Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Clinical Packet
November 12, 2014

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Pharmacy and Therapeutics (P&T) Committee
Helpful Hints/Reference Document

P&T Charge

As defined by §22-6-122

The Medicaid Pharmacy and Therapeutics (P&T) Committee shall review and recommend classes of drugs to the Medicaid Commissioner for inclusion in the Medicaid Preferred Drug Plan. Class means a therapeutic group of pharmaceutical agents approved by the FDA as defined by the American Hospital Formulary Service.

The P&T Committee shall develop its preferred drug list recommendations by considering the clinical efficacy, safety and cost effectiveness of a product. Within each covered class, the Committee shall review and recommend drugs to the Medicaid Commissioner for inclusion on a preferred drug list. Medicaid should strive to insure any restriction on pharmaceutical use does not increase overall health care costs to Medicaid.

The recommendations of the P&T Committee regarding any limitations to be imposed on any drug or its use for a specific indication shall be based on sound clinical evidence found in labeling, drug compendia and peer reviewed clinical literature pertaining to use of the drug. Recommendations shall be based upon use in the general population. Medicaid shall make provisions in the prior approval criteria for approval of non-preferred drugs that address needs of sub-populations among Medicaid beneficiaries. The clinical basis for recommendations regarding the PDL shall be made available through a written report that is publicly available. If the recommendation of the P&T Committee is contrary to prevailing clinical evidence found in labeling, drug compendia and/or peer-reviewed literature, such recommendation shall be justified in writing.

Preferred Drug List/Program Definitions

Preferred Drug: Listed on the Agency's Preferred Drug Lists and will not require a prior authorization (PA).

Non Preferred Drug: Covered by the Agency, if it is determined and supported by medical records to be medically necessary, but will require a PA.

Non Covered Drug: In accordance with Medicaid Drug Amendments contained in the Omnibus Budget Reconciliation Act of 1990 (OBRA 90 federal legislation), the Agency has the option to not cover (or pay for) some drugs. Alabama Medicaid does not cover/pay for the following:

- Drugs used for anorexia, weight loss or weight gain, with the exception of those specified by the Alabama Medicaid Agency
- Drugs used to promote fertility with the exception of those specified by the Alabama Medicaid Agency
- Drugs used for cosmetic purposes or hair growth
- Over-the-counter/non prescription drugs, with the exception of those specified by the Alabama Medicaid Agency
- Covered outpatient drugs when the manufacturer requires as a condition of sale that associated test and/or monitoring services be purchased exclusively from the manufacturer or designee
- DESI (Drug Efficacy Study Implementation [less than effective drugs identified by the FDA]) and IRS (Identical, Related and Similar [drugs removed from the market]) drugs which may be restricted in accordance with Section 1927(d) (2) of the Social Security Act
- Agents when used for the symptomatic relief of cough and colds except for those specified by the Alabama Medicaid Agency
- Prescription vitamin and mineral products, except prenatal vitamins and fluoride preparations and others as specified by the Alabama Medicaid Agency
- Benzodiazepines and barbiturates with the exception of those specified by the Alabama Medicaid Agency
- Agents used to promote smoking cessation, unless authorized for pregnant females or plan first recipients
- Agents when used for the treatment of sexual or erectile dysfunction, unless authorized for pulmonary hypertension.

(From Alabama Medicaid Agency Administrative Code, Chapter 16 and Alabama Medicaid Agency Provider Billing Manual, Chapter 27.)

Prior Authorization (PA): Process that allows drugs that require approval prior to payment to be reimbursed for an individual patient. Drugs may require PA if they are in Non-preferred status or if they required PA prior to the PDL

Medicaid may require prior authorization for generic drugs only in instances when the cost of the generic product is significantly greater than the net cost of the brand product in the same AHFS therapeutic class or when there is a clinical concern regarding safety, overuse or abuse of the product.

Although a product may require PA, the product is considered a covered product and Medicaid will pay for the product only once the PA has been approved.

Override: Process where drugs require approval prior to payment to be reimbursed for an individual patient if the claim falls outside a predetermined limit or criteria. Overrides differ from PA in that drugs or drug classes that require an override will automatically allow payment of the drug unless something on the claim hits a predetermined limit or criteria. The different types of overrides include:

Maximum Unit Limitations
Early Refill
Brand Limit Switchover
Therapeutic Duplication

Electronic PA (EPA): The EPA system checks patient-specific claims history to determine if pharmacy and medical PA requirements are met at the Point-of-Sale claim submission for a non-preferred drug. If it is determined that all criteria are met and the request is approved, the claim will pay and no manual PA request will be required. Electronic PA results in a reduction in workload for providers because the claim is electronically approved within a matter of seconds with no manual PA required.

Prior Authorization Criteria Definitions

Appropriate Diagnosis: Diagnosis(es) that justifies the need for the drug requested. Diagnosis(es) **or** ICD-9 code(s) may be used. Use of ICD-9 codes provides specificity and legibility and will usually expedite review.

Prior Treatment Trials: Prior authorization requires that two (2) prescribed generic or brand name drugs have been utilized unsuccessfully relative to efficacy and/or safety within six (6) months prior to requesting the PA. The PA request must indicate that two (2) generic or other brand drugs have been utilized for a period of at least thirty (30) days each (14 days for Triptans, 3 days for EENT Vasoconstrictor Agents), **unless** there is an adverse/allergic response or contraindication. If the prescribing practitioner feels there is a medical reason for which the patient should not be on a generic or brand drug or drug trial, medical justification may be submitted in lieu of previous drug therapy. One prior therapy is acceptable in those instances when a class has only one preferred agent, either generic, or brand.

Stable Therapy: Allows for approval of a PA for patients who have been determined to be stable on a medication (same drug, same strength) for a specified timeframe and who continue to require therapy. Medications provided through a government or state sponsored drug assistance program for uninsured patients may be counted toward the stable therapy requirement. Medications paid for through insurance, private pay or Medicaid are also counted toward the requirement. Providers will be required to document this information on the PA request form and note the program or method through which the medication was dispensed.

Medical Justification: An explanation of the reason the drug is required and any additional information necessary. Medical justification is documentation to support the physician's choice of the requested course of treatment. Documentation from the patient record (history and physical, tests, past or current medication/treatments, patient's response to treatment, etc) illustrates and supports the physician's request for the drug specified. For example, if a recommended therapy trial is contraindicated by the patient's condition or a history of allergy to a first-line drug, and the physician wants to order a non-preferred drug, documentation from the patient record would support that decision. In addition, medical justification may include peer reviewed literature to support the use of a non-preferred medication.

External Criteria

Anti-infective Agents

Appropriate Diagnosis

- The patient must have an appropriate diagnosis supported by documentation in the patient record.

Prior Treatment Trials

- The patient must also have failed two treatment trials of no less than three-days each, with at least two prescribed and preferred anti-infectives, either generic, OTC, or brand, for the above diagnosis within the past 30 days or have a documented allergy or contraindication to all preferred agents for the diagnosis submitted.

- For Olysio® and Victrelis®, in lieu of prior usage requirements, approval may be obtained for adjunctive therapy to hepatitis C treatment with peginterferon alfa and ribavirin in patients ≥18 years of age with genotype 1 chronic hepatitis C and a documented Sovaldi® contraindication.

- For Sovaldi®, please see Form 415 for specific information.

Stable Therapy

- Patients on anti-infective therapy while institutionalized once discharged or transferred to another setting or patients having a 60 day consecutive stable therapy may continue on that therapy with supportive medical justification or documentation.

Medical Justification

- Medical justification may include peer-reviewed literature, medical record documentation, or other information specifically requested. Approval may also be given, with medical justification, if the medication requested is indicated for first line therapy when there are no other indicated preferred agents available or if indicated by susceptibility testing or evidence of resistance to all preferred agents.

PA Approval Timeframes

- Approval may be given for up to 12 months.

Electronic Prior Authorization (EPA)

- Not Applicable

Verbal PA Requests

- PA requests that meet prior usage requirement for approval may be accepted verbally.

AGENDA

ALABAMA MEDICAID AGENCY
PHARMACY AND THERAPEUTICS (P&T) COMMITTEE

November 12, 2014
9:00 a.m. – 12:00 noon

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1. Opening remarks…….....…..Chair
2. Approval of August 13, 2014 P&T Committee Meeting minutes…….……...…Chair
3. Pharmacy program update…….…...….…….....…...Alabama Medicaid
4. Oral presentations by manufacturers/manufacturers' representatives (prior to each respective class review)
5. Pharmacotherapy class re-reviews……..…….……..University of Massachusetts Clinical Pharmacy Services
    - Allylamines – AHFS 081404
    - Azoles – AHFS 081408
    - Echinocandins – AHFS 081416
    - Polyenes – AHFS 081428
    - Pyrimidines – AHFS 081432
    - Antifungals, Miscellaneous – AHFS 081492
    - Antituberculosis Agents – AHFS 081604
    - Antimycobacterials, Miscellaneous – AHFS 081692
    - Adamantanes – AHFS 081804
    - Interferons – AHFS 081820
    - Neuraminidase Inhibitors – AHFS 081828
    - Nucleosides and Nucleotide – AHFS 081832
    - HCV Antivirals – AHFS 081840
    - Antivirals, Miscellaneous – AHFS 081892
    - Amebicides – AHFS 083004
    - Antimalarials – AHFS 083008
    - Antiprotozoals, Miscellaneous – AHFS 083092
    - Urinary anti-infectives – AHFS 083600
6. Results of voting announced……...…….....…….Chair
7. Upcoming meeting dates
    - February 11, 2015
    - May 20, 2015
    - August 12, 2015
    - November 18, 2015
8. Adjourn

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Allylamines
AHFS Class 081404
November 12, 2014

I. Overview

Serious fungal infections are relatively rare, but in recent years they have taken on greater importance in clinical practice because of an increased number of opportunistic fungal infections in immunocompromised patients. Contributing factors have been the advent of human immunodeficiency virus and the more frequent use of immunosuppressive drugs as part of other therapies. For instance, those receiving immunosuppressive drug regimens for the management of organ transplantation or autoimmune inflammatory conditions, or those undergoing chemotherapy for hematologic malignancies, are potential hosts for systemic fungal invasion.[1] Fungal infections can also be brought on by antibiotic use, particularly with broad-spectrum antibiotics which kill organisms that inhibit fungal growth, or with the use of antibiotics for long-term prophylaxis.[1]

The systemic antifungals are categorized into six different American Hospital Formulary Service (AHFS) classes, including allylamines, azoles, echinocandins, polyenes, pyrimidines, and miscellaneous agents. The agents which make up these classes differ in their structure, pharmacokinetics, spectrum of activity, and Food and Drug Administration-approved indications.

Terbinafine is the only allylamine currently available, and it is approved for the treatment of onychomycosis and tinea capitis.[2-6] It inhibits biosynthesis of ergosterol via inhibition of squalene epoxidase enzyme. This results in fungal cell death, which is primarily due to increased membrane permeability.

The allylamines that are included in this review are listed in Table 1. This review encompasses all systemic dosage forms and strengths. The topical antifungals were previously reviewed with the skin and mucous membrane agents (AHFS 840408) and are not included in this review. Terbinafine (tablet formulation) is available in a generic formulation. This class was last reviewed in May 2012.

Table 1. Allylamines Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Terbinafine	granules, tablet	Lamisil®*	terbinafine

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List

The allylamines have been shown to be active against the strains of microorganisms indicated in Table 2. This activity has been demonstrated in clinical infections and is represented by the Food and Drug Administration (FDA)-approved indications for the allylamines that are noted in Table 4. These agents may also have been found to show activity to other microorganisms in vitro; however, the clinical significance of this is unknown since their safety and efficacy in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials. Although empiric anti-infective therapy may be initiated before culture and susceptibility test results are known, once results become available, appropriate therapy should be selected.

Table 2. Microorganisms Susceptible to the Allylamines[2-6]

Organism	Terbinafine
Trichophyton mentagrophytes	✔
Trichophyton rubrum	✔

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the allylamines are summarized in Table 3.

Table 3. Treatment Guidelines Using the Allylamines

Clinical Guideline	Recommendation(s)
European Academy of Dermatology and Venereology: **Onychomycosis Treatment Guidelines (2005)**[7]	• Prior to initiating treatment, it is important that the diagnosis be confirmed and the etiological agent identified. • Topical monotherapy is indicated when the matrix area is not involved. Topical treatment is also suitable for patients who are reluctant to take oral medications or have swallowing difficulties. The only case in which it is not recommended is if nail penetration may be suboptimal. • Oral antifungal drugs are generally considered to be more effective than topical treatments. However, they are accompanied by a higher risk of systemic adverse effects and drug interactions. • Oral monotherapy (terbinafine, itraconazole, or fluconazole) or combined oral and topical (nail lacquer) is recommended when 1) at least 50% of the distal nail plate is involved; 2) the nail matrix area is involved; 3) mycological criteria such as the causative agent or agents are known and oral agents can target specific fungi; 4) topical drugs are not indicated when topical drug transport is suboptimal; and 5) oral or combined therapy is also recommended in cases of nail matrix area involvement. • Combination therapy with systemic and topical treatments may be considered when a large portion of the nail plate is affected (>50%), when the nail matrix is involved, and in cases of treatment failure. • Griseofulvin is associated with the poorest mycological cure rate (<30%) and is rarely used. Terbinafine is associated with the highest mycological cure rate (77 to 100%).
British Association of Dermatologists: **Guidelines for the Treatment of Onychomycosis (2003)**[8]	• Both topical and oral agents are available for the treatment of fungal nail infection. The primary aim of treatment is to eradicate the organism as demonstrated by microscopy and culture. • Systemic therapy is almost always more successful than topical treatment, which should only be used in superficial white onychomycosis, possibly very early distal and lateral subungual onychomycosis, or when systemic therapy is contraindicated. • Both terbinafine and itraconazole have been shown to be more effective than griseofulvin in dermatophyte onychomycosis and the optimal choice of treatment lies between terbinafine and itraconazole. • Terbinafine is more effective than itraconazole for dermatophyte infection of the nails and should be first-line treatment. Itraconazole may be considered a second-line treatment. • Expected cure rates vary and range from 80 to 90% for fingernail infections and 70 to 80% for toenail infections.
European Society for Pediatric Dermatology: **Guidelines for the Management of Tinea Capitis in Children (2010)**[9]	• Tinea capitis always requires systemic treatment because topical antifungal agents do not penetrate the hair follicle. • Topical treatment is only used as adjuvant therapy to systemic antifungals. • Griseofulvin has been the gold standard for systemic therapy of tinea capitis. The main disadvantage of griseofulvin is the long duration of treatment required (six to 12 weeks or longer) which may lead to reduced compliance. • The newer oral antifungal agents including terbinafine, itraconazole, and fluconazole appear to have efficacy rates and potential adverse effects similar to those of griseofulvin in children with tinea capitis due to *Trichophyton* species, while requiring much shorter duration of

Clinical Guideline	Recommendation(s)
	treatment. The decision between griseofulvin and newer antifungal agents for children with *Trichophyton* species can be based on the balance between duration of treatment and compliance. • Griseofulvin is still the treatment of choice for cases caused by *Microsporum* species. • Adjunctive topical therapies, such as selenium sulfide or ketoconazole shampoos, as well as fungicidal creams or lotions have been shown to decrease the carriage of viable spores responsible for the disease contagion and reinfection and may shorten the cure rate with oral antifungals. • The topical fungicidal cream/lotion should be applied to the lesions once daily for a week. The shampoo should be applied to the scalp and hair for five minutes twice weekly for two to four weeks or three times weekly until the patient is clinically and mycologically cured. The latter in conjunction with one week of topical fungicidal cream or lotion application is recommended.

British Association of Dermatologists: **Guidelines for the Management of Tinea Capitis (2000)**[10]	• The aim of treatment is to achieve a clinical and mycological cure as quickly as possible.
	• Oral antifungal therapy is generally needed. Topical treatment alone is not recommended for the management of tinea capitis.
	• Oral therapy options include griseofulvin, terbinafine, itraconazole, fluconazole, and ketoconazole.
	• If there has been no clinical response and signs persist at the end of the treatment period, then the options include:
	  o Increase the dose or duration of the original drug (both griseofulvin and terbinafine have been used successfully and safely at higher doses or for longer courses to clear resistant infections)
	  o Change to an alternative antifungal (e.g., switch from griseofulvin to terbinafine or itraconazole).
	• Symptom-free carriers with light growth/low spore count on culture may be treated with twice weekly selenium or povidone shampoo.
	• The definitive end-point for adequate treatment is not clinical response but mycological cure; therefore, follow-up with repeat mycology sampling is recommended at the end of the standard treatment period and then monthly until mycological clearance is documented. Treatment should, therefore, be tailored for each individual patient according to response.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the allylamines are noted in Table 4. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 4. FDA-Approved Indications for the Allylamines[2-6]

Indication	Terbinafine Tablets	Terbinafine Granules
Treatment of onychomycosis of the toenail or fingernail due to dermatophytes (tinea unguium)	✔	
Treatment of tinea capitis		✔

IV. Pharmacokinetics

The pharmacokinetic parameters of the allylamines are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Allylamines[2-6]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Terbinafine	40	99	Hepatic	Renal (70 to 80) Bile (20)	22 to 26

V. Drug Interactions

Significant drug interactions with the allylamines are listed in Table 6.

Table 6. Significant Drug Interactions with the Allylamines[2]

Generic Name(s)	Significance Level	Interaction	Mechanism
Terbinafine	2	Serotonin reuptake blockers	Plasma concentrations and pharmacologic effects of serotonin reuptake blockers may be increased when co-administered with terbinafine. The potential for adverse effects due to serotonin reuptake blockers may be increased. Inhibition of CYP2D6-mediated metabolism of serotonin reuptake blockers by terbinafine is suspected.
Terbinafine	2	Tricyclic antidepressants	Terbinafine may increase pharmacologic effects and plasma concentrations of tricyclic antidepressants. Toxic signs may occur. Inhibition of cytochrome P450 2D6 isoenzymes by terbinafine may decrease the metabolic elimination of tricyclic antidepressants.
Terbinafine	2	Cyclosporine	Terbinafine may decrease cyclosporine concentrations by increasing cyclosporine metabolism.

Significance level 1 = major severity; significance level 2 = moderate severity

VI. Adverse Drug Events

The most common adverse drug events reported with the allylamines are listed in Table 7.

Table 7. Adverse Drug Events (%) Reported with the Allylamines[2-6]

Adverse Events	Terbinafine Granules	Terbinafine Tablets
Central Nervous System		
Fatigue	✔	✔
Fever	7	✔
Headache	7	-
Malaise	✔	✔
Dermatological		
Alopecia	✔	✔
Exanthematous pustulosis	✔	✔
Photosensitivity reaction	✔	✔
Pruritus	1	3
Psoriasiform eruption	✔	✔
Psoriasis exacerbation	✔	✔
Rash	2	6
Stevens-Johnson syndrome	✔	✔
Toxic epidermal necrolysis	✔	✔
Urticaria	1	1
Gastrointestinal		
Abdominal pain	2 to 4	2
Diarrhea	3	6
Dyspepsia	-	4
Flatulence	-	2
Nausea	2	3
Taste disturbance	✔	3
Taste loss	✔	✔
Toothache	1	-
Vomiting	5	✔
Hematological		
Agranulocytosis	✔	✔
Anemia	✔	✔
Neutropenia	✔	✔
Pancytopenia	✔	✔
Thrombocytopenia	✔	✔
Hepatic		
Hepatic failure	✔	✔
Hepatic injury	✔	✔
Liver enzyme abnormalities	-	3
Musculoskeletal		
Arthralgia	✔	✔
Myalgia	✔	✔
Rhabdomyolysis	✔	✔
Respiratory		
Cough	6	-
Nasal congestion	2	-
Nasopharyngitis	10	-
Pharyngolaryngeal pain	2	-
Rhinorrhea	2	-
Upper respiratory tract infection	5	-
Other		
Allergic reactions	✔	✔

Adverse Events	Terbinafine Granules	Terbinafine Tablets
Angioedema	✔	✔
Creatine phosphokinase increased	✔	✔
Influenza-like illness	2	✔
Lupus erythematosus exacerbation	✔	✔
Ocular lens and retina changes	✔	-
Pancreatitis	✔	✔
Serum sickness-like reaction	✔	✔
Smell disturbance	✔	✔
Smell loss	✔	✔
Vasculitis	✔	✔
Visual disturbance	✔	1

✔ Percent not specified
- Event not reported

VII. Dosing and Administration

The usual dosing regimens for the allylamines are listed in Table 8.

Table 8. Usual Dosing Regimens for the Allylamines[2-6]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Terbinafine	Treatment of onychomycosis of the fingernail due to dermatophytes (tinea unguium): Tablet: 250 mg once daily for six weeks Treatment of onychomycosis of the toenail due to dermatophytes (tinea unguium): Tablet: 250 mg once daily for 12 weeks Treatment of tinea capitis Granules: <25 kg, 125 mg once daily for six weeks; 25 to 35 kg, 187.5 mg once daily for six weeks; >35 kg, 250 mg once daily for six weeks	Treatment of tinea capitis in children ≥4 years of age: Granules: <25 kg, 125 mg once daily for six weeks; 25 to 35 kg, 187.5 mg once daily for six weeks; >35 kg, 250 mg once daily for six weeks	Granules: 125 mg 187.5 mg Tablet: 250 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the allylamines are summarized in Table 9.

Table 9. Comparative Clinical Trials with the Allylamines

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Onychomycosis				
Haneke et al.[11] (1995) Terbinafine 250 mg daily for 12 weeks vs griseofulvin microsize 500 mg daily for 12 weeks After 12 weeks of treatment, all patients received an additional 12 weeks of placebo followed by 6 months follow-up	DB, MC, RCT Patients 18 years of age and older with clinically confirmed distal subungual onychomycosis of the fingernails	N=180 1 year	Primary: Clinical response (outgrowth from the border of healthy and infected nails), mean global score (based on onycholysis, hyperkeratosis, brittleness, and paronychial inflammation), mycological cure (negative culture), mean time to negative culture Secondary: Not reported	Primary: Mycological cure rates increased in both groups during active treatment and continued in the terbinafine group during follow-up while remaining steady in the griseofulvin group. At week 24, 90% of patients in the terbinafine group and 64% in the griseofulvin group were mycologically cured. At the end of the study, 92% of patients in the terbinafine group and 63% in the griseofulvin group were mycologically cured (P<0.001). Mean time to negative culture was 73 days in the terbinafine group and 93 days in the griseofulvin group. The length of unaffected nail increased in the terbinafine group from 3.2 to 11.4 mm (week 24) and 12.4 mm (end of study). In the griseofulvin group, it increased from 2.6 to 9.5 mm (week 24) and decreased to 8.7 mm at the end of the study (P=0.006 between groups at the end of the study). The mean global scores decreased in the terbinafine group from 5.8 to 0.9 (week 24) and 0.4 (end of study). In the griseofulvin group, the scores decreased from 5.7 to 1.8 (week 24) and increased to 2.2 at the end of the study (P=0.028 at week 24; P<0.001 at end of study). Secondary: Not reported
Faergemann et al.[12] (1995) Terbinafine 250	DB, PG, RCT Adult patients with culture-proven tinea of the toenails	N=89 52 weeks	Primary: Complete cure (no signs and symptoms of infection and	Primary: Significantly more patients in the terbinafine group were completely cured (42%) compared to the griseofulvin group (2%) at the end of the study (P<0.0005).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg daily for 16 weeks vs griseofulvin 500 mg daily for 52 weeks Patients who did not respond after 16 weeks were switched to OL terbinafine for 16 to 20 weeks of follow-up			negative culture), mycological cure (negative culture) Secondary: Not reported	Significantly more patients in the terbinafine group experienced mycological cure (84%) compared to the griseofulvin group (45%) at the end of the study (P<0.0005). Of the patients who switched to open-label treatment with terbinafine, 44% were cured at the end of the study (week 52 or 20 weeks after cessation of open-label terbinafine) compared to 18% in the griseofulvin group. Secondary: Not reported
Hoffman et al.[13] (1995) Terbinafine 250 mg daily for 24 weeks, followed by placebo for 24 weeks vs griseofulvin micronized 1,000 mg daily for 48 weeks	DB, RCT Patients 21 to 93 years of age with clinically confirmed distal subungual onychomycosis of the toenails	N=195 72 weeks	Primary: Mycological cure (negative culture), clinical response (global score based on growth of unaffected nail and presence of onycholysis, hyperkeratosis, brittleness, and paronychial inflammation), time to mycological cure Secondary: Not reported	Primary: Mycological cure increased during active therapy in both groups and slightly decreased in the terbinafine group while sharply decreasing in the griseofulvin group during the follow-up period. At week 48, 88% of terbinafine patients and 82% of griseofulvin patients had negative cultures, while these numbers decreased to 81 and 62%, respectively, at the end of the study (P=0.02). The time to negative culture was 130 days in the terbinafine group and 172 days in the griseofulvin group (P=0.036). The mean global score in the terbinafine group decreased from 6.3 to 1.4 at week 48 and 0.8 at the end of the study, compared to 7.0 in the griseofulvin group decreasing to 1.7 at week 48 and 1.8 at the end of the study (P=0.010). Secondary: Not reported
Haugh et al.[14] (2002)	MA	N=2,063	Primary: Mycological cure	Primary: <u>Terbinafine vs placebo (three trials)</u>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Terbinafine 250 mg daily for 3 to 6 months vs griseofulvin 500 to 1,000 mg daily for 3 months to 11 months vs itraconazole 200 mg daily or 400 mg intermittently (for 1 of every 4 weeks) for 3 to 4 months vs placebo	Patients diagnosed with onychomycosis	3 to 11 months	at the end of the studies (negative microscopy or culture), negative microscopy or culture at specified time points Secondary: Not reported	After 12 weeks, a significant advantage in mycological cure rates was seen in favor of the terbinafine group compared to the placebo group. <u>Terbinafine vs itraconazole (four trials)</u> At the end of the study periods, a statistically significant advantage in achieving negative culture and microscopy was seen in favor of terbinafine compared to itraconazole. No significant differences in the occurrence of adverse events were reported. <u>Terbinafine vs griseofulvin (two trials)</u> Significantly higher rates of negative microscopy and culture were observed in the terbinafine groups at week 24 compared to the griseofulvin groups. Secondary: Not reported
Brautigam[15] (1998) Terbinafine 250 mg daily for 12 weeks vs itraconazole 200 mg daily for 12 weeks	DB, MC, PG, RCT Patients 18 years of age and older with a clinical diagnosis of distal subungual or proximal onychomycosis of the toenails	N=195 52 weeks	Primary: Mycologic cure (culture negative for dermatophytes and hyphae), clinical efficacy (length of unaffected area on the target nail) Secondary: Not reported	Primary: Significantly more patients in the terbinafine group had experienced mycological cure (81.4%) compared to the itraconazole group (63.1%, P<0.01) at week 52. At week 52, 91.9% of cultures were negative for dermatophytes in the terbinafine group compared to 66.6% in the itraconazole group (P<0.0001). The mean time to the first negative culture was significantly shorter in the terbinafine group (8.52 weeks) compared to the itraconazole group (11.64 weeks; P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Terbinafine was significantly more effective in increasing the length of unaffected nail compared to itraconazole. At week 52, a significantly lower number of patients in the terbinafine group had >60% of the nail plate affected (3.5% of patients) compared to the number in the itraconazole group (15.5% of patients; P<0.05). Secondary: Not reported
Evans et al.[16] (1999) Terbinafine 250 mg daily for 12 to 16 weeks vs itraconazole 200 mg daily for 1 of every 4 weeks for 12 (3 cycle) or 16 weeks (4 cycle)	DB, MC, PG, RCT Patients 18 to 75 years of age with a clinical diagnosis of onychomycosis of the toenail confirmed by positive results on mycological cure and microscopy	N=496 72 weeks	Primary: Mycologic cure (negative results on microscopy and culture) Secondary: Clinical cure (100% toenail clearing), complete cure (mycological and clinical cure), clinical effective-ness (mycological cure and at least 5 mm of new clear toenail growth), and global assessments by physician and patient	Primary: Mycologic cure rates were significantly higher in both terbinafine groups (81 and 80%, respectively) compared to the itraconazole groups (41 and 53% for the 3-cycle and 4-cycle itraconazole groups, respectively; P<0.0001). Secondary: Clinical cure rates were significantly higher in the terbinafine groups compared to the itraconazole groups (P<0.0022). Complete cure rates were significantly higher in the continuous terbinafine group compared to both itraconazole groups (P<0.0044). Clinical effectiveness and global assessments were significantly higher for the continuous terbinafine groups compared to the itraconazole groups (P<0.0001).
Degreef et al[17] (1999) Terbinafine 250 mg daily for 12 weeks	DB, MC, PG, RCT Patients 18 to 65 years of age with clinically suspected and microscopically and culturally	N=297 36 weeks	Primary: Mycologic cure (culture negative) Secondary: Investigator's global clinical	Primary: A similar number of patients were mycologically cured (79 in the terbinafine group and 78 in the itraconazole group). Secondary: Clinical response rates were similar between the groups (P<0.1).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs itraconazole 200 mg daily for 12 weeks	proven onychomycosis of the toenail		evaluation of response to treatment defined as clinical response (cured or markedly improved, ≥50% clinical improve-ment), percentage of total affected nail area, total number of infected nails, signs and symptoms of onycholysis, hyperkeratosis, paronychial inflammation and discoloration	Complete clinical cure rates were similar between the groups. The mean percentage of affected nail area and the mean number of nails infected decreased similarly in the two groups. Signs and symptoms of infections improved comparably in the two groups.
Gupta et al.[18] (2001) Terbinafine 250 mg daily for 12 weeks vs itraconazole 200 mg 2 times daily for 1 week given as 3 pulses	CS, PRO, RCT, SB Patients 60 years of age and older with dermatophyte onychomycosis of at least 1 great toe	N=101 18 months	Primary: Mycologic cure (negative cultures), clinical efficacy (mycological cure and either clinical cure or reduction of involved nail plate to 10% or less) Secondary: Not reported	Primary: At month 18, the mycological cure rate in the terbinafine group was 64% and 62.7% in the itraconazole group. No significant difference was found between groups. At month 18, clinical efficacy was 62% in the terbinafine group and 60.8% in the itraconazole group. No significant difference was found between groups. Secondary: Not reported
Sigurgeirsson et al.[19] (2002) Terbinafine 250 mg daily for 12 or	DB, PRO, RCT Patients 18 to 75 years of age with onychomycosis of the toenail	N=158 72 weeks	Primary: Proportion of patients who remained mycologically cured (negative	Primary: Significantly more patients originally treated with terbinafine were mycologically cured at the end of the study compared to patients originally treated with itraconazole (46% compared to 13%; P<0.001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
16 weeks vs itraconazole 400 mg daily for 1 of every 4 weeks for 12 (3 cycles) or 16 (4 cycles) weeks	confirmed by culture finding infection with a dermatophyte		culture) at the end of follow-up without requiring continued treatment with terbinafine Secondary: Clinical cure (100% normal-appearing nail), complete cure (mycological plus clinical cure), clinical and mycological relapse over time, mycological and clinical cure over time, effect of subsequent terbinafine treatment on clinical and mycological outcome Secondary: Not reported	Significantly more patients originally treated with terbinafine were clinically cured at the end of the study compared to patients originally treated with itraconazole (42% compared to 18%; P<0.002). Significantly more patients in the terbinafine group maintained complete cure at the end of the study compared to patients in the itraconazole group (P<0.005). At the end of the study, significantly fewer terbinafine patients had mycologically relapsed compared to itraconazole patients (23% compared to 53%; P<0.01). At the end of the study, significantly fewer terbinafine patients had clinically relapsed compared to itraconazole patients (21% compared to 48%; P<0.05). Ninety-two percent of patients who originally received terbinafine and subsequently received a second course of treatment with terbinafine after 18 months achieved mycological cure compared to 85% of those originally treated with itraconazole. Similar results were seen with clinical cure rates: it was achieved in 76% of patients originally treated with terbinafine and 77% of patients originally treated with itraconazole. Secondary: Not reported
Sigurgeirsson et al.[20] (1999) Terbinafine 250 mg daily for 12 weeks (group T_{12}) or 16 weeks (group T_{16})	DB, DD, MC, PG, PRO, RCT Patients 18 to 75 years of age with distal subungual or total dystrophic onychomycosis of the toenails	N=507 72 weeks	Primary: Mycological cure (negative microscopy and cultures) Secondary: Clinical cure (100% toenail	Primary: Mycological cure rates were 75.7% in the T_{12} group, 80.8% in the T_{16} group, 38.3% in the I_3 group and 49.1% in the I_4 group. Results were statistically significant in favor of the terbinafine regimens (P<0.0001). Secondary: Clinical cure was 53.6, 60.2, 31.8, and 32.1% for the T_{12}, T_{16}, I_3, and I_4 groups respectively, and all were significantly in favor of the terbinafine regimens (P<0.002).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs itraconazole 400 mg/day for 1 week every 4 weeks for 12 weeks (group I_3) or 16 weeks (group I_4)	confirmed mycologically		clearing), complete cure (mycological and clinical cure), clinical efficacy (mycological cure and at least 5 mm of new clear toenail growth), global assessment of efficacy by patient and physician	Complete cure rates were 45.8, 55.1, 23.4, and 25.9% for the T_{12}, T_{16}, I_3, and I_4 groups respectively, and all were significantly in favor of the terbinafine regimens (P<0.0007). Clinical efficacy rates were significantly in favor of the terbinafine regimens (P<0.0001). Global assessment of efficacy by patients was very good or excellent in 78.9, 78.8, 43.9, and 52.3% of patients in the T_{12}, T_{16}, I_3, and I_4 groups, respectively, and were statistically in favor of the terbinafine regimens (P<0.0001). Global assessment of efficacy by physicians was very good or excellent in 78.9, 78.8, 43.9, and 52.3% of patients in the T_{12}, T_{16}, I_3, and I_4 groups, respectively, and these assessments statistically favored the terbinafine regimens (P<0.0001).
Heikkila et al.[21] (2002) Terbinafine 250 mg daily for 12 or 16 weeks vs itraconazole 400 mg daily for 1 of every 4 weeks for 12 (3 cycles) or 16 (4 cycles) weeks	DB, MC, RCT Finnish participants 18 to 75 years of age with a clinical diagnosis of onychomycosis of the toenail confirmed by culture	N=76 4 years	Primary: Mycologic cure (microscopy and culture negative), clinical cure (100% clearing of all toenails), complete cure (mycological and complete cure) Secondary: Not reported	Primary: At four years, terbinafine was shown to be more effective than itraconazole. At four years, negative microscopy and culture remained unchanged in the terbinafine group treated for 16 weeks, but fell to <50% in all other groups. At four years, clinical and complete cure rates in the terbinafine group treated for 16 weeks was better than the rates seen at 72 weeks (78% compared to 50%), but remained unchanged or worsened in all other groups. Secondary: Not reported
De Backer et al.[22] (1998) Terbinafine 250 mg daily for 12	DB, RCT Patients 18 years of age and older with clinically suspected	N=372 48 weeks	Primary: Percentage of patients with negative culture at week 48, length of	Primary: At week 48, significantly more patients in the terbinafine group had negative microscopy results (77.9%) compared to the itraconazole group (55.4%; P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
weeks vs itraconazole 200 mg daily for 12 weeks	subungual dermato-phyte infections of the toenails confirmed by microscopy and culture		healthy nail, hyperkeratosis, onycholysis, paronychial inflammation, investigator and patient assessment of efficacy of treatment Secondary: Not reported	At week 48, significantly more patients in the terbinafine group had negative dermatophyte culture results (84%) compared to the itraconazole group (64.3%; P<0.0001). At week 48, significantly more patients in the terbinafine group had negative mycology results (73%) compared to the itraconazole group (45.8%; P<0.0001). At week 48, patients in the terbinafine group had significantly more healthy nail in the big toe compared to the itraconazole group (8.1 and 6.4 mm, respectively; P=0.026). At week 48, onycholysis score significantly favored terbinafine compared to itraconazole (P=0.001). There was no significant difference in hyperkeratosis scores between groups (P=0.27). Paronychial inflammation was absent in the majority of patients in both groups. The global clinical evaluation of the target nail at week 48 was significantly higher in the terbinafine group (cleared or minimal symptoms) compared to the itraconazole group (76.2 and 58.1%, respectively; P=0.001). Secondary: Not reported
De Backer et al.[23] (1996) Terbinafine 250 mg daily for 12 weeks vs	DB, RCT Patients with a clinical diagnosis of toenail onychomycosis	N=372 48 weeks	Primary: Clinical symptoms, rate of negative mycology (negative microscopy and negative culture) Secondary:	Primary: Clinical symptoms in the target nail improved significantly more in the terbinafine group compared to the itraconazole group (P=0.001). The unaffected nail length for big toes was significantly greater in the terbinafine group compared to the itraconazole group (9.1 and 7.7 mm, respectively; P=0.0298). Onycholysis was less frequent in the terbinafine group compared to the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
itraconazole 200 mg daily for 12 weeks			Not reported	itraconazole group (P=0.001). No significant difference was seen between groups in hyperkeratosis. Negative mycology was observed in 73% of terbinafine patients compared to 45.8% of itraconazole patients at week 48 (P<0.0001). Secondary: Not reported
Arenas et al.[24] (1995) Terbinafine 250 mg daily for 3 months vs itraconazole 200 mg daily for 3 months	CS, OL, PRO Patients 18 years of age and older with onychomycosis	N=53 9 months	Primary: Culture and potassium hydroxide (KOH) smear results, affected nail area, medical evaluation of treatment (cure, improvement, no changes, deterioration) Secondary: Nail changes, nail growth, patient evaluation of treatment	Primary: At the end of treatment, rates of positive KOH smears were similar between groups (21.7% for itraconazole and 23.5% for terbinafine). At the end of treatment, there was one positive culture in the terbinafine group and at the end of follow-up, there was one positive culture in the itraconazole group. Both treatment groups showed improvement in nail area affected compared to baseline (P<0.01) and there was no significant difference between groups. There was no significant difference between groups in the medical evaluation of treatment. There was no significant difference in cure and improvement between groups. Secondary: There were no significant differences in nail changes or nail growth between groups. There was no significant difference between groups in the patients' evaluation of treatment.
Bahadir et al.[25] (2000) Terbinafine 250	RCT Patients with clinically and	N=60 24 week posttreatment	Primary: Therapeutic response (healing, remission, or	Primary: Healing was achieved in 60% of itraconazole patients and 68.5% of terbinafine patients (P=0.50).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg daily for 3 months vs itraconazole 100 mg 2 times daily for the first week of 3 consecutive months	mycologically confirmed onychomycosis	follow-up	failure, undefined) Secondary: Not reported	Remission was achieved in 28% of itraconazole patients and 25.7% of terbinafine patients (P=0.50). Failure was reported in 4% of itraconazole patients and 2.85% of terbinafine patients (P=0.50). Secondary: Not reported
Honeyman et al.[26] (1997) Terbinafine 250 mg daily for 4 months vs itraconazole 200 mg daily for 4 months Patients in both groups received placebo for an additional 8 months after initial therapy.	DB, MC, PG, RCT Patients with toenail onychomycosis	N=179 12 months	Primary: Clinical response (symptom scores), mycological response (negative culture), clinical global evaluation scores [CGE, defined as complete cure, improvement (reduction of >50%), unchanged, or worsening], effectively cured patient scores (ECP, defined as complete mycological cure plus clinical improvement or complete cure) Secondary: Not reported	Primary: At the end of treatment (four months), mycological cure was similar for terbinafine and itraconazole (54.9 and 51.8%, respectively). At 12 months, the mycological cure was 95.3% for terbinafine and 84.3% for itraconazole (P=0.04). No significant differences in clinical response were observed between groups at month four or 12 (P>0.05). There was no significant difference in the CGE at month four or 12 between groups when clinical cure was considered, though when clinical improvement was also considered, terbinafine showed significantly better scores (P<0.02). At four months, there was no difference in the proportion of patients considered to be ECP, though at 12 months significantly more patients in the terbinafine group were considered ECP (95.3 and 75.7%, respectively; P<0.001). Secondary: Not reported
Brautigam et al.[27] (1995)	MC, RCT	N=170	Primary: Mycological	Primary: Mycological cure rates were 81% in the terbinafine group and 63% in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Terbinafine 250 mg daily for 12 weeks vs itraconazole 200 mg daily for 12 week	Patients with a clinical diagnosis of distal subungual or proximal onychomycosis and a growth of dermatophytes	40 week posttreatment follow-up	response (negative culture), area of unaffected nail Secondary: Not reported	itraconazole group (P<0.01). The length of unaffected nail increased to 9.4 mm in the terbinafine group and to 7.9 mm in the itraconazole group (P<0.05). Secondary: Not reported
Tosti et al.[28] (1996) Terbinafine 250 mg daily (T250) vs terbinafine 500 mg daily for 1 week every month (T500) vs itraconazole 400 mg daily for 1 week every month (I) Treatment was continued for 4 months for toenail infections and for 2 months for fingernail infections.	OL, RCT Patients with onychomycosis of the toenails or fingernails	N=63 6 month posttreatment follow-up	Primary: Mycological response (not cured, cured with residual malformations, cured without residual malformations) Secondary: Not reported	Primary: At the end of the follow-up period, 76.5% of patients in the T250 group were cured without residual malformations compared to 50% in the T500 group and 38.1% in the I group (P=0.013 between T250 and I). At the end of the follow-up period, significantly more patients in the I group were considered cured with residual malformations compared to those in the T250 group (P=0.013). At the end of the follow-up period, significantly more patients in the I group were considered failures compared to those in the T250 group (P=0.013). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Gupta et al.[29] (2013) Itraconazole 200 mg/day for weeks 1 to 4 and terbinafine 250 mg/day for weeks 3 to 6 (2-week overlap of itraconazole and terbinafine) (COMBO) vs Continuous terbinafine 250 mg/day for 12 weeks (CTERB) vs Intermittent terbinafine (250 mg/day for 4 weeks on, 4 weeks off, 4 weeks on) (TOT) vs Pulsed itraconazole (one pulse = 200 mg twice daily for	PRO, SB Patients with toenail onychomycosis caused by dermatophytes mycologically cured at 48 weeks after the beginning of therapy based on a last observation carry forward analysis and both clinically and mycologically assessed after week 48	N=106 1.25 to 7 years	Primary: Proportions of participants with mycologic recurrence and recurrence (clinical and/or mycologic) at a post–week 48 visit Secondary: Not reported	Primary: Mycologic recurrence was found to occur in 43% (46 of 106) of all subjects. Mycologic recurrence rates were similar for the CTERB (32%) and TOT (36%) regimens, as well as for the III (59%) and the COMBO (57%) regimens. About half (22 of 43; 51%) of the participants completely cured had recurrence post–week 48. The recurrence rates for complete cure by regimen were similar and ranged from 40 (CTERB) to 67% (COMBO). Similar recurrence rates were generally obtained when participants who received booster therapy were excluded from the analyses. However, the mycologic recurrence rates for CTERB (21%) and III (46%) were lower when the participants requiring booster were excluded. No statistically significant difference was detected between the four treatment groups. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
7 days on, 21 days off) for three pulses (III)				
Chang et al.[30] (2007) Terbinafine, itraconazole, fluconazole (with or without topical agents)	MA Patients aged ≥18 years with superficial dermatophytosis (tinea pedis, tinea manus, tinea corpora, and tinea cruris) or onychomycosis who were receiving oral antifungal therapy for 2 or more weeks	N=19,298 (122 trials) Variable duration	Primary: Cumulative incidence of patients who withdrew from the study because of adverse reactions Secondary: Cumulative incidence of patients stopping treatment because of elevation of serum transaminase levels and cumulative incidence of patients developing elevation of serum transaminase levels during treatment but not requiring discontinuation	Primary: For continuous oral antifungal therapy, the pooled risks of treatment discontinuation because of adverse reactions were 3.44% (95% CI, 2.28 to 4.61%) for terbinafine 250 mg/day; 1.96% (95% CI, 0.35 to 3.57%) for itraconazole 100 mg/day; 4.21% (95% CI, 2.33 to 6.09%) for itraconazole 200 mg/day; and 1.51% (95% CI, 0 to 4.01%) for fluconazole 50 mg/day. For intermittent or pulse therapy, the pooled risks of treatment discontinuation because of adverse reactions were 2.09% (95% CI, 0 to 4.42%) for terbinafine; 2.58% (95% CI, 1.15 to 4.01%) for itraconazole; 1.98% (95% CI, 0.05 to 3.92%) for fluconazole 150 mg/week and 5.76% (95% CI, 2.42 to 9.10%) for fluconazole 300 to 450 mg/week. Secondary: The incidence of liver injury associated with oral antifungal therapy was less than 2% in general. For the risks of having elevated serum transaminase levels that required treatment termination, the pooled risk estimates for continuous therapy ranged from 0.11% (itraconazole 100 mg/day) to 1.22% (fluconazole 50 mg/day). The pooled risk estimates for pulse therapy ranged from 0.39% (fluconazole 150 mg/week and itraconazole 400 mg/day) to 0.85% (fluconazole 300 to 450 mg/week). The pooled risks of developing elevated serum transaminase levels not requiring treatment discontinuation was on the order of 1.5% for continuous regimens and 1% for intermittent regimens evaluated.
Tinea Capitis				
Elewski et al.[31] (2008) Terbinafine granules 125 to 250 mg (5 to 8	RCT, SB, MC (Pooled analysis of 2 trials) Children between 4 and 12 years of age	N=1,549 10 weeks	Primary: End-of-study complete cure rate defined as mycologic cure (negative culture	Primary: The complete cure rate at the end-of-study (week 10) was statistically higher in the terbinafine group (45.1%) compared to the griseofulvin group (39.2%; P=0.024) in the pooled analysis. In the individual analyses, terbinafine was more effective than griseofulvin in trial 1 (46.23 vs 34.01%, respectively; P<0.01) but not in trial 2 (43.99 vs 43.46%,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/kg) once daily for 6 weeks vs griseofulvin suspension 125 to 500 mg (10 to 20 mg/kg) once daily for 6 weeks	with a clinical diagnosis of tinea capitis confirmed by positive potassium hydroxide microscopy at baseline		and microscopy) and clinical cure Secondary: End-of-study mycologic cure rate, end-of-study clinical cure rate, and adverse events	respectively; P=0.95). Secondary: The end-of-study mycologic cure rate was higher in the terbinafine group (61.5%) compared to the griseofulvin group (55.5%; P=0.029). In the individual analyses, terbinafine was more effective than griseofulvin in trial 1 (62.29 vs 50.25%; P<0.01) but not in trial 2 (60.77 vs 59.92%; P=0.89). The end-of-study clinical cure rate were similar between terbinafine and griseofulvin in the pooled analysis (63 vs 58.8%; P=0.10) as well as in the individual trials (trial 1: 62.77 vs 56.35%; P=0.06; trial 2: 63.27 vs 60.76%; P=0.59). Overall, 51.9% of patients in the terbinafine group and 49.1% of patients in the griseofulvin group reported an adverse event during the study. The incidence of adverse events by organ class was similar in the two treatment groups.
Lipozencic et al.[32] (2002) Terbinafine tablets 125 to 250 mg daily for 6 to 12 weeks vs griseofulvin oral suspension 20 mg/kg/day for 12 weeks	DB, MC, PG, RCT Patients 4 years of age and older diagnosed with tinea capitis clinically confirmed by positive culture for *Microsporum* species	N=134 16 weeks	Primary: Complete cure at the end of study (EOS) defined by negative culture and no residual signs and symptoms Secondary: Effective treatment (negative culture and minimal signs and symptoms), clinical cure (no clinical signs and symptoms), mycological cure (negative	Primary: There was no significant difference between any of the terbinafine treatment groups in complete cure at EOS (P=0.12). Higher daily doses of terbinafine (>4.5 mg/kg/day) had a positive effect on complete cure rates at EOS compared to lower doses (<4.5 mg/kg/day) (P=0.048). Open-label, high-dose griseofulvin showed a high rate of complete cure at EOS of 84%. No comparisons were made between griseofulvin group and terbinafine groups. Secondary: At EOS, no significant differences were observed between any of the terbinafine treatment groups in any secondary endpoint (P>0.05). Open-label, high-dose griseofulvin produced effective treatment in 88% of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			microscopy and culture)	patients, mycological cure in 76%, and clinical cure in 96%. No comparisons were made between the griseofulvin and terbinafine groups.
Fuller et al.[33] (2001) Terbinafine tablets 62.5 mg to 125 mg daily for 4 weeks vs griseofulvin suspension 10 mg/kg/day for 4 weeks Patients used selenium sulfide shampoo at least 2 times weekly for the first 2 weeks.	MC, OL, PG, RCT Patients 2 to 16 years of age with a diagnosis of tinea capitis confirmed by culture	N=210 24 weeks	Primary: Clinical response (complete cure= microscopy and culture negative, no residual signs and symptoms; cure= microscopy and culture negative and total symptom score ≤2) Secondary: Not reported	Primary: No significant differences were observed between groups in clinical response (P>0.2). Graphical representation of cure rates shows a numerically higher response to terbinafine at earlier time points. Significantly more children weighing over 20 kg and infected with *Trichophyton* species were rated as cured at week 4 compared to children in the griseofulvin group (36 and 13%, respectively; P=0.03). Secondary: Not reported
Caceres-Rios et al.[34] (2000) Terbinafine tablets 62.5 to 250 mg daily for 4 weeks, then 4 weeks of placebo vs griseofulvin 125 to 500 mg daily for 8	DB, PRO, RCT Patients 1 to 14 years of age with a clinical and mycological diagnosis of non-inflammatory tinea capitis	N=50 12 weeks	Primary: Clinical outcomes (complete cure= negative culture and resolution of signs and symptoms; mycological cure= negative mycological findings and slight erythema, desquamation or pruritus)	Primary: At the end of week eight, the efficacy (as measured by complete cure) of griseofulvin was 76 and 72% for terbinafine. No significant difference between groups was observed. At the end of week eight, no significant difference was observed between the groups with respect to proportion of patients with negative cultures. At the end of week 12, the proportion of patients with negative cultures decreased in the griseofulvin group and increased or remained steady in the terbinafine group. A significant difference in favor of the terbinafine group was observed (P<0.05). At the end of week 12, the efficacy (as measured by complete cure) of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
weeks			Secondary: Not reported	griseofulvin had decreased to 44% and terbinafine had risen to 76% (P<0.05). Secondary: Not reported
Memisoglu et al.[35] (1999) Terbinafine once daily for 4 weeks vs griseofulvin once daily for 8 weeks	RCT, DB Children with mycologically proven tinea capitis	N=78 12 weeks	Primary: Mycological cure, effective treatment (complete disappearance of signs/symptoms and negative mycology, or not >2 signs/symptoms of mild erythema, desquamation or pruritus) Secondary: Not reported	Primary: At week 12, a mycological cure was recorded in 88.0% of the terbinafine-treated group, compared to 91.0% of the griseofulvin-treated group. Effective treatment was recorded in 78% of patients in the terbinafine-treated group compared to 74% of patients in the griseofulvin-treated group. *Trichophyton* species and *Microsporum canis* showed similar responsiveness to terbinafine treatment. Secondary: Not reported
Fleece et al.[36] (2004) Terbinafine administered for 2 to 4 weeks vs griseofulvin administered for 6 to 8 weeks	MA Patients with tinea capitis	N=603 (6 trials) 12 to 16 weeks	Primary: Clinical outcomes Secondary: Not reported	Primary: Three separate meta-analyses were performed. Analysis I included all six studies using culture status at least 12 weeks after enrollment in the study as the outcome. The OR was 0.86 (95% CI, 0.57 to 1.27; P=0.444). Analysis II included only the five studies in which *Trichophyton* species were the predominant pathogens and outcome was assessed at least 12 weeks post-enrollment. The OR was 0.65 (95% CI, 0.042 to 1.01; P=0.054). Analysis III included the four studies that provided outcome data at eight weeks post-enrollment. The OR was 0.84 (95% CI, 0.54 to 1.32; P=0.462). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Grover et al.[37] (2012) Terbinafine 3 to 5 mg/kg/day for two weeks vs griseofulvin 15 to 20 mg/kg/day administered in two doses per day for 6 weeks vs fluconazole 6 to 8 mg/kg administered weekly for 6 weeks Treatment in each group could be prolonged	OL, PRO Children aged ≤12 years with tinea capitis confirmed on microscopic examination	N=75 Variable duration	Primary: Clinical cure Secondary: Not reported	Primary: Cure rates of 96, 88, and 84% were achieved with griseofulvin, terbinafine, and fluconazole, respectively. Overall, seven patients required prolonged therapy. No side effects to therapy were seen. Griseofulvin remains the drug of choice in the treatment of tinea capitis. Terbinafine was the second best agent and offered the advantage of a shorter course of therapy. Fluconazole had comparatively low cure rates but was easier to administer than the other two medications. Secondary: Not reported
González et al.[38] (2007) Terbinafine, itraconazole, fluconazole, ketoconazole, griseofulvin	MA Children <18 years of age with tinea capitis confirmed by microscopy or growth of dermatophytes in culture or both	N=1,812 (21 trials) 6 to 26 weeks	Primary: The proportion of participants with complete cure (clinical and mycological) Secondary: Not reported	Primary: <u>Terbinafine vs griseofulvin:</u> A pooled analysis of the five trials found that the difference in the cure rates between four weeks of terbinafine and eight weeks griseofulvin was not statistically significant (RR, 1.11; 95% CI, 0.96 to 1.29). <u>Itraconazole vs griseofulvin:</u> In the pooled analysis, there was no significant difference in cure rates between itraconazole and griseofulvin (RR, 0.94; 95% CI, 0.80 to 1.09).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Itraconazole vs terbinafine: In the pooled analysis, there was no significant difference in cure rates between itraconazole and terbinafine (as treatment of *Trichophyton* species) when used for periods of two to three weeks (RR, 0.93; 95% CI, 0.72 to 1.19). Ketoconazole vs griseofulvin: In the pooled analysis, there was no significant difference in cure rates between ketoconazole and griseofulvin (RR, 0.72; 95% CI, 0.50 to 1.02). Fluconazole vs griseofulvin: In the pooled analysis, there was no significant difference in cure rates between fluconazole and griseofulvin (RR, 0.92; 95% CI, 0.80 to 1.05). Fluconazole vs terbinafine: In one study, the cure rates were found to be similar between fluconazole and terbinafine (RR, 0.87; 95% CI, 0.75 to 1.01). Fluconazole vs itraconazole: In one study, the cure rates were found to be similar between fluconazole and itraconazole (RR, 1.00; 95% CI, 0.83 to 1.20). Secondary: Not reported
Tey et al.[39] (2011) Terbinafine vs griseofulvin	MA Children and adults with a diagnosis of tinea capitis	N=2,163 (7 trials) Variable duration	Primary: Complete cure rate (defined as the achievement of both clinical and mycological cure) Secondary: Mycological cure rate (defined as the absence of dermatophytes on microscopy and	Primary: The pooled OR did not significantly favor griseofulvin or terbinafine when all studies were pooled (OR, 1.22; 95% CI, 0.785 to 1.919; P=0.37). For those studies with *Trichophyton* species being the predominant pathogen, the pooled OR favored terbinafine, but did not reach statistical significance (OR, 1.49; 95% CI, 0.975 to 2.277; P=0.065). For those studies with *Microsporum* species being the predominant pathogen, the pooled OR significantly favored griseofulvin (OR, 0.408; 95% CI, 0.254 to 0.656; P<0.001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			culture), clinical cure rate (defined as the resolution of clinical symptoms and signs), adverse events	Griseofulvin was associated with a small number of adverse effects including gastrointestinal symptoms, headache, upper respiratory tract symptoms, and rash. Severe adverse effects did not occur. The most frequent adverse events reported with terbinafine were gastrointestinal symptoms and upper respiratory tract symptoms. One patient developed asymptomatic neutropenia that was reversible after treatment was terminated prematurely.
Gupta et al.[40] (2013) Terbinafine (3.125 to 6.250 mg/kg/day) for 4 weeks vs griseofulvin (6.25 to 12.50 mg/kg/day) for 8 weeks	MA Patients with mycologically confirmed tinea capitis	N=272 (3 trials) 8 weeks	Primary: Efficacy (clinical and mycologic cure at week 8) Secondary: Efficacy of each treatment in infections caused by different dermatophyte genera	Primary: No statistically significant difference was detected between the two interventions (P=0.81) when considering all cases regardless of organism. Secondary: For *Trichophyton* species, terbinafine is significantly more efficacious than griseofulvin (OR, 0.50; 95% CI, 0.26 to 0.98; P=0.04). For *Microsporum* species, griseofulvin is significantly more efficacious than terbinafine (OR, 6.39; 95% CI, 1.09 to 37.47; P=0.04).
Miscellaneous				
Francesconi et al.[41] (2011) Terbinafine 250 to 500 mg/day vs itraconazole 100 to 200 mg/day	Cohort Patients diagnosed with cutaneous sporotrichosis	N=304 12 months	Primary: Clinical cure rate (defined as complete healing of the lesions) Secondary: Frequency of recurrence	Primary: The clinical cure rate was similar with terbinafine (92.7%) and itraconazole (92.0%; RR, 1.01; 95% CI, 0.93 to 1.09). Secondary: The mean time until achieving clinical cure did not differ between the two groups (terbinafine: 11.5 weeks; itraconazole: 11.8 weeks). In the terbinafine group, the duration of treatment until cure ranged from two to 24 months. One patient presented recurrence three months after the end of treatment. In the itraconazole group, 92.0% of patients were cured within a period of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				time of 2 to 44 months. Three patients presented recurrence. No difference in the frequency of adverse events was observed between the two groups (terbinafine group: 7.3%; itraconazole group: 7.6%; RR, 0.91; 95% CI, 0.39 to 2.07).

Study abbreviations: CI=confidence interval, CS=comparative study, DB=double blind, DD=double dummy, MA=meta-analysis, MC=multi-center, OL=open label, OR=odds ratio, PG=parallel group, PRO=prospective trial, RCT=randomized controlled trial, RR=relative risk, SB=single blind

Additional Evidence

Dose Simplification:
Several studies have compared the continuous use of terbinafine with pulse doses of itraconazole.[16,18-21,25,28-29] Three studies demonstrated similar clinical and mycological outcomes between terbinafine and itraconazole.[18,25,29] Whereas, five other studies have demonstrated greater efficacy with the continuous use of terbinafine compared to pulse dosing with itraconazole.[16,19-21,28]

Stable Therapy:
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits:
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 10. Relative Cost of the Allylamines

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Terbinafine	granules, tablet	Lamisil®*	$$$$$	$

*Generic is available in at least one dosage form or strength.

X. Conclusions

Terbinafine is approved for the treatment of onychomycosis and tinea capitis.[2-6] The tablet formulation is available generically. For the treatment of onychomycosis, guidelines recommend the use of systemic antifungals as they are generally more effective than topical treatments.[7-8] Oral monotherapy or combined oral/topical therapy is recommended as initial therapy.[7] Terbinafine should be considered as a first-line treatment option and itraconazole may be considered as a second-line treatment.[8] Numerous clinical trials have demonstrated improved clinical and/or mycological cure rates with terbinafine compared to itraconazole and griseofulvin.[11-16,19-23,26-28] Relatively few studies have demonstrated similar cure rates between terbinafine and itraconazole.[17-18,24-26]

For the treatment of tinea capitis, guidelines recommend the use of systemic antifungals because topical agents do not penetrate the hair follicle.[9-10] Fluconazole, itraconazole, griseofulvin, and terbinafine have similar efficacy and safety profiles for the treatment tinea capitis due to *Trichophyton* species.[9-10] Griseofulvin is recommended as initial therapy for the treatment of tinea capitis due to *Microsporum* species.[9] Two studies evaluated the efficacy

and safety of terbinafine granules. A pooled analysis demonstrated a higher cure rate with terbinafine granules compared to griseofulvin suspension.[31] However, in the individual analyses of the studies, terbinafine was more effective than griseofulvin in trial 1, but not in trial 2. Similar results were found when the investigators evaluated mycological cure rates. Studies conducted with terbinafine tablets have demonstrated similar cure rates compared to griseofulvin.[33-36,38-39] There were no studies found in the medical literature that directly compared terbinafine tablets and granules for the treatment of tinea capitis.

There is insufficient evidence to support that one brand allylamine is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand allylamines within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand allylamine is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Azoles
AHFS Class 081408
November 12, 2014

I. Overview

The azoles are approved to treat a variety of fungal infections, including aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, cryptococcal disease, histoplasmosis, sporotrichosis, and tinea infections.[1-8] They exert their antifungal activity by interfering with cytochrome P450 activity, decreasing ergosterol synthesis and inhibiting cell membrane formation.

The azoles that are included in this review are listed in Table 1. This review encompasses all systemic dosage forms and strengths. The topical antifungals were previously reviewed with the skin and mucous membrane agents (AHFS 840408) and are not included in this review. All of the products are available in a generic formulation, with the exception of posaconazole. This class was last reviewed in May 2012.

Table 1. Azoles Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Fluconazole	injection, suspension, tablet	Diflucan®*	fluconazole
Itraconazole	capsule, solution	Sporanox®*, Onmel®	itraconazole
Ketoconazole	tablet	N/A	ketoconazole
Posaconazole	injection, suspension, tablet	Noxafil®	none
Voriconazole	injection, suspension, tablet	Vfend®*, Vfend IV®*	voriconazole

*Generic is available in at least one dosage form or strength.
N/A=Not available, PDL=Preferred Drug List

The azoles have been shown to be active against the strains of microorganisms indicated in Table 2. This activity has been demonstrated in clinical infections and is represented by the Food and Drug Administration-approved indications for the azoles that are noted in Table 4. These agents may also have been found to show activity to other microorganisms in vitro; however, the clinical significance of this is unknown since their safety and efficacy in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials. Although empiric anti-infective therapy may be initiated before culture and susceptibility test results are known, once results become available, appropriate therapy should be selected.

Table 2. Microorganisms Susceptible to the Azoles[1-8]

Organism	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Voriconazole
Aspergillus flavus				✔	✔
Aspergillus fumigatus		✔		✔	✔
Aspergillus niger					✔
Aspergillus terreus					✔
Blastomyces dermatitidis		✔	✔		
Candida albicans	✔			✔	✔
Candida glabrata	✔				✔
Candida krusei					✔
Candida parapsilosis	✔				✔
Candida tropicalis	✔				✔
Candida species		✔	✔		
Coccidioides immitis		✔	✔		
Cryptococcus neoformans	✔	✔			
Epidermophyton species			✔		
Fusarium solani					✔
Fusarium species					✔

Organism	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Voriconazole
Histoplasma capsulatum			✔		
Histoplasma duboisii		✔			
Microsporum species			✔		
Paracoccidioides brasiliensis		✔	✔		
Phialophora species			✔		
Scedosporium apiospermum					✔
Sporothrix schenckii		✔			
Trichophyton mentagrophytes		✔			
Trichophyton rubrum		✔			
Trichophyton species			✔		

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the azoles are summarized in Table 3.

Table 3. Treatment Guidelines Using the Azoles

Clinical Guideline	Recommendation(s)
American Thoracic Society: **Treatment of Fungal Infections in Adult Pulmonary and Critical Care Patients (2011)**[9]	<u>Aspergillomas</u> • In patients with aspergillomas, it is recommended that antifungal agents not be used. • Antifungals should only be used only in patients suspected of having a component of semi-invasive disease. <u>Invasive Aspergillosis</u> • When invasive disease is suspected or confirmed, prompt, aggressive antifungal treatment is essential. • Although amphotericin B deoxycholate had historically been the "gold standard" for the treatment of invasive aspergillosis, most clinicians and the most recent Infectious Diseases Society of America guidelines recommend voriconazole as the primary treatment option. • There are no definitive data or consensus opinions indicating improved efficacy of any of the lipid amphotericin formulations over amphotericin B deoxycholate in the treatment of invasive aspergillosis. Thus, the best indication for using a lipid formulation appears to be for reducing renal toxicity to allow the administration of high doses of amphotericin for a prolonged time. • Voriconazole has recently emerged as a standard therapy for the treatment of invasive aspergillosis based on the results of a randomized trial comparing the outcomes to amphotericin B deoxycholate; however, whether outcomes are superior to lipid formulations of amphotericin B has not been determined. In many instances voriconazole may be considered the treatment of choice. The patient can be transitioned to oral formulations of this drug. • Oral itraconazole is not recommended for initial therapy for invasive aspergillosis. However, after disease progression is arrested with either voriconazole or amphotericin, the patient can be transitioned to oral itraconazole. • Caspofungin use in invasive aspergillosis is largely limited to salvage therapy, often in combination with other antifungal agents, after primary therapy with amphotericin-based regimens have failed. • There is currently insufficient clinical support to recommend combination therapy, although many clinicians are employing this approach as a "last option," or in settings of particularly advanced disease.

Clinical Guideline	Recommendation(s)

	<u>Chronic necrotizing aspergillosis</u>
	• In patients with chronic necrotizing aspergillosis, with mild to moderate disease, voriconazole (200 mg every 12 hours) or itraconazole (400 to 600 mg/day) is recommended until resolution or stabilization of all clinical and radiographic manifestations.
	• If clinically severe, consider beginning therapy of chronic necrotizing aspergillosis with either liposomal amphotericin B or intravenous voriconazole as described above for invasive disease.
	• In select patients at high risk of invasive fungal infection, some anti-*Aspergillus* prophylaxis is warranted. Data support the use of posaconazole 200 mg orally three times daily until recovery from neutropenia and clinical remission is established. Other prophylaxis approaches have utilized itraconazole, micafungin, and inhaled liposomal amphotericin B.
	
	<u>Invasive Pulmonary Aspergillosis</u>
	• In patients with invasive pulmonary aspergillosis, the following are recommended:
	  o Intravenous voriconazole six mg/kg every 12 hours for one day, followed by four mg/kg every 12 hours until improvement, followed by oral voriconazole 200 mg every 12 hours (preferred) or oral itraconazole 400 to 600 mg/day until resolution or stabilization of all clinical and radiographic manifestations OR
	  o Intravenous liposomal amphotericin B three to five mg/kg/day until improvement, followed by oral voriconazole 200 mg every 12 hours (preferred) or oral itraconazole 400 to 600 mg/day until resolution or stabilization of all clinical and radiographic manifestation.
	• In patients with invasive pulmonary aspergillosis who have failed front line therapy and are requiring salvage therapy, the following are recommended:
	  o Intravenous caspofungin 70 mg on day one and 50 mg/day intravenously thereafter, or intravenous micafungin 100 to 150 mg/day until improvement, followed by oral voriconazole 200 mg every 12 hours or oral itraconazole 400 to 600 mg/day until resolution of disease OR
	  o Posaconazole 200 mg four times per day initially, then 400 mg twice daily orally after stabilization of disease.
	
	<u>Hypersensitivity pneumonitis related to *Aspergillus*</u>
	• In patients with hypersensitivity pneumonitis, it is recommended that antifungal therapy not be used.
	
	<u>Blastomycosis (immunocompetent hosts)</u>
	• In patients with mild to moderate pulmonary blastomycosis, oral itraconazole 200 mg twice daily is recommended for six months.
	• In patients with severe pulmonary blastomycosis, amphotericin B 0.7 to 1.0 mg/kg/day daily is recommended until clinical improvement is observed, followed by continuation of amphotericin B 0.7 to 1.0 mg/kg three times weekly, until a cumulative dose of 1.5 to 2.5 grams is reached. Once clinical improvement is observed, oral itraconazole 200 mg twice daily is recommended for six months.
	• In patients with pulmonary blastomycosis and bone involvement, it is recommended to prolong treatment with itraconazole to 12 months.

Clinical Guideline	Recommendation(s)

	• In patients with pulmonary blastomycosis and concomitant central nervous system involvement, the following are recommended:
	  o Liposomal amphotericin B 0.7 mg/kg/day until a cumulative dose of two grams is reached.
	  o Triazoles should not be used as monotherapy for meningeal blastomycosis.
	  o High dose intravenous or oral fluconazole 400 to 800 mg daily may be provided as an add-on therapy to intravenous amphotericin B in patients with severe or refractory disease, with the total duration of fluconazole therapy extended for at least six months.
	
	<u>Blastomycosis (immunocompromised hosts)</u>
	• In patients with severe pulmonary blastomycosis without central nervous system involvement, amphotericin B 0.7 mg/kg/day is recommended until clinical improvement is observed. Once clinical improvement is observed, oral itraconazole 200 mg twice daily is recommended for at least 12 months.
	• In patients with mild to moderate pulmonary blastomycosis without central nervous system involvement, oral itraconazole 200 mg twice daily is recommended for at least 12 months.
	• When acquired immunodeficiency syndrome is involved, oral itraconazole 200 mg/day is recommended indefinitely or until immunity is fully restored.
	• In patients with pulmonary blastomycosis and concomitant central nervous system involvement, the following are recommended:
	  o Combined therapy with amphotericin B 0.7 mg/kg/day together with intravenous or oral fluconazole 400 to 800 mg daily from the onset until clinical improvement is observed.
	  o Use of fluconazole for at least 12 months total after discontinuation of combined intravenous treatment with amphotericin B and high-dose fluconazole.
	  o Use of liposomal amphotericin B rather than amphotericin B deoxycholate should be considered due to theoretic better central nervous system penetration.
	  o Triazoles are not used as monotherapy.
	  o Patients with acquired immunodeficiency syndrome should continue to receive oral fluconazole 400 mg per day indefinitely or until immunity is restored.
	• In patients with pulmonary blastomycosis with new or progressing central nervous system involvement despite amphotericin B monotherapy, the following are recommended:
	  o Combined therapy with liposomal amphotericin B five mg/kg/day until clinical improvement is observed, together with intravenous or oral fluconazole 800 mg/day.
	  o Fluconazole is used for at least six months in immunocompetent patients, and at least 12 months in immunocompromised patients, after discontinuation of combined treatment with amphotericin B and fluconazole.
	  o Patients with acquired immunodeficiency syndrome receive oral fluconazole 400 mg daily indefinitely or until immunity is restored.
	• In critically ill patients with pulmonary blastomycosis, the following are recommended:
	  o Combined therapy with amphotericin B (0.7 to 1.0 mg/kg amphotericin B deoxycholate or five mg/kg daily liposomal

Clinical Guideline	Recommendation(s)
	amphotericin B) until clinical improvement is observed, together with oral itraconazole 200 mg/day. o Following the initial intravenous therapy, oral itraconazole is used for at least six months in immunocompetent patients, and at least 12 months in immunocompromised patients, after discontinuation of combined treatment with amphotericin B and itraconazole. o After initial therapy is complete, patients with acquired immunodeficiency syndrome should receive oral itraconazole 200 mg/day indefinitely, or until immunity is restored. Voriconazole 200 mg twice daily may be used as an alternative to itraconazole. • In patients with pulmonary blastomycosis with new or progressing central nervous system involvement despite amphotericin B monotherapy, the following are recommended: o Combined therapy with liposomal amphotericin B five mg/kg/day until clinical improvement is observed, together with intravenous or oral fluconazole 800 mg/day. o Fluconazole is used for at least six months in immunocompetent patients, and at least 12 months in immunocompromised patients, after discontinuation of combined treatment with amphotericin B and fluconazole. o Patients with acquired immunodeficiency syndrome receive oral fluconazole 400 mg daily indefinitely or until immunity is restored. o Voriconazole 200 mg twice daily may be considered as an alternative to fluconazole, though extensive disease-specific data are currently lacking. • In critically ill patients with pulmonary blastomycosis, the following are recommended: o Combined therapy with amphotericin B (0.7 to 1.0 mg/kg amphotericin B deoxycholate or five mg/kg daily liposomal amphotericin B) until clinical improvement is observed, together with oral itraconazole 200 mg/day. o Following the initial intravenous therapy, oral itraconazole is used for at least six months in immunocompetent patients, and at least 12 months in immunocompromised patients, after discontinuation of combined treatment with amphotericin B and itraconazole. o After initial therapy is complete, patients with AIDS should receive oral itraconazole 200 mg/day indefinitely, or until immunity is restored. o Voriconazole 200 mg twice daily may be considered as an alternative to itraconazole, though this is based largely on in vitro sensitivities and limited case based data. <u>Coccidioidomycosis (immunocompetent hosts)</u> • In most immunocompetent patients with primary pulmonary coccidioidomycosis and no additional risk factors for dissemination, we suggest no antifungal treatment. • In immunocompetent patients with primary pulmonary coccidioidomycosis and moderate to severe symptoms, or those in whom symptoms persist for more than six weeks, treatment with triazole antifungal drugs are recommended for at least three to six months or longer if symptoms and radiographic abnormalities persist.

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	<u>Coccidioidomycosis (immunocompromised hosts and others at risk for disseminated disease)</u> • In many patients with pulmonary coccidioidomycosis and pulmonary nodules only, observation is recommended for at least one year without antifungal treatment. However, fluconazole (400 mg/day) or itraconazole (400 mg/day) may be considered during periods of significant immune suppression (i.e., chemotherapy, systemic corticosteroid therapy, or CD4 counts <250/µL). • In patients with pulmonary coccidioidomycosis and pulmonary nodules who have additional risk factors for disseminated disease, patients with cavities, and those presenting with hemoptysis, treatment with triazole antifungal drugs are recommended, either fluconazole (400 mg/day) or itraconazole (400 mg/day). • For diffuse pulmonary coccidioidomycosis with significant impairment of gas exchange, initial liposomal amphotericin B (five mg/kg/day) or amphotericin B (0.7 to 1.0 mg/kg/day) is recommended until clinical improvement, followed by fluconazole (400 mg/day) or itraconazole (400 mg/day) for at least another year. In patients with ongoing immune suppression, azole therapy may be continued indefinitely. • All patients, whether immunocompetent or immunocompromised, with any form of disseminated coccidioidomycosis require treatment. For non-meningeal disseminated disease, treatment with fluconazole (400 mg/day) or itraconazole (400 mg/day) is recommended for at least a year and until clinical improvement and stabilization. Itraconazole is preferred in bone disease. In severe or refractory cases, liposomal amphotericin B (five mg/kg/day) or amphotericin B (0.7 to 1.0 mg/kg/day) may be initiated until clinical improvement, followed by fluconazole (400 mg/day) or itraconazole (400 mg/day) for at least another year. • In patients with meningitis, fluconazole (400 to 1,000 mg/day) or itraconazole (400 to 600 mg/day) for life. In patients with meningitis in whom treatment with triazole antifungal drugs failed, intrathecal amphotericin B is recommended in select cases. <u>Cryptococcosis (immunocompetent hosts)</u> • In asymptomatic immunocompetent patients with respiratory tract colonization by *Cryptococcus neoformans*, no antifungal treatment is recommended. • In immunocompetent patients with pulmonary cryptococcosis and no evidence of other organ involvement, fluconazole 400 mg/day initially is recommended, tapering to 200 mg/day after clinical improvement is assured and with total treatment for six months. Alternatively, itraconazole 400 mg/day may be considered for six months. Fluconazole treatment is recommended for longer than six months in patients with documented *Cryptococcus gattii* infection. <u>Cryptococcosis (immunocompromised hosts and immunocompetent hosts with disseminated or central nervous system involvement)</u> • In patients with disseminated cryptococcosis or central nervous system involvement, amphotericin B (0.7 to 1.0 mg/kg/day) plus flucytosine (100 mg/kg/day) is recommended for two weeks, then fluconazole or itraconazole (400 mg/day) for eight to 10 weeks. Alternatively, amphotericin B (0.7 to 1.0 mg/kg/day) plus flucytosine (100 mg/kg/day) may be administered for six to 10 weeks in patients in whom azoles cannot be used. • In patients with disseminated cryptococcosis or central nervous system

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	involvement, it is recommended that azoles not be used as monotherapy. • In patients with refractory disease not responding to fluconazole and itraconazole, voriconazole or posaconazole can be considered as salvage therapy on a case by case basis. • In patients with acquired immunodeficiency syndrome and CD4+ T cell count < 200/µL who have disseminated cryptococcosis or central nervous system involvement, fluconazole 200 mg/day is recommended to be used indefinitely, after successful primary therapy as outlined above, or until CD4+ T cell count is greater than 200/µL, human immunodeficiency virus ribonucleic acid is undetectable and sustained for three months, and the patient is stable for one to two years. <u>Histoplasmosis (immunocompetent hosts with *Histoplasma*-related pulmonary nodules, broncholithiasis, or fibrosing mediastinitis)</u> • Among asymptomatic patients with pulmonary nodules in whom *Histoplasma* cannot be cultured, antifungal treatment is not recommended. • In most patients with broncholithiasis, antifungal treatment is not recommended. • In patients with fibrosing mediastinitis, some clinicians recommend itraconazole 200 mg twice daily for 12 weeks. In patients with radiographic or physiologic improvement after an initial 12 weeks of therapy, longer treatment, up to 12 months, is recommended. <u>Histoplasmosis (immunocompetent hosts with symptomatic, progressive, or severe pulmonary histoplasmosis)</u> • In asymptomatic patients, no antifungal treatment is recommended. • In symptomatic patients with mild pulmonary histoplasmosis, who remain symptomatic after three weeks of observation, itraconazole 200 mg twice daily for up to 12 weeks is recommended. • In selected patients with mild to moderate pulmonary histoplasmosis, initiating treatment with itraconazole 200 mg twice daily rather than with amphotericin B is recommended. • In patients with severe pulmonary histoplasmosis, amphotericin B 0.7 mg/kg/day is recommended until clinical improvement is observed or until a cumulative dose of two grams of amphotericin B is reached. In patients who improve clinically after initial treatment with amphotericin B, maintenance itraconazole 200 mg twice daily for at least 12 weeks is recommended. <u>Histoplasmosis (immunocompromised hosts with pulmonary histoplasmosis or with progressive or disseminated disease, or with chronic pulmonary histoplasmosis)</u> • In patients with mild to moderate histoplasmosis, itraconazole 200 mg three times daily for three days is recommended, followed by 200 mg twice daily for 12 months. • In patients with severe progressive disseminated histoplasmosis requiring hospitalization, amphotericin B 0.7 to 1.0 mg/kg/day (or a lipid formulation of amphotericin three to five mg/kg/day) is recommended until clinical improvement is observed or until a cumulative dose of two grams of amphotericin B is reached. In patients who improve clinically after initial treatment with amphotericin B, itraconazole 200 mg twice daily for 12 months is recommended. • In patients with acquired immunodeficiency syndrome and progressive

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	disseminated histoplasmosis who completed 12 months of initial itraconazole therapy, itraconazole 200 mg twice daily is recommended until effective immune reconstitution occurs.
	• In patients with chronic pulmonary histoplasmosis, itraconazole 200 mg twice daily for 12 to 24 months is recommended rather than no antifungal treatment.
	• In patients with severe chronic pulmonary histoplasmosis, initial treatment with amphotericin B is recommended over itraconazole.
	
	<u>Paracoccidioidomycosis</u>
	• In critically ill patients with disseminated paracoccidioidomycosis, initial amphotericin B (0.7 to 1.0 mg/kg/day) therapy is recommended until clinical stabilization or until two grams total dose administered. This may be followed by azole therapy as listed below.
	• In patients with disseminated paracoccidioidomycosis and mild to moderate or slowly progressive symptoms, one of the following options is recommended until clinical stabilization and resolution of symptoms. The total duration of therapy must be individualized to clinical response, but generally therapy for six to 12 months or longer is employed. Potential regimens include:
	  o Ketoconazole 200 to 400 mg daily
	  o Itraconazole 100 to 400 mg daily
	  o Sulfadiazine four to six grams daily
	
	<u>Sporotrichosis</u>
	• In patients with mild to moderately severe pulmonary sporotrichosis, itraconazole 200 mg twice daily is recommended, with a total duration of therapy generally of three to six months based upon overall clinical response.
	• In patients with severe pulmonary sporotrichosis, amphotericin B 0.7 mg/kg/day is recommended until clinical improvement is observed or until a cumulative dose of one to two grams of amphotericin B is reached, followed by itraconazole 200 mg twice daily, with total duration of therapy generally of three to six months based upon overall clinical response.
	
	<u>Candidemia</u>
	• Candidemia should be treated with antifungal agents, selecting one of the following agents: fluconazole, an amphotericin B formulation, an echinocandin, voriconazole, or the combination regimen of fluconazole and amphotericin B.
	• For patients who are clinically stable and have not recently received azole therapy, the following are recommended:
	  o Fluconazole (400 mg/day or ~6 mg/kg/day) OR
	  o Caspofungin (70 mg loading dose day one, then 50 mg/day) OR
	  o Micafungin (100 mg/day) OR
	  o Anidulafungin (200 mg on day one, then 100 mg/day).
	• For patients who are clinically unstable and for whom identification of the *Candida* species in the blood is unknown, there is no definitive recommendation. Several options are available and include:
	  o Amphotericin B deoxycholate (0.6 to 1.0 mg/kg/day) or a lipid formulation of amphotericin B (three to five mg/kg/day) OR
	  o High-dose fluconazole (800 mg/kg/day or ~12 mg/kg/day) OR

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	o Caspofungin (70 mg loading dose day one, then 50 mg/day) OR o Micafungin (100 mg/day) OR o Anidulafungin (200 mg on day one, then 100 mg/day) OR o Voriconazole (six mg/kg every 12 hours for two doses, then three mg/kg every 12 hours) OR o A combination regimen with fluconazole (800 mg/day) and amphotericin B (0.6 to 1.0 mg/kg/day, for the first five to six days) • For *Candida albicans* and also possibly *Candida tropicalis*, the drugs of choice are fluconazole (400 mg/day), amphotericin B (0.6 to 1.0 mg/kg/day), and an echinocandin. • For *Candida parapsilosis*, the drugs of choice are fluconazole (400 mg/day) or amphotericin B (0.6 to 1.0 mg/kg/day). • For *Candida glabrata*, the drugs of choice are an echinocandin or amphotericin B. High-dose fluconazole (800 mg/day) may be a suitable alternative. • For *Candida krusei*, the drugs of choice are an echinocandin or amphotericin B. • For *Candida lusitaniae*, fluconazole is the preferred therapy. • Lipid formulations of amphotericin B are usually indicated for patients intolerant of, or refractory to, conventional antifungal therapy. <u>Other Fungi</u> • In patients with zygomycosis, lipid formulations of amphotericin B are recommended at five mg/kg/day or amphotericin B deoxycholate at 0.7 to 1.0 mg/kg/day. • In patients who are intolerant of, or refractory to, amphotericin B, posaconazole 200 mg orally four times per day is recommended.
Infectious Diseases Society of America: **Treatment of Aspergillosis (2008)**[10]	<u>Invasive pulmonary aspergillosis</u> • For primary treatment of invasive pulmonary aspergillosis, intravenous or oral voriconazole is recommended for most patients. For seriously ill patients, the parenteral formulation is recommended. • Liposomal amphotericin B may be considered as alternative primary therapy in some patients. For salvage therapy, agents include lipid formulations of amphotericin, posaconazole, itraconazole, caspofungin, or micafungin. • In the absence of a well-controlled, prospective clinical trial, routine administration of combination therapy for primary therapy is not routinely recommended. For salvage therapy, an additional antifungal agent might be added to current therapy, or combination antifungal drugs from different classes other than those in the initial regimen may be used. • For patients with successfully treated invasive aspergillosis who will require subsequent immunosuppression, resumption of antifungal therapy can prevent recurrent infection. <u>Tracheobronchial aspergillosis</u> • Voriconazole is recommended as initial therapy in the treatment of tracheobronchial aspergillosis. • Because the use of deoxycholate amphotericin B may result in increased nephrotoxicity in association with calcineurin inhibitors, a lipid formulation of amphotericin B is recommended if a polyene is considered in the patient (e.g., lung transplant recipient).

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	Chronic necrotizing pulmonary aspergillosis • The greatest body of evidence regarding effective therapy supports the use of orally administered itraconazole. • Although voriconazole (and presumably posaconazole) is also likely to be effective, there is less published information available. Single-organ, extrapulmonary forms of invasive aspergillosis • Voriconazole is recommended for primary treatment of these uncommon manifestations of invasive aspergillosis. Aspergillosis of the central nervous system • The weight of evidence supports voriconazole as the primary recommendation for systemic antifungal therapy of central nervous system aspergillosis. • Itraconazole, posaconazole, or lipid formulations of amphotericin are recommended for patients who are intolerant or refractory to voriconazole. Invasive sinonasal aspergillosis • If the infection is known to be due to *Aspergillus* species, voriconazole should be initiated. • If the etiological organism is not known or histopathologic examination is still pending, an amphotericin B formulation should be initiated in anticipation of possible sinus zygomycosis. Aspergillus endocarditis, pericarditis, and myocarditis • Voriconazole has been successfully used in case reports and may be the preferred agent. • Because of the potential for recurrent infections following replacement of an infected prosthetic valve, strong consideration should be given to lifelong antifungal therapy with an antifungal triazole, such as oral voriconazole or posaconazole. *Aspergillus* osteomyelitis and septic arthritis • Combined medical and surgical intervention is recommended, where feasible, for management of *Aspergillus* osteomyelitis and arthritis. • Although there is currently limited experience with voriconazole for treatment of *Aspergillus* osteomyelitis, voriconazole appears to be effective for this indication. • Historically, amphotericin B has been used and would be appropriate therapy. *Aspergillus* endophthalmitis and *Aspergillus* keratitis • Following a diagnostic vitreal tap, intravenous amphotericin B and, where appropriate, intravitreal amphotericin B plus pars plana vitrectomy may be sight saving in *Aspergillus* endophthalmitis. • Voriconazole administered intravitreally or systemically is an alternative regimen. Management of *Aspergillus* keratitis requires emergency ophthalmologic intervention with ophthalmologic examination, topical antifungal therapy, and systemic antifungal therapy with amphotericin B, voriconazole, or itraconazole. Cutaneous aspergillosis • Therapy for secondary cutaneous lesions reflects that of disseminated infection, with systemic voriconazole recommended as primary

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	therapy. • Alternative agents include liposomal amphotericin B, posaconazole, itraconazole, or an echinocandin. *Aspergillus* peritonitis • Removal of peritoneal dialysis catheter and intraperitoneal dialysis with amphotericin B, in addition to intravenous administration of amphotericin B, are recommended. • Itraconazole or an extended-spectrum azole (voriconazole or posaconazole) may be used as a salvage therapy. Esophageal and gastrointestinal aspergillosis • Once a diagnosis is established, medical and, where appropriate, surgical therapy is needed to prevent the complications of potentially fatal hemorrhage, perforation, obstruction, and infarction. • Systemic antifungal therapy, as used for disseminated invasive aspergillosis, is appropriate. Hepatic aspergillosis • Medical therapy of hepatic aspergillosis should be considered as initial therapy. • For extrahepatic or perihepatic biliary obstruction, surgical intervention is warranted. Empirical antifungal therapy of neutropenic patients • Empirical antifungal therapy with amphotericin B, lipid formulations of amphotericin, itraconazole, voriconazole, or caspofungin is recommended for high-risk patients with prolonged neutropenia who remain persistently febrile despite broad-spectrum antibiotic therapy. • Empirical antifungal therapy is not recommended for patients who are anticipated to have short durations of neutropenia (duration of neutropenia, <10 days), unless other findings indicate the presence of an invasive fungal infection. Prophylaxis against invasive aspergillosis • Antifungal prophylaxis with posaconazole can be recommended in hematopoietic stem cell transplantation recipients with graft-vs-host disease who are at high risk for invasive aspergillosis and in patients with acute myelogenous leukemia or myelodysplastic syndrome who are at high risk for invasive aspergillosis. • Itraconazole may be effective, but tolerability limits its use. Aspergilloma and chronic pulmonary aspergillosis • Antifungal chemotherapy with itraconazole, voriconazole, or presumably, posaconazole provides some potential for therapeutic benefit with comparatively minimal risk. *Aspergillus* otomycosis (otic aspergillosis) • Topical therapy with irrigating solutions of boric acid, acetic acid, or azole cream may be effective in eradicating *Aspergillus* otomycosis. • For refractory cases and in contexts of perforated tympanic membranes, use of voriconazole, posaconazole, or itraconazole may be appropriate. Allergic bronchopulmonary aspergillosis

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	• Treatment of allergic bronchopulmonary aspergillosis should consist of a combination of corticosteroids and itraconazole. Allergic *Aspergillus* sinusitis • Itraconazole is recommended for consideration in allergic *Aspergillus* sinusitis. Renal aspergillosis • Because none of the available antifungal agents are excreted primarily into the pelvis of the kidney or urine, the management of pelvicaliceal and ureteral infection may require nephrostomy with instillation of amphotericin B.
Infectious Diseases Society of America: **Clinical Practice Guidelines for the Management of Blastomycosis (2008)**[11] **Reviewed and deemed current as of April 2013**	Pulmonary blastomycosis • For moderately severe to severe disease, initial treatment with a lipid formulation of amphotericin B at a dosage of three to five mg/kg/day or amphotericin B deoxycholate at a dosage of 0.7 to 1.0 mg/kg/day for one to two weeks or until improvement is noted, followed by oral itraconazole, 200 mg three times per day for three days and then 200 mg twice per day, for a total of six to 12 months, is recommended. • For mild to moderate disease, oral itraconazole, 200 mg three times per day for three days and then once or twice per day for six to 12 months, is recommended. Disseminated extrapulmonary blastomycosis • For moderately severe to severe disease, lipid formulation amphotericin B, three to five mg/kg/day, or amphotericin B deoxycholate, 0.7 to 1.0 mg/kg/day, for one to two weeks or until improvement is noted, followed by oral itraconazole, 200 mg three times per day for three days and then 200 mg twice per day for a total of at least 12 months, is recommended. • For mild to moderate disease, oral itraconazole, 200 mg three times per day for three days and then once or twice per day for six to 12 months, is recommended. • Patients with osteoarticular blastomycosis should receive a total of at least 12 months of antifungal therapy. • Serum levels of itraconazole should be determined after the patient has received this agent for at least two weeks, to ensure adequate drug exposure. Central nervous system blastomycosis • Amphotericin B, given as a lipid formulation at a dosage of five mg/kg/day over four to six weeks followed by an oral azole, is recommended. Possible options for azole therapy include fluconazole, 800 mg per day, itraconazole, 200 mg two or three times per day, or voriconazole, 200 to 400 mg twice per day, for at least 12 months and until resolution of cerebrospinal fluid abnormalities. Treatment for immunosuppressed patients with blastomycosis • Amphotericin B, given as a lipid formulation, three to five mg/kg/day, or amphotericin B deoxycholate, 0.7 to 1.0 mg/kg/day, for one to two weeks or until improvement is noted, is recommended as initial therapy for patients who are immunosuppressed, including those with acquired immunodeficiency syndrome. • Itraconazole, 200 mg three times daily for three days and then twice daily, is recommended as step-down therapy after the patient has

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	responded to initial treatment with amphotericin B and should be given to complete a total of at least 12 months of therapy. • Serum levels of itraconazole should be determined after the patient has received this agent for at least two weeks, to ensure adequate drug exposure. • Lifelong suppressive therapy with oral itraconazole, 200 mg per day, may be required for immunosuppressed patients if immunosuppression cannot be reversed and in patients who experience relapse despite appropriate therapy. <u>Treatment for blastomycosis in pregnant women and in children</u> • During pregnancy, lipid formulation amphotericin B, three to five mg/kg/day, is recommended. Azoles should be avoided because of possible teratogenicity. • If the newborn shows evidence of infection, treatment is recommended with amphotericin B deoxycholate, 1.0 mg/kg/day. • For children with severe blastomycosis, amphotericin B deoxycholate, 0.7 to 1.0 mg/kg/day, or lipid formulation amphotericin B, at a dosage of three to five mg/kg/day, is recommended for initial therapy, followed by oral itraconazole, 10 mg/kg/day (up to 400 mg daily) as step-down therapy, for a total of 12 months. • For children with mild to moderate infection, oral itraconazole, at a dosage of 10 mg/kg/day (to a maximum of 400 mg orally daily) for six to 12 months, is recommended. • Serum levels of itraconazole should be determined after the patient has received this agent for at least two weeks, to ensure adequate drug exposure.
Infectious Diseases Society of America: **Clinical Practice Guidelines for the Management of Candidiasis (2009)**[12]	<u>Candidemia in non-neutropenic patients</u> • Fluconazole or an echinocandin (caspofungin, micafungin, or anidulafungin) is recommended as initial therapy for most adult patients. An echinocandin is recommended for patients with moderately severe to severe illness or for patients who have had recent azole exposure. Fluconazole is recommended for patients who are less critically ill and who have had no recent azole exposure. The same therapeutic approach is advised for children, with attention to differences in dosing regimens. • Transition from an echinocandin to fluconazole is recommended for patients who have isolates that are likely to be susceptible to fluconazole (e.g., *Candida albicans*) and who are clinically stable. • For infection due to *Candida glabrata,* an echinocandin is preferred. Transition to fluconazole or voriconazole therapy is not recommended without confirmation of isolate susceptibility. For patients who have initially received fluconazole or voriconazole, are clinically improved, and whose follow-up culture results are negative, continuing use of an azole to completion of therapy is reasonable. • For infection due to *Candida parapsilosis,* treatment with fluconazole is recommended. For patients who have initially received an echinocandin, are clinically improved, and whose follow-up culture results are negative, continuing use of an echinocandin is reasonable. • Amphotericin B deoxycholate or a lipid formulation of amphotericin B are alternatives if there is intolerance to or limited availability of other antifungals. Transition from amphotericin B deoxycholate or lipid formulation of amphotericin B to fluconazole is recommended for patients who have isolates that are likely to be susceptible to fluconazole (e.g., *Candida albicans*) and who are clinically stable.

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	• Voriconazole is effective for candidemia, but it offers little advantage over fluconazole and is recommended as step-down oral therapy for selected cases of candidiasis due to *Candida krusei* or voriconazole-susceptible *Candida glabrata*. <u>Candidemia in neutropenic patients</u> • An echinocandin (caspofungin, micafungin, or anidulafungin) or lipid formulation of amphotericin B is recommended for most patients. • For patients who are less critically ill and who have no recent azole exposure, fluconazole is a reasonable alternative. Voriconazole can be used in situations in which additional mold coverage is desired. • For infections due to *Candida glabrata,* an echinocandin is preferred. Lipid formulations of amphotericin B are an alternative treatment option. For patients who were already receiving voriconazole or fluconazole, are clinically improved, and whose follow-up culture results are negative, continuing use of the azole to completion of therapy is reasonable. • For infections due to *Candida parapsilosis*, fluconazole or lipid formulation of amphotericin B is preferred as initial therapy. If the patient is receiving an echinocandin, is clinically stable, and follow-up culture results are negative, continuing the echinocandin until completion of therapy is reasonable. For infections due to *Candida krusei*, an echinocandin, lipid formulation of amphotericin B, or voriconazole is recommended. <u>Empirical treatment for suspected invasive candidiasis in non-neutropenic patients</u> • Empirical therapy for suspected candidiasis in non-neutropenic patients is similar to that for proven candidiasis. Fluconazole, caspofungin, anidulafungin, or micafungin is recommended as initial therapy. An echinocandin is preferred for patients who have had recent azole exposure, whose illness is moderately severe or severe, or who are at high risk of infection due to *Candida glabrata* or *Candida krusei*. • Amphotericin B deoxycholate or a lipid formulation of amphotericin B are alternatives if there is intolerance to other antifungals or limited availability of other antifungals. <u>Empirical treatment for suspected invasive candidiasis in neutropenic patients</u> • Lipid formulations of amphotericin B, caspofungin, or voriconazole are recommended. • Fluconazole and itraconazole are alternative agents. • Azoles should not be used for empirical therapy in patients who have received an azole for prophylaxis. <u>Chronic disseminated candidiasis</u> • Fluconazole is recommended for clinically stable patients. Lipid formulation of amphotericin B or amphotericin B deoxycholate can be used to treat acutely ill patients or patients with refractory disease. Induction therapy with amphotericin B for one to two weeks, followed by oral fluconazole is also recommended. • Anidulafungin, micafungin, or caspofungin are alternatives for initial therapy, followed by oral fluconazole when clinically appropriate. • Therapy should be continued for weeks to months, until calcification

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	occurs or lesions resolve. Premature discontinuation of antifungal therapy can lead to recurrent infection. • Patients with chronic disseminated candidiasis who require ongoing chemotherapy or undergo stem cell transplantation should continue to receive antifungal therapy throughout the period of high risk to prevent relapse. <u>Treatment for neonatal candidiasis</u> • Amphotericin B deoxycholate is recommended for neonates with disseminated candidiasis. If urinary tract involvement is excluded, lipid formulation of amphotericin B can be used. Fluconazole is a reasonable alternative. The recommended length of therapy is three weeks. • Echinocandins should be used with caution and are generally limited to situations in which resistance or toxicity precludes the use of fluconazole or amphotericin B deoxycholate. • In nurseries with high rates of invasive candidiasis, fluconazole prophylaxis may be considered in neonates whose birth weight is <1000 grams. Antifungal drug resistance, drug-related toxicity, and neurodevelopmental outcomes should be observed. <u>Osteoarticular *Candida* infections</u> • For osteomyelitis, fluconazole at a dosage of 400 mg daily for six to 12 months or lipid formulation of amphotericin B at a dosage of three to five mg/kg/day for at least two weeks, followed by fluconazole at a dosage of 400 mg daily for six to 12 months is recommended. Alternatives include an echinocandin or amphotericin B deoxycholate at a dosage of 0.5 to 1.0 mg/kg/day for at least two weeks, followed by fluconazole at a dosage of 400 mg daily for six to 12 months. • For septic arthritis, treatment for at least six weeks with fluconazole at a dosage of 400 mg daily or lipid formulation of amphotericin B at a dosage of three to five mg/kg/day for at least two weeks, followed by fluconazole at a dosage of 400 mg daily is recommended. Alternatives include an echinocandin or amphotericin B deoxycholate at a dosage of 0.5 to 1.0 mg/kg/day for at least two weeks, followed by fluconazole at a dosage of 400 mg daily for the remainder of therapy. • For infection involving a prosthetic device, device removal is recommended for most cases. Therapy for at least six weeks with the above dosages of fluconazole, lipid formulation of amphotericin B, an echinocandin, or amphotericin B deoxycholate is recommended. If the device cannot be removed, chronic suppression with fluconazole is recommended. <u>Central nervous system candidiasis</u> • Lipid formulation of amphotericin B with or without flucytosine is recommended for the initial several weeks of treatment. • Fluconazole is recommended as step-down therapy after the patient responds to initial treatment with lipid formulation of amphotericin B and flucytosine. Therapy should continue until all signs and symptoms, cerebrospinal fluid abnormalities, and radiologic abnormalities have resolved. <u>*Candida* endophthalmitis</u> • Amphotericin B deoxycholate combined with flucytosine is recommended for advancing lesions or lesions threatening the macula. Fluconazole is an acceptable alternative for less severe

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	endophthalmitis. Lipid formulation of amphotericin B, voriconazole, or an echinocandin can be used to treat patients who are intolerant of or experiencing treatment failure with amphotericin B deoxycholate in combination with flucytosine or fluconazole. • The recommended duration of therapy is at least four to six weeks and is determined by the stabilization or resolution of lesions as documented by repeated ophthalmological examinations. <u>Cardiovascular *Candida* infections</u> • For native valve endocarditis, lipid formulation of amphotericin B with or without flucytosine is recommended. Alternatives include amphotericin B deoxycholate with or without flucytosine or an echinocandin (caspofungin or anidulafungin). Step-down therapy to fluconazole should be considered among patients with susceptible *Candida* isolates who have demonstrated clinical stability and clearance of *Candida* from the bloodstream. Valve replacement is recommended, and treatment should continue for at least six weeks after valve replacement and should continue for a longer duration in patients with perivalvular abscesses and other complications. • For patients who cannot undergo valve replacement, long-term suppression with fluconazole is recommended. • For prosthetic valve endocarditis, the recommendations above apply, and suppressive therapy should be indefinite if valve replacement is not possible. • For pericarditis, lipid formulation of amphotericin B, amphotericin B deoxycholate, an echinocandin, or fluconazole for as long as several months, in combination with either a pericardial window or pericardiectomy, is recommended. Step-down therapy to fluconazole should be considered for patients who have initially responded to amphotericin B or an echinocandin and who are clinically stable. • For myocarditis, treatment as for endocarditis (as stated above) is recommended. • For suppurative thrombophlebitis, catheter removal and incision and drainage or resection of the vein, if feasible, is recommended. Lipid formulation of amphotericin B, amphotericin B deoxycholate, fluconazole, or an echinocandin for at least two weeks after candidemia has cleared is recommended. Step-down therapy to fluconazole should be considered for patients who have initially responded to amphotericin B or an echinocandin and who are clinically stable. Resolution of the thrombus can be used as evidence to discontinue antifungal therapy if clinical and culture data are supportive. • For pacemaker and implantable cardiac defibrillator wire infections, removal of the entire device and systemic antifungal therapy with lipid formulation of amphotericin B with or without flucytosine, amphotericin B deoxycholate with or without flucytosine, or an echinocandin is recommended. Step-down therapy to fluconazole should be considered for patients with susceptible *Candida* isolates who have demonstrated clinical stability and clearance of *Candida* from the bloodstream. For infections limited to generators and/or pockets, four weeks of antifungal therapy after removal of the device is recommended. For pacemaker and implantable cardiac defibrillator wire infections, at least six weeks of antifungal therapy after wire removal is recommended. • For ventricular assist devices that cannot be removed, treatment with lipid formulation of amphotericin B, amphotericin B deoxycholate, or an echinocandin is recommended. After candidemia has cleared and the

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	patient has responded clinically, fluconazole is recommended as step-down therapy. Chronic suppressive therapy with fluconazole is warranted until the device is removed. <u>Esophageal candidiasis</u> • Systemic antifungal therapy is always required. Oral fluconazole for 14 to 21 days is recommended. Intravenous fluconazole, amphotericin B deoxycholate, or an echinocandin should be used for patients who cannot tolerate oral therapy. A diagnostic trial of antifungal therapy is appropriate before performing an endoscopic examination. • For fluconazole-refractory disease, itraconazole solution, posaconazole suspension, or voriconazole (administered intravenously or orally) for 14 to 21 days is recommended. Micafungin, anidulafungin, or amphotericin B deoxycholate are acceptable alternatives. • Suppressive therapy with fluconazole is recommended for recurrent infections. • In patients with acquired immunodeficiency syndrome, treatment with highly active antiretroviral therapy is recommended to reduce recurrent infections. <u>Oropharyngeal candidiasis</u> • For mild disease, clotrimazole troches, nystatin suspension, or nystatin pastilles for seven to 14 days is recommended. • For moderate to severe disease, oral fluconazole for seven to 14 days is recommended. • For fluconazole-refractory disease, either itraconazole solution or posaconazole suspension for up to 28 days is recommended. Voriconazole or amphotericin B deoxycholate is recommended when treatment with other agents has failed. Intravenous echinocandin or amphotericin B deoxycholate can be used in treating patients with refractory disease. • Chronic suppressive therapy is usually unnecessary for patients with human immunodeficiency virus infection. If suppressive therapy is required, fluconazole three times weekly is recommended. Treatment with highly active antiretroviral therapy is recommended to reduce recurrent infections. • For denture-related candidiasis, disinfection of the denture, in addition to antifungal therapy, is recommended. <u>Antifungal prophylaxis for solid-organ transplant recipients, patients hospitalized in intensive care units, neutropenic patients receiving chemotherapy, and stem cell transplant recipients at risk of candidiasis</u> • For solid-organ transplant recipients, fluconazole or liposomal amphotericin B is recommended as postoperative antifungal prophylaxis for liver, pancreas, and small bowel transplant recipients at high risk of candidiasis. • For patients hospitalized in the intensive care unit, fluconazole is recommended for high-risk patients in adult units that have a high incidence of invasive candidiasis. • For patients with chemotherapy-induced neutropenia, fluconazole, posaconazole, or caspofungin is recommended during induction chemotherapy for the duration of neutropenia. Oral itraconazole is an effective alternative, but it offers little advantage over other agents and is less well tolerated. • For stem cell transplant recipients with neutropenia, fluconazole,

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	posaconazole, or micafungin is recommended during the period of risk of neutropenia. <u>Urinary tract infections – asymptomatic candiduria</u> • Treatment is not recommended unless the patient belongs to a group at high risk of dissemination. Elimination of predisposing factors often results in resolution of candiduria. • High-risk patients include neutropenic patients, infants with low birth weight, and patients who will undergo urologic manipulations. Neutropenic patients and neonates should be managed as described for invasive candidiasis. For those patients undergoing urologic procedures, fluconazole, or amphotericin B deoxycholate for several days before and after the procedure is recommended. <u>Urinary tract infections – symptomatic candiduria</u> • For candiduria with suspected disseminated candidiasis, treatment as described for candidemia is recommended. • For cystitis due to a fluconazole-susceptible *Candida* species, oral fluconazole for two weeks is recommended. For fluconazole-resistant organisms, amphotericin B deoxycholate for one to seven days or oral flucytosine for seven to 10 days are alternatives. Amphotericin B deoxycholate bladder irrigation is generally not recommended but may be useful for treatment of patients with fluconazole-resistant *Candida* species, especially *Candida glabrata.* • For pyelonephritis due to fluconazole-susceptible organisms, oral fluconazole daily for two weeks is recommended. For patients with fluconazole-resistant *Candida* strains, especially *Candida glabrata*, alternatives include amphotericin B deoxycholate with or without flucytosine or flucytosine alone for two weeks. • For fungus balls, surgical intervention is strongly recommended in non-neonates. Fluconazole is recommended. Amphotericin B deoxycholate with or without flucytosine is an alternative. If access to the renal collecting system is available, an adjunct to systemic therapy is irrigation with amphotericin B deoxycholate. Treatment duration should be until symptoms have resolved and urine cultures no longer yield *Candida* species. <u>Vulvovaginal candidiasis</u> • Several topical antifungal agents are effective therapy for vulvovaginal candidiasis, and no agent is clearly more effective than another. • A single 150 mg dose of fluconazole is recommended for the treatment of uncomplicated *Candida* vulvovaginal candidiasis. • For recurring *Candida* vulvovaginal candidiasis, 10 to 14 days of induction therapy with a topical or oral azole, followed by fluconazole once per week for six months, is recommended.
Infectious Diseases Society of America: **Practice Guidelines for the Treatment of Coccidioidomycosis (2005)**[13]	<u>Uncomplicated acute coccidioidal pneumonia</u> • Commonly prescribed therapies include oral azole antifungal agents at dosages of 200 to 400 mg per day. Courses of therapy are typically administered for three to six months. • During pregnancy, amphotericin B is the treatment of choice because fluconazole (and likely other azole antifungals) are teratogenic. <u>Diffuse pneumonia</u> • Therapy is usually begun either with amphotericin B or high-dose fluconazole.

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	• Amphotericin B is more frequently used as initial therapy if significant hypoxia is present or if deterioration is rapid. • Several weeks of therapy are often required to produce clear evidence of improvement. After this time, amphotericin B therapy may be discontinued and replaced with treatment with an oral azole antifungal. • In combination, the total length of therapy should be at least one year, and for patients with severe immunodeficiency, oral azole therapy should be continued as secondary prophylaxis. <u>Symptomatic pulmonary cavity infections</u> • Complications of coccidioidal cavities include local discomfort, superinfection with other fungi or possibly bacteria, or hemoptysis. Should these complications occur, oral therapy with azole antifungals may result in improvement, although recurrence of symptoms may occur on cessation of therapy. • Rupture of a coccidioidal cavity into the pleural space, resulting in a pyopneumothorax, is an infrequent but serious complication of coccidioidal pneumonia. In young, otherwise-healthy patients, surgical closure by lobectomy with decortication is the preferred management. • Antifungal therapy is recommended for treatment, particularly in cases with delay of diagnosis and coexistent diseases. • For patients in whom the diagnosis was delayed a week or more, or for patients in whom there are coexistent diseases, management approaches are less uniform and may include courses of therapy with amphotericin B or oral azole antifungal drugs prior to surgery or chest tube drainage without surgery. <u>Chronic progressive fibrocavitary pneumonia</u> • Initial treatment with oral azole antifungal agents is recommended. • If the patient improves sufficiently, therapy should be continued for at least one year. If therapy is not satisfactory, switching to an alternative azole antifungal, raising the dosage of the azole, or therapy with amphotericin B are alternative strategies. • Surgical resection may be a useful option for refractory lesions that are well localized or in cases in which significant hemoptysis has occurred. <u>Non-meningeal disseminated infection (extrapulmonary)</u> • Initial therapy is usually initiated with oral azole antifungal agents. • Amphotericin B is recommended for alternative therapy, especially if lesions are appearing to worsen rapidly and are in particularly critical locations, such as the vertebral column. • In patients experiencing failure of conventional deoxycholate amphotericin B therapy, or experiencing intolerable drug-related toxicities, lipid amphotericin B formulations have been demonstrated to be safe and to cause less nephrotoxicity and may be considered. • Combination therapy with amphotericin B and an azole has been administered to some patients, especially when infection is widespread or in cases in which there has been disease progression during treatment with a single agent. Although combination therapy may improve responses, there is no evidence that such an approach is more effective than treatment with a single agent. <u>Meningeal disseminated infection (extrapulmonary)</u> • Therapy with oral fluconazole is preferred by most clinicians.

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	Itraconazole, administered in dosages of 400 to 600 mg per day, has also been reported to be comparably effective. • Some physicians also initiate therapy with intrathecal amphotericin B in addition to an azole on the basis that responses are more prompt with this approach. Patients who respond to azole therapy should continue this treatment indefinitely. Patients who do not respond to fluconazole or itraconazole would be candidates for intrathecal amphotericin B therapy with or without continuation of azole treatment.
Infectious Diseases Society of America: **Clinical Practice Guidelines for the Management of Cryptococcal Disease (2010)**[14] **Reviewed and deemed current as of April 2013**	<u>Cryptococcal meningoencephalitis (human immunodeficiency virus-infected individuals)</u> • Primary therapy: induction and consolidation: o Amphotericin B deoxycholate (0.7 to 1.0 mg/kg per day IV) plus flucytosine (100 mg/kg/day orally in four divided doses; IV formulations may be used in severe cases and in those without oral intake where the preparation is available) for at least two weeks, followed by fluconazole (400 mg [six mg/kg] per day orally) for a minimum of eight weeks. o Lipid formulations of amphotericin B, including liposomal amphotericin B (three to four mg/kg/day IV) and amphotericin B lipid complex (five mg/kg/day IV) for at least two weeks, could be substituted for amphotericin B deoxycholate among patients with or predisposed to renal dysfunction. • Alternative regimens for induction and consolidation (listed in order of highest recommendation top to bottom): o Amphotericin B deoxycholate (0.7 to 1.0 mg/kg/day IV), liposomal amphotericin B (three to four mg/kg/day IV), or amphotericin B lipid complex (5 mg/kg/day IV) for four to six weeks. Liposomal amphotericin B has been given safely at six mg/kg/day IV in cryptococcal meningoencephalitis and could be considered in the event of treatment failure or high–fungal burden disease. o Amphotericin B deoxycholate (0.7 mg/kg/day IV) plus fluconazole (800 mg/day orally) for two weeks, followed by fluconazole (800 mg/day orally) for a minimum of eight weeks. o Fluconazole (≥800 mg/day orally; 1200 mg/day is favored) plus flucytosine (100 mg/kg/day orally) for six weeks. o Fluconazole (800 to 2000 mg/day orally) for 10 to 12 weeks; a dosage of ≥1200 mg/day is encouraged if fluconazole alone is used. o Itraconazole (200 mg twice/day orally) for 10 to 12 weeks, although use of this agent is discouraged. <u>Non-meningeal, pulmonary cryptococcosis (immunosuppressed):</u> • For mild-to-moderate symptoms, absence of diffuse pulmonary infiltrates, absence of severe immunosuppression, and negative results of a diagnostic evaluation for dissemination, use fluconazole (400 mg [six mg/kg] per day orally) for six to 12 months. • In human immunodeficiency virus-infected patients who are receiving highly active antiretroviral therapy with a CD4 cell count >100 cells/μL and a cryptococcal antigen titer that is ≤1:512 and/or not increasing, consider stopping maintenance fluconazole after one year of treatment.

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	Cryptococcal meningoencephalitis (non-human immunodeficiency virus-infected, non-transplant hosts) • Amphotericin B deoxycholate (0.7 to 1.0 mg/kg/day IV) plus flucytosine (100 mg/kg/day orally in four divided doses) for at least four weeks for induction therapy. The four-week induction therapy is reserved for persons with meningoencephalitis without neurological complications and cerebrospinal fluid yeast culture results that are negative after two weeks of treatment. For amphotericin B deoxycholate toxicity issues, lipid formulations of amphotericin B may be substituted in the second two weeks. In patients with neurological complications, consider extending induction therapy for a total of six weeks, and lipid formulations of amphotericin B may be given for the last four weeks of the prolonged induction period. Then, start consolidation with fluconazole (400 mg per day) for eight weeks. • If patient is amphotericin B deoxycholate intolerant, substitute liposomal amphotericin B (three to four mg/kg/day IV) or amphotericin B lipid complex (five mg/kg/day IV). • If flucytosine is not given or treatment is interrupted, consider lengthening amphotericin B deoxycholate or lipid formulations of amphotericin B induction therapy for at least two weeks. • In patients at low risk for therapeutic failure, consider induction therapy with combination of amphotericin B deoxycholate plus flucytosine for only two weeks, followed by consolidation with fluconazole (800 mg [12 mg/kg] per day orally) for eight weeks. • After induction and consolidation therapy, use maintenance therapy with fluconazole (200 mg [three mg/kg] per day orally) for six to 12 months. Non-meningeal, pulmonary cryptococcosis (non-immunosuppressed): • For mild-to-moderate symptoms, administer fluconazole (400 mg per day orally) for six to 12 months; persistently positive serum cryptococcal antigen titers are not criteria for continuance of therapy. • For severe disease, treat similarly to central nervous system disease. • Itraconazole (200 mg twice/day orally), voriconazole (200 mg twice/day orally), and posaconazole (400 mg twice/day orally) are acceptable alternatives if fluconazole is unavailable or contraindicated. Organ transplant recipients • For central nervous system disease, liposomal amphotericin B (three to four mg/kg/day IV) or amphotericin B lipid complex (five mg/kg/day IV) plus flucytosine (100 mg/kg/day in four divided doses) for at least two weeks for the induction regimen, followed by fluconazole (400 to 800 mg [six to 12 mg/kg] per day orally) for eight weeks and by fluconazole (200 to 400 mg/day orally) for six to 12 months. If induction therapy does not include flucytosine, consider lipid formulations of amphotericin B for at least four to six weeks of induction therapy, and liposomal amphotericin B (six mg/kg/day) might be considered in high–fungal burden disease or relapse. • For mild-to-moderate non-central nervous system disease, fluconazole (400 mg [six mg/kg] per day) for six to 12 months. • For moderately severe–to-severe non-central nervous system or disseminated disease without central nervous system involvement, treat the same as central nervous system disease. • In the absence of any clinical evidence of extrapulmonary or disseminated cryptococcosis, severe pulmonary disease is treated the

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	same as central nervous system disease. For mild-to-moderate symptoms without diffuse pulmonary infiltrates, use fluconazole (400 mg [six mg/kg] per day) for six to 12 months. • Fluconazole maintenance therapy should be continued for at least six to 12 months. <u>Cryptococcal meningoencephalitis (management of complications-persistence)</u> • Reinstitute induction phase of primary therapy for longer course (four to 10 weeks). • Consider increasing the dose if the initial dosage of induction therapy was ≤0.7 mg/kg IV of amphotericin B deoxycholate per day or ≤3 mg/kg of lipid formulations of amphotericin B per day, up to one mg/kg IV of amphotericin B deoxycholate per day or six mg/kg of liposomal amphotericin B per day; in general, combination therapy is recommended. • If the patient is polyene intolerant, consider fluconazole (≥800 mg/day orally) plus flucytosine (100 mg/kg/day orally in four divided doses). • If patient is flucytosine intolerant, consider amphotericin B deoxycholate (0.7 mg/kg/day IV) plus fluconazole (800 mg [12 mg/kg] per day orally). • Use of intrathecal or intraventricular amphotericin B deoxycholate is generally discouraged and is rarely necessary. <u>Cerebral cryptococcomas</u> • Induction therapy with amphotericin B deoxycholate (0.7 to 1.0 mg/kg/day IV), liposomal amphotericin B (three to four mg/kg/day IV), or amphotericin B lipid complex (5 mg/kg/day IV) plus flucytosine (100 mg/kg/day orally in four divided doses) for at least six weeks. • Consolidation and maintenance therapy with fluconazole (400 to 800 mg/day orally) for 6 to 18 months. <u>Non-meningeal, non-pulmonary cryptococcosis</u> • If central nervous system disease is ruled out, fungemia is not present, infection occurs at single site, and there are no immunosuppressive risk factors, consider fluconazole (400 mg [six mg/kg] per day orally) for six to 12 months.
Infectious Diseases Society of America: **Clinical Practice Guidelines for the Management of Patients with Histoplasmosis (2007)**[15] **Reviewed and deemed current as of June 2011**	<u>Moderately severe to severe acute pulmonary histoplasmosis (adults)</u> • Lipid formulation of amphotericin B (3.0 to 5.0 mg/kg/day intravenously for one to two weeks) followed by itraconazole (200 mg three times daily for three days and then 200 mg twice daily, for a total of 12 weeks) is recommended. • The deoxycholate formulation of amphotericin B is an alternative to a lipid formulation in patients who are at a low risk for nephrotoxicity. <u>Mild-to-moderate acute pulmonary histoplasmosis (adults)</u> • Treatment is usually unnecessary. Itraconazole (200 mg three times daily for three days and then 200 mg once or twice daily for six to 12 weeks) is recommended for patients who continue to have symptoms for 11 month. <u>Acute pulmonary histoplasmosis (children)</u> • Treatment indications and regimens are similar to those for adults, except that amphotericin B deoxycholate (1.0 mg/kg/day) is usually

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	well tolerated, and the lipid preparations are not preferred. • Itraconazole dosage in children is 5.0 to 10.0 mg/kg/day in two divided doses (not to exceed 400 mg daily), generally using the solution formulation. <u>Chronic cavitary pulmonary histoplasmosis</u> • Itraconazole (200 mg three times daily for three days and then once or twice daily for at least one year) is recommended, but some prefer 18 to 24 months in view of the risk for relapse. • Blood levels of itraconazole should be obtained after the patient has been receiving this agent for at least two weeks to ensure adequate drug exposure. <u>Pericarditis</u> • Nonsteroidal anti-inflammatory therapy is recommended in mild cases. • Prednisone (0.5 to 1.0 mg/kg daily [maximum, 80 mg daily] in tapering doses over one to two weeks) is recommended for patients with evidence of hemodynamic compromise or unremitting symptoms after several days of therapy with nonsteroidal anti-inflammatory therapy. • Pericardial fluid removal is indicated for patients with hemodynamic compromise. • Itraconazole (200 mg three times daily for three days and then once or twice daily for six to 12 weeks) is recommended if corticosteroids are administered. <u>Rheumatologic syndromes</u> • Nonsteroidal anti-inflammatory therapy is recommended in mild cases. • Prednisone (0.5 to 1.0 mg/kg/day [maximum, 80 mg daily] in tapering doses over one to two weeks) is recommended in severe cases. • Itraconazole (200 mg three times daily for three days and then once or twice daily for six to 12 weeks) is recommended only if corticosteroids are administered. <u>Mediastinal lymphadenitis</u> • Treatment is usually unnecessary. Itraconazole (200 mg three times daily for three days and then 200 mg once or twice daily for six to 12 weeks) is recommended in patients who have symptoms that warrant treatment with corticosteroids and in those who continue to have symptoms for 11 month. • Prednisone (0.5 to 1.0 mg/kg/day [maximum, 80 mg daily] in tapering doses over one to two weeks) is recommended in severe cases with obstruction or compression of contiguous structures. <u>Mediastinal granuloma</u> • Treatment is usually unnecessary. Itraconazole (200 mg three times daily for three days and then once or twice daily for six to 12 weeks) is recommended for symptomatic cases. <u>Mediastinal fibrosis</u> • Antifungal treatment is not recommended. The placement of intravascular stents is recommended for selected patients with pulmonary vessel obstruction. • Itraconazole (200 mg once or twice daily for 12 weeks) is recommended if clinical findings cannot differentiate mediastinal

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	fibrosis from mediastinal granuloma. <u>Progressive disseminated histoplasmosis (adults)</u> • For moderately severe to severe disease, liposomal amphotericin B (3.0 mg/kg/day) is recommended for one to two weeks, followed by oral itraconazole (200 mg three times daily for three days and then 200 mg twice daily for a total of at least 12 months). • Substitution of another lipid formulation may be preferred in some patients because of tolerability. • The deoxycholate formulation of amphotericin B is an alternative to a lipid formulation in patients who are at a low risk for nephrotoxicity. • For mild-to-moderate disease, itraconazole (200 mg three times daily for three days and then twice daily for at least 12 months) is recommended. • Lifelong suppressive therapy with itraconazole (200 mg daily) may be required in immunosuppressed patients if immunosuppression cannot be reversed and in patients who relapse despite receipt of appropriate therapy. • Blood levels of itraconazole should be obtained to ensure adequate drug exposure. <u>Progressive disseminated histoplasmosis (children)</u> • Amphotericin B deoxycholate (1.0 mg/kg/day for four to six weeks) is recommended. • Amphotericin B deoxycholate (1.0 mg/kg/day for two to four weeks) followed by itraconazole (5.0 to 10.0 mg/kg/day in two divided doses) to complete three months of therapy is an alternative. • Longer therapy may be needed for patients with severe disease, immunosuppression, or primary immunodeficiency syndromes. • Lifelong suppressive therapy with itraconazole (5.0 mg/kg/day, up to 200 mg daily) may be required in immunosuppressed patients if immunosuppression cannot be reversed and in patients who experience relapse despite receipt of appropriate therapy. • Blood levels of itraconazole should be obtained to ensure adequate drug exposure. <u>Prophylaxis for immunosuppressed patients</u> • Prophylaxis with itraconazole (200 mg daily) is recommended in patients with human immunodeficiency virus with CD4 cell counts <150 cells/mm^3 in specific areas of endemicity where the incidence of histoplasmosis is 110 cases per 100 patient-years. • Prophylaxis with itraconazole (200 mg daily) may be appropriate in specific circumstances in other immunosuppressed patients. <u>Central nervous system histoplasmosis</u> • Liposomal amphotericin B (5.0 mg/kg/day for a total of 175 mg/kg given over four to six weeks) followed by itraconazole (200 mg two or three times daily) for at least one year and until resolution of cerebrospinal fluid abnormalities, including *Histoplasma* antigen levels, is recommended. • Blood levels of itraconazole should be obtained to ensure adequate drug exposure. <u>Histoplasmosis in Pregnancy</u> • Lipid formulation amphotericin B is recommended. The deoxycholate

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	formulation of amphotericin B is an alternative to a lipid formulation in patients who are at a low risk for nephrotoxicity. • If the newborn shows evidence for infection, treatment is recommended with amphotericin B deoxycholate.
Infectious Diseases Society of America: **Clinical Practice Guidelines for the Management of Sporotrichosis (2007)**[16] **Reviewed and deemed current as of April 2013**	Lymphocutaneous and cutaneous sporotrichosis • For cutaneous and lymphocutaneous sporotrichosis, itraconazole 200 mg orally daily is recommended to be given for two to four weeks after all lesions have resolved, usually for a total of three to six months. • Patients who do not respond should be given a higher dosage of itraconazole (200 mg twice daily); terbinafine, administered at a dosage of 500 mg orally twice daily; or saturated solution of potassium iodide, initiated at a dosage of five drops (using a standard eye-dropper) three times daily and increasing, as tolerated, to 40 to 50 drops three times daily. • Fluconazole (400 to 800 mg daily) should be used only if the patient cannot tolerate these other agents. Osteoarticular sporotrichosis • Itraconazole, administered at 200 mg orally twice daily for at least 12 months, is recommended. • Amphotericin B, given as a lipid formulation at a dosage of three to five mg/kg/day, or amphotericin B deoxycholate, administered at a dosage of 0.7 to 1.0 mg/kg/day, can be used for initial therapy. After the patient has shown a favorable response, therapy can be changed to itraconazole administered at a dosage of 200 mg orally twice daily to complete a total of at least 12 months of therapy. • Serum levels of itraconazole should be determined after the patient has been receiving this agent for at least two weeks to ensure adequate drug exposure. Pulmonary sporotrichosis • For severe or life-threatening pulmonary sporotrichosis, amphotericin B, given as a lipid formulation at three to five mg/kg/day, is recommended. Amphotericin B deoxycholate, administered at a dosage of 0.7 to 1.0 mg/kg/day, could also be used. • After the patient has shown a favorable response to amphotericin B, therapy can be changed to itraconazole (200 mg orally twice daily) to complete a total of at least 12 months of therapy. • For less severe disease, itraconazole administered at 200 mg orally twice daily for at least 12 months is recommended. • Serum levels of itraconazole should be determined after the patient has been receiving this agent for at least two weeks to ensure adequate drug exposure. • Surgery combined with amphotericin B therapy is recommended for localized pulmonary disease. Meningeal sporotrichosis • Amphotericin B, given as a lipid formulation at a dosage of five mg/kg/day for four to six weeks, is recommended for the initial treatment of meningeal sporotrichosis. Amphotericin B deoxycholate, administered at a dosage of 0.7 to 1.0 mg/kg/day, could also be used but was not preferred by the panel. • Itraconazole (200 mg twice daily) is recommended as step-down therapy after the patient responds to initial treatment with amphotericin B and should be given to complete a total of at least 12 months of

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	therapy. • Serum levels of itraconazole should be determined after the patient has been receiving this agent for at least two weeks to ensure adequate drug exposure. • For patients with acquired immunodeficiency syndrome and other immunosuppressed patients, suppressive therapy with itraconazole at a dosage of 200 mg daily is recommended to prevent relapse. <u>Disseminated (systemic) sporotrichosis</u> • Amphotericin B, given as a lipid formulation at a dosage of three to five mg/kg/day, is recommended for disseminated sporotrichosis. Amphotericin B deoxycholate (0.7 to 1.0 mg/kg/day) could also be used but was not preferred by the panel. • Itraconazole (200 mg twice daily) is recommended as step-down therapy after the patient responds to initial treatment with amphotericin B and should be given to complete a total of at least 12 months of therapy. • Serum levels of itraconazole should be determined after the patient has been receiving this agent for at least two weeks to ensure adequate drug exposure. • Lifelong suppressive therapy with itraconazole (200 mg daily) may be required for patients with acquired immunodeficiency syndrome and other immunosuppressed patients if immunosuppression cannot be reversed. <u>Sporotrichosis in pregnant women and in children</u> • Amphotericin B, given as a lipid formulation at a dosage of three to five mg/kg/day, or amphotericin B deoxycholate, given at a dosage of 0.7 to 1.0 mg/kg/day, is recommended for severe sporotrichosis that must be treated during pregnancy; azoles should be avoided. • Itraconazole, administered at a dosage of six to 10 mg/kg to a maximum of 400 mg orally daily, is recommended for children with cutaneous or lymphocutaneous sporotrichosis. • For children with disseminated sporotrichosis, amphotericin B (0.7 mg/kg/day) should be the initial therapy, followed by itraconazole (six to 10 mg/kg, up to a maximum of 400 mg daily) as step-down therapy.
National Institutes of Health, the Centers for Disease Control and Prevention, and the Human Immunodeficiency Virus Medicine Association of the Infectious Diseases Society of America: **Guidelines for Prevention and Treatment of Opportunistic Infections in Human Immunodeficiency Virus - Infected Adults and Adolescents (2013)**[17]	<u>Aspergillosis</u> • Voriconazole is the drug of choice but should be used cautiously with human immunodeficiency virus protease inhibitors and efavirenz. Amphotericin B deoxycholate at 1 mg/kg daily or lipid-formulation amphotericin B at 5 mg/kg daily are alternatives, as is caspofungin at 50 mg daily and posaconazole. • Other echinocandins, such as micafungin and anidulafungin, are reasonable alternatives. • For treatment failure (if voriconazole was used initially) substitution with amphotericin B, posaconazole, or echinocandins might be considered; the amphotericin B or echinocandins would be rational for those who began therapy with voriconazole or posaconazole. <u>Candidiasis (mucocutaneous)</u> • Oral fluconazole is as effective as topical therapy for oropharyngeal candidiasis and is considered the drug of choice. Initial episodes of oropharyngeal candidiasis can be adequately treated with topical therapy, including clotrimazole troches, nystatin suspension or pastilles, or miconazole mucoadhesive tablets. Itraconazole oral

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	solution for seven to 14 days is as effective as oral fluconazole but less well tolerated. Posaconazole oral solution is also as effective as fluconazole and is generally better tolerated than itraconazole. Intravenous amphotericin B is usually effective and can be used among patients with refractory disease. Both conventional amphotericin B and lipid complex and liposomal amphotericin B have been used. • Systemic antifungals are required for effective treatment of esophageal candidiasis. A 14 to 21-day course of either fluconazole (oral or intravenous) or oral itraconazole solution is highly effective. Oral ketoconazole or itraconazole capsules are less effective than fluconazole because of variable absorption. Although intravenous caspofungin or intravenous voriconazole are effective in treating esophageal candidiasis among human immunodeficiency virus -infected patients, oral or intravenous fluconazole remain the preferred therapies. Azole-refractory esophageal candidiasis can be treated with posaconazole, amphotericin B, anidulafungin, caspofungin, micafungin, or voriconazole. • Vulvovaginal candidiasis in human immunodeficiency virus -infected women is usually uncomplicated (90%) and responds readily to short-course oral or topical treatment with any of several therapies, including oral fluconazole, topical azoles, and itraconazole oral solution. Severe or recurrent episodes of vaginitis require oral fluconazole or topical antifungal therapy for ≥7 days. <u>Coccidioidomycosis</u> • For patients with clinically mild infection, such as focal pneumonia or a positive coccidioidal serologic test alone, initial therapy with a triazole antifungal is appropriate. • For patients with either diffuse pulmonary involvement or severely ill patients with extrathoracic disseminated disease, amphotericin B is the preferred initial therapy. Therapy with amphotericin B should continue until clinical improvement is observed. Some specialists would use a triazole antifungal concurrently with amphotericin B and continue the triazole once amphotericin B is stopped. <u>Cryptococcosis</u> • The recommended initial standard treatment is amphotericin B combined with flucytosine for ≥2 weeks for those with normal renal function. • The combination of amphotericin B with fluconazole is less effective than amphotericin B combined with flucytosine in terms of clearing *Cryptococcus* from the cerebrospinal fluid but is better than amphotericin B alone. • Fluconazole combined with flucytosine is an alternative to amphotericin B plus flucytosine, but is less effective than amphotericin B and is recommended only for persons unable to tolerate or unresponsive to standard treatment. • After at least a two-week period of successful induction therapy, amphotericin B and flucytosine may be discontinued and follow-up therapy initiated with fluconazole. This should continue for eight weeks. Itraconazole is an acceptable though less effective alternative. • The optimal therapy for those with treatment failure is not established. For those initially treated with fluconazole, therapy should be changed to amphotericin B, with or without flucytosine, and continued until a clinical response occurs. Liposomal amphotericin B may have improved efficacy over the deoxycholate formulation and should be

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	considered in treatment failures. Higher doses of fluconazole in combination with flucytosine might also be useful. Cryptosporidiosis • In the setting of severe immunosuppression, antiretroviral therapy with immune restoration to a CD4+ count >100 cells/µL leads to resolution of clinical cryptosporidiosis and is the mainstay of treatment. • All patients with cryptosporidiosis should be offered antiretroviral therapy as part of the initial management of their infection. • Management should include symptomatic treatment of diarrhea. Rehydration and repletion of electrolyte losses by either the oral or intravenous route are important. Severe diarrhea can exceed >10 L/day among patients with acquired immunodeficiency syndrome, often requiring intensive support. Aggressive efforts at oral rehydration should be made with oral rehydration solutions. Prevention of Cytomegalovirus • Cytomegalovirus end-organ disease is best prevented by using antiretroviral therapy to maintain the CD4+ count >100 cells/µL. • Although oral valganciclovir would likely prevent the occurrence of cytomegalovirus retinitis in patients with CD4+ counts <50 cells/µL, such therapy is not generally recommended because of the potential to induce cytomegalovirus resistance, the utility of treating disease when it occurs, and the lack of demonstrated survival advantage. Treatment of Cytomegalovirus disease • Oral valganciclovir, intravenous ganciclovir, intravenous ganciclovir followed by oral valganciclovir, intravenous foscarnet, and intravenous cidofovir are all effective treatments for cytomegalovirus retinitis. • The ganciclovir implant, a surgically-implanted reservoir of ganciclovir, which lasts approximately six months, also is very effective but it no longer is being manufactured. In its absence, some clinicians will use intravitreal injections of ganciclovir or foscarnet in conjunction with oral valganciclovir, at least initially, to provide immediate high intraocular levels of drug and presumably faster control of the retinitis. • Systemic therapy has been shown to reduce morbidity in the contralateral eye. This should be considered when choosing between the oral, intravenous, and local options. • The choice of initial therapy for cytomegalovirus retinitis should be individualized based on the location and severity of the lesion(s), the level of underlying immune suppression, and other factors such as concomitant medications and ability to adhere to treatment. • No one regimen has been proven in a clinical trial to have greater efficacy in terms of protecting vision, and thus clinical judgment must be used when choosing a regimen. • In studies conducted in the pre-antiretroviral therapy era, ganciclovir intraocular implant plus oral ganciclovir was superior to once-daily intravenous ganciclovir for treatment of cytomegalovirus retinitis; however, the implant is no longer manufactured. Assuming that this observation can be extended to other combinations of systemically and locally administered drugs, human immunodeficiency virus-specialists often recommend intravitreal ganciclovir or foscarnet injections plus oral valganciclovir as the preferred initial therapy for patients with immediate sight-threatening lesions. Intravitreal injections deliver high concentrations of the drug to the target organ immediately while

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	steady-state concentrations in the eye are achieved with systemically delivered medications. For patients with small peripheral lesions, oral valganciclovir alone often is adequate. • After induction therapy, secondary prophylaxis (i.e., chronic maintenance therapy) should be continued until immune reconstitution occurs as a result of antiretroviral therapy. Regimens demonstrated to be effective for chronic suppression in randomized, controlled clinical trials include parenteral ganciclovir, oral valganciclovir, parenteral foscarnet, combined parenteral ganciclovir and foscarnet, and parenteral cidofovir. Management of Cytomegalovirus retinitis treatment failures • When patients relapse while receiving maintenance therapy, induction with the same drug followed by reinstitution of maintenance therapy can control the retinitis, although for progressively shorter periods of time with each relapse. • Ganciclovir and foscarnet in combination appear to be superior in efficacy to either agent alone and should be considered for patients whose disease does not respond to single-drug therapy, and for patients with multiple relapses of retinitis. This drug combination, however, is associated with substantial toxicity. Treatment of Hepatitis B Virus coinfection in patients not receiving antiretroviral therapy • For patients with CD4+ counts >350 cells/µL who are not receiving antiretroviral therapy but meet criteria for hepatitis B virus treatment, adefovir or peginterferon alfa-2a monotherapy for 48 weeks might be considered, with close monitoring of hepatitis B virus deoxyribonucleic acid levels and follow-up to evaluate for hepatitis B e antigen seroconversion. However, early initiation of antiretroviral therapy should also be considered for human immunodeficiency virus/hepatitis B virus -coinfected persons with CD4+ counts >350 cells/µL. Treatment of Hepatitis B Virus coinfection in patients who require antiretroviral therapy • For human immunodeficiency virus-infected persons, some experts recommend combination therapy with two agents active against hepatitis B virus to reduce the risk of hepatitis B virus drug resistance; although, there are no results from controlled trials as yet to support this strategy. • Among patients infected with hepatitis B virus, hepatitis C virus, and human immunodeficiency virus, consideration of the need for antiretroviral therapy should be the first priority. If antiretroviral therapy is not required, interferon-based therapy, which suppresses both hepatitis C virus and hepatitis B virus, should be considered. If interferon-based therapy for hepatitis C virus has failed, treatment of chronic hepatitis B with nucleoside or nucleotide analogs is recommended. Treatment of Hepatitis C coinfection • Antiviral treatment for hepatitis C virus infection should be considered for all human immunodeficiency virus-infected persons with acute or chronic hepatitis C virus infection. • The combination of peginterferon alfa (PegIFN) plus ribavirin is the recommended backbone of therapy for HIV/HCV-co-infected patients

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	regardless of HCV genotype.
	• Antiviral treatment with PegIFN is not recommended in patients with decompensated liver disease.
	• For HCV-genotype-1-infected patients who are not co-infected with HIV, a HCV NS3/4A protease inhibitor (PI), either boceprevir or telaprevir, in combination with PegIFN/ribavirin is recommended on the basis of large clinical trials demonstrating significantly higher SVR rates with an acceptable safety/tolerability profile compared to PegIFN/ribavirin alone.
	• For HIV/HCV co-infected patients, preliminary data from small, ongoing clinical trials of boceprevir or telaprevir plus PegIFN/ribavirin for the treatment of HCV genotype 1 infection in HIV/HCV co-infected patients demonstrate greater efficacy than PegIFN/ribavirin alone, with a safety and tolerability profile similar to that observed in HCV monoinfected patients treated with boceprevir or telaprevir plus PegIFN/ribavirin. Preliminary recommendations are as follows:
	  o PegIFN is recommended for use for all HCV genotypes
	  o Ribavirin is recommended for use with PegIFN for all HCV genotypes.
	  o Boceprevir is approved for use in combination with PegIFN/ribavirin in HCV-genotype-1-monoinfected-patients. For HIV/HCV-co-infected patients, the regimen being evaluated is PegIFN/ribavirin administered for four weeks (lead-in phase) followed by boceprevir 800 mg orally every 7 to 9 hours (with a light snack) added to PegIFN/ribavirin for an additional 44 weeks.
	  o Telaprevir is approved for use in combination with PegIFN/ribavirin in HCV-genotype-1-monoinfected-patients. Dosing regimens lasting 48 weeks are being evaluated.
	• Patients with contraindications to the use of ribavirin can be treated with peginterferon alfa (2a or 2b) monotherapy. However, substantially lower sustained viral response rates are expected in persons not receiving ribavirin. HCV PIs should not be administered without ribavirin because of the high likelihood of virologic failure.
	
	<u>Treatment of herpes simplex virus disease</u>
	• Orolabial lesions can be treated with oral valacyclovir, famciclovir, or acyclovir for five to 10 days.
	• Severe mucocutaneous herpes simplex virus lesions are best treated initially with intravenous acyclovir. Patients may be switched to oral therapy after the lesions have begun to regress. Therapy should be continued until the lesions have completely healed.
	• Genital herpes simplex virus infection should be treated with oral valacyclovir, famciclovir, or acyclovir for five to 14 days. Short-course therapy (one, two, or three days) should not be used in patients with human immunodeficiency virus infection.
	• Most recurrences of genital herpes can be prevented by use of daily anti- herpes simplex virus therapy, and this is recommended for persons who have frequent or severe recurrences.
	• Suppressive therapy with oral acyclovir, valacyclovir, or famciclovir is effective in preventing recurrences. Suppressive therapy with valacyclovir should be 500 mg twice daily in human immunodeficiency virus -infected persons or twice-daily regimens with acyclovir or famciclovir should be used.
	
	<u>Management of herpes simplex virus treatment failure</u>

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	• The treatment of choice for acyclovir-resistant herpes simplex virus is intravenous foscarnet. Topical trifluridine, cidofovir, and imiquimod also have been used successfully for lesions on external surfaces, although prolonged application for 21 to 28 days or longer might be required.
	
	Histoplasmosis
	• Patients with moderately severe to severe disseminated histoplasmosis should be treated with an intravenous lipid formulation of amphotericin B for ≥2 weeks or until they clinically improve followed by oral itraconazole (200 mg three times daily for three days and then 200 mg twice daily for a total of ≥12 months).
	• In patients with less severe disseminated histoplasmosis, oral itraconazole at 200 mg three times daily for three days followed by 200 mg twice daily is appropriate initial therapy.
	
	Treatment of Isosporiasis (also known as Cystoisosporiasis)
	  • Sulfamethoxazole-trimethoprim is the antimicrobial agent of choice for treatment of isosporiasis. It is the only agent whose use is supported by substantial published data and clinical experience. Therefore, potential alternative therapies should be reserved for patients with documented sulfa intolerance or in whom treatment fails. The traditional treatment regimen has been a 10-day course of Sulfamethoxazole-trimethoprim (800-160 mg) administered orally four times daily.
	  • Intravenous administration of Sulfamethoxazole-trimethoprim should be considered for patients with potential or documented malabsorption.
	  • Single-agent therapy with pyrimethamine has been used, with anecdotal success for treatment and prevention of isosporiasis. Pyrimethamine (50 to 75 mg/day) plus leucovorin (10 to 25 mg/day) to prevent myelosuppression may be an effective treatment alternative; it is the option for sulfa-intolerant patients.
	
	Leishmaniasis
	• Due to similar efficacy and a better toxicity profile, clinicians consider liposomal amphotericin B as the drug of choice for visceral leishmaniasis in human immunodeficiency virus-coinfected patients. The optimal amphotericin B dosage has not been determined.
	• Regimens with efficacy include conventional amphotericin B 0.5 to 1.0 mg/kg body weight/day intravenous to achieve a total dose of 1.5 to 2.0 g, or liposomal or lipid complex preparations of two to four mg/kg body weight administered on consecutive days or in an interrupted schedule (e.g., 4 mg/kg on Days 1 to 5, 10, 17, 24, 31, and 38) to achieve a total cumulative dose of 20 to 60 mg/kg body weight. A higher daily dosage is recommended for liposomal or lipid complex preparations than for conventional amphotericin B.
	
	Preventing disseminated *Mycobacterium avium* complex disease
	• Human immunodeficiency virus-infected adults and adolescents should receive chemoprophylaxis against disseminated *Mycobacterium avium* complex disease if they have a CD4+ count <50 cells/µL.
	• Azithromycin or clarithromycin are the preferred prophylactic agents.
	• The combination of clarithromycin and rifabutin is no more effective than clarithromycin alone for chemoprophylaxis, is associated with a higher rate of adverse effects than either drug alone, and should not be

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	used. • The combination of azithromycin with rifabutin is more effective than azithromycin alone; however, the additional cost, increased occurrence of adverse effects, potential for drug interactions, and absence of a survival difference compared to azithromycin alone do not warrant a routine recommendation for this regimen. • Azithromycin and clarithromycin also each confer protection against respiratory bacterial infections. • If azithromycin or clarithromycin cannot be tolerated, rifabutin is an alternative prophylactic agent for *Mycobacterium avium* complex disease, although drug interactions may make this agent difficult to use. • Primary *Mycobacterium avium* complex disease prophylaxis should be discontinued among adult and adolescent patients who have responded to antiretroviral therapy with an increase in CD4+ counts to >100 cells/µL for ≥3 months. Primary prophylaxis should be reintroduced if the CD4+ count decreases to <50 cells/µL. <u>Treatment of disseminated *Mycobacterium avium* Complex Disease</u> • Initial treatment of *Mycobacterium avium* complex disease should consist of two or more antimycobacterial drugs to prevent or delay the emergence of resistance. • Clarithromycin is the preferred first agent; however, azithromycin can be substituted for clarithromycin when drug interactions or clarithromycin intolerance preclude the use of clarithromycin. • Testing of *Mycobacterium avium* complex disease isolates for susceptibility to clarithromycin or azithromycin is recommended for all patients. <u>Treatment of Penicilliosis marneffei</u> • Penicilliosis is caused by the dimorphic fungus *Penicillium marneffei*, which is known to be endemic in Southeast Asia (especially Northern Thailand and Vietnam) and southern China. • The recommended treatment is liposomal amphotericin B, three to five mg/kg body weight/day intravenously for two weeks, followed by oral itraconazole, 400 mg/day for a subsequent duration of 10 weeks, followed by secondary prophylaxis. • Patients with mild disease can be initially treated with oral itraconazole 400 mg/day for eight weeks, followed by 200 mg/day for prevention of recurrence. • The alternative drug for primary treatment in the hospital is intravenous voriconazole, 6 mg/kg every 12 hours on day one and then 4 mg/kg every 12 hours for at least three days, followed by oral voriconazole, 200 mg twice daily for a maximum of 12 weeks. • Patients with mild disease can be initially treated with oral voriconazole 400 mg twice a day on day one, and then 200 mg twice daily for 12 weeks. The optimal dose of voriconazole for secondary prophylaxis after 12 weeks has not been studied. <u>Primary prophylaxis of *Pneumocystis (carinii) jiroveci* pneumonia</u> • Sulfamethoxazole-trimethoprim is the recommended prophylactic agent. One double-strength tablet daily is the preferred regimen. However, one single-strength tablet daily is also effective and might be better tolerated than one double-strength tablet daily. One double-

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	strength tablet three times weekly is also effective. Sulfamethoxazole-trimethoprim at a dose of one double-strength tablet daily confers cross-protection against toxoplasmosis and selected common respiratory bacterial infections. Lower doses of sulfamethoxazole-trimethoprim likely also confer such protection. • For patients who have an adverse reaction that is not life threatening, chemoprophylaxis with sulfamethoxazole-trimethoprim should be continued if clinically feasible; for those who have discontinued such therapy because of an adverse reaction, reinstituting sulfamethoxazole-trimethoprim should be strongly considered after the adverse event has resolved. Patients who have experienced adverse events, including fever and rash, might better tolerate reintroduction of the drug with a gradual increase in dose (i.e., desensitization), according to published regimens or reintroduction of sulfamethoxazole-trimethoprim at a reduced dose or frequency; as many as 70% of patients can tolerate such reinstitution of therapy. • If sulfamethoxazole-trimethoprim cannot be tolerated, alternative prophylactic regimens include dapsone, dapsone/pyrimethamine plus leucovorin, aerosolized pentamidine and atovaquone. • Primary *Pneumocystis (carinii) jiroveci* pneumonia prophylaxis should be discontinued for adult and adolescent patients who have responded to antiretroviral therapy with an increase in CD4+ counts to >200 cells/µL for >3 months. Prophylaxis should be reintroduced if the CD4+ count decreases to <200 cells/µL. <u>Treatment of *Pneumocystis (carinii) jiroveci* pneumonia</u> • Sulfamethoxazole-trimethoprim is the treatment of choice. The dose must be adjusted for abnormal renal function. Multiple randomized clinical trials indicate that sulfamethoxazole-trimethoprim is as effective as parenteral pentamidine and more effective than other regimens. Adding leucovorin to prevent myelosuppression during acute treatment is not recommended because of questionable efficacy and some evidence for a higher failure rate. Oral outpatient therapy of sulfamethoxazole-trimethoprim is highly effective among patients with mild-to-moderate disease. • Patients who have *Pneumocystis (carinii) jiroveci* despite sulfamethoxazole-trimethoprim prophylaxis are usually effectively treated with standard doses of sulfamethoxazole-trimethoprim. • Patients with documented or suspected *Pneumocystis (carinii) jiroveci* and moderate-to-severe disease, as defined by room air pO_2 <70 mm Hg or arterial-alveolar O_2 gradient >35 mm Hg, should receive adjunctive corticosteroids as early as possible, and certainly within 72 hours after starting specific *Pneumocystis (carinii) jiroveci* therapy. • The recommended duration of therapy for *Pneumocystis (carinii) jiroveci* is 21 days. • Patients who have a history of *Pneumocystis (carinii) jiroveci* should be administered chemoprophylaxis for life (i.e., secondary prophylaxis or chronic maintenance therapy) with sulfamethoxazole-trimethoprim unless immune reconstitution occurs as a result of antiretroviral therapy. • Secondary prophylaxis should be discontinued for adult and adolescent patients whose CD4+ count has increased from <200 cells/µL to >200 cells/µL for >3 months as a result of antiretroviral therapy. Prophylaxis should be reintroduced if the CD4+ count decreases to <200 cells/µL. If *Pneumocystis (carinii) jiroveci* recurs at a CD4+ count of ≥200 cells/µL, lifelong prophylaxis should be administered.

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	Primary prophylaxis of *Toxoplasma* encephalitis
	• The double-strength tablet daily dose of sulfamethoxazole-trimethoprim recommended as the preferred regimen for *Pneumocystis (carinii) jiroveci* prophylaxis is effective against *Toxoplasma* encephalitis as well and is therefore recommended. Sulfamethoxazole-trimethoprim, one double-strength tablet three times weekly, is an alternative.
	• If patients cannot tolerate sulfamethoxazole-trimethoprim, the recommended alternative is dapsone-pyrimethamine plus leucovorin, which is also effective against *Pneumocystis (carinii) jiroveci* pneumonia.
	• Atovaquone with or without pyrimethamine/leucovorin can also be considered.
	• Prophylactic monotherapy with dapsone, pyrimethamine, azithromycin, or clarithromycin cannot be recommended on the basis of available data. Aerosolized pentamidine does not protect against *Toxoplasma* encephalitis and is not recommended.
	• Prophylaxis against *Toxoplasma* encephalitis should be discontinued among adult and adolescent patients who have responded to antiretroviral therapy with an increase in CD4+ counts to >200 cells/µL for >3 months. Prophylaxis for *Toxoplasma* encephalitis should be reintroduced if the CD4+ count decreases to <100–200 cells/µL.
	
	Treatment of *Toxoplasma* encephalitis
	• The initial therapy of choice for *Toxoplasma* encephalitis consists of the combination of pyrimethamine plus sulfadiazine plus leucovorin.
	• The preferred alternative regimen for patients with *Toxoplasma* encephalitis who are unable to tolerate or who fail to respond to first-line therapy is pyrimethamine plus clindamycin plus leucovorin.
	• Sulfamethoxazole-trimethoprim was reported in a small randomized trial to be effective and better tolerated than pyrimethamine-sulfadiazine. On the basis of less in vitro activity and less experience with sulfamethoxazole-trimethoprim, treatment with this drug may be considered an option.
	• Acute therapy for *Toxoplasma* encephalitis should be continued for at least six weeks, if there is clinical and radiologic improvement.
	
	Treatment of latent tuberculosis infection
	• Human immunodeficiency virus-infected persons, regardless of age, should be treated for latent tuberculosis infection if they have no evidence of active tuberculosis and:
	  o A positive diagnostic test for latent tuberculosis infection and no prior history of treatment for active or latent tuberculosis.
	  o A negative diagnostic test for latent tuberculosis infection but are close contacts of persons with infectious pulmonary tuberculosis.
	  o A history of untreated or inadequately treated healed tuberculosis (i.e., old fibrotic lesions on chest radiography) regardless of diagnostic tests for latent tuberculosis infection.
	• Treatment options for latent tuberculosis infection include isoniazid daily or twice weekly for nine months.
	• Due to an increased risk of fatal and severe hepatotoxicity, a two-month regimen of daily rifampin and pyrazinamide is not

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	recommended for latent tuberculosis infection treatment regardless of human immunodeficiency virus status. • Human immunodeficiency virus-infected persons receiving isoniazid should receive pyridoxine to minimize the risk of developing peripheral neuropathy. Alternatives for individuals who cannot take isoniazid or who have been exposed to a known isoniazid-resistant index case include either rifampin or rifabutin alone for four months. • For persons exposed to isoniazid- and/or rifampin-resistant tuberculosis, decisions to treat with one or two drugs other than isoniazid, rifampin, or rifabutin should be based on the relative risk of exposure to organisms broadly resistant to other antimycobacterial drugs and should be made in consultation with public health authorities. • Directly observed therapy should be used with intermittent dosing regimens when otherwise feasible to maximize regimen completion rates. • There is no evidence to suggest that latent tuberculosis infection treatment should be continued beyond the recommended duration in persons with human immunodeficiency virus infection. Therefore, latent tuberculosis infection treatment should be discontinued after completing the appropriate number of doses. <u>Treatment of active tuberculosis disease</u> • Recommendations for anti-tuberculosis treatment regimens in human immunodeficiency virus -infected adults follow the same principles as for adults without human immunodeficiency virus -infection. • Treatment of drug susceptible tuberculosis disease should include a six-month regimen with an initial phase of isoniazid, rifampin or rifabutin, pyrazinamide, and ethambutol administered for two months followed by isoniazid and rifampin (or rifabutin) for four additional months. • When drug-susceptibility testing confirms the absence of resistance to isoniazid, rifampin, and pyrazinamide, ethambutol may be discontinued before two months of treatment have been completed. • For patients with cavitary lung disease and cultures positive for *Mycobacterium tuberculosis* after completion of two months of therapy, treatment should be extended with isoniazid and rifampin for an additional three months for a total of nine months. • All human immunodeficiency virus-infected patients treated with isoniazid should receive pyridoxine supplementation. • For patients with extrapulmonary tuberculosis, a six- to nine-month regimen (two months of isoniazid, rifampin, pyrazinamide, and ethambutol followed by four to seven months of isoniazid and rifampin) is recommended. • Exceptions to the recommendation for a six- to nine-month regimen for extrapulmonary tuberculosis include central nervous system disease (tuberculoma or meningitis) and bone and joint tuberculosis, for which many experts recommend nine to 12 months. • Adjuvant corticosteroids should be added when treating central nervous system and pericardial disease. • Treatment with corticosteroids should be started intravenously as early as possible with change to oral therapy individualized according to clinical improvement. • Recommended corticosteroid regimens are dexamethasone 0.3 to 0.4 mg/kg tapered over six to eight weeks or prednisone 1 mg/kg for three

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	weeks, then tapered for three to five weeks. Treatment of varicella zoster virus disease • For uncomplicated varicella, the preferred treatment options are valacyclovir (1 gram orally three times daily), or famciclovir (500 mg orally three times daily) for five to seven days. Oral acyclovir (20 mg/kg body weight up to a maximum dose of 800 mg five times daily) can be an alternative. • Prompt antiviral therapy should be instituted in all human immunodeficiency virus-seropositive patients whose herpes zoster is diagnosed within one week of rash onset (or any time before full crusting of lesions). The recommended treatment options for acute localized dermatomal herpes zoster in human immunodeficiency virus-infected patients are oral valacyclovir, famciclovir, or acyclovir (doses as above) for seven to 10 days, although longer durations of therapy should be considered if lesions resolve slowly. Valacyclovir or famciclovir are preferred because of their improved pharmacokinetic properties and simplified dosing schedule. • If cutaneous lesions are extensive or if visceral involvement is suspected, intravenous acyclovir should be initiated and continued until clinical improvement is evident. A switch from intravenous acyclovir to oral antiviral therapy (to complete a 10 to 14 day treatment course) is reasonable when formation of new cutaneous lesions has ceased and the signs and symptoms of visceral varicella zoster virus infection are clearly improving. • Optimal antiviral therapy for progressive outer retinal necrosis remains undefined. Specific treatment should include systemic therapy with at least one intravenous drug (selected from acyclovir, ganciclovir, foscarnet, and cidofovir) coupled with injections of at least one intravitreal drug (selected from ganciclovir and foscarnet). Treatment regimens for progressive outer retinal necrosis recommended by certain specialists include a combination of intravenous ganciclovir and/or foscarnet plus intravitreal injections of ganciclovir and/or foscarnet. The prognosis for visual preservation in involved eyes is poor, despite aggressive antiviral therapy. • Other infectious disease states mentioned within these guidelines note that the treatment guidelines for that disease state should be utilized. • The guideline specifies that detailed recommendations for the treatment of human herpesvirus-8 and associated malignancies are beyond the scope of these guidelines. • Other excluded infectious disease states offer no specific therapy or utilize medications not licensed in the United States.
National Comprehensive Cancer Network: **Prevention and Treatment of Cancer-Related Infections[18] (2014)**	Initial Therapy for Fever and Neutropenia • Fluconazole may be used as an addition to initial empiric broad-spectrum antibiotics if patients present with thrush. • Voriconazole or posaconazole may be used if refractory to fluconazole. Empiric Antifungal Therapy in Persistent Neutropenic Fever • Fluconazole has been used successfully as empiric therapy for neutropenic fever in patients not receiving prophylaxis but is limited by a lack of activity against molds. • Itraconazole in the capsule formulation has erratic bioavailability and is therefore not suitable as empiric antifungal therapy.

Clinical Guideline	Recommendation(s)
	• Voriconazole is an option for empiric therapy in patients at high risk for invasive mold infection. Empiric therapy for uncomplicated fever and neutropenia with site-specific involvement • Fluconazole is first-line therapy for thrush. Voriconazole, posaconazole, or echinocandin if refractory to fluconazole. • For sinus/nasal findings, add vancomycin if periorbital cellulitis is noted. Add lipid amphotericin B preparation to cover possible aspergillosis and mucormycosis in high-risk patients with suspicious computed tomography/magnetic resonance imaging findings. Posaconazole can be considered for patients who have invasive, refractory infections or who have intolerance to amphotericin B. • For vesicular lesions, use anti-herpes simplex virus therapy. Antifungal prophylaxis in cancer patients with an intermediate to high overall infection risk • Consider fluconazole during neutropenia and for anticipated mucositis. • Patients with acute lymphoblastic leukemia may use fluconazole until resolution of neutropenia. • Posaconazole is recommended in neutropenic patients with acute myelogenous leukemia and myelodysplastic syndromes until resolution of neutropenia. • Patients undergoing autologous hematopoietic stem cell transplantation with mucositis may use fluconazole or micafungin until resolution of neutropenia. • Recommended agents for patients undergoing allogeneic hematopoietic stem cell transplantation include fluconazole and micafungin during neutropenia and for at least 75 days after transplant. • Patients with significant graft-vs-host disease may use posaconazole until resolution of significant graft-vs-host disease. Antiviral prophylaxis in cancer patients with an intermediate to high overall infection risk • Initiate antiviral therapy during neutropenia and at least 30 days after hematopoietic stem cell transplantation. • For intermediate risk patients, consider acyclovir, famciclovir, or valacyclovir for herpes simplex virus prophylaxis during active therapy and at least 30 days after hematopoietic stem cell transplantation. Consider varicella zoster virus prophylaxis for at least one year after hematopoietic stem cell transplantation. • High risk patients may use acyclovir, famciclovir, or valacyclovir for herpes simplex virus and varicella zoster virus prophylaxis during active therapy including periods of neutropenia. • In allogenic transplant recipients, acyclovir prophylaxis should be considered for at least one year after hematopoietic stem cell transplantation for varicella. • Herpes simplex virus prophylaxis is recommended for a minimum of two months after alemtuzumab and until CD4 ≥200 cells/µL, during active therapy including neutropenia, and at least 30 days after hematopoietic stem cell transplantation. Prevention of cytomegalovirus in cancer patients at high risk • For allogenic stem cell transplant recipients, monitor weekly for cytomegalovirus for one to six months after transplant and during

Clinical Guideline	Recommendation(s)
	graft-vs-host disease requiring therapy. • For patients receiving alemtuzumab, monitor weekly for cytomegalovirus for a minimum of two months after therapy. • Pre-emptive therapy agents include ganciclovir (intravenous), valganciclovir (PO), foscarnet (intravenous), or cidofovir (intravenous) for at least two weeks and until cytomegalovirus is no longer detected. Prevention of hepatitis B virus in cancer patients at high risk • For allogenic stem cell transplant candidates with active hepatitis B infection, consider delaying transplant. Treat with antivirals (adefovir, entecavir, lamivudine, telbivudine, or tenofovir) for three to six months and then reevaluate. • Use prophylactic treatment for at least six to 12 months after allogenic stem cell transplant. • For allogenic stem cell transplant candidates with no active hepatitis B infection, consider antiviral prophylaxis (adefovir, entecavir, lamivudine, telbivudine, or tenofovir) if HBsAg+ (without HBeAg+), or HBcAb+, or increasing hepatitis B viral load. • For patients treated with anti-CD20 monoclonal antibodies (rituximab, ofatumumab) or alemtuzumab, consider antiviral treatment (adefovir, entecavir, lamivudine, telbivudine, or tenofovir) if HBsAg+ or HBcAb+ or increasing viral load for at least six to 12 months following last dose of antibody therapy. Miscellaneous Recommendations • Fluconazole or an echinocandin is recommended as initial therapy for most non-neutropenic adult patients with candidiasis. • An echinocandin is preferred as initial therapy for candidemia in most neutropenic patients. • Voriconazole is the recommended agent as primary therapy for invasive aspergillosis. • Data on posaconazole as primary therapy for invasive fungal infections are limited.
Infectious Diseases Society of America: **Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer (2010)**[19] **Reviewed and deemed current as of April 2013**	Antifungal therapy in high risk patients • Empirical antifungal therapy and investigation for invasive fungal infections should be considered for patients with persistent or recurrent fever after four to seven days of antibiotics and whose overall duration of neutropenia is expected to be greater than seven days. • Data are insufficient to recommend a specific empirical antifungal agent for a patient already receiving antifungal prophylaxis, but switching to a different class of antifungals that is given intravenously should be considered. • Preemptive antifungal management is acceptable as an alternative to empirical antifungal therapy in a subset of high-risk neutropenic patients. Those who remain febrile after four to seven days of broad-spectrum antibiotics but are clinically stable, have no clinical or chest and sinus computed tomography signs of fungal infection, have negative serologic assay results for evidence of invasive fungal infection, and have no recovery of fungi from any body site may have antifungal agents withheld. Antifungal therapy should be instituted if any of these indicators of possible invasive fungal infection are identified. • Prophylaxis against *Candida* infection is recommended in patient groups in whom the risk of invasive candidal infection is substantial, such as allogeneic hematopoietic stem cell transplant recipients or

Clinical Guideline	Recommendation(s)
	those undergoing intensive remission-induction or salvage-induction chemotherapy for acute leukemia. Fluconazole, itraconazole, voriconazole, posaconazole, micafungin, and caspofungin are all acceptable alternatives. • Prophylaxis against invasive *Aspergillus* infections with posaconazole should be considered for selected patients >13 years of age who are undergoing intensive chemotherapy for acute myeloid leukemia or myelodysplastic syndrome in whom the risk of invasive aspergillosis without prophylaxis is substantial. <u>Antifungal therapy in low risk patients</u> • In low-risk patients, the risk of invasive fungal infection is low, and therefore routine use of empirical antifungal therapy is not recommended. • Antifungal prophylaxis is not recommended for patients in whom the anticipated duration of neutropenia is less than seven days. <u>Antiviral prophylaxis</u> • Herpes simplex virus–seropositive patients undergoing allogeneic hematopoietic stem cell transplantation or leukemia induction therapy should receive acyclovir antiviral prophylaxis. • Antiviral treatment for herpes simplex or varicella-zoster virus infection is only indicated if there is clinical or laboratory evidence of active viral disease.
Center for International Blood and Marrow Transplant Research /National Marrow Donor Program /European Blood and Marrow Transplant Group /American Society of Blood and Marrow Transplantation / Canadian Blood and Marrow Transplant Group / Infectious Diseases Society of America /Society for Healthcare Epidemiology of America /Association of Medical Microbiology and Infectious Diseases Canada /Centers for Disease Control and Prevention: **Guidelines for Preventing Infectious Complications Among Hematopoietic Stem Cell Transplantation Recipients: A Global Perspective (2009)**[20]	<u>Cytomegalovirus (CMV) recommendations</u> • Hematopoietic cell transplantation (HCT) candidates should be tested for CMV antibodies prior to transplant to determine their risk for primary CMV infection and reactivation after HCT. • CMV-seropositive HCT recipients and CMV-seronegative recipients with CMV-seropositive donors should be placed on CMV preventative therapy from time of engraftment until at least 100 days after HCT. • A prophylaxis strategy against early CMV replication for allogeneic recipients involves administering prophylaxis to all allogeneic recipients at risk throughout the period from engraftment to 100 days after HCT. Ganciclovir, high-dose acyclovir, and valacyclovir are all effective at reducing the risk for CMV infection after HCT. • Ganciclovir is often used as a first-line drug for preemptive therapy. Although foscarnet is as effective as ganciclovir, it is currently more commonly used as a second-line drug, because of the requirement for pre-hydration and electrolyte monitoring. Preemptive therapy should be given for a minimum of two weeks. Patients who are ganciclovir-intolerant should be treated with foscarnet. <u>Fungal infection recommendations</u> • Fluconazole is the drug of choice for the prophylaxis of invasive candidiasis before engraftment in allogeneic hematopoietic cell transplant recipients, and may be started from the beginning or just after the end of the conditioning regimen. • The optimal duration of fluconazole prophylaxis is not defined. • Fluconazole is not effective against *Candida krusei* and *Candida glabrata* and should not be used for prophylaxis against these strains. • Micafungin is an alternative prophylactic agent. • Itraconazole oral solution has been shown to prevent invasive fungal infections, but use of this drug is limited by poor tolerability and toxicities.

Clinical Guideline	Recommendation(s)
	• Voriconazole and posaconazole may be used for prevention of candidiasis post-engraftment. • Oral amphotericin B, nystatin, and clotrimazole troches may control superficial infection and control local candidiasis but have not been shown to prevent invasive candidiasis. • Transplant patients with candidemia or candidiasis may still receive transplants if their infection is diagnosed early and treated aggressively with amphotericin B or appropriate doses of fluconazole. • Autologous recipients have a lower risk of infection compared to allogeneic recipients and may not require prophylaxis, though it is still recommended in patients who have underlying hematologic malignancies, those who will have prolonged neutropenia and mucosal damage, or have recently received fludarabine. Itraconazole oral solution has been shown to prevent mold infections. • In patients with graft-vs-host disease, posaconazole has been reported to prevent invasive mold infections. • Patients with prior invasive aspergillosis should receive secondary prophylaxis with a mold-active drug. The optimal drug has not been determined, but voriconazole has been shown to have benefit for this indication. <u>Hepatitis B virus (HBV) recommendations</u> • Limited data suggests HCT donors with detectable HBV DNA should receive antiviral therapy for four weeks or until viral load is undetectable. Expert opinion suggests entecavir for this use. • HCT recipients with active HBV posttransplant should be treated with lamivudine for at least six months in autologous HCT recipients and for six months after immunosuppressive therapy has stopped in allogenic HCT recipients. <u>Hepatitis C virus (HCV) recommendations</u> • Treatment for chronic HCV should be considered in all HCV-infected HCT recipients. • The patient must be in complete remission from the original disease, be >2 years posttransplant without evidence of either protracted GVHD, have been off immunosuppression for 6 months, and have normal blood counts and serum creatinine. • Treatment should consist of full-dose peginterferon and ribavirin and should be continued for 24 to 48 weeks, depending on response. <u>Herpes simplex virus (HSV) recommendations</u> • Acyclovir prophylaxis should be offered to all HSV-seropositive allogenic recipients to prevent HSV reactivation during the early transplant period for up to 30 days. • Routine acyclovir prophylaxis is not indicated for HSV-seronegative allogenic recipients. • Use of ganciclovir for CMV prophylaxis will provide sufficient prophylaxis for HSV. • Foscarnet is the treatment of choice for acyclovir-resistant HSV. • Valacyclovir is equally effective at HSV prophylaxis when compared to acyclovir. • Foscarnet is not recommended for routine HSV prophylaxis among HCT recipients due to renal and infusion-related toxicity. Patients who receive foscarnet for other reasons (e.g., CMV prophylaxis) do not require additional acyclovir prophylaxis.

Clinical Guideline	Recommendation(s)
	• There is inadequate data to make recommendations regarding the use of famciclovir for HSV prophylaxis. • HSV prophylaxis lasting >30 days after HCT might be considered for persons with frequent recurrences of HSV infection. Acyclovir or valacyclovir can be used during phase I (pre-engraftment) for administration to HSV-seropositive autologous recipients who are likely to experience substantial mucositis from the conditioning regimen. <u>Respiratory syncytial virus (RSV) recommendations</u> • Some researchers recommend preemptive aerosolized ribavirin for patients with RSV upper respiratory infection (URI), especially those with lymphopenia (during the first three months after HCT) and preexisting obstructive lung disease (late after HCT). • Although a definitive, uniformly effective preemptive therapy for RSV infection among HCT recipients has not been identified, certain other strategies have been proposed, including systemic ribavirin, RSV antibodies (i.e., passive immunization with high-RSV-titer IVIG, RSV immunoglobulin) in combination with aerosolized ribavirin, and RSV monoclonal antibody. • No randomized trial has been completed to test the efficacy of these strategies; therefore, no specific recommendation regarding any of these strategies can be given at this time. <u>Varicella zoster virus (VZV) recommendations</u> • Long-term acyclovir prophylaxis to prevent recurrent VZV infection is recommended for the first year after HCT for VZV-seropositive allogenic and autologous HCT recipients. Acyclovir prophylaxis may be continued beyond one year in allogenic HCT recipients who have graft-vs-host disease or require systemic immunosuppression. • Valacyclovir may be used in place of acyclovir when oral medications are tolerated. • There is not enough data to recommend use of famciclovir in place of valacyclovir or acyclovir for VZV prophylaxis. • Any HCT recipient with VZV-like rash should receive preemptive intravenous acyclovir therapy until two days after the lesions have crusted • Acyclovir or valacyclovir may be used in place of VZV immunoglobulin for post-exposure therapy.
European Academy of Dermatology and Venereology: **Onychomycosis Treatment Guidelines (2005)**[21]	• Prior to initiating treatment, it is important that diagnosis be confirmed and the etiological agent identified. • Topical monotherapy is indicated when the matrix area is not involved. Topical treatment is also suitable for patients who are reluctant to take oral medications or have swallowing difficulties. The only case in which it is not recommended is if nail penetration may be suboptimal. • Oral antifungal drugs are generally considered to be more effective than topical treatments. However, they are accompanied by a higher risk of systemic adverse effects and drug interactions. • Oral monotherapy (terbinafine, itraconazole, or fluconazole) or combined oral and topical (nail lacquer) is recommended when 1) at least 50% of the distal nail plate is involved; 2) the nail matrix area is involved; 3) mycological criteria such as the causative agent or agents are known and oral agents can target specific fungi; 4) topical drugs are not indicated when topical drug transport is suboptimal; and 5) oral or combined therapy is also recommended in cases of nail matrix area

Clinical Guideline	Recommendation(s)
	involvement. • Combination therapy with systemic and topical treatments may be considered when a large portion of the nail plate is affected (>50%), when the nail matrix is involved, and in cases of treatment failure. • Griseofulvin is associated with the poorest mycological cure rate (<30%) and is rarely used. Terbinafine is associated with the highest mycological cure rate (77 to 100%).
British Association of Dermatologists: **Guidelines for the Treatment of Onychomycosis (2003)**[22]	• Both topical and oral agents are available for the treatment of fungal nail infection. The primary aim of treatment is to eradicate the organism as demonstrated by microscopy and culture. • Systemic therapy is almost always more successful than topical treatment, which should only be used in superficial white onychomycosis, possibly very early distal and lateral subungual onychomycosis or when systemic therapy is contraindicated. • Both terbinafine and itraconazole have been shown to be more effective than griseofulvin in dermatophyte onychomycosis and therefore the optimum choice of treatment lies between terbinafine and itraconazole. • Terbinafine is more effective than itraconazole for dermatophyte infection of the nails and should be first-line treatment. Itraconazole may be considered a second-line treatment. • Expected cure rates vary and range from 80 to 90% for fingernail infections and 70 to 80% for toenail infections.
European Society for Pediatric Dermatology: **Guidelines for the Management of Tinea Capitis in Children (2010)**[23]	• Tinea capitis always requires systemic treatment because topical antifungal agents do not penetrate the hair follicle. • Topical treatment is only used as adjuvant therapy to systemic antifungals. • Griseofulvin has been the gold standard for systemic therapy of tinea capitis. The main disadvantage of griseofulvin is the long duration of treatment required (six to 12 weeks or longer) which may lead to reduced compliance. • The newer oral antifungal agents including terbinafine, itraconazole, and fluconazole appear to have efficacy rates and potential adverse effects similar to those of griseofulvin in children with tinea capitis due to *Trichophyton* species, while requiring much shorter duration of treatment. The decision between griseofulvin and newer antifungal agents for children with *Trichophyton* species can be based on the balance between duration of treatment and compliance. • Griseofulvin is still the treatment of choice for cases caused by *Microsporum* species. • Adjunctive topical therapies, such as selenium sulfide or ketoconazole shampoos, as well as fungicidal creams or lotions have been shown to decrease the carriage of viable spores responsible for the disease contagion and reinfection and may shorten the cure rate with oral antifungals. • The topical fungicidal cream/lotion should be applied to the lesions once daily for a week. The shampoo should be applied to the scalp and hair for five minutes twice weekly for two to four weeks or three times weekly until the patient is clinically and mycologically cured. The latter in conjunction with one week of topical fungicidal cream or lotion application is recommended.
British Association of Dermatologists: **Guidelines for the Management of Tinea Capitis**	• The aim of treatment is to achieve a clinical and mycological cure as quickly as possible. • Oral antifungal therapy is generally needed. Topical treatment alone is not recommended for the management of tinea capitis.

Clinical Guideline	Recommendation(s)
(2000)[24]	• Oral therapy options include griseofulvin, terbinafine, itraconazole, fluconazole, and ketoconazole. • If there has been no clinical response and signs persist at the end of the treatment period, then the options include: o Increase the dose or duration of the original drug (both griseofulvin and terbinafine have been used successfully and safely at higher doses or for longer courses to clear resistant infections) o Change to an alternative antifungal (e.g. switch from griseofulvin to terbinafine or itraconazole). • Symptom-free carriers with light growth/low spore count on culture may be treated with twice weekly selenium or povidone shampoo. • The definitive end-point for adequate treatment is not clinical response but mycological cure; therefore, follow-up with repeat mycology sampling is recommended at the end of the standard treatment period and then monthly until mycological clearance is documented. Treatment should, therefore, be tailored for each individual patient according to response.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the azoles are noted in Table 4. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 4. FDA-Approved Indications for the Azoles[1-8]

Indication	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Voriconazole
Aspergillosis (invasive)					✔
Aspergillosis in patients intolerant of or refractory to amphotericin B therapy		✔ †			
Blastomycosis		✔ †	✔		
Candida pneumonia	✔				
Candida wound infections					✔
Candidemia	✔				✔
Candidiasis			✔		
Candidiasis (abdominal)					✔
Candidiasis (bladder wall)					✔
Candidiasis (kidney)					✔
Candidiasis (Peritoneum)	✔				
Candidiasis (skin, disseminated)					✔
Candidiasis (disseminated)	✔				
Candidiasis (esophageal)	✔	✔ ‡			✔
Candidiasis (mucocutaneous)			✔		
Candidiasis (oropharyngeal)	✔	✔ ‡	✔	✔	
Candidiasis (vaginal)	✔				
Candiduria	✔		✔		
Chromomycosis			✔		
Coccidioidomycosis			✔		
Cryptococcal meningitis	✔				
Histoplasmosis		✔ †	✔		
Onychomycosis of the fingernail		✔ †			
Onychomycosis of the toenail (with or		✔ †			

Indication	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Voriconazole
without fingernail involvement)					
Onychomycosis of the toenail caused by *Trichophyton rubrum* or *Trichophyton mentagrophytes*		✔ ^			
Paracoccidioidomycosis			✔		
Prophylaxis of candidiasis in patients undergoing bone marrow transplantation receiving cytotoxic chemotherapy and/or radiation	✔				
Prophylaxis of invasive *Aspergillus* and *Candida* infections in severely immunocompromised patients				✔	
Recalcitrant cutaneous dermatophyte infections who have not responded to topical therapy or oral griseofulvin or who are unable to take oral griseofulvin			✔		
Serious fungal infections caused by *Scedosporium apiospermum* and *Fusarium* species in patients intolerant of or refractory to other therapy					✔

† Capsule formulation only
‡ Solution formulation only
^Tablet formulation only

IV. Pharmacokinetics

The pharmacokinetic parameters of the azoles are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Azoles[1-8]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Fluconazole	Oral: >90	11 to 12	Liver	Renal (80)	30
Itraconazole	55 to 68	>99	Liver	Renal (40) Feces (3 to 18)	64
Ketoconazole	75	91-99	Liver	Feces (75) Renal (13)	2 to 12
Posaconazole	Variable	>98	Liver	Feces (71 to 77) Renal (13 to 14)	35
Voriconazole	96	58	Liver	Renal (>94)	Variable

V. Drug Interactions

Significant drug interactions with the azoles are listed in Table 6.

Table 6. Significant Drug Interactions with the Azoles[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Azoles (fluconazole, itraconazole, ketoconazole, voriconazole)	1	Alfentanil, fentanyl, sufentanil	The pharmacological adverse effects of the opioid analgesics may be increased.
Azoles (fluconazole, itraconazole,	1	Cisapride	Increased cisapride plasma concentrations resulting in cardiotoxicity may occur.

Generic Name(s)	Significance Level	Interaction	Mechanism
ketoconazole, posaconazole, voriconazole)			
Azoles (itraconazole, ketoconazole)	1	Conivaptan	Increased levels and adverse effects of conivaptan may occur.
Azoles (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)	1	Crizotinib	May result in increased crizotinib concentrations and an increased risk of QT interval prolongation.
Azoles (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)	1	Dasatinib	May result in an increased risk of QT interval prolongation.
Azoles (itraconazole, ketoconazole)	1	Dofetilide	Increased levels and adverse effects of dofetilide may occur, including ventricular arrhythmias and torsades de pointes.
Azoles (voriconazole)	1	Efavirenz	Voriconazole concentrations may be decreased, decreasing therapeutic effects, and efavirenz concentrations may be increased, increasing the risk of side effects.
Azoles (itraconazole, ketoconazole)	1	Eplerenone	Increased eplerenone plasma concentrations may occur, increasing the risk of hyperkalemia and serious arrhythmias.
Azoles (itraconazole, ketoconazole, posaconazole, voriconazole)	1	Ergot derivatives	An increased risk of ergot toxicity has been observed.
Azoles (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)	1	Lapatinib	May result in increased lapatinib plasma concentrations and increased risk of QT interval prolongation.
Azoles (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)	1	Nilotinib	May result in increased nilotinib plasma concentrations and an increased risk of QT interval prolongation.
Azoles (itraconazole, ketoconazole, posaconazole, voriconazole)	1	Pimozide	The risk of life-threatening arrhythmias is increased.
Azoles (fluconazole,	1	Quetiapine	May result in increased quetiapine serum concentrations

Generic Name(s)	Significance Level	Interaction	Mechanism
itraconazole, ketoconazole, posaconazole, voriconazole)			and an increased risk of QT prolongation.
Azoles (itraconazole, posaconazole, voriconazole)	1	Quinidine	Quinidine levels may be increased, increasing the risk of cardiovascular events.
Azoles (itraconazole, ketoconazole)	1	Ranolazine	Ranolazine levels may be increased, increasing the risk of QT prolongation, torsades de pointes, and sudden death.
Azoles (voriconazole)	1	Ritonavir	Therapeutic effect of voriconazole may be decreased.
Azoles (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)	1	Salmeterol	May result in increased salmeterol plasma concentrations and increased risk of QT interval prolongation.
Azoles (fluconazole, posaconazole, voriconazole)	1	Serotonin antagonists (ondansetron, granisetron)	May result in an increased risk of QT interval prolongation.
Azoles (fluconazole, posaconazole, voriconazole)	1	Sorafenib	May result in increased risk of QT interval prolongation and risk of ventricular arrhythmias.
Azoles (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)	1	Sparfloxacin	May result in an increased risk of QT interval prolongation and torsade de pointes.
Azoles (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)	1	Sunitinib	May result in an increased risk of QT interval prolongation.
Azoles (ketoconazole)	1	Taxoids	Increased levels and adverse effects of the taxoids may occur.
Azoles (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)	1	Terfenadine	May result in increased serum concentrations of terfenadine and its active metabolite, and an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
Azoles (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)	1	Vinblastine, vincristine	Vinca alkaloid toxicity may be increased when co-administered with azole antifungals.
Azoles (fluconazole,	1	Warfarin	Anticoagulant effect of warfarin may be increased.

Generic Name(s)	Significance Level	Interaction	Mechanism
itraconazole, ketoconazole, voriconazole)			
Azoles (itraconazole, ketoconazole)	2	Alfuzosin	Increased levels and adverse effects of alfuzosin may occur.
Azoles (fluconazole, itraconazole, ketoconazole)	2	Almotriptan, eletriptan	Increased levels and adverse effects of almotriptan and eletriptan may occur.
Azoles (ketoconazole)	2	Antacids	Therapeutic effects of ketoconazole may be decreased.
Azoles (itraconazole, ketoconazole)	2	Aripiprazole	Increased levels and adverse effects of aripiprazole may occur.
Azoles (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)	2	Benzodiazepines	Increased serum levels of benzodiazepines with central nervous system depression and psychomotor impairment is possible.
Azoles (fluconazole, itraconazole, ketoconazole, voriconazole)	2	Bosentan	Increased levels of bosentan and increased adverse effects may occur.
Azoles (fluconazole, itraconazole, ketoconazole)	2	Buspirone	Increased buspirone levels and increased adverse effects may occur.
Azoles (itraconazole)	2	Busulfan	Increased levels and adverse effects of busulfan may occur.
Azoles (fluconazole, itraconazole, ketoconazole, voriconazole)	2	Carbamazepine	Increased carbamazepine levels and increased adverse effects may occur.
Azoles (Posaconazole)	2	Cimetidine	Plasma concentrations and therapeutic effect of posaconazole may be decreased.
Azoles (itraconazole, ketoconazole)	2	Cimetidine, famotidine, nizatidine, ranitidine	Effects of itraconazole and ketoconazole may be attenuated.
Azoles (fluconazole, itraconazole, ketoconazole, voriconazole)	2	Corticosteroids	Corticosteroid effects and toxicity may be increased.
Azoles (fluconazole, itraconazole, ketoconazole)	2	Cyclophosphamide	Increased adverse effects of cyclophosphamide may occur.
Azoles (fluconazole, itraconazole,	2	Cyclosporine	Cyclosporine levels and toxicity may increase and persist more than 1 week after stopping

Generic Name(s)	Significance Level	Interaction	Mechanism
ketoconazole, posaconazole, voriconazole)			antifungal therapy.
Azoles (itraconazole, ketoconazole)	2	Didanosine	Therapeutic effects of azole antifungals may be decreased.
Azoles (itraconazole)	2	Digoxin	Serum digoxin concentrations and adverse effects may be increased.
Azoles (itraconazole, ketoconazole, posaconazole, voriconazole)	2	Felodipine	Felodipine concentrations may be increased, leading to peripheral edema and adverse effects.
Azoles (fluconazole, itraconazole, ketoconazole, voriconazole)	2	Gefitinib	Increased gefitinib adverse reactions may occur.
Azoles (fluconazole, itraconazole, ketoconazole)	2	Haloperidol	Elevated haloperidol plasma concentrations and adverse effects may occur.
Azoles (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)	2	HMG-CoA reductase inhibitors	Increased plasma levels of HMG-CoA reductase inhibitors and rhabdomyolysis may occur.
Azoles (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)	2	Nisoldipine	Increased nisoldipine levels and adverse reactions may occur.
Azoles (fluconazole, voriconazole)	2	Nonsteroidal anti-inflammatory drugs (NSAIDs)	Elevated plasma concentrations of nonsteroidal anti-inflammatory drugs and increases in adverse reactions may occur.
Azoles (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)	2	Phenytoin	Increased phenytoin levels and toxicity may occur.
Azoles (itraconazole, ketoconazole, posaconazole, voriconazole)	2	Phosphodiesterase (PDE) 5 inhibitors	Increased levels and adverse effects of PDE5 inhibitors may occur.
Azoles (fluconazole, itraconazole, ketoconazole, posaconazole)	2	Protease inhibitors	Increased levels and adverse effects of protease inhibitors may occur.
Azoles (itraconazole,	2	Proton-pump inhibitors	Plasma levels of azole antifungals may be reduced, decreasing the

Generic Name(s)	Significance Level	Interaction	Mechanism
ketoconazole)			therapeutic effect.
Azoles (fluconazole, itraconazole, ketoconazole, voriconazole)	2	Quetiapine	Increased levels and adverse effects of quetiapine may occur.
Azoles (fluconazole, itraconazole, ketoconazole, posaconazole)	2	Rifamycins	Plasma levels of azole antifungals may be decreased, ketoconazole may interfere with rifamycin absorption, and itraconazole may inhibit rifabutin metabolism.
Azoles (fluconazole, itraconazole, ketoconazole)	2	Risperidone	Increased levels and adverse effects of risperidone may occur.
Azoles (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)	2	Sirolimus	Increased levels and adverse effects of sirolimus may occur.
Azoles (ketoconazole)	2	Solifenacin	Increased levels and adverse effects of solifenacin may occur.
Azoles (fluconazole, ketoconazole)	2	Sulfonylureas	Hypoglycemic effects of tolbutamide and glimepiride may occur.
Azoles (fluconazole, itraconazole, ketoconazole, posaconazole, voriconazole)	2	Tacrolimus	Increased levels and adverse effects of tacrolimus may occur.
Azoles (fluconazole, itraconazole, ketoconazole)	2	Tolterodine	Tolterodine plasma concentrations may be elevated, increasing the pharmacologic and adverse effects of tolterodine.
Azoles (fluconazole, ketoconazole)	2	Tricyclic antidepressants	Increased levels and adverse effects of tricyclic antidepressants may occur, including cardiac arrhythmias.
Azoles (fluconazole, itraconazole, ketoconazole, voriconazole)	2	Venlafaxine	Venlafaxine levels may be elevated, leading to an increase in adverse effects.

Significance level 1 = major severity; significance level 2 = moderate severity

VI. Adverse Drug Events

The most common adverse drug events reported with the azoles are listed in Table 7. The boxed warning for itraconazole is listed in Table 8 and the boxed warning for ketoconazole is listed in Table 9.

Table 7. Adverse Drug Events (%) Reported with the Azoles[1-8]

Adverse Events	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Voriconazole
Cardiovascular System					

Adverse Events	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Voriconazole
Atrial arrhythmia	-	-	-	-	<2
Atrial fibrillation	-	-	-	-	<2
Atrioventricular block	-	-	-	-	<2
Bigeminy	-	-	-	-	<2
Bradycardia	-	-	-	-	<2
Bundle branch block	-	-	-	-	<2
Cardiomegaly	-	-	-	-	<2
Cardiomyopathy	-	-	-	-	<2
Chest pain	-	3	-	-	<2
Congestive heart failure	-	✔	-	-	<2
Endocarditis	-	-	-	-	<2
Extrasystoles	-	-	-	-	<2
Hypertension	-	2 to 3	-	1 to 18	<2
Hypotension	-	1	-	14	<2
Myocardial infarction	-	-	-	-	<2
Nodal arrhythmia	-	-	-	-	<2
Orthostatic hypotension	-	1	-	-	-
Palpitation	-	-	-	-	<2
Phlebitis	-	-	-	-	<2
Postural hypotension	-	-	-	-	<2
QT prolongation	✔	-	✔	4	<2
Substernal chest pain	-	-	-	-	<2
Supraventricular extrasystoles	-	-	-	-	<2
Supraventricular tachycardia	-	-	-	-	<2
Syncope	-	-	-	-	<2
Tachycardia	-	1	-	12	2
Torsades de pointes	✔	-	-	✔	<2
Ventricular dysrhythmias	-	-	✔	-	<2
Ventricular fibrillation	-	-	-	-	<2
Ventricular tachycardia	-	-	-	-	<2
Central Nervous System					
Abnormal dreaming	-	2	-	-	<2
Acute brain syndrome	-	-	-	-	<2
Agitation	-	-	-	-	<2
Akathisia	-	-	-	-	<2
Amnesia	-	-	-	-	<2
Anxiety	-	3	-	9	<2
Asthenia	-	2	-	1 to 2	<2
Ataxia	-	-	-	-	<2
Brain edema	-	-	-	-	<2
Cerebral hemorrhage	-	-	-	-	<2
Cerebral ischemia	-	-	-	-	<2
Cerebrovascular accident	-	-	-	-	<2
Coma	-	-	-	-	<2
Confusion	-	-	-	-	<2
Convulsion	-	-	-	-	<2
Delirium	-	-	-	-	<2
Dementia	-	-	-	-	<2
Depersonalization	-	-	-	-	<2
Depression	-	3	✔	-	<2
Diplopia	-	-	-	-	<2
Dizziness	1	1 to 4	<1	1 to 11	<2
Encephalitis	-	-	-	-	<2
Encephalopathy	-	-	-	-	<2

Adverse Events	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Voriconazole
Euphoria	-	-	-	-	<2
Extrapyramidal syndrome	-	-	-	-	<2
Guillain-Barre syndrome	-	-	-	-	<2
Hallucinations	-	-	-	-	2
Headache	2 to 13	1 to 10	<1	1 to 8	3
Hypertonia	-	-	-	-	<2
Hypoesthesia	-	✔	-	-	<2
Insomnia	-	✔	-	1 to 17	<2
Intracranial hypertension	-	-	-	-	<2
Neuralgia	-	-	-	-	<2
Neuropathy	-	✔	-	-	<2
Nystagmus	-	-	-	-	<2
Oculogyric crisis	-	-	-	-	<2
Psychosis	-	-	-	-	<2
Seizures	✔	-	-	-	<2
Somnolence	-	1	<1	1	<2
Suicidal tendencies	-	-	✔	-	<2
Tremor	-	1 to 2	-	-	<2
Vertigo	-	1	-	-	<2
Dermatological					-
Alopecia	✔	✔	✔	-	<2
Cellulitis	-	-	-	-	✔
Contact dermatitis	-	-	-	-	<2
Discoid lupus erythematosus	-	-	-	-	<2
Dry skin	-	-	-	-	<2
Eczema	-	-	-	-	<2
Erythema multiforme	-	✔	-	-	✔
Erythematous rash	-	1 to 2	-	-	-
Exfoliative dermatitis	-	✔	-	-	<2
Fixed drug eruption	-	-	-	-	<2
Furunculosis	-	-	-	-	<2
Maculopapular rash	-	-	-	-	<2
Melanosis	-	-	-	-	<2
Petechiae	-	-	-	11	-
Photosensitivity skin reaction	-	✔	-	-	<2
Pruritus	✔	1 to 5	2	1 to 11	<2
Psoriasis	-	-	-	-	<2
Rash	2	3 to 9	-	1 to 19	5-7
Skin discoloration	-	-	-	-	<2
Skin disorder	-	2	-	-	<2
Stevens-Johnson syndrome	✔	✔	-	-	✔
Toxic epidermal necrolysis	✔	✔	-	-	✔
Urticaria	-	✔	✔	-	<2
Endocrine and Metabolic					
Adrenal insufficiency	-	✔	-	✔	<2
Dehydration	-	<2	-	1	-
Diabetes insipidus	-	-	-	-	<2
Edema	-	2 to 4	-	9 to 15	<2
Erectile dysfunction	-	✔	-	-	-
Fluid overload	-	1	-	-	-
Gynecomastia	-	✔	<1	-	-
Male breast pain	-	✔	-	-	-
Menstrual disorder	-	✔	-	-	-
Weight loss	-	<2	-	1	-

Adverse Events	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Voriconazole
Gastrointestinal					
Abdomen enlarged	-	-	-	-	<2
Abdominal pain	2 to 6	2 to 6	1	1 to 27	<2
Anorexia	-	1	-	1 to 15	<2
Appetite increased	-	2	-	-	-
Ascites	-	-	-	-	<2
Cheilitis	-	-	-	-	<2
Cholecystitis	-	-	-	-	<2
Cholelithiasis	-	-	-	-	<2
Cholestasis	✔	-	-	-	1
Constipation	-	1 to 3	-	1 to 21	<2
Diarrhea	2 to 3	3 to 11	<1	3 to 42	<2
Dry mouth	✔	-	-	1	<2
Duodenal ulcer perforation	-	-	-	-	<2
Duodenitis	-	-	-	-	<2
Dyspepsia	1	<2 to 4	-	1 to 10	<2
Dysphagia	-	<2	-	-	<2
Esophageal ulcer	-	-	-	-	<2
Esophagitis	-	-	-	-	<2
Flatulence	-	<2 to 4	-	1	<2
Gastritis	-	2	-	-	-
Gastroenteritis	-	2	-	-	<2
Gastrointestinal disorders	-	4	-	-	-
Gastrointestinal hemorrhage	-	-	-	-	<2
Gingivitis	-	-	-	-	<2
Glossitis	-	-	-	-	<2
Gum hemorrhage	-	-	-	-	<2
Gum hyperplasia	-	-	-	-	<2
Hematemesis	-	-	-	-	<2
Hemorrhoids	-	<2	-	-	-
Intestinal perforation	-	-	-	-	<2
Intestinal ulcer	-	-	-	-	<2
Melena	-	-	-	-	<2
Mouth ulceration	-	-	-	-	<2
Mucositis	-	-	-	2 to 17	-
Nausea	2 to 7	3 to 11	3	5 to 38	5
Pancreatitis	-	-	-	-	<2
Parotid gland enlargement	-	-	-	-	<2
Periodontitis	-	-	-	-	<2
Proctitis	-	-	-	-	<2
Pseudomembranous colitis	-	-	-	-	<2
Rectal disorder	-	-	-	-	<2
Rectal hemorrhage	-	-	-	-	<2
Stomach ulcer	-	-	-	-	<2
Stomatitis	-	-	-	-	<2
Taste loss	-	-	-	-	<2
Taste perversion	1	<2	-	1	<2
Tongue edema	-	-	-	-	<2
Ulcerative stomatitis	-	3	-	-	-
Vomiting	2 to 5	5 to 7	3	4 to 29	4
Genitourinary					
Albuminuria	-	1	-	-	<2
Anuria	-	-	-	-	<2
Blighted ovum	-	-	-	-	<2

Adverse Events	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Voriconazole
Creatinine clearance decreased	-	-	-	-	<2
Cystitis	-	3	-	-	-
Dysmenorrhea	-	-	-	-	<2
Dysuria	-	-	-	-	<2
Epididymitis	-	-	-	-	<2
Glycosuria	-	-	-	-	<2
Hematuria	-	<2	-	-	<2
Hemolytic uremic syndrome	-	-	-	✔	-
Hemorrhagic cystitis	-	-	-	-	<2
Hydronephrosis	-	-	-	-	<2
Impotence	-	1	<1	-	<2
Kidney function abnormal	-	1	-	-	<1
Kidney pain	-	-	-	-	<2
Kidney tubular necrosis	-	-	-	-	<2
Libido decreased	-	1	-	-	<2
Metrorrhagia	-	-	-	-	<2
Nephritis	-	-	-	-	<2
Nephrosis	-	-	-	-	<2
Oligospermia	-	-	<1	-	-
Oliguria	-	-	-	-	<2
Pelvic pain	-	-	-	-	<2
Pollakiuria	-	✔	-	-	-
Renal failure	-	-	-	1	<1
Scrotal edema	-	-	-	-	<2
Urinary incontinence	-	✔	-	-	<2
Urinary retention	-	-	-	-	<2
Urinary tract infection	-	3	-	-	<2
Uterine hemorrhage	-	-	-	-	<2
Vaginal hemorrhage	-	-	-	10	<2
Hematological					
Agranulocytosis	✔	-	-	-	<2
Anemia	-	-	-	2 to 25	<2
Aplastic anemia	-	-	-	-	<2
Bleeding time increased	-	-	-	-	<2
Cyanosis	-	-	-	-	<2
Disseminated intravascular coagulation	-	-	-	-	<2
Ecchymosis	-	-	-	-	<2
Eosinophilia	-	-	-	-	<2
Hemolytic anemia	-	-	<1	-	<2
Hypervolemia	-	-	-	-	<2
Leukopenia	✔	✔	<1	-	<2
Lymphadenopathy	-	-	-	-	<2
Lymphangitis	-	-	-	-	<2
Marrow depression	-	-	-	-	<2
Neutropenia	✔	✔	-	2 to 23	-
Pancytopenia	-	-	-	-	<2
Petechia	-	-	-	-	<2
Purpura	-	-	-	-	<2
Splenomegaly	-	-	-	-	<2
Thrombocytopenia	✔	✔	<1	1 to 29	<2
Thrombotic thrombocytopenic purpura	-	-	-	✔	<2
Hepatic					
Hepatic coma	-	-	-	-	<2
Hepatic failure	✔	✔	-	-	<2

Adverse Events	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Voriconazole
Hepatic function abnormal	-	3	<1	1	-
Hepatitis	✔	✔	-	1	<2
Hepatomegaly	-	-	-	-	<2
Hepatotoxicity	-	✔	-	-	-
Jaundice	✔	-	-	-	<2
Laboratory Test Abnormalities					
Alkaline phosphatase increased	✔	2 to 4	-	1 to 3	4
Bilirubinemia	-	6	-	1 to 10	<1
Blood urea nitrogen increased	-	1	-	-	<2
Creatinine increased	-	3	-	3	<1
Creatinine phosphokinase increased	-	-	-	-	<2
Hypercalcemia	-	-	-	-	<2
Hypercholesterolemia	✔	-	-	-	<2
Hyperglycemia	-	-	-	11	<2
Hyperkalemia	-	-	-	-	<2
Hypermagnesemia	-	-	-	-	<2
Hypernatremia	-	-	-	-	<2
Hyperthyroidism	-	-	-	-	<2
Hypertriglyceridemia	✔	3	✔	-	-
Hyperuricemia	-	-	-	-	<2
Hypocalcemia	-	1	-	9	<2
Hypoglycemia	-	-	-	-	<2
Hypokalemia	✔	2 to 9	-	1 to 30	2
Hypomagnesemia	-	2	-	18	<2
Hyponatremia	-	-	-	-	<2
Hypophosphatemia	-	1-2	-	-	<2
Hypothyroidism	-	-	-	-	<2
Lactate dehydrogenase increased	-	2	-	-	-
Transaminases increased	✔	✔	-	2 to 17	2-3
Uremia	-	-	-	✔	<2
Musculoskeletal					
Arthralgia	-	✔	-	11	<2
Arthritis	-	-	-	-	<2
Back pain	-	<2	-	10	<2
Bone necrosis	-	-	-	-	<2
Bone pain	-	-	-	-	<2
Bursitis	-	3	-	-	-
Leg cramps	-	-	-	-	<2
Malaise	✔	1 to 3	-	-	-
Musculoskeletal pain	-	-	-	16	-
Myalgia	✔	1 to 3	-	1	<2
Myasthenia	-	-	-	-	<2
Myopathy	-	-	-	-	<2
Osteomalacia	-	-	-	-	<2
Osteoporosis	-	-	-	-	<2
Respiratory					
Coughing	-	4	-	1 to 24	<2
Dyspnea	-	1 to 2	-	1 to 20	<2
Epistaxis	-	-	-	14	<2
Hemoptysis	-	-	-	-	<2
Hypoxia	-	-	-	-	<2
Lung edema	-	-	-	-	<2
Pharyngitis	-	2	-	12	-
Pleural effusion	-	-	-	-	<2

Adverse Events	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Voriconazole
Pneumonia	-	2	-	3	<2
Pulmonary edema	-	✔	-	-	-
Pulmonary embolus	-	-	-	✔	<2
Pulmonary infiltration	-	1 to 2	-	-	-
Respiratory disorder	-	-	-	-	<2
Respiratory distress syndrome	-	-	-	-	<2
Rhinitis	-	<2-9	-	-	<2
Sinusitis	-	2 to 7	-	-	<2
Sputum increased	-	2	-	-	-
Upper respiratory tract infection	-	<2 to 8	-	7	<2
Special Senses					
Abnormality of accommodation	-	-	-	-	<2
Blepharitis	-	-	-	-	<2
Blurred vision	-	✔	-	1	-
Conjunctivitis	-	-	-	-	<2
Corneal opacity	-	-	-	-	<2
Chromatopsia	-	-	-	-	1
Deafness	-	-	-	-	<2
Diplopia	-	✔	-	-	-
Dry eyes	-	-	-	-	<2
Ear pain	-	-	-	-	<2
Eye hemorrhage	-	-	-	-	<2
Eye pain	-	-	-	-	<2
Keratitis	-	-	-	-	<2
Mydriasis	-	-	-	-	<2
Night blindness	-	-	-	-	<2
Optic atrophy	-	-	-	-	<2
Optic neuritis	-	-	-	-	<2
Otitis externa	-	-	-	-	<2
Photophobia	-	-	<1	-	2
Retinitis	-	-	-	-	<2
Scleritis	-	-	-	-	<2
Tinnitus	-	✔	-	-	<2
Uveitis	-	-	-	-	<2
Visual disturbances	-	<2	-	-	19
Other					
Allergic reactions	-	✔	-	✔	<2
Anaphylactoid reaction	-	✔	-	-	✔
Anaphylaxis	✔	✔	-	-	-
Angioedema	✔	✔	-	-	<2
Angioneurotic edema	-	✔	-	-	-
Bacteremia	-	-	-	18	-
Bulging fontanelles	-	-	<1	-	-
Candidiasis, oral	-	-	-	1	-
Chills	-	-	<1	-	4
Cytomegalovirus infection	-	-	-	14	-
Facial edema	✔	-	-	-	<2
Fatigue	✔	2 to 3	-	1 to 17	-
Fever	✔	2 to 7	<1	2 to 45	6
Flank pain	-	-	-	-	<2
Flu syndrome	-	-	-	-	<2
Gingivitis	-	3	-	-	-
Graft vs host disease	-	-	-	-	<2
Granuloma	-	-	-	-	<2

Adverse Events	Fluconazole	Itraconazole	Ketoconazole	Posaconazole	Voriconazole
Herpes simplex	-	-	-	3 to 15	<2
Herpes zoster	-	2	-	-	-
Hot flashes	-	<2	-	-	-
Hypoacusis	-	-	-	-	<2
Implantation complication	-	<2	-	-	-
Increased intracranial pressure	-	-	✔	-	-
Infection	-	<2	-	-	<2
Injection site pain	-	-	-	-	<2
Injury	-	3 to 7	-	-	-
Mucous membrane disorder	-	-	-	-	<2
Multi organ failure	-	-	-	-	<2
Pain	-	2 to 3	-	1	<2
Papilledema	-	-	✔	-	<2
Paresthesia	-	✔	✔	✔	<2
Peripheral edema	-	✔	-	-	<2
Peritonitis	-	-	-	-	<2
Pneumocystis carinii infection	-	2	-	-	-
Rigors	-	1	-	<1 to 20	-
Sepsis	-	-	-	-	<2
Serum sickness	-	✔	-	-	-
Sweating	-	2 to 3	-	2	<2
Thrombophlebitis	-	-	-	-	<2
Vasculitis	-	1	-	-	-
Vasodilation	-	-	-	-	<2
Weakness	-	-	-	1 to 8	-

✔ Percent not specified
- Event not reported

Table 8. Boxed Warning for Itraconazole[1]

WARNING
Congestive Heart Failure: If signs or symptoms of CHF occur during administration of itraconazole, reassess continued itraconazole use. Do not administer itraconazole capsules for the treatment of onychomycosis in patients with evidence of ventricular dysfunction such as CHF or a history of CHF. If signs or symptoms of CHF occur during administration of itraconazole capsules, discontinue administration. When itraconazole was administered intravenously (IV) to dogs and healthy human volunteers, negative inotropic effects were seen. Drug interactions: Coadministration of cisapride, pimozide, quinidine, or dofetilide with itraconazole is contraindicated. Itraconazole, a potent cytochrome P450 3A4 isoenzyme system (CYP3A4) inhibitor, may increase plasma concentrations of drugs metabolized by this pathway. Serious cardiovascular events, including QT prolongation, torsades de pointes, ventricular tachycardia, cardiac arrest, and/or sudden death have occurred in patients using cisapride, pimozide, or quinidine concomitantly with itraconazole and/or other CYP3A4 inhibitors.

Table 9. Boxed Warning for Ketoconazole[1]

WARNING
Hepatotoxicity: When used orally, ketoconazole has been associated with hepatic toxicity, including some fatalities. Patients receiving this drug should be informed by the physician of the risk and should be closely monitored. Drug interactions: Terfenadine: Coadministration of terfenadine with ketoconazole tablets is contraindicated. Rare cases of serious cardiovascular adverse events, including death, ventricular tachycardia and torsades de pointes have been observed in patients taking ketoconazole tablets concomitantly with terfenadine, due to increased terfenadine concentrations induced by ketoconazole tablets. Astemizole: Pharmacokinetic data indicate that oral ketoconazole inhibits the metabolism of astemizole, resulting in elevated plasma levels of astemizole and its active metabolite desmethylastemizole which may prolong QT intervals. Coadministration of astemizole with ketoconazole tablets is therefore contraindicated. Cisapride: Coadministration of cisapride with ketoconazole is contraindicated. Serious cardiovascular adverse events including ventricular tachycardia, ventricular fibrillation and torsades de pointes have occurred in patients taking ketoconazole concomitantly with cisapride.

VII. Dosing and Administration

The usual dosing regimens for the azoles are listed in Table 10.

Table 10. Usual Dosing Regimens for the Azoles[1-8]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Fluconazole	Cryptococcal meningitis: Injection, suspension, tablet: 400 mg on the first day, followed by 200 to 400 mg once daily for 10 to 12 weeks after the cerebrospinal fluid becomes culture negative Esophageal candidiasis: Injection, suspension, tablet: 200 mg on the first day, followed by 100 to 400 mg once daily. Treatment should be continued for at least three weeks, and for at least two weeks following resolution of symptoms Oropharyngeal candidiasis: Injection, suspension, tablet: 200 mg on the first day, followed by 100 mg once daily. Treatment should be continued for at least two weeks Prophylaxis of candidiasis in patients undergoing bone marrow transplantation	Cryptococcal meningitis: Injection, suspension, tablet: 12 mg/kg on the first day, followed by six to 12 mg/kg once daily for 10 to 12 weeks after the cerebrospinal fluid becomes culture negative Esophageal candidiasis: Injection, suspension, tablet: 6 mg/kg on the first day, followed by 3 to 12 mg/kg once daily for at least three weeks, and for at least two weeks following resolution of symptoms Oropharyngeal candidiasis: Injection, suspension, tablet: 6 mg/kg on the first day, followed by 3 mg/kg once daily for at least two weeks Systemic *Candida* infections: Injection, suspension, tablet: Daily doses of 6 to 12 mg/kg/day have been used in an open, non-comparative study of a small number of	Injection: 100 mg/50 mL 200 mg/100 mL 400 mg/200 mL Suspension: 10 mg/mL 40 mg/mL Tablet: 50 mg 100 mg 150 mg 200 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	receiving cytotoxic chemotherapy and/or radiation: Injection, suspension, tablet: 400 mg once daily starting several days before expected neutropenia and continuing for seven days after the neutrophil count rises above 1,000 cells/mm^3 Systemic *Candida* infections: Injection, suspension, tablet: For systemic *Candida* infections including candidemia, disseminated candidiasis, and pneumonia, optimal therapeutic dosage and duration of therapy have not been established. In open, non-comparative studies of small numbers of patients, doses of up to 400 mg daily have been used. Urinary tract infections and peritonitis: Injection, suspension, tablet: 50 to 200 mg daily have been used in non-comparative studies with small numbers of patients Vaginal candidiasis: Suspension, tablet: 150 mg orally as a single dose	children for the treatment of candidemia and disseminated *Candida* infections	
Itraconazole	Aspergillosis in patients intolerant of or refractory to amphotericin B therapy: Capsule: 200 to 400 mg daily for a minimum of three months and until clinical parameters and laboratory tests indicate that the active fungal infection has subsided Blastomycosis and histoplasmosis: Capsule: 200 mg once daily; may be increased by 100 mg increments to a total daily dose of 400 mg. Continue treatment for a minimum of 3 months and until clinical parameters and laboratory tests indicate that the active fungal infection has subsided	Safety and efficacy in children have not been established	Capsule: 100 mg Solution: 10 mg/mL Tablet: 200 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Esophageal candidiasis: Solution: 100 mg daily for a minimum of three weeks. Treatment should continue for two weeks after the resolution of symptoms Onychomycosis of the fingernail: Capsule: Two treatment pulses, each consisting of 200 mg twice daily for one week. The pulses are separated by a three-week period without itraconazole Onychomycosis of the toenail (with or without fingernail involvement): Capsule: 200 mg once daily for 12 consecutive weeks Onychomycosis of the toenail caused by *Trichophyton rubrum* or *Trichophyton mentagrophytes*: Tablet: 200 mg once daily for 12 consecutive weeks Oropharyngeal candidiasis: Solution: 200 mg daily for one to two weeks Oropharyngeal candidiasis (unresponsive/refractory to fluconazole): Solution: 100 mg twice daily. For patients responding to therapy, clinical response will be seen in two to four weeks		
Ketoconazole	Fungal infections: Tablet: 200 mg once daily; maximum, 400 mg daily. Treatment should be continued until active fungal infection has subsided. The usual duration for systemic infection is six months	Fungal infections: Tablet: >2 years of age: 3.3 to 6.6 mg/kg once daily. Treatment should be continued until active fungal infection has subsided. The usual duration for systemic infection is six months	Tablet: 200 mg
Posaconazole	Oropharyngeal candidiasis: Suspension: 100 mg twice daily on day one, then 100 mg once daily for 13 days Oropharyngeal candidiasis (refractory to itraconazole and/or fluconazole):	Children ≥13 years of age follow usual adult dosing. Safety and efficacy in children <13 years of age have not been established.	Injection: 300 mg Suspension: 200 mg/5 mL Tablet (delayed-release):

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Suspension: 400 mg twice daily, duration of therapy is based on clinical response Prophylaxis of invasive *Aspergillus* and *Candida* infections in severely immunocompromised patients: Delayed-release tablet: 300 mg twice a day on the first day, then 300 mg once a day, starting on the second day. Suspension: 200 mg three times daily. Duration of therapy is based on recovery from neutropenia and immunosuppression.		100 mg
Voriconazole	Candidemia in non-neutropenic patients and other deep tissue *Candida* infections: Injection: Six mg/kg every 12 hours for the first 24 hours then three to four mg/kg intravenous every 12 hours. Suspension, tablet: Patients may be switched to the oral formulation when indicated at a dose of 200 mg every 12 hours if weight ≥40 kg, or 100 mg every 12 hours if weight <40 kg Esophageal candidiasis: Suspension, tablet: 200 mg every 12 hours for 14 days, and at least seven days following resolution of symptoms Invasive aspergillosis and serious fungal infections caused by *Scedosporium apiospermum* and *Fusarium* species in patients intolerant of or refractory to other therapy: Injection: Six mg/kg every 12 hours for the first 24 hours, then four mg/kg IV every 12 hours. Suspension, tablet: Patients may be switched to oral therapy when indicated at a dose of 200 mg every 12 hours if weight ≥40 kg, or 100 mg every 12 hours if weight <40 kg	Children ≥12 years of age follow usual adult dosing. Safety and efficacy in children <12 years of age have not been established.	Injection: 200 mg Suspension: 200 mg/5 mL Tablet: 50 mg 200 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the azoles are summarized in Table 11.

Table 11. Comparative Clinical Trials with the Azoles

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Aspergillosis				
Maertens et al.[25] (2006) Caspofungin 70 mg IV daily in combination with either an azole (itraconazole or voriconazole) or a polyene (amphotericin B deoxycholate or an amphotericin B lipid preparation) All patients received active treatment with combination therapy.	MC, OL Patients 16 years of age and older with definite or probable invasive aspergillosis refractory or intolerant to standard antifungal therapy (amphotericin B deoxycholate, lipid preparations of amphotericin B, caspofungin, itraconazole, voriconazole, or posaconazole)	N=53 12 months posttreatment follow-up	Primary: Clinical response (favorable= complete or partial response; complete response= resolution of all signs, symptoms, radiologic and/or bronchoscopic evidence; partial response= clinically meaningful improvement in the above measures) Secondary: Not reported	Primary: At the end of combination therapy, 55% of patients had a favorable response. Of the patients with a favorable response (29), four showed a complete response and 25 showed a partial response. At day 84, 49% of patients had a favorable response. Success at the end of combination therapy ranged from 43% in the caspofungin plus itraconazole group to 60% in the caspofungin plus voriconazole group. In the caspofungin plus polyene group, success rates were 80, 29, and 50% for amphotericin B deoxycholate, amphotericin B lipid complex, and liposomal amphotericin B, respectively. Of 46 refractory patients, the addition of caspofungin to the initially refractory antifungal agent demonstrated a favorable response in 66% of patients. Success was observed in 20% of patients who were initially refractory to caspofungin and had a non-echinocandin antifungal agent added. Of the patients who were refractory to voriconazole therapy, 73% had a favorable response when caspofungin was added to voriconazole compared to a 40% favorable response rate in patients who discontinued voriconazole and switched to two new antifungal agents. Secondary: Not reported
Caillot et al.[26] (2003) Itraconazole 200	MC, OL Patients ≥18 years of age with proven	N=21 14 weeks or last day of	Primary: Clinical response (complete= resolution of signs	Primary: Complete or partial response was observed in 47% and 90% of patients at weeks two and 14, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg IV every 12 hours for 2 days, 200 mg IV daily for 12 days, then 200 mg orally twice daily for 12 weeks	or probable active invasive pulmonary aspergillosis who were immuno-compromised and refractory to amphotericin B	treatment or neutropenia	and symptoms and radiographic and bronchoscopic abnormalities; partial=major improvement in above listed criteria without complete resolution) Secondary: Total number of patients responding, median time to achieve response, microbiological results from anterior nares and sputum Secondary: Not reported	Secondary: Overall, 62% of patients had a complete or partial response at any time point and 86% had a complete or partial response or stable disease (i.e., minor or no improvement in disease without deterioration) at any time point. The median time to achieve response was 14 days. At week 14, there were no positive cultures obtained. Secondary: Not reported
Caillot et al.[27] (2001) Itraconazole 200 mg IV every 12 hours for 2 days, 200 mg IV daily for 12 days, then 200 mg orally twice daily for 12 weeks	MC, OL Patients 25-78 years of age with active invasive pulmonary aspergillosis and who were immuno-compromised	N=31 14 weeks	Primary: Clinical response Secondary: Median time to achieve response, microbiological results from anterior nares and sputum	Primary: Complete or partial response was observed in 32.3, 38.7, and 48% of patients at week two, week 14 and at study end, respectively. Overall, 58% of patients experienced a complete or partial response at any time during the study. When stable disease was considered as a positive response, the success rate was 67.7% at day 14, 45.2% at the end of oral therapy, and 68% at the end of the study. A total of 87% of patients achieved a complete, partial, or stable response at any time during the study. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The median time to achieve global response was 55 days. At week 14, there were no positive cultures.
Raad et al.[28] (2008) Posaconazole 800 mg/day in divided doses vs amphotericin B liposome 7.5 mg/kg/day (L-AMB) vs amphotericin B liposome 7.5 mg/kg/day plus caspofungin 70 mg on day 1, followed by 50 to 100 mg daily	RCT Patients with hematologic malignancies and invasive aspergillosis enrolled in a compassionate-use trial of antifungal salvage therapy	N=143 Up to 12 weeks	Primary: Response rate to salvage therapy Secondary: Deaths related to aspergillosis within 12 months after initiation of salvage therapy and adverse events	Primary: The overall response rate to salvage therapy was 40% for posaconazole, 8% for L-AMB (P≤0.001) and 11% for combination therapy (P<0.002). Secondary: Aspergillosis contributed to the death of 40% of posaconazole group, 65% of the L-AMB group and 68% of the combination group (P≤0.008). By multivariate analysis, posaconazole therapy independently improved response (95% CI, 2.8 to 32.5; P<0.001). L-AMB alone or in combination with caspofungin was associated with a significantly higher rate of nephrotoxicity (P≤0.02) and hepatotoxicity (P<0.03) than monotherapy with posaconazole.
Sambatakou et	MC, OL	N=36	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
al.[29] (2006) Voriconazole 200 mg orally twice daily (with an increase to 250 mg twice daily based on response and tolerability) for 4 to 24 weeks	Patients >18 years of age with definite or probable subacute invasive aspergillosis at different body sites or chronic pulmonary aspergillosis	12 week posttreatment follow-up	Clinical response Secondary: Not reported	Response rates at the end of treatment in subacute invasive aspergillosis and chronic pulmonary aspergillosis patients were 43% and 80%, respectively. Secondary: Not reported
Mouas et al.[30] (2005) Voriconazole 6 mg/kg IV every 12 hours on day 1, followed by 4 mg/kg IV every 12 hours or 200 mg orally twice daily vs voriconazole 400 mg orally twice daily on day 1, then 200 mg twice daily	RETRO Patients 4 to 78 years of age with definite or probable invasive bone aspergillosis	N=20 End of therapy (4 to 395 days)	Primary: Response at end of therapy Secondary: Not reported	Primary: Overall response rates were similar in both treatment groups (55%). Secondary: Not reported
Herbrecht et al.[31] (2002) Voriconazole 6 mg/kg IV twice daily on day 1, followed by	RCT, DB, MC Immuno-compromised patients ≥12 years of age with definite or probable invasive	N=277 12 weeks	Primary: Clinical response Secondary: Response at end of initial therapy, safety outcomes,	Primary: Successful response rates at week 12 in patients receiving voriconazole and amphotericin B deoxycholate were 52.8 and 31.6%, respectively, and were significantly better in the voriconazole group. Secondary: Successful response rates at end of initial therapy in patients receiving

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
4 mg/kg IV twice daily for ≥7 days, then 200 mg orally twice daily vs amphotericin B deoxycholate 1.0 to 1.5 mg/kg/day	aspergillosis		survival up to week 12	voriconazole and amphotericin B deoxycholate were 49.7 and 27.8%, respectively. There were significantly fewer adverse events in the voriconazole group compared to the amphotericin B group (P=0.02). Visual disturbances (44.8 vs 4.3%; P<0.001), chills and/or fever (3.1 vs 24.9%; P<0.001) and severe adverse events (13.4 vs 24.3%; P=0.008), including renal impairment (1.0 vs 10.3%; P<0.001), hypokalemia (0 vs 3.2%; P=0.01) and systemic events (0.5 vs 3.8%; P=0.03) occurred in patients receiving voriconazole and amphotericin B deoxycholate, respectively. The survival rates for patients receiving voriconazole and amphotericin B deoxycholate were 70.8 and 57.9%, respectively.
Blastomycosis and Histoplasmosis				
Wheat et al.[32] (1995) Itraconazole 300 mg orally twice daily for 3 days then 200 mg twice daily with meals for 12 weeks	MC, OL, PRO Patients 13 years of age and older with serologically documented human immunodeficiency virus and first-episode disseminated histoplasmosis	N=59 12 weeks	Primary: Clinical response (resolution of signs and symptoms and clearance of positive cultures), clearance of positive cultures, drug tolerance Secondary: Effect of therapy on *Histoplasma capsulatum* variant *capsulatum* antigen levels	Primary: Clinical response was observed in 85% of patients. Fungemia cleared after a median of one week. Secondary: *Histoplasma capsulatum* variant *capsulatum* antigen levels cleared from the urine and serum at rates of 0.2 and 0.3 units per week, respectively. Initial antigen levels reverted to negative in serum and urine in 46% and 9% of patients, respectively (P<0.001). The mean reduction in antigen was significantly higher in serum compared to urine (3.7 units and 2.0 units, respectively; P=0.032).
Dismukes et al.[33] (1992) Itraconazole 200 mg, 300 mg, or	MC, RCT Patients 18 years of age and older with a diagnosis of	N=85 12 month posttreatment follow-up	Primary: Clinical response Secondary: Not reported	Primary: Among patients with blastomycosis, 90% were reported as having clinical success. For patients treated for more than two months, the clinical success rate was 95%.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
400 mg daily	histoplasmosis or blastomycosis			Among patients with histoplasmosis, 81% were reported as having clinical success. For patients treated for more than two months, the clinical success rate was 86%. Secondary: Not reported
Hecht et.al.[34] (1997) Itraconazole 200 mg orally daily vs itraconazole 400 mg orally daily	MC, OL, PRO Patients >13 years of age with first episode of mild-moderate disseminated histoplasmosis with human immunodeficiency virus who had successfully completed induction itraconazole therapy for 12 weeks	N=46 ≥52 weeks	Primary: Relapse of histoplasmosis, survival Secondary: Drug-limiting toxicity, change in serum and urine *Histoplasma* polysaccharide antigen levels	Primary: The relapse-free rate at one year for all patients was 95.3%. The survival rate for all patients at one year and at study completion was 73.0 and 41%, respectively. Secondary: Toxicity leading to withdrawal occurred in eight of 46 patients. The median change in serum and urine antigen levels of all patients who did not relapse by end of maintenance therapy was a decrease of 0.2 units and 2.1 units, respectively (P=0.0001).
Wheat et al.[35] (2001) Itraconazole 300 mg orally twice daily for 3 days then 200 mg twice daily for 12 weeks vs amphotericin B liposomal 3 mg/kg/day IV for 2 weeks, followed by itraconazole	CS Human immunodeficiency virus-infected patients ≥13 years of age with a first episode of disseminated histoplasmosis	N=110 12 weeks	Primary: Mycological response (negative blood cultures), time to negative blood cultures Secondary: Not reported	Primary: By the end of the second week of therapy, blood cultures were negative in over 85% of amphotericin B patients compared to 53% of itraconazole patients (P=0.0008). By 12 weeks of therapy, cultures were negative in all patients in both groups. After two weeks of therapy, serum antigen levels fell by a significantly greater amount in the amphotericin B group compared to the itraconazole group (P=0.02). After two weeks of treatment, serum antigen levels were negative in 28% of the amphotericin B group and 20% of the itraconazole group (P=0.55). After two weeks of therapy, urine antigen levels were below the detection

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
200 mg twice daily for 10 weeks				limit in 19% of amphotericin B patients and 3% of itraconazole patients (P=0.06). After two weeks of therapy, urine antigen levels fell by a significantly greater amount in the amphotericin B group compared to the itraconazole group (P<0.0005). By 12 weeks of therapy, there was no significant difference in the proportion of patients with undetectable serum and urine antigen levels in either group (P<0.80). Secondary: Not reported
Dismukes et al.[36] (1985) Ketoconazole 400 mg PO QD ≥6 months vs ketoconazole 800 mg PO QD ≥6 months	MC, PRO, RCT Patients 17 to 80 years of age with presumptive or culture-proven blastomycosis or histoplasmosis	N=134 6 month posttreatment follow-up	Primary: Clinical response (cure=resolution or reduction in symptoms and signs in addition to resolution or 50% reduction in size of lesion and negative cultures; improved= undefined clinical and mycological response and non-compliant with protocol) Secondary: Response in patients treated for 6 months or more	Primary: Clinical response rates in blastomycosis patients receiving low- and high-dose ketoconazole were 70 and 85%, respectively (P=0.12). Clinical response rates in histoplasmosis patients receiving low- and high-dose ketoconazole were 77 and 43%, respectively, and were significantly higher in the low-dose group (P=0.02). Secondary: Clinical response rates in blastomycosis patients adherent to low- and high-dose ketoconazole therapy for ≥6 months were 79 and 100%, respectively (P=0.01). Response rates in histoplasmosis patients adherent to low- and high-dose ketoconazole therapy for ≥6 months were 92 and 71%, respectively (P=0.16).
Candidiasis (Esophageal/Oropharyngeal)				
Akova et al.[37] (1994)	OL, PRO	N=129	Primary: Clinical response	Primary: The overall clinical cure rate was 82%. Cure rates were similar in patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Fluconazole 200 mg daily IV during neutropenia, then 100 mg orally daily for 14 days (oropharyngeal involvement) or 21 days (esophageal involvement)	Adult patients with a hematological malignancy or solid tumor with oropharyngeal and/or esophageal candidiasis	4 week posttreatment follow-up	Secondary: Not reported	with and without esophageal involvement (75 and 83%, respectively; P>0.1). The overall mycological eradication rate was 56%. Secondary: Not reported
Pagani et al.[38] (2002) Fluconazole 150 mg weekly (secondary prophylaxis) vs placebo	DB, PC, PRO, RCT Patients ≥16 years of age with HIV and oropharyngeal candidiasis who had responded to a 7 day course of fluconazole 200 mg daily	N=138 37 months	Primary: Third relapse of oropharyngeal candidiasis, occurrence of adverse events requiring discontinuation of the drug, development of microbiological resistance to fluconazole Secondary: Not reported	Primary: The duration of secondary prophylaxis for patients receiving fluconazole and placebo were 347 and 197 days, respectively (P<0.001). The median time interval to relapse for patients receiving fluconazole and placebo were: first relapse (175 and 35 days; P<0.001), second relapse (68 and 43 days; P=0.027), and third relapse (41 and 41 days), respectively. Significantly more patients in the placebo group experienced a third relapse by day 196 compared to the number of patients in the fluconazole group suffering a third relapse by day 382 (50 and 25%, respectively; P<0.001). Relapse rates were 61 and 90% for patients receiving fluconazole and placebo, respectively (P<0.001). No adverse events led to drug discontinuation. The difference in microbiological resistance between patients receiving fluconazole and those receiving placebo was not statistically significant (P=0.20). Secondary: Not reported
Wilcox et al.[39] (1997) Fluconazole 100 mg to 200 mg	DB, MC, RCT Patients ≥13 years of age with endoscopically	N=126 4 week posttreatment follow-up	Primary: Clinical response Secondary: Severity of	Primary: Clinical response rates (cured or improved) in patients receiving itraconazole and fluconazole were 94 and 91%, respectively. The difference was not statistically significant.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
orally daily for 3 to 8 weeks vs itraconazole 100 mg to 200 mg orally daily for 3 to 8 weeks	confirmed esophageal candidiasis and predisposing risk factors for fungal infection		symptoms, mycological assessment (eradication), fungal culture, global efficacy at 4 week follow-up (Persistent response or relapse), time to clinical response, time to relapse	Secondary: Clearance of all symptoms in patients receiving itraconazole and fluconazole occurred in 94 and 93%, respectively. Of those receiving itraconazole and fluconazole, 78 and 74%, respectively, remained symptom-free at the end of follow-up. The endoscopic assessment classified 94% of patients in both groups as cured or improved, respectively. Mycological eradication in patients receiving itraconazole and fluconazole occurred in 92 and 78%, respectively. Neither endoscopic nor mycological assessment demonstrated a statistically significant difference between treatment groups. Relapse rate at end of four weeks for patients receiving itraconazole and fluconazole was 18 and 27%, respectively. There was no significant difference between groups in time to relapse or response.
De Wit et al.[40] (1998) Fluconazole 150 mg orally for 1 dose vs itraconazole 100 mg daily for 7 days	CS, OL, RCT Patients 16 to 65 years of age with human immunodeficiency virus infection and oropharyngeal candidiasis	N=40 30-day posttreatment follow-up	Primary: Clinical response and mycological eradication Secondary: Not reported	Primary: At the end of treatment, clinical cure was observed in 75% of fluconazole patients and 24% of itraconazole patients. Improvement was observed in 15 and 12% of patients, respectively. Cure plus improvement was seen in significantly more fluconazole patients compared to itraconazole patients (P=0.0006). On the day of relapse or day 30, clinical success (cure plus improvement) was significantly higher in the fluconazole group compared to the itraconazole group (42 and 12% respectively; P=0.0013). Eradication was observed in one patient in each group. Secondary: Not reported
Oude Lashof et al.[41]	MC, OL, RCT	N=252	Primary: Clinical response	Primary: Clinical cure was observed in 74% of fluconazole patients and 62% of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2004) Fluconazole 100 mg daily for 10 days vs itraconazole 200 mg daily for 15 days	Patients 16 years of age and older with cancer and oropharyngeal candidiasis	42 days	(cure=resolution of signs and symptoms) and mycological response Secondary: Not reported	itraconazole patients (P=0.04). Mycological eradication was observed in 80% of fluconazole patients and 68% of itraconazole patients (P=0.03). Both clinical cure and mycological eradication was observed in 66% of fluconazole patients and 54% of itraconazole patients (P=0.054). Secondary: Not reported
Phillips et al.[42] (1998) Fluconazole 100 mg daily for 14 days vs itraconazole 100 mg daily for 14 days (itraconazole QD) vs itraconazole 100 mg twice daily for 7 days (itraconazole BID)	DB, MC, PC, RCT Human immunodeficiency virus-infected patients ≥18 years of age with pseudomembranous oropharyngeal candidiasis	N=194 2 week posttreatment follow-up	Primary: Clinical response (complete= clearance of signs and symptoms except erythema, or markedly improved based on investigator ratings) and mycological response Secondary: Not reported	Primary: Clinical response (complete or marked improvement) in patients receiving fluconazole, itraconazole QD and itraconazole BID was 90, 90, and 82%, respectively. There was no significant difference in efficacy between the treatment groups. At day seven, cultures were negative in 56% of patients in the itraconazole BID group, 58% in the itraconazole QD group, and 44% in the fluconazole group. At day 14, cultures were negative in 44% of patients in the itraconazole BID group, 57% in the itraconazole QD group, and 53% in the fluconazole group. Secondary: Not reported
Graybill et al.[43] (1998) Fluconazole 100 mg daily for 14 days	MC, OL, RCT Patients ≥13 years of age with human immunodeficiency virus and	N=179 6 weeks	Primary: Clinical response (cured=clearance of all signs and symptoms; improved=	Primary: Cure was achieved in 97, 86, and 87% of patients receiving itraconazole for 14 days, itraconazole for seven days and fluconazole, respectively. Differences in clinical response were not statistically significant. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs itraconazole 200 mg daily for 7 days vs itraconazole 200 mg daily for 14 days	oropharyngeal candidiasis		minimal signs and symptoms with no visible lesions) Secondary: Symptom severity, quantification of colony-forming units of *Candida* (cure ≤20 colony forming units/mL), culture results	No significant differences were observed between groups in any secondary endpoint. Mycological cure was 52, 88, and 77% in patients receiving itraconazole for 14 days, itraconazole for seven days and fluconazole, respectively.
Meunier et al.[44] (1990) Fluconazole 100 mg daily vs ketoconazole 400 mg daily	CS, DB, RCT Patients with cancer and mycologically proven oropharyngeal candidiasis	N=40 4 to 27 days	Primary: Clinical response and mycological response Secondary: Not reported	Primary: Clinical cure was observed in 15 of 19 patients in the fluconazole group and 14 of 18 patients in the ketoconazole group. Mycological eradication was reported in 10 patients in both groups. Secondary: Not reported
Hernandez-Sampelayo et al.[45] (1994) Fluconazole suspension 3 mg/kg/day (for 5 to 49 days) vs ketoconazole suspension 7 mg/kg/day (for 5 to 49 days)	MC, OL, RCT Pediatric patients with acquired immunodeficiency syndrome or human immunodeficiency virus infection and oropharyngeal candidiasis	N=46 4 week posttreatment follow-up	Primary: Clinical response (cure=resolution of signs and symptoms), mycological response (cure= negative culture) Secondary: Not reported	Primary: Clinical cure at the end of therapy was observed in 87.5% of fluconazole patients and 81% of ketoconazole patients. At the four week posttreatment follow-up, 44.4% of fluconazole and 58.8% of ketoconazole patients were clinically cured. At the end of therapy, mycological cure was observed in 71.4% of fluconazole patients and 57.1% of ketoconazole patients. At the four week posttreatment follow-up, 41.2% of fluconazole and 50.0% of ketoconazole patients were mycologically cured. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Vazquez et al.[46] (2006) Fluconazole 200 mg on day one, then 100 mg daily for 13 days vs posaconazole 200 mg on day one, then 100 mg daily for 13 days	MC, RCT, SB Patients ≥18 years of age with human immunodeficiency virus and pseudomembranous oropharyngeal candidiasis	N=350 42 days	Primary: Clinical success (cure=absence of plaques and no or minimal symptoms, or improvement= partial resolution) on day 14 Secondary: Clinical durability or relapse on day 42, clinical response after 7 days of therapy, mycological response rate by visit (success= culture yielding <20 CFU/mL of *Candida* species, eradication= negative culture)	Primary: Clinical success rates observed in patients receiving posaconazole and fluconazole at day 14 were 91.7 and 92.5%, respectively. The difference was not statistically significant. Secondary: Clinical relapse rates at day 42 in patients receiving posaconazole and fluconazole were 31.5 and 38.2%, respectively (P=0.24). Response rates in patients receiving posaconazole and fluconazole at day seven were 97.0 and 96.9%, respectively. On day 14, 68% of patients in both groups achieved mycological response. At day 42, significantly more patients in the posaconazole group continued to have mycological response compared to the fluconazole group (40.6 and 26.4%, P=0.038). Mycological eradication was observed in 35.6% of posaconazole patients and 24.2% of fluconazole patients at day 42 (P=0.084).
Ally et al.[47] (2001) Fluconazole 400 mg orally daily on day 1, then 200 mg daily vs voriconazole 200 mg orally twice daily	DB, MC, PC, RCT Immuno-compromised patients 18 to 75 years of age with esophageal and/or oropharyngeal candidiasis	N=391 43 days	Primary: Endoscopic response to treatment (cure= normal endoscopy, improved= improvement in lesions of 1 or more grades) Secondary: Symptomatic response of	Primary: The incidence of endoscopically proven cure in patients receiving voriconazole and fluconazole was 94.8% and 90.1%, respectively. Combined cured or improved response rates in patients receiving voriconazole and fluconazole were 98.3 and 95.1%, respectively. Secondary: Symptomatic cure was observed in 82.0 and 83.2% of voriconazole and fluconazole patients, respectively. The success rates for esophageal candidiasis were 88.0 and 91.1% in the voriconazole and fluconazole groups, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			esophageal and oropharyngeal candidiasis, time to symptomatic cure	The success rates for oropharyngeal candidiasis were 88.4 and 93.8% in the voriconazole and fluconazole groups, respectively. There was no significant difference in time to symptomatic cure.
Krause et al.[48] (2004) Fluconazole 200 mg oral loading dose on day 1, then 100 mg daily for 14 to 21 days vs anidulafungin 100 mg loading dose on day 1, then 50 mg IV daily	DB, MC, RCT Patients 18 to 65 years of age with esophageal candidiasis and a predisposing risk factor for fungal infection	N=601 Up to 35 weeks	Primary: Endoscopic response at the end of therapy (cure= complete resolution of lesions; improvement= decrease of >1 grade from baseline) Secondary: Clinical response (absence or improvement in symptoms), mycological response (eradication)	Primary: Endoscopic success was observed in 97.2% of patients in the anidulafungin group and 98.8% of patients in the fluconazole group. No significant difference was observed. Secondary: Clinical success was observed in 97.2% of patients in the anidulafungin group and in 98% in the fluconazole group. No significant difference was observed. Mycological success was observed in 86.7% of patients in the anidulafungin group and in 90.9% in the fluconazole group.
Villanueva et al.[49] (2002) Fluconazole 200 mg IV daily for 7 to 21 days vs caspofungin 50 mg IV daily for 7 to 21 days	DB, MC, RCT Patients with symptomatic, endoscopically and microbiologically documented *Candida* esophagitis	N=177 5 to 7 day posttreatment follow-up	Primary: Combined clinical and endoscopic response (favorable= complete resolution of signs and symptoms and total clearing of esophageal lesions or reduction in endoscopy score	Primary: Combined response rates in patients receiving caspofungin and fluconazole were 81% and 85%, respectively. No significant difference was seen between groups. Microbiological response was observed in 59% of patients in the caspofungin group and 76% of patients in the fluconazole group. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			by at least 2 points), microbiological response (negative stains and culture) Secondary: Not reported	
de Wet et al.[50] (2004) Fluconazole 200 mg IV daily for up to 14 to 21 days vs micafungin 50 mg, 100 mg, or 150 mg IV daily for up to 14 to 21 days	DB, MC, PG, RCT Patients 18 years of age or older with human immunodeficiency virus infection and endoscopically confirmed esophageal candidiasis (EC)	N=245 2 week posttreatment follow-up	Primary: Endoscopic cure rate and eradication rates Secondary: Change in endoscopic cure rate compared to baseline at day 14, clinical response at end of treatment, EC severity score, overall therapeutic success, incidence of relapse	Primary: Comparisons of micafungin groups showed a dose-response relationship for endoscopic cure. Cure rates were 68.8, 77.4, and 89.9% for the 50, 100, and 150 mg doses, respectively (P=0.024 for comparison between the three groups, P=0.007 for the comparison of the 50 and 150 mg groups). There was no significant difference seen between the fluconazole group and either the 100 or 150 mg micafungin groups (P=0.136 and P=0.606, respectively). Fluconazole had a lower endoscopic cure rate than micafungin 150 mg in patients with an endoscopic grade 3 at baseline (77.8 and 100% respectively). Eradication rates were 35.1, 78.3, 57.1, and 67.3% for the micafungin 50, 100, and 150 mg groups and the fluconazole group, respectively. Eradication rates for the micafungin 100 mg group were higher than for the 150 mg group (P=0.031). No significant difference was observed between micafungin 100 mg and fluconazole or micafungin 150 mg and fluconazole (P=0.263 and P=0.312, respectively). Secondary: All treatment groups showed an improvement in endoscopic findings at the end of treatment compared to baseline (P=0.003 for the micafungin groups). Endoscopic cure rate at day 14 and clinical response at the end of treatment were dose dependent in the micafungin groups and comparable

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				in the 100 and 150 mg micafungin group and the fluconazole group (P=0.574). Therapeutic success rates were comparable among the 100 and 150 mg micafungin groups and the fluconazole group (P=0.463). The rates of improvement in EC severity scores were comparable in the 100 and 150 mg micafungin groups and the fluconazole group. Worsening EC severity or use of non-prophylactic antifungal therapy was observed in nine patients in the micafungin group during follow-up and in no patients in the fluconazole group.
de Wet et al.[51] (2005) Fluconazole 200 mg IV for up to 42 days vs micafungin 150 mg IV daily for up to 42 days	DB, MC, PG, RCT Patients 16 years of age and older with endoscopically confirmed esophageal candidiasis (EC)	N=523 4 week posttreatment follow-up	Primary: Treatment success at the end of therapy (endoscopic cure, mucosal grade=0) Secondary: Clinical and mucosal response at the end of therapy (cleared or improved), therapeutic response at the end of therapy, relapse at 2 and 4 weeks posttreatment	Primary: Endoscopic cure rate was 87.7% at the end of therapy in the micafungin group compared to 88.0% for fluconazole patients and no significant differences were observed. Secondary: The clinical success rates (cleared or improved) for micafungin and fluconazole were 94.2 and 94.6% respectively. Overall therapeutic success rates for micafungin and fluconazole were 87.3 and 87.2%, respectively. The overall incidence of relapse at two and four weeks posttreatment was 15.2 and 11.3% in the micafungin and fluconazole groups, respectively (P>0.313).
Blomgren et al.[52] (1998) Fluconazole 50 mg orally daily for 7 days	RCT Patients with a diagnosis of oral candidiasis	N=71 6 month posttreatment follow-up	Primary: Clinical response (cure=healthy oral mucosa and no signs and symptoms)	Primary: No significant differences were observed between groups in clinical response. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs nystatin rinse with 1 mL for 5 minutes 4 times daily for 3 weeks			Secondary: Not reported	
Flynn et al.[53] (1995) Fluconazole 4 mg/kg oral loading dose, followed by 2 mg/kg daily for 14 days vs nystatin 400,000 units 4 times daily for 14 days The dose of fluconazole was increased half-way through the study to 6 mg/kg loading dose followed by 3 mg/kg daily.	MC, RCT, SB Children 5 months to 14 years of age with oral thrush	N=182 42 days	Primary: Clinical response (cure=resolution of symptoms and signs of infection; improvement= reduction in signs and symptoms), mycological response (negative culture) Secondary: Not reported	Primary: Significantly more patients treated with fluconazole were clinically cured (78 and 37%, respectively; P<0.001). Significantly more patients treated with fluconazole experienced mycological eradication (55 and 6%, respectively; P<0.001). At the end of therapy, significantly more patients taking the higher dose of fluconazole had mycological eradication compared to the lower dose (P<0.01). Secondary: Not reported
Goins et al.[54] (2002) Fluconazole 3 mg/kg/day orally for 7 days vs	OL, PRO, RCT Infants 1 to 12 months of age with signs of oral thrush	N=34 28 days	Primary: Clinical response (cure=absence of oral plaques), microbiologic response (cure= negative culture)	Primary: At the end of therapy, 28.6% of nystatin patients and 100% of fluconazole patients were clinically cured (P<0.0001). At the end of therapy, 5.6% of nystatin patients and 73.3% of fluconazole patients were microbiologically cured (P<0.0001). By day 28, 23% of fluconazole patients had evidence of clinical relapse

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
nystatin 100,000 units 4 times daily for 10 days			Secondary: Not reported	(relapse not evaluated in nystatin group). Secondary: Not reported
Pons et al.[55] (1997) Fluconazole 200 mg oral loading dose, followed by 100 mg orally once daily for 14 days vs nystatin 500,000 units four times daily for 14 days	MC, PRO, RCT Patients with acquired immunodeficiency syndrome or human immunodeficiency virus and typical signs and symptoms of oropharyngeal candidiasis	N=167 42 days	Primary: Clinical response (cure=complete resolution of signs and symptoms), mycological response (cure= eradication) Secondary: Not reported	Primary: Significantly more patients in the fluconazole group were considered clinically cured compared to patients in the nystatin group (87% and 52% respectively, P<0.001). Significantly more patients in the fluconazole group experienced mycological eradication compared to the nystatin group (60% and 6% respectively, P<0.001). Secondary: Not reported
Saag et al.[56] (1999) Itraconazole 100 mg orally twice daily for 14 days Patients not responding completely were treated with an additional 14 days of itraconazole solution.	MC, OL Patients 18 to 65 years of age with human immunodeficiency virus and oropharyngeal candidiasis who had failed ≥14 days treatment of fluconazole ≥200 mg daily within past 14 days	N=74 6 week posttreatment follow-up	Primary: Clinical response at end of treatment (no lesions or symptoms) Secondary: Not reported	Primary: Clinical response was observed in 55% of patients. All patients who did not receive maintenance itraconazole therapy after initial therapy relapsed within six weeks. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Queiros-Telles et al.[57] (2001) Itraconazole 100 mg orally twice daily for 7 to 14 days	MC, OL Patients >18 years of age with human immunodeficiency virus and pseudomembranous oropharyngeal candidiasis	N=50 4 weeks	Primary: Clinical response at end of therapy (success=cured or improved, undefined), mycological cure (negative culture) Secondary: Not reported	Primary: Clinical response was observed in 86 and 92% of patients after seven and 14 days, respectively, and maintained for 21 days following therapy in 52% of patients. Mycological cure was observed in 40% of patients at the end of therapy but *Candida* colonization occurred in 84% of patients at day 28. Secondary: Not reported
Smith et al.[58] (1991) Itraconazole 200 mg daily for 28 days vs ketoconazole 200 mg twice daily for 28 days	DB, RCT Patients with human immunodeficiency virus infection and clinical and mycological diagnoses of buccal or esophageal candidiasis	N=111 3 month posttreatment follow-up	Primary: Clinical response (resolution of signs or improvement in signs by 2 or more grades), mycological response (negative culture) Secondary: Not reported	Primary: There was no significant difference between groups in clinical response rates (P>0.4497). There was no significant difference between groups in mycological response rates by week four. At week one, the mycological response rate was greater in the ketoconazole group compared to the itraconazole group (P=0.0028), but this difference did not persist. Secondary: Not reported
de Repentigny et al.[59] (1996) Itraconazole 200 mg daily vs ketoconazole 200 mg daily Patients were	DB, MC, PC, RCT Patients 16 years of age and older with symptoms and signs of oropharyngeal and/or esophageal candidiasis and human immunodeficiency virus	N=143 6 week posttreatment follow-up	Primary: Clinical response (cure=no signs and symptoms of disease), mycological response for oropharyngeal patients only (cure=negative culture) Secondary:	Primary: There was no significant difference in clinical cure rates with itraconazole compared to ketoconazole for patients with oropharyngeal or esophageal candidiasis (P=0.0614 and P=0.0781, respectively). Mycological cure occurred in 63% of itraconazole patients and 62% of ketoconazole patients with oropharyngeal candidiasis (P=0.8589). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
treated for 2 weeks (oropharyngeal candidiasis) or 4 weeks (esophageal candidiasis).			Not reported	
Murray et al.[60] (1997) Itraconazole 200 mg orally daily for 14 days vs clotrimazole troches 10 mg five times daily for 14 days	MC, OL Patients ≥13 years of age with oropharyngeal candidiasis and predisposing risk factors for immunosuppression	N=149 6 weeks	Primary: Clinical response (cured=clearance of all symptoms; improved= minimal symptoms and no lesions), mycological response (negative culture) Secondary: Not reported	Primary: Clinical (77 and 70%; P=0.349), mycological (60 and 32%; P<0.001), and clinical and mycological (53 and 30%; P=0.006) responses were observed in patients receiving itraconazole and clotrimazole, respectively. Mycological (64 and 29%) and clinical plus mycological (55 and 28%) responses were observed in the subset of human immunodeficiency virus / acquired immunodeficiency syndrome patients receiving itraconazole and clotrimazole, respectively (P<0.01). Secondary: Not reported
Linpiyawan et al.[61] (2000) Itraconazole 100 mg orally twice daily for 7 days vs clotrimazole troches 10 mg five times daily for 7 days	PRO, RCT Patients 15 to 62 years of age with acquired immunodeficiency syndrome and oropharyngeal candidiasis	N=29 4 weeks	Primary: Global evaluation of response, mycological response Secondary: Not reported	Primary: Clinical cure rates in patients receiving itraconazole and clotrimazole were 66.7 and 73.3%, respectively. Differences in reduction in clinical severity scores and clinical plus mycological response were not statistically significant between the treatment groups. Secondary: Not reported
Petersen et al.[62] (1980) Ketoconazole 100 mg (<40 kg) or	DB, PC, RCT Patients 7 to 31 years of age with chronic	N=12 6 months	Primary: Clinical response Secondary: Not reported	Primary: Symptom remission and regression of mucosal, nail and skin lesions of patients receiving ketoconazole and placebo occurred in 100% and 0%, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
200 mg (≥40 kg) orally daily vs placebo	mucocutaneous candidiasis for ≥3 years			Temporary mucosal clearing occurred in 33.3% of patients receiving placebo. The response was significantly more favorable in patients receiving ketoconazole than placebo (P=0.001). Secondary: Not reported
Skiest et al.[63] (2007) Posaconazole 400 mg orally twice daily for 3 days, then 400 mg daily for 25 days (regimen A) vs posaconazole 400 mg orally twice daily for 28 days (regimen B) Patients responding to initial treatment received 400 mg twice daily 3 times per week as maintenance therapy	MC, OL Patients ≥18 years of age with human immunodeficiency virus and oropharyngeal or esophageal candidiasis who had failed fluconazole or itraconazole treatment for mucosal candidiasis	N=176 4 week posttreatment follow-up	Primary: Rate of cure or improvement after 28 days of therapy Secondary: Clinical response on day 14, clinical response at day 14 stratified by the presence or absence of in vitro resistance to fluconazole or itraconazole at baseline	Primary: Clinical response rates at 28 days in patients receiving regimen A and regimen B were 75.3 and 74.7%, respectively. Secondary: At day 14, 52.8% of patients were considered responders. Clinical response in all patients with baseline fluconazole resistance, itraconazole resistance, or resistance to both agents was 73, 74, and 74%, respectively. Relapse rates were 80% and 68% of all patients receiving posaconazole once daily and twice daily, respectively.
Candidiasis (Systemic)				
Phillips et al.[64] (1997) Fluconazole 800 mg IV loading	RCT, SB Patients ≥18 years of age with one or more blood cultures	N=106 6 months	Primary: Clinical response (success=absence of death within the first 7 days of	Primary: Successful response was seen in 50% of fluconazole patients and 58% of amphotericin B patients (P=0.39). Therapy failed in one amphotericin B patient during the sixth months of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
dose on day 1, then 400 mg IV daily for 4 week vs amphotericin B 0.6 mg/kg/day IV Patients could be switched to oral fluconazole after 10 days of IV therapy if fungemia had cleared and they could tolerate oral therapy.	positive for a yeast species		treatment, progressive fungal infection, and withdrawal from study due to drug toxicity, inadequate response, or superinfection) Secondary: Not reported	follow-up. Secondary: Not reported
Abele-Horn et al.[65] (1996) Fluconazole 400 mg on day 1, then 200 mg daily IV for 14 days vs amphotericin B 1 to 1.5 mg/kg/day every other day for 14 days plus flucytosine 3×2.5 g as a total daily dose	MC, PRO, RCT Patients 18 to 80 years of age in the intensive care unit with evidence of systemic *Candida* infection	N=72 14 days	Primary: Clinical response (cure=resolution of all symptoms and signs of infection), microbiological response (cure= eradication of *Candida* species) Secondary: Not reported	Primary: No significant differences were seen between the treatment groups in the treatment of pneumonia and sepsis/fungemia. In the treatment of peritonitis, amphotericin B plus flucytosine was more effective than fluconazole, as seen in clinical and microbiological response ($P<0.05$). Secondary: Not reported
Kujath et al.[66] (1993)	OL, PRO, RCT	N=40	Primary: Microbiological	Primary: No statistical difference was observed between groups in microbiological

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Fluconazole 400 mg on day 1, then 300 mg IV daily vs amphotericin B 0.5 mg/kg/day IV plus flucytosine 3×2.5 g as a total daily dose	Patients ≥18 years of age with systemic candidiasis	Variable duration	response (elimination or improvement [reduction of fungal density by 2 stages on a 6-stage scale]), time to elimination of all fungi Secondary: Not reported	elimination or improvement (P=0.44). Fungal elimination was observed significantly sooner in the amphotericin B plus flucytosine group compared to the fluconazole group (5.5 and 8.5 days respectively, P=0.03). Secondary: Not reported
Rex et al.[67] (1994) Fluconazole 400 mg daily IV for 7 days, followed by oral therapy vs amphotericin B 0.5 to 0.6 mg/kg/day IV for the first 7 days, then 3 times per week	MC, RCT Patients 13 years of age and older with at least 1 positive blood culture for *Candida* species	N=237 12 week posttreatment follow-up	Primary: Response rates (success= resolution of signs and symptoms and negative blood cultures) Secondary: Response rates in the intent-to-treat population, outcome in patients who received at least 5 days of therapy	Primary: No significant difference was observed between fluconazole and amphotericin B in successful response to therapy (70 and 79%, respectively; P=0.22). Secondary: No significant difference was observed in the intent-to-treat population between fluconazole and amphotericin B in successful response to therapy (72 and 80%, respectively; P=0.17). In patients who had received at least five days of treatment, 75% of fluconazole patients and 86% of amphotericin B patients had a successful outcome (P=0.05).
Reboli et al.[68] (2007) Fluconazole 800 mg IV on day 1 then 400 mg daily for 14 to 42 days vs	DB, MC, RCT Patients 16 years of age and older with candidemia or other forms of invasive candidiasis	N=261 6 week posttreatment follow-up	Primary: Global response at the end of IV therapy (success= resolution of signs and symptoms and no need for additional antifungal therapy	Primary: Significantly more patients in the anidulafungin group achieved a successful global response compared to the fluconazole group (75.6 and 60.2%, respectively; P=0.01). Secondary: Significantly more patients in the anidulafungin group had a successful global response at the end of all therapy compared to the fluconazole group (74 and 56.8%, respectively; P<0.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
anidulafungin 200 mg IV on day 1, then 100 mg daily for 14 to 42 days All patients could receive oral fluconazole after 10 days of IV therapy if they could tolerate oral medication, if they were afebrile for 24 hours, last blood culture was negative for *Candida*, and if there was clinical improvement.			and eradication of *Candida* species) Secondary: Global response at the end of all therapy and at 2 and 6 weeks follow-up, per-patient and per-pathogen microbiological response at all time points, death from all causes	Significantly more patients in the anidulafungin group had a successful global response at the 2-week follow-up compared to the fluconazole group (64.6 and 49.2%, respectively; P<0.02). There was no significant difference in the proportion of patients in either group who had a successful global response at the 6-week follow-up (55.9 and 44.1%, respectively). Microbiological success was observed for 88.1% of all pathogens in the anidulafungin group compared to 76.2% in the fluconazole group (P=0.02). There was no significant difference in death from all causes between groups (P=0.13).
Reboli et al.[69] (2011) Fluconazole 800 mg IV on day 1 then 400 mg daily for 14 to 42 days vs anidulafungin 200 mg IV on day 1, then 100 mg daily for 14 to 42 days All patients could receive oral	DB, MC, RCT (Post-hoc analysis) Patients 16 years of age and older with candidemia or other forms of invasive candidiasis	N=261 6 week posttreatment follow-up	Primary: Baseline characteristics predictive of treatment success Secondary: Not reported	Primary: There were no significant imbalances in any baseline clinical or demographic characteristics between the two treatment groups (P≤ 0.05). Study treatment and APACHE II score were identified as significant and independent predictors of global response at the end of the IV study treatment in patients with invasive *C. albicans* infection. The odds ratio for study treatment was 2.60 (95% CI, 1.14 to 5.91) in favor of anidulafungin, and the odds ratio for APACHE II score was 0.935 (95% CI, 0.885 to 0.987), with poorer responses associated with higher baseline APACHE II scores. The proportion of patients who died during the six week period from study entry was 20.3% in the anidulafungin arm and 21.3% in the fluconazole arm. The Kaplan-Meier estimates of survival at six weeks were not significantly different between treatment groups (P=0.842).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fluconazole after 10 days of IV therapy if they could tolerate oral medication, if they were afebrile for 24 hours, last blood culture was negative for *Candida*, and if there was clinical improvement.				Secondary: Not reported
Kulberg et al.[70](2005) Voriconazole 6 mg/kg IV every 12 hours for 1 day, then 3 mg/kg every 12 hours vs amphotericin B 0.7 to 1.0 mg/kg/day Patients in the voriconazole could be switched to oral voriconazole 200 mg twice daily after 3 days, and patients in the amphotericin group were switched to IV or oral fluconazole	MC, RCT Patients 12 years of age and older with candidemia	N=370 12 week posttreatment follow-up	Primary: Response to treatment (clinical cure or improvement and microbiological eradication) Secondary: Time to first negative blood culture, time from randomization to death	Primary: No significant difference between groups was observed in successful response to treatment (P=0.96). Significantly more patients in the voriconazole group infected with *C. tropicalis* were considered to have a successful response compared to the amphotericin group (32 and 6%, respectively; P=0.032). Secondary: No significant difference between groups was observed in the time to first negative blood culture (two days in each group). No significant difference between groups was observed in the time from randomization to death (36% in the voriconazole group died in the first 14 days compared to 42% in the amphotericin B group).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
after 3 to 7 days.				
Gafter-Gvili et al.[71] (2008) Group 1 Echinocandins vs other antifungal agents Group 2 Fluconazole vs other antifungal agents	MA Patients with confirmed invasive candidiasis	N=3,265 (15 trials) Variable duration	Primary: 30-day all-cause mortality Secondary: Treatment failure, microbiological failure, adverse events	Primary: Fluconazole vs other antifungal agents (9 studies) No difference in mortality was observed with fluconazole vs amphotericin B (RR, 0.92; 95% CI, 0.72 to 1.17). No difference in mortality was observed between fluconazole and itraconazole (RR, 1.91; 95% CI, 0.39 to 9.35) or between fluconazole and a combination of fluconazole and amphotericin B (RR, 0.98; 95% CI, 0.70 to 1.35). Echinocandins vs other antifungal agents (4 studies) There was no difference in mortality with anidulafungin vs fluconazole (RR, 0.73; 95% CI, 0.48 to 1.10). There was no difference in mortality with caspofungin vs amphotericin B (RR, 1.08; 95% CI, 0.75 to 1.55) or with micafungin vs liposomal amphotericin B (RR, 1.04; 95% CI, 0.75 to 1.43). Other comparisons (2 studies) There was no difference in mortality with micafungin vs caspofungin (100 mg/d: RR, 1.10; 95% CI, 0.80 to 1.51; 150 mg/d: RR, 1.27; 95% CI, 0.93 to 1.72). There was no difference in mortality with amphotericin B plus fluconazole vs voriconazole (RR, 1.18; 95% CI, 0.90 to 1.54). Secondary: Fluconazole vs other antifungal agents (9 studies) No significant difference in treatment failure was found with fluconazole and amphotericin B (RR, 1.22; 95% CI, 0.97 to 1.54) or with fluconazole vs a combination of fluconazole and amphotericin B (RR, 1.41; 95% CI, 0.99 to 1.99). Microbiological failure was higher in patients treated with fluconazole compared to amphotericin B (RR, 1.52; 95% CI, 1.12 to 2.07) or with fluconazole vs a combination of fluconazole and amphotericin B (RR,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				2.69; 95% CI, 1.17 to 6.18). No difference in adverse events requiring discontinuation was noted with fluconazole vs amphotericin B (RR, 0.45; 95% CI, 0.13 to 1.56), itraconazole (RR, 0.32; 95% CI, 0.04 to 2.82) or with fluconazole vs a combination of fluconazole and amphotericin B (RR, 1.16; 95% CI, 0.49 to 2.75). Fluconazole caused less nephrotoxicity than amphotericin B (RR, 0.11; 95% CI, 0.03 to 0.48) or the combination of amphotericin B and fluconazole (RR, 0.12; 95% CI, 0.04 to 0.39). <u>Echinocandins vs other antifungal agents (4 studies)</u> Treatment failure significantly decreased with anidulafungin vs fluconazole (RR, 0.61; 95% CI, 0.42 to 0.89). There was no difference in treatment failure with caspofungin vs amphotericin B (RR, 0.70; 95% CI, 0.47 to 1.03) or with micafungin vs liposomal amphotericin B (RR, 0.93; 95% CI, 0.74 to 1.19). Microbiological failure was significantly reduced with anidulafungin vs fluconazole (RR, 0.50; 95% CI, 0.29 to 0.86). No difference in microbiological failure was noted for caspofungin vs amphotericin B (RR, 0.95; 95% CI, 0.40 to 2.25) or with micafungin vs liposomal amphotericin B (RR, 1.01; 95% CI, 0.53 to 1.92). A significant decrease in adverse events requiring discontinuation was observed with anidulafungin vs fluconazole (RR, 0.52; 95% CI, 0.29 to 0.92). Caspofungin was associated with a significantly lower rate of adverse events requiring discontinuation when compared to amphotericin B (RR, 0.11; 95% CI, 0.04 to 0.36) or liposomal amphotericin B (RR, 0.45; 95% CI, 0.26 to 0.80). <u>Other comparisons (2 studies)</u> There was no difference in treatment failure with micafungin and caspofungin (100 mg/d: RR, 0.85; 95% CI, 0.60 to 1.20; 150 mg/d: RR, 1.04; 95% CI, 0.74 to 1.42). There was no difference in treatment failure with amphotericin B plus fluconazole vs voriconazole (RR, 1.00; 95% CI, 0.83 to 1.19).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was no difference in microbiological failure with micafungin and caspofungin (100 mg/d: RR, 0.73; 95% CI, 0.41 to 1.22; 150 mg/d: RR, 1.10; 95% CI, 0.70 to 1.73). There was no difference in adverse events requiring discontinuation with micafungin and caspofungin. Adverse events requiring discontinuation were significantly lower (RR, 0.47; 95% CI, 0.23 to 0.93) and nephrotoxicity was significantly higher (RR, 2.64; 95% CI, 1.57 to 4.44) with the amphotericin B-fluconazole arm compared to voriconazole.
Candidiasis (Vaginal)				
Sobel et al.[72] (1995) Fluconazole 150 mg orally as a single dose vs clotrimazole tablet 100 mg intravaginally for 7 days	MC, PRO, RCT, SB Female patients 17 to 64 years of age with symptomatic *Candida* vaginitis	N=358 35 days	Primary: Clinical response at day 14 and 35 (cured=absence of signs and symp-toms of vaginitis; improved= reduction of >50% of the clinical severity score) Secondary: Not reported	Primary: Clinical response at 14 days in patients receiving fluconazole and clotrimazole were 94 and 97%, respectively (P=0.307). At day 35, 75% of patients in both treatment groups were still clinically cured (P=0.890). Secondary: Not reported
van Heusden et al.[73] (1994) Fluconazole 150 mg orally for one dose vs clotrimazole 500 mg intravaginally for one dose	CS, MC, RCT Patients 18 to 65 years of age with symptomatic vaginal candidosis	N=741 28 days	Primary: Clinical efficacy (symptom scores from 0=absent to 3=severe) Secondary: Not reported	Primary: No significant difference was observed between groups in clinical efficacy (P=0.48). There was no significant difference observed between groups in mycological efficacy (tests not performed on all patients and not required by study protocol). Secondary: Not reported
O-Prasertsawat et	PRO, RCT, SB	N=103	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
al.[74] (1995) Fluconazole 150 mg orally for one dose vs clotrimazole 100 mg suppository intravaginally twice daily for 3 days	Patients with a clinical diagnosis of vulvovaginal candidiasis	1- and 4-week posttreatment follow-up	Clinical improvement (Patient self-assessment based on symptoms, not further defined), mycological cure (negative culture) Secondary: Not reported	At week one, clinical improvement was reported in 87% of fluconazole patients and 90% of clotrimazole patients (P=0.92). At week one, mycological cure was reported in 79.2% of fluconazole patients and 80% of clotrimazole patients (P=0.88). At week four, clinical improvement was reported in 69.8% of fluconazole patients and 68% of clotrimazole patients (P=0.99). At week four, mycological cure was reported in 60.4% of fluconazole patients and 66% of clotrimazole patients (P=0.70). Secondary: Not reported
Mendling et al.[75] (2004) Fluconazole 150 mg orally as single dose vs clotrimazole tablet 500 mg intravaginally as single dose plus clotrimazole 1% cream applied to vulval area as needed vs clotrimazole 10% cream intravaginally as	AC, MC, RCT, SB Female patients with vulvovaginal mycosis caused by *Candida*	N=679 8 weeks	Primary: Overall response (clinical cure and mycological response, undefined) at 14 days Secondary: Time to meaningful symptom relief and complete symptom relief	Primary: Overall response rates at 14 days in patients receiving clotrimazole tablet, clotrimazole cream and fluconazole were 65.8, 60.5, and 59.1%, respectively. Secondary: The difference in time to meaningful or complete symptom relief was not statistically significant among groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
single dose plus clotrimazole 2% cream applied to vulval area as needed				
Sekhavat et al.[76] (2011) Fluconazole 150 mg as a single dose vs clotrimazole 200 mg daily intravaginally for 6 days	RCT Patients >15 years of age with acute clinical and mycologically verified vulvovaginal candidiasis	N=142 1 month	Primary: Clinical cure (defined as absence of signs and symptoms) and mycological cure (defined as microscopic absence of yeast) Secondary: Not reported	Primary: On the first visit, *Candida* was clinically treated in 73.6% of patients in the fluconazole group and 58.6% of patients in the clotrimazole group. *Candida* was eradicated in 83.3% of patients in the fluconazole group and in 70% of patients in the clotrimazole group (P=0.001). After one month, *Candida* was recurrent symptomatically in one patient in the fluconazole group and 17 patients in clotrimazole group (P=0.001). Mycological symptoms were positive in one patient in the fluconazole group and seven patients in clotrimazole group (P=0.01). Secondary: Not reported
Pitsouni et al.[77] (2008) Fluconazole 150 mg orally for 1 dose vs itraconazole 200 mg twice daily for 1 day, itraconazole 200 mg once for 3 days, or itraconazole 200 mg twice daily for 7 days	MA Nonpregnant women with uncomplicated acute vaginal or vulvovaginal candidiasis	N=1092 (6 trials) 60 days	Primary: Clinical cure and mycologic cure at the first and second assessment visits after treatment was completed (7-28 days and 21-60 days, respectively) Secondary: Adverse events	Primary: There was no difference between itraconazole and fluconazole regarding clinical cure and improvement at the first and second scheduled visit assessments (OR, 0.94; 95% CI, 0.6 to 1.48 and OR, 1.09; 95% CI, 0.68 to 1.75, respectively). There was no difference between itraconazole and fluconazole regarding mycological cure at the first and second scheduled visit assessments (OR, 0.73; 95% CI, 0.31 to 1.7 and OR, 0.71; 95% CI, 0.49 to 1.03, respectively). Secondary: There was no difference between itraconazole and fluconazole regarding adverse events (OR, 1.07; 95% CI, 0.42 to 2.73 and OR, 1.84; 95% CI, 0.3 to 11.27, respectively). The proportion of patients with skin and subcutaneous tissues adverse events was 0 and 2% for fluconazole and 0 and 12% for itraconazole, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
van Heusden et al.[78] (1990) Fluconazole 150 mg orally as a single dose vs miconazole 1,200 mg capsule intravaginally as a single dose	DB, MC, PG, RCT Patients 18 to 65 years of age with symptomatic and mycologically verified vaginal candidosis	N=99 3 to 12 day posttreatment follow-up (short-term follow-up), and 22 to 60 day posttreatment follow-up (long-term follow-up)	Primary: Clinical efficacy (cure, improve-ment, or failure assessed by investigator, not further defined, combined with patient-rating of excellent, good, fair, or not effective), mycological efficacy (cure= negative culture) Secondary: Not reported	Primary: At the short-term follow-up, 100% of fluconazole patients and 94% of miconazole patients were considered cured or improved by investigators. At the long-term follow-up, 95% of fluconazole patients and 90% of miconazole patients were considered cured or improved by investigators. At the short-term follow-up, 81% of fluconazole patients and 84% of miconazole patients considered the treatment excellent or good. At the long-term follow-up, 81% of fluconazole patients and 76% of miconazole patients considered the treatment excellent or good. At the short-term follow-up, mycological cure was observed in 98% of fluconazole patients and 96% of miconazole patients. At the long-term follow-up, mycological cure was observed in 74% of fluconazole patients and 82% of miconazole patients. Secondary: Not reported
Cryptococcal Disease				
Saag et al.[79] (1992) Fluconazole 400 mg oral loading dose, followed by 200 mg daily vs amphotericin B 0.3 mg/kg/day or an equivalent dose every other day	MC, RCT Patients 18 years of age and older with HIV and a positive cerebrospinal fluid culture for *Cryptococcus neoformans*	N=194 10 weeks	Primary: Rate of treatment success (sterilization of cerebrospinal fluid cultures) Secondary: Not reported	Primary: Treatment was successful in 40% of the amphotericin B patients and 34% of the fluconazole patients (P=0.40). Disease progression occurred more frequently in the fluconazole group while discontinuation of study drug occurred more frequently in the amphotericin B group though neither difference was statistically significant. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Patients in the amphotericin B group may also have been treated with flucytosine 150 mg/kg/day according to investigator discretion.				
Larsen et al.[80](1990) Fluconazole 400 mg orally for 10 weeks vs amphotericin B 0.7 mg/kg/day IV for 7 days, followed by 3 times weekly for 9 weeks plus flucytosine 150 mg/kg/day orally in 4 doses for 10 weeks	PRO, RCT Patients 18 years of age and older with evidence of cryptococcal meningitis, with or without acquired immunodeficiency syndrome (AIDS)	N=26 62 weeks	Primary: Clinical outcome (success=blood and cerebrospinal fluid cultures negative) Secondary: Not reported	Primary: At 10 weeks of treatment, eight of 14 patients receiving fluconazole were considered failures while zero of six patients taking amphotericin B plus flucytosine were considered failures (P=0.04). Conversion from positive to negative cerebrospinal fluid cultures was significantly slower in patients taking fluconazole compared to amphotericin B and flucytosine (P=0.02). No significant difference was seen in the time to achieve mycological success for blood cultures (P=0.19). Secondary: Not reported
van der Horst et al.[81] (1997) <u>Step 1</u> Amphotericin B 0.7 mg/kg/day plus flucytosine 100 mg/kg/day in 4	DB, MC, RCT Patients ≥13 years of age with first episode of acquired immunodeficiency syndrome-associated cryptococcal	N=381 (Step 1) N=306 (Step 2) 10 weeks	Primary: Mycological response (negative culture) at 2 and 10 weeks, clinical outcome (success= resolution of fever, headache, and meningismus) at 2	Primary: Mycological response at the end of step one in patients receiving amphotericin B plus flucytosine or amphotericin B alone was 60% and 51%, respectively (P=0.06). Clinical response at the end of step one in patients receiving amphotericin B plus flucytosine or amphotericin B alone was 78% and 83%, respectively (P=0.18).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
doses for 2 weeks vs amphotericin B 0.7 mg/kg/day for 2 weeks Patients who were stabilized or improved after step 1 moved on to step 2. <u>Step 2</u> Fluconazole 800 mg daily for 2 days, followed by 400 mg daily for 8 weeks vs itraconazole 600 mg daily for 3 days, followed by 200 mg twice daily for 8 weeks	meningitis		and 10 weeks Secondary: Not reported	There was no significant difference between the treatments in combined mycological and clinical response (P=0.12). Mycological response at the end of step two in patients receiving fluconazole and itraconazole was 72 and 60%, respectively. Clinical response at the end of step two in patients receiving fluconazole and itraconazole was 68 and 70%, respectively. There was no significant difference between fluconazole and itraconazole in mycological or clinical response. Secondary: Not reported
Brouwer et al.[82] (2004) Fluconazole 400 mg daily plus amphotericin B 0.7 mg/kg/day vs	OL, RCT Adult patients with first episode of cryptococcal meningitis and human immunodeficiency virus	N=64 10 weeks	Primary: Rate of reduction of cerebrospinal fluid cryptococcal colony-forming units Secondary: Not reported	Primary: Early fungicidal activity occurred faster for patients receiving amphotericin B plus flucytosine than amphotericin B alone (P=0.0006), amphotericin B plus fluconazole (P=0.03), or amphotericin B plus flucytosine plus fluconazole (P=0.01). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fluconazole 400 mg daily plus flucytosine 100 mg/kg/day plus amphotericin B 0.7 mg/kg/day vs amphotericin B 0.7 mg/kg/day plus flucytosine 100 mg/kg/day vs amphotericin B 0.7 mg/kg/day After 2 weeks, all arms received treatment with fluconazole 400 mg daily for 8 weeks, followed by 200 mg daily.				
Nussbaum et al.[83] (2010) Fluconazole 1,200 mg daily for 14 days vs fluconazole 1,200 mg daily plus	OL, RCT human immunodeficiency virus-positive adults with their first episode of cryptococcal meningitis	N=41 24 days	Primary: Rate of cerebrospinal fluid infection clearance Secondary: Not reported	Primary: The rate of clearance of infection was more rapid in the combination arm compared to fluconazole alone. The difference in early fungicidal activity was 0.18 (95% CI, 0.085 to 0.27; P=0.0005). Four patients in the combination arm and one in the monotherapy arm had sterile cerebrospinal fluid cultures by day 14. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
flucytosine 100 mg/kg/day, followed by fluconazole 800 mg/day				
Dermatophyte Infections				
Dehghan et al.[84] (2010) Fluconazole 400 mg as a single dose (G1) vs clotrimazole 1% cream twice daily for 2 weeks (G2)	RCT, DB Patients with pityriasis versicolor	N=105 12 weeks	Primary: Clinical response and recurrence rates Secondary: Not reported	Primary: After two weeks, the rate of complete resolution of disease was significantly higher in the clotrimazole group than in the fluconazole group (49.1 vs 30.0%, respectively; P=0.16). After 4 weeks, 81.2% of patients in the fluconazole group and 94.9% of patients in the clotrimazole group showed complete resolution (P=0.044). After 12 weeks, 92% of patients in the fluconazole group and 81.8% of patients in the clotrimazole group showed complete resolution. Recurrence rate in the fluconazole and clotrimazole groups were 6.0 and 18.2%, respectively (P=0.77). No complications were seen in either group. Secondary: Not reported
Roberts et al.[85] (1987) Ketoconazole 200 mg daily for up to 8 weeks vs griseofulvin 1 g daily for up to 8 weeks	RCT Patients with mycologically proven tinea pedis	N=29 8 weeks	Primary: Mycological cure (negative culture) Secondary: Not reported	Primary: At four weeks, the mycological cure rate was 33% in the ketoconazole group and 29% in the griseofulvin group. At eight weeks, the mycological cure rate was 53% in the ketoconazole group and 57% in the griseofulvin group. Secondary: Not reported
Jolly et al.[86] (1983)	DB, RCT	N=137	Primary: Clinical response	Primary: Clinical response was observed in 20 of 21 patients in the ketoconazole

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ketoconazole 200 mg daily for 2 to 16 weeks vs griseofulvin ultramicrosize 250 mg daily for 2 to 16 weeks	Patients with mycologically confirmed dermatophyte infections	16 weeks	and mycological response Secondary: Not reported	group compared to nine of 11 in the griseofulvin group. Mycological response was better in the ketoconazole group compared to the griseofulvin group. In the ketoconazole group, 61% achieved remission compared to 39% in the griseofulvin group (P=0.02). In the ketoconazole group, 9% of patients relapsed compared to 43% in the griseofulvin group (P<0.01). Secondary: Not reported
Stratigos et al.[87] (1983) Ketoconazole 200 mg daily until negative culture or 6 weeks vs griseofulvin 500 mg daily until negative culture or 6 weeks	DB, RCT Patients with clinical symptoms and cultures for dermatophytes	N=50 6 weeks	Primary: Cure rate (no symptoms and negative culture results) Secondary: Not reported	Primary: After two weeks of treatment, 50% of patients in the ketoconazole group and 25% in the griseofulvin group had negative cultures and this difference was not statistically significant between groups. At three weeks, 88.5% of patients in the ketoconazole group and 66.6% in the griseofulvin group had negative cultures and this difference was not statistically significant between groups. There was no significant difference in cure rates between groups. Secondary: Not reported
Tanz et al.[88] (1988) Ketoconazole 3.3 to 6.6 mg/kg/day for 12 weeks vs	DB, RCT Patients 2 to 16 years of age with tinea capitis or mycological evidence of dermatophyte infection of the scalp	N=79 12 weeks	Primary: Clinical response (success=clinical improvement and negative cultures), mycological response, symptom severity score Secondary:	Primary: Treatment success was observed in 73% of patients in the ketoconazole group and in 96% of patients in the griseofulvin group (P<0.10). There were no significant differences in symptom severity scores between groups (P>0.20). There were no significant differences between groups in mycological response (P<0.90).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
griseofulvin 10 to 20 mg/kg/day for 12 weeks			Not reported	Secondary: Not reported
Legendre et al.[89] (1980) Ketoconazole 200 mg daily for 28 to 60 days vs griseofulvin ultramicrosize 250 mg daily for 28 to 60 days	DB, RCT Patients with microscopically confirmed dermatophyte infection of the skin	N=58 28-day posttreatment follow-up	Primary: Response to therapy (cure= clearance of lesions and negative culture), relapse rates	Primary: Cure was obtained in 38% of patients in the ketoconazole group and 24% of patients in the griseofulvin group after four weeks of therapy. After 60 days of therapy, cure was obtained in 83% of ketoconazole patients and 32% of griseofulvin patients (P<0.001). Of the patients cured after four weeks of treatment, none of the ketoconazole patients relapsed and all of the griseofulvin patients relapsed (P=0.001). Of all the patients cured regardless of duration of therapy, 7% of ketoconazole patients relapsed within 28 days compared to 80% in the griseofulvin group (P=0.006).
Gan et al.[90] (1987) Ketoconazole 5 mg/kg/day until clearance of lesions and negative culture or for 6 months vs griseofulvin 15 mg/kg/day until clearance of lesions and negative culture or for 6 months	RCT Patients 1 to 12 years of age with a diagnosis of tinea capitis	N=63 6 months	Primary: Negative cultures, relapse rates	Primary: After one month of therapy, fungal cultures were negative in 69% of patients treated with griseofulvin and 29% of patients treated with ketoconazole (P<0.01). This statistical difference persisted throughout the follow-up period. At the end of 12 weeks of therapy, 4% of griseofulvin patients continued to have positive cultures compared to 26% in the ketoconazole group. Seven patients (1 in the griseofulvin group and six in the ketoconazole group) reverted to negative samples between the 12th and 26th week of treatment. The median time from initiation of therapy to negative culture was significantly longer in the ketoconazole group compared to the griseofulvin group (eight weeks and four weeks, respectively, P<0.01).
Martinez-Roig et al.[91]	DB, RCT	N=47	Primary: Response to	Primary: After six weeks of therapy, clinical and mycological cure or improvement

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1988) Ketoconazole 100 mg daily divided every 12 hours until lesions had cleared and negative culture was obtained vs griseofulvin 350 mg daily every 12 hours until lesions had cleared and negative culture was obtained	Patients 3 months to 14 years of age with dermatophyte infections who had not received previous antifungal therapy	2 week posttreatment follow-up	therapy (clinical cure=clearance of lesions and mycological cure= negative culture), time to clinical cure and negative culture Secondary: Not reported	was seen in 92% of patients treated with ketoconazole and 76% of patients treated with griseofulvin. The time to clinical cure and negative cultures was shorter for patients treated with ketoconazole compared to griseofulvin for tinea capitis and shorter for griseofulvin compared to ketoconazole for tinea corporis, though no significant difference was observed in overall response to therapy. Secondary: Not reported
Tanz et al.[92] (1985) Ketoconazole 200 mg daily vs griseofulvin 500 mg daily	DB, RCT Children 2 to 16 years of age with mycologically proven tinea capitis	N=22 6 weeks	Primary: Symptom severity score, mycological response (negative cultures) Secondary: Not reported	Primary: The total severity scores decreased in all patients during the course of the study (P<0.05 compared to baseline) and the decrease was similar between groups (P=0.62). After 6 weeks of therapy, 57% of patients in each group were culture negative. Secondary: Not reported
Yazdanpanah et al.[93] (2007) Ketoconazole 400 mg orally as a single dose vs	OL Patients with extensive pityriasis versicolor	N=90 1 month	Primary: Clinical evaluation for extension and localization of lesions, hyperhidrosis, and greasiness of the skin	Primary: The improvement rate for ketoconazole (87.9%) was not significantly different from fluconazole (81.5%; P=0.37). Equal improvement response was detected in all over areas of the body except forearms involvement, which showed better results in ketoconazole rather than fluconazole treatment group (P=0.049). Total improvement rate did not show any relation to individual

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fluconazole 300 mg orally as a single dose, repeated after 2 weeks			Secondary: Not reported	characteristics such as age, gender, hyperhidrosis, greasiness of the skin and body involved area (P=0.520, 0.407, 0.614, 0.083, 0.897). Adverse reactions to treatments were seen in three patients (9.09%) in ketoconazole treatment group (flatulence, urine color change and itching) and four patients (14.8%) in the fluconazole treatment group (flatulence, urticaria, exertional dyspnea and perspiration). There was not any significant correlation between presence of side effects and the patient's age (Chi-square: P=0.500). Secondary: Not reported
Onychomycosis				
Ginter et al.[94] (1998) Itraconazole 400 mg daily for 1 week per month for 3 months	OL Patients with toenail onychomycosis	N=354 10 months	Primary: Clinical cure (complete clearance or clearance with a few small residual lesions), mycological cure (negative culture) Secondary: Not reported	Primary: Clinical cure was achieved in 64% of patients with proximal nail involvement in the big toenails, 77% of patients with proximal nail involvement in other toenails, and in 87% of patients without proximal nail involvement. Mycological cure was achieved in 77% of the patients who were examined (197). Secondary: Not reported
Odom et al.[95] (1997) Itraconazole 200 mg twice daily for 1 week each month for 2 months vs placebo	DB, MC, PC, RCT Patients 18 to 70 years of age with clinically and mycologically diagnosed fingernail onychomycosis	N=73 24 weeks	Primary: Clinical response (success=cleared or markedly improved nail involvement), mycological response (success= negative culture) Secondary: Not reported	Primary: Significantly more patients in the itraconazole group achieved clinical success compared to the placebo group (77% compared to 0%, P<0.001). Significantly more patients in the itraconazole group achieved mycological success compared to the placebo group (73 and 13% respectively, P<0.001). The proportion of patients achieving overall success (clinical and mycological success) was significantly greater in the itraconazole group compared to the placebo group (68 and 0% respectively, P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Haneke et al.[96] (1998) Itraconazole 400 mg/day for 1 week every 4 weeks for 3 months in patients with toenail or fingernail onychomycosis (Group A) vs itraconazole 400 mg/day for 1 week per month for 2 months in patients with fingernail onychomycosis (Group B)	MC, RCT Patients with onychomycosis of the fingernail, toenail, or both	N=683 18 weeks posttreatment follow-up	Primary: Clinical cure rates, mycological cure rates (undefined) Secondary: Not reported	Primary: Clinical and mycological cure rates at the end of the study were 89% and 68.4% respectively for toenails, 91.4 and 85.3% respectively for fingernails in Group A, and 84.4 and 77.1% respectively for Group B fingernails. Secondary: Not reported
Korting et al.[97] (1993) Itraconazole 100 mg daily for up to 18 months vs griseofulvin ultramicrosize (UMSG) 660 mg	OL, RCT Patients with clinically confirmed tinea unguium of the toenails, fingernails, or both	N=109 18 months	Primary: Clinical response, compliance, adverse effects Secondary: Not reported	Primary: There was no significant difference in the cure or partial cure rates between the USMG 660 mg, USMG 990 mg, and itraconazole groups (6, 14, and 19% respectively; P=0.2097). There was no significant difference in the rates of marked improvement between the USMG 660 mg, USMG 990 mg, and itraconazole 100 mg groups (36, 44, and 39% respectively). No significant difference in compliance was observed between groups. Itraconazole was significantly better tolerated compared to both USMG

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
daily for up to 18 months vs griseofulvin ultramicrosize (UMSG) 990 mg daily for up to 18 months				groups (P<0.0322). Secondary: Not reported
Haugh et al.[98] (2002) Itraconazole 200 mg daily or 400 mg intermittently (for 1 of every 4 weeks) for 3 or 4 months vs griseofulvin 500 mg or 1,000 mg daily for 3 months or 11 months vs terbinafine 250 mg daily for 3 or 6 months vs placebo	MA Patients diagnosed with onychomycosis	N=2,063 3 to 11 months	Primary: Mycological cure at the end of the studies (negative microscopy or culture) Secondary: Negative microscopy or culture at specified time points	Primary: <u>Terbinafine vs placebo (3 trials)</u> After 12 weeks, a significant advantage in mycological cure rates was seen in favor of the terbinafine group compared to the placebo group. <u>Terbinafine vs itraconazole (4 trials)</u> At the end of the study periods, a statistically significant advantage in achieving negative culture and microscopy was seen in favor of terbinafine compared to itraconazole. No significant differences in tolerability were reported. <u>Terbinafine vs griseofulvin (2 trials)</u> Significantly higher rates of negative microscopy and culture were observed in the terbinafine groups at week 24 compared to the griseofulvin groups.
Brautigam[99]	DB, MC, PG, RCT	N=195	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1998) Itraconazole 200 mg daily for 12 weeks vs terbinafine 250 mg daily for 12 weeks	Patients 18 years of age and older with a clinical diagnosis of distal subungual or proximal onychomycosis of the toenails	52 weeks	Mycologic cure (culture negative for dermatophytes and hyphae), clinical efficacy (length of unaffected area on the target nail) Secondary: Not reported	Significantly more patients in the terbinafine group had experienced mycologic cure (81.4%) compared to the itraconazole group (63.1%; P<0.01) at week 52. At week 52, 91.9% of cultures were negative for dermatophytes in the terbinafine group compared to 66.6% in the itraconazole group (P<0.0001). The mean time to the first negative culture was significantly shorter in the terbinafine group (8.52 weeks) compared to the itraconazole group (11.64 weeks; P<0.05). Terbinafine was significantly more effective in increasing the length of unaffected nail compared to itraconazole. At week 52, a significantly lower number of patients in the terbinafine group had >60% of the nail plate affected (3.5% of patients) compared to the number in the itraconazole group (15.5% of patients; P<0.05).
Evans et al.[100] (1999) Itraconazole 200 mg daily for 1 week every 4 weeks for 12 or 16 weeks vs terbinafine 250 mg daily for 12 or 16 weeks	DB, MC, PG, RCT Patients 18 to 75 years of age with a clinical diagnosis of onychomycosis of the toenail confirmed by positive results on mycologic cure and microscopy	N=496 72 weeks	Primary: Mycologic cure (negative results on microscopy and culture) Secondary: Clinical cure (100% toenail clearing), complete cure (mycologic and clinical cure), clinical effective-ness (mycologic cure and at least 5 mm of new clear toenail growth),	Primary: Mycologic cure rates were significantly higher in both terbinafine groups (81 and 80% respectively) compared to the itraconazole groups (41 and 53% for the 3-cycle and 4-cycle itraconazole groups respectively, P<0.0001). Secondary: Clinical cure rates were significantly higher in the terbinafine groups compared to the itraconazole groups (P<0.0022). Complete cure rates were significantly higher in the continuous terbinafine group compared to both itraconazole groups (P<0.0044). Clinical effectiveness and global assessments were significantly higher for the continuous terbinafine groups compared to the itraconazole groups (P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			and global assessments by physician and patient	
Degreef et al.[101] (1999) Itraconazole 200 mg daily for 12 weeks vs terbinafine 250 mg daily for 12 weeks	DB, MC, PG, RCT Patients 18 to 65 years of age with clinically suspected and microscopically and culturally proven onychomycosis of the toenail	N=297 36 weeks	Primary: Mycologic cure (culture negative) Secondary: Investigator's global clinical evaluation of response to treatment, percentage of total affected nail area, total number of infected nails, signs and symptoms of onycholysis, hyperkeratosis, paronychial inflammation and discoloration	Primary: A similar number of patients were mycologically cured (79 in the terbinafine group and 78 in the itraconazole group). Secondary: Clinical response rates were similar between the groups (P<0.1). Complete clinical cure rates were similar between the groups. The mean percentage of affected nail area and the mean number of nails infected decreased similarly in the two groups. Signs and symptoms of infections improved comparably in the two groups.
Gupta et al.[102] (2001) Itraconazole 200 mg twice daily for 1 week given as 3 pulses vs terbinafine 250 mg daily for 12 weeks	CS, PRO, RCT, SB Patients 60 years of age and older with dermatophyte onychomycosis of at least 1 great toe	N=101 18 months	Primary: Mycologic cure (negative cultures), clinical efficacy (mycologic cure and either clinical cure or reduction of involved nail plate to 10% or less) Secondary:	Primary: At month 18, the mycologic cure rate in the terbinafine group was 64% and 62.7% in the itraconazole group. No significant difference was found between groups. At month 18, clinical efficacy was 62% in the terbinafine group and 60.8% in the itraconazole group. No significant difference was found between groups. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Not reported	
Sigurgeirsson et al.[103] (2002) Itraconazole 400 mg daily for 1 week every 4 weeks for 12 (3 cycles) or 16 (4 cycles) weeks vs terbinafine 250 mg daily for 12 or 16 weeks	DB, PRO, RCT Patients 18 to 75 years of age with onychomycosis of the toenail confirmed by culture finding infection with a dermatophyte	N=158 72 weeks	Primary: Proportion of patients who remained mycologically cured (negative culture) at the end of follow-up without requiring continued treatment with terbinafine Secondary: Clinical cure (100% normal-appearing nail), complete cure (mycologic plus clinical cure), clinical and mycologic relapse over time, mycologic and clinical cure over time, effect of subsequent terbinafine treat-ment on clinical and mycologic outcome	Primary: Significantly more patients treated with terbinafine were mycologically cured at the end of the study compared to patients treated with itraconazole (46% compared to 13%; P<0.001). Secondary: Significantly more patients treated with terbinafine were clinically cured at the end of the study compared to patients treated with itraconazole (42% compared to 18%; P<0.002). Significantly more patients in the terbinafine group maintained complete cure at the end of the study compared to patients in the itraconazole group (P<0.005). At the end of the study, significantly fewer terbinafine patients had relapsed mycologically compared to itraconazole patients (23% compared to 53%; P<0.01). At the end of the study, significantly fewer terbinafine patients had relapsed clinically compared to itraconazole patients (21% compared to 48%; P<0.05). For patients who originally received terbinafine and subsequently received a second course of treatment with terbinafine after 18 months, 92% achieved mycologic cure compared to 85% of those originally treated with itraconazole. Similar results were seen with clinical cure rates: it was achieved in 76% of patients originally treated with terbinafine and 77% of patients originally treated with itraconazole.
Sigurgeirsson et al.[104] (1999) Itraconazole 400	DB, MC, PG, RCT Patients 18 to 75 years of age with distal subungual or	N=507 72 weeks	Primary: Mycological cure (negative microscopy and cultures)	Primary: Mycological cure rates were 75.7% in the T_{12} group, 80.8% in the T_{16} group, 38.3% in the I_3 group and 49.1% in the I_4 group. Results were statistically significant in favor of the terbinafine regimens (P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day for 1 week every 4 weeks for 12 weeks (group I_3) or 16 weeks (group I_4) vs terbinafine 250 mg daily for 12 weeks (group T_{12}) or 16 weeks (group T_{16})	total dystrophic onychomycosis of the toenails confirmed mycologically		Secondary: Clinical cure (100% toenail clearing), complete cure (mycological and clinical cure), clinical efficacy (mycological cure and at least 5 mm of new clear toenail growth), global assessment of efficacy by patient and physician	Secondary: Clinical cure was 53.6%, 60.2%, 31.8%, and 32.1% for the T_{12}, T_{16}, I_3, and I_4 groups respectively, and all significantly favored the terbinafine regimens (P<0.002). Complete cure rates were 45.8%, 55.1%, 23.4%, and 25.9% for the T_{12}, T_{16}, I_3, and I_4 groups respectively, and all significantly favored the terbinafine regimens (P<0.0007). Clinical efficacy rates significantly favored the terbinafine regimens (P<0.0001). Global assessment of efficacy by patients was very good or excellent in 78.9%, 78.8%, 43.9%, and 52.3% of patients in the T_{12}, T_{16}, I_3, and I_4 groups, respectively, and these assessments statistically favored the terbinafine regimens (P<0.0001). Global assessment of efficacy by physicians was very good or excellent in 78.9%, 78.8%, 43.9%, and 52.3% of patients in the T_{12}, T_{16}, I_3, and I_4 groups, respectively, and these assessments statistically favored the terbinafine regimens (P<0.0001).
Heikkila et al.[105] (2002) Itraconazole 400 mg daily for 1 of every 4 weeks for 12 (3 cycles), or 16 (4 cycles) weeks vs terbinafine 250 mg daily for 12 or 16 weeks	DB, MC, RCT Finnish participants 18 to 75 years of age with a clinical diagnosis of onychomycosis of the toenail confirmed by culture	N=76 4 years	Primary: Mycologic cure (microscopy and culture negative), clinical cure (100% clearing of all toenails), complete cure (mycologic and complete cure) Secondary: Not reported	Primary: At 4 years, terbinafine was shown to be more effective than itraconazole. At 4 years, negative microscopy and culture remained unchanged in the terbinafine group treated for 16 weeks, but fell to <50% in all other groups. At 4 years, clinical and complete cure rates in the terbinafine group treated for 16 weeks was better than the rates seen at 72 weeks (78% compared to 50%), but remained unchanged or worsened in all other groups. Secondary: Not reported
De Backer et al.[106] (1998)	DB, RCT	N=372	Primary: Percentage of	Primary: At week 48, significantly more patients in the terbinafine group had

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Itraconazole 200 mg daily for 12 weeks vs terbinafine 250 mg daily for 12 weeks	Patients 18 years of age and older with clinically suspected subungual dermatophyte infections confirmed by microscopy and culture	48 weeks	patients with negative culture at week 48, length of healthy nail, hyperkeratosis, onycholysis, paronychial inflammation, investigator and patient assessment of efficacy of treatment Secondary: Not reported	negative microscopy results (77.9%) compared to the itraconazole group (55.4%; P<0.0001). At week 48, significantly more patients in the terbinafine group had negative dermatophyte culture results (84%) compared to the itraconazole group (64.3%; P<0.0001). At week 48, significantly more patients in the terbinafine group had negative mycology results (73%) compared to the itraconazole group (45.8%; P<0.0001). At week 48, patients in the terbinafine group had significantly more healthy nail in the big toe compared to the itraconazole group (8.1 and 6.4 mm, respectively; P=0.026). At week 48, onycholysis score significantly favored terbinafine compared to itraconazole (P=0.001). There was no significant difference in hyperkeratosis scores between groups (P=0.27). Paronychial inflammation was absent in the majority of patients in both groups. The global clinical evaluation of the target nail at week 48 was significantly higher in the terbinafine group (cleared or minimal symptoms) compared to the itraconazole group (76.2 and 58.1%, respectively; P=0.001). Secondary: Not reported
De Backer et al.[107] (1996) Itraconazole 200 mg daily for 12 weeks	DB, RCT Patients with a clinical diagnosis of toenail onychomycosis	N=372 48 weeks	Primary: Clinical symptoms, rate of negative mycology (negative microscopy and	Primary: Clinical symptoms in the target nail improved significantly more in the terbinafine group compared to the itraconazole group (P=0.001). The unaffected nail length for big toes was significantly greater in the terbinafine group compared to the itraconazole group (9.1 and 7.7 mm

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs terbinafine 250 mg daily for 12 weeks			negative culture)	respectively; P=0.0298). Onycholysis was less frequent in the terbinafine group compared to the itraconazole group (P=0.001). No significant difference was seen between groups in hyperkeratosis. Negative mycology was observed in 73% of terbinafine patients compared to 45.8% of itraconazole patients at week 48 (P<0.0001).
Arenas et al.[108] (1995) Itraconazole 200 mg daily for 3 months vs terbinafine 250 mg daily for 3 months	CS, OL, PRO Patients 18 years of age and older with onychomycosis	N=53 9 months	Primary: Culture and potassium hydroxide (KOH) smear results, affected nail area, medical evaluation of treatment (cure, improvement, no changes, or deterioration Secondary: Nail changes, nail growth, patient evaluation of treatment	Primary: At the end of treatment, rates of positive KOH smears were similar between groups (21.7% for itraconazole and 23.5% for terbinafine). At the end of treatment, there was 1 positive culture in the terbinafine group; at the end of follow-up, there was 1 positive culture in the itraconazole group. Both treatment groups showed improvement in nail area affected compared to baseline (P<0.01) and there was no significant difference between groups. There was no significant difference between groups in the medical evaluation of treatment. There was no significant difference in cure and improvement between groups. Secondary: There were no significant differences in nail changes or nail growth between groups. There was no significant difference between groups in the patients' evaluation of treatment.
Bahadir et al.[109] (2000) Itraconazole 100	RCT Patients with clinically and	N=60 24 week posttreatment	Primary: Therapeutic response (healing, remission, or	Primary: Healing was achieved in 60% of itraconazole patients and 68.5% of terbinafine patients (P=0.50).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg twice daily for the first week of 3 consecutive months vs terbinafine 250 mg daily for 3 months	mycologically confirmed onychomycosis	follow-up	failure, undefined) Secondary: Not reported	Remission was achieved in 28% of itraconazole patients and 25.7% of terbinafine patients (P=0.50). Failure was reported in 4% of itraconazole patients and 2.85% of terbinafine patients (P=0.50). Secondary: Not reported
Honeyman et al.[110] (1997) Itraconazole 200 mg daily for 4 months vs terbinafine 250 mg daily for 4 months	DB, MC, PG, RCT Patients with toenail onychomycosis	N=179 12 months	Primary: Clinical response (symptom scores), mycological response (negative culture), clinical global evaluation scores, effectively cured patient scores (ECP, defined as complete mycological cure plus clinical improvement or complete cure) Secondary: Not reported	Primary: At the end of treatment, mycological cure was similar for terbinafine and itraconazole (54.9 and 51.8% respectively). At 12 months, the mycological cure was 95.3% for terbinafine and 84.3% for itraconazole (P=0.04). No significant differences in clinical response were observed between groups at month 4 or 12 (P>0.05). There was no significant difference in the CGE at month 4 or 12 between groups when clinical cure was considered, though when clinical improvement was also considered, terbinafine showed significantly better scores (P<0.02). At 4 months, there was no difference in the proportion of patients considered to be ECP, though at 12 months significantly more patients in the terbinafine group were considered ECP (95.3 and 75.7%, respectively; P<0.001). Secondary: Not reported
Brautigam et al.[111] (1995) Itraconazole 200 mg daily for 12 week	MC, RCT Patients with a clinical diagnosis of distal subungual or proximal	N=170 40 week posttreatment follow-up	Primary: Mycological response (negative culture), area of unaffected nail	Primary: Mycological cure rates were 81% in the terbinafine group and 63% in the itraconazole group (P<0.01). The length of unaffected nail increased to 9.4 mm in the terbinafine group and to 7.9 mm in the itraconazole group (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs terbinafine 250 mg daily for 12 weeks	onychomycosis and a growth of dermatophytes			
Tosti et al.[112] (1996) Itraconazole 400 mg daily for 1 week every month (I) vs terbinafine 250 mg daily (T250) vs terbinafine 500 mg daily for 1 week every month (T500)	OL, RCT Patients with onychomycosis of the toenails or fingernails	N=63 6 month posttreatment follow-up	Primary: Mycological response (not cured, cured with residual malformations, cured without residual malformations) Secondary: Not reported	Primary: At the end of the follow-up period, 76.5% of patients in the T250 group were cured without residual malformations compared to 50% in the T500 group and 38.1% in the I group (P=0.013 between T250 and I). At the end of the follow-up period, significantly more patients in the I group were considered cured with residual malformations compared to those in the T250 group (P=0.013). At the end of the follow-up period, significantly more patients in the I group were considered failures compared to those in the T250 group (P=0.013). Secondary: Not reported
Gupta et al.[113] (2013) Itraconazole 200 mg/day for weeks 1 to 4 and terbinafine 250 mg/day for weeks 3 to 6 (2-week overlap of itraconazole and terbinafine) (COMBO)	PRO, SB Patients with toenail onychomycosis caused by dermatophytes mycologically cured at 48 weeks after the beginning of therapy based on a last observation carry forward analysis and both	N=106 1.25 to 7 years	Primary: Proportions of participants with mycologic recurrence and recurrence (clinical and/or mycologic) at a post–week 48 visit Secondary: Not reported	Primary: Mycologic recurrence was found to occur in 43% (46 of 106) of all subjects. Mycologic recurrence rates were similar for the CTERB (32%) and TOT (36%) regimens, as well as for the III (59%) and the COMBO (57%) regimens. About half (22 of 43; 51%) of the participants completely cured had recurrence post–week 48. The recurrence rates for complete cure by regimen were similar and ranged from 40 (CTERB) to 67% (COMBO). Similar recurrence rates were generally obtained when participants who received booster therapy were excluded from the analyses. However, the mycologic recurrence rates for CTERB (21%) and III (46%) were lower

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs Continuous terbinafine 250 mg/day for 12 weeks (CTERB) vs Intermittent terbinafine (250 mg/day for 4 weeks on, 4 weeks off, 4 weeks on) (TOT) vs Pulsed itraconazole (one pulse = 200 mg twice daily for 7 days on, 21 days off) for three pulses (III)	clinically and mycologically assessed after week 48			when the participants requiring booster were excluded. No statistically significant difference was detected between the four treatment groups. Secondary: Not reported
Chang et al.[114] (2007) Itraconazole, fluconazole, terbinafine (with or without topical agents)	MA Patients aged ≥18 years with superficial dermatophytosis (tinea pedis, tinea manus, tinea corpora, and tinea cruris) or	N=19,298 (122 trials) Variable duration	Primary: Cumulative incidence of patients who withdrew from the study because of adverse reactions Secondary: Cumulative	Primary: For continuous oral antifungal therapy, the pooled risks of treatment discontinuation because of adverse reactions were 3.44% (95% CI, 2.28 to 4.61%) for terbinafine 250 mg/day; 1.96% (95% CI, 0.35 to 3.57%) for itraconazole 100 mg/day; 4.21% (95% CI, 2.33 to 6.09%) for itraconazole 200 mg/day; and 1.51% (95% CI, 0 to 4.01%) for fluconazole 50 mg/day. For intermittent or pulse therapy, the pooled risks of treatment discontinuation because of adverse reactions were 2.09% (95% CI, 0 to 4.42%) for terbinafine; 2.58% (95% CI, 1.15 to 4.01%) for itraconazole;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	onychomycosis who were receiving oral antifungal therapy for 2 or more weeks		incidence of patients stopping treatment because of elevation of serum transaminase levels and cumulative incidence of patients developing elevation of serum transaminase levels during treatment but not requiring discontinuation	1.98% (95% CI, 0.05 to 3.92%) for fluconazole 150 mg/week and 5.76% (95% CI, 2.42 to 9.10%) for fluconazole 300 to 450 mg/week. Secondary: The incidence of liver injury associated with oral antifungal therapy was less than 2% in general. For the risks of having elevated serum transaminase levels that required treatment termination, the pooled risk estimates for continuous therapy ranged from 0.11% (itraconazole 100 mg/day) to 1.22% (fluconazole 50 mg/day). The pooled risk estimates for pulse therapy ranged from 0.39% (fluconazole 150 mg/week and itraconazole 400 mg/day) to 0.85% (fluconazole 300 to 450 mg/week). The pooled risks of developing elevated serum transaminase levels not requiring treatment discontinuation was on the order of 1.5% for continuous regimens and 1% for intermittent regimens evaluated.
Empirical Therapy				
Marr et al.[115] (2000) Fluconazole 400 mg daily for 75 days after bone marrow transplant (BMT) vs placebo	DB, PC, RCT Patients 11 to 65 years of age who were autologous or allogeneic bone marrow transplant recipients	N=300 8 years	Primary: Mortality, cause of death, incidence of invasive fungal infections early (<100 days) and late (>100 days) after BMT Secondary: Not reported	Primary: Survival was significantly better for fluconazole compared to placebo (P=0.0001). The survival benefit of fluconazole was significant for patients receiving allogeneic grafts (P=0.0018) but not for those receiving autologous grafts (P=0.60). The overall incidence of invasive candidiasis was increased in patients in the placebo group compared to the fluconazole group (P<0.001). More patients in the placebo group died of invasive candidiasis early and late after BMT (P<0.0068). The incidence of severe graft vs host disease (GVHD) of the gut was significantly higher in the placebo group (P=0.02). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Slavin et al.[116] (1995) Fluconazole 400 mg daily vs placebo	DB, PC, RCT Patients >12 years of age and >34 kg undergoing autologous or allogeneic bone marrow transplantation	N=300 110 days post-transplant	Primary: Incidence of systemic fungal infections, incidence of superficial fungal infections, incidence of fungal colonization, incidence of empiric amphotericin B use, survival Secondary: Not reported	Primary: Systemic fungal infections occurred in 7% of fluconazole patients and 18% of placebo patients (P=0.004). No cases of *Candida albicans* infections were seen in the fluconazole group compared to 18 cases in placebo patients (P<0.001). Significantly fewer patients in the fluconazole group experienced superficial fungal infections (P<0.001) and fungal colonization (P=0.037). Significantly fewer patients in the fluconazole group required empiric amphotericin B therapy (P=0.005). Significantly fewer deaths occurred in fluconazole patients up to 110 days posttransplant compared to placebo patients (P=0.004). Secondary: Not reported
Bodey et al.[117] (1990) Fluconazole 50 mg daily vs placebo	DB, PC, RCT Patients with a diagnosis of lymphoma, melanoma, sarcoma, breast carcinoma, or bronchogenic carcinoma	N=146 End of hospitalization or 4 weeks	Primary: Development of oral candidiasis Secondary: Not reported	Primary: Oropharyngeal candidiasis developed in 2% of patients receiving fluconazole and 28% receiving placebo (P=0.0003). Secondary: Not reported
Benjamin et al.[118] (2014) Fluconazole (6 mg/kg of body weight) vs placebo	DB, PC, RCT Premature infants weighing <750 grams at brith	N=361 Treatment for 42 days, evaluations at 18 to 22 months	Primary: Composite of death or definite or probable invasive candidiasis prior to study day 49 (one week after completion of study drug)	Primary: Among infants receiving fluconazole, the composite primary end point of death or invasive candidiasis was 16% (95% CI, 11 to 22) vs 21% in the placebo group (95% CI, 15 to 28; OR, 0.73 [95% CI, 0.43 to 1.23]; P=0.24). Invasive candidiasis occurred less frequently in the fluconazole group (3% [95% CI, 1 to 6]) vs the placebo group (9% [95% CI, 5 to 14]; P=0.02). Secondary: The cumulative incidences of secondary outcomes were not statistically

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: Safety outcomes	different between groups.
MacMillan et al.[119] (2002) <u>Phase 1</u> Fluconazole 400 mg daily (high dose) until neutrophil engraftment (or 6 mg/kg/day for patients weighing <40 kg) vs fluconazole 200 mg daily (low dose) until neutrophil engraftment (or 3 mg/kg/day for patients weighing <40 kg) Engrafted, non-neutropenic patients with no active fungal infection went on to phase 2. <u>Phase 2</u> Fluconazole 100 mg daily (or 1.5 mg/kg/day if <40	RCT Patients 2 to 67 years of age who were bone marrow transplantation recipients	N=253 2 week posttreatment follow-up	Primary: Incidence of fungal infection during early and maintenance prophylaxis Secondary: Not reported	Primary: During early prophylaxis, 16% of high-dose patients and 18% of low-dose patients had a post-surveillance culture that was positive for yeast (P=0.35). Superficial fungal infections developed in 16% of the high-dose patients and 18% of the low-dose patients (P=0.66). Systemic fungal infections occurred in 8% of the high-dose patients and 2% of the low-dose patients (P=0.06). There was no significant difference between the low- and high-dose groups in the incidence of systemic candidiasis or aspergillosis (P>0.08). Early prophylaxis was discontinued in 60% of high-dose patients and 59% of low-dose patients (P>0.80).There was no significant difference in clinical outcomes between groups (P=0.57). There was no significant difference between groups in rates of fungal colonization at any time during the maintenance prophylaxis (P>0.58). There was no significant difference between groups in survival after maintenance prophylaxis. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
kg) until 100 days posttransplant vs clotrimazole troches 10 mg 4 times daily until 100 days posttransplant				
Johansen et al.[120] (2002) Fluconazole IV/oral at various doses vs amphotericin B IV/oral at various doses	MA Patients with cancer complicated by neutropenia	N=3,798 (17 trials) Variable duration	Primary: Mortality, invasive fungal infections, colonization, use of additional antifungal therapy, adverse effects leading to discontinuation Secondary: Not reported	Primary: No significant difference was observed between fluconazole and amphotericin B with regards to mortality (P>0.1). No significant difference was observed between fluconazole and amphotericin B on the rate of invasive fungal infection (P>0.4). No significant difference was observed between fluconazole and amphotericin B on fungal colonization (P>0.3). No significant difference was observed overall between groups in the use of additional antifungal therapy (P>0.1). Significantly more patients receiving amphotericin B dropped out of the study due to adverse effects (P<0.009). Secondary: Not reported
Gotzsche et al.[121] (2002) Fluconazole IV/oral at various doses vs	MA Patients with cancer and neutropenia from chemotherapy or bone marrow transplants	N=4,155 (31 trials) Variable duration	Primary: Mortality Secondary: Invasive fungal infections, colonization, use of additional antifungal therapy	Primary: No significant differences were observed between group on mortality (P>0.08). Secondary: Invasive fungal infections decreased significantly with amphotericin B, fluconazole, and itraconazole (P<0.04) but not with miconazole or ketoconazole (P>0.2).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
amphotericin B IV/oral at various doses vs amphotericin B liposome IV at various doses vs ketoconazole orally at various doses vs itraconazole orally at various doses vs miconazole orally at various doses vs placebo				Definitions of fungal colonization differed greatly between studies, though the effect of prophylaxis on colonization was significant for amphotericin B, fluconazole, itraconazole, and ketoconazole (P<0.02) but not for miconazole (P=0.8) Significantly more patients who received placebo or no treatment required additional antifungal therapy.
Ito et al.[122] (2007) Fluconazole 200 mg orally once daily vs	MC, RCT Adult patients with acute myeloid leukemia (AML) or myelodysplastic syndromes (MDS), receiving	N=218 4 weeks	Primary: Frequency of systemic fungal infections Secondary: Not reported	Primary: Among the evaluable patients, 64 (62.1%) of 103 episodes in the itraconazole group developed febrile neutropenia, compared to 73 (68.9%) of 106 episodes in the fluconazole group. In 21 (20.4%) of 103 episodes in the itraconazole group and 20 (18.9%) of 106 episodes in the fluconazole group, intravenous antifungal drugs were empirically used instead of discontinuing the prophylactic use of oral

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
itraconazole 200 mg orally once daily	conventional chemotherapy as remission-induction or consolidation therapy			antifungals. According to the diagnostic criteria, 4 possible and no probable cases of systemic fungal infection were noted in the itraconazole group, and 8 possible and 3 probable cases were seen in the fluconazole group. There were no cases of proven systemic fungal infection in either group. In patients receiving remission-induction therapy, probable and possible systemic fungal infections were found in 2 (4.9%) of 41 episodes in the itraconazole group, and 7 (15.9%) of 44 episodes were found in the fluconazole group. The numbers of patients who received consolidation therapy were similar in the 2 groups. Among patients with MDS, there was no episode (0%) of probable or possible systemic fungal infection among 15 episodes in the itraconazole group, whereas 3 episodes (23.1%) of possible infection were noted among 13 episodes in the fluconazole group. In patients with AML, no difference between the 2 groups in the development fungal disease was found. Secondary: Not reported
Ullmann et al.[123] (2007) Fluconazole 400 mg orally once daily vs posaconazole 200 mg three times daily	DB, MC, PG, RCT Patients ≥13 years of age, having undergone allogeneic hematopoietic stem cell transplantation and either acute or chronic extensive graft-vs-host disease (GVHD)	N=600 112 days	Primary: Incidence of proven or probable invasive fungal infections Secondary: Incidence of proven or probable aspergillosis, incidence of breakthrough proven or probable invasive fungal	Primary: At 112 days, posaconazole was found to be as effective as fluconazole in preventing all invasive fungal infections (incidence, 5.3 and 9.0%, respectively; OR, 0.56; 95 % CI, 0.30 to 1.07; P=0.07). Secondary: Posaconazole was more effective than fluconazole in preventing proven or probable invasive aspergillosis (2.3 vs 7.0%, respectively; OR, 0.31; 95% CI, 0.13 to 0.75; P=0.006). There were fewer breakthrough invasive fungal infections in the posaconazole group compared to fluconazole (2.4 vs 7.6%, respectively; P=0.004), particularly for invasive aspergillosis (1.0 vs 5.9%; P=0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			infections, mortality, and incidence of adverse events	Overall mortality was similar in the two groups, but the number of deaths from invasive fungal infections was lower in the posaconazole group (1%) compared to the fluconazole group (4%; P=0.046). The incidence of treatment-related adverse events was similar in the two groups (36% in the posaconazole group and 38% in the fluconazole group), and the rates of treatment-related serious adverse events were 13% and 10% in the posaconazole and fluconazole treatment groups, respectively.
Day et al.[124] (2013) Amphotericin B IV (1 mg/kg/day) for 4 weeks (Group 1) vs amphotericin B deoxycholate (1 mg/kg/day) combined with oral flucytosine (100 mg/kg/day in 3 to 4 divided doses) for 2 weeks (Group 2) vs amphotericin B deoxycholate (1 mg/kg/day) combined with oral fluconazole (400 mg twice	OL, RCT Patients >14 years of age with HIV and signs and symptoms consistent with cryptococcal Meningitis, as well as a lab test indicative of *Cryptococcus*	N=299 6 months	Primary: All cause mortality in the first 14 and 70 days after randomization Secondary: Mortality at 6 months, disability status at 70 days and at 6 months, changes in CSF fungal counts in the first 2 weeks after randomization, time to CSF sterilization, and adverse events during the first 10 weeks of the study	Primary: By day 70, a total of 44 patients treated with amphotericin B monotherapy had died, as compared with 30 patients treated with amphotericin B and flucytosine and 33 patients treated with amphotericin B and fluconazole. Treatment with amphotericin B and flucytosine was associated with a significantly reduced hazard of death by day 70 in the intention-to-treat analysis (HR, 0.61; 95% CI, 0.39 to 0.97; P=0.04); this benefit was maintained in the per-protocol analysis and after adjustment for predefined baseline covariates. Fewer patients receiving combination therapy with high-dose fluconazole died, as compared with those treated with amphotericin B monotherapy, but this finding was not significant (HR, 0.71; 95% CI, 0.45 to 1.11; P=0.13). Secondary: The survival benefit seen for patients receiving amphotericin B and flucytosine, as compared with those receiving amphotericin B monotherapy, was more marked at six months (HR, 0.56; 95% CI, 0.36 to 0.86; P=0.01). Treatment with amphotericin B and fluconazole did not confer a survival advantage, as compared with monotherapy. Patients receiving amphotericin B and flucytosine had a significantly higher chance of being free of disability at six months, as compared with those receiving monotherapy (OR, 2.01; 95% CI, 1.04 to 3.88; P=0.04). The time to fungal clearance was significantly shorter in patients receiving amphotericin B plus flucytosine than in those receiving amphotericin B alone or in combination with fluconazole, with more rapid rates of decline in the colony count (P<0.001 for both comparisons).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
daily) for 2 weeks (Group 3) each treatment was followed by fluconazole (400 mg/day) to achieve a 10-week treatment course				Adverse events occurred with similar frequency among all the treatment groups.
Hiramatsu et al.[125] (2008) Fluconazole 400 mg IV daily vs micafungin 150 mg IV daily Patients received treatment within 48 hours of the transplant-related conditioning regimen.	RCT, OL Adult patients with a hematological malignancy who were undergoing high-dose combination chemotherapy with autologous or allogeneic hematopoietic stem cell transplantation	N=104 4-week posttreatment follow-up	Primary: Treatment success (defined as the absence of proven, probable, or suspected systemic fungal infection through the end of prophylaxis and as the absence of a proven or probable systemic fungal infection through the end of the 4-week posttreatment period) Secondary: Not reported	Primary: The overall treatment success rate for patients in the micafungin arm was comparable to that in the fluconazole arm (94.0 and 88.0%, respectively; 95% CI, -5.4 to 17.4; P=0.295). Suspected invasive fungal infections were reported to occur in 4% of patients in the micafungin arm and 12% of patients in the fluconazole arm (P=0.14). More fluconazole-treated patients received empirical antifungal therapy compared to micafungin-treated patients during the post-treatment period only (12.0 vs 4.0%; P=0.14), although there was no significant difference. In total, 4.0% of micafungin-treated patients and 1.0% of fluconazole-treated patients died during course of the study. None of the deaths were related to the study drug. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Aydemir et al.[126] (2011) Fluconazole 3 mg/kg every 3 days vs nystatin 100,000 units every 8 hours vs placebo	RCT Very-low birth weight infants admitted to the neonatal intensive-care unit	N=278 Treatment from birth to day 30 (or 45 if <1,000 g at birth)	Primary: Prevention of fungal colonization and infection Secondary: Incidence of bacterial sepsis, necrotizing enterocolitis, threshold retinopathy of prematurity requiring surgery, severe intraventricular hemorrhage, bronchopulmonary dysplasia and mortality	Primary: Fungal colonization occurred less frequently in the fluconazole (10.8%) and nystatin (11.7%) groups than in the control group (42.9%; P<0.001). Invasive fungal infection was less frequent in the fluconazole (3.2%) and nystatin groups (4.3%), as compared to in the control group (16.5%; P<0.001). Secondary: There were no significant differences in secondary outcomes. No serious adverse effects of the fluconazole or nystatin therapy were documented.
Vehreschild et al.[127] (2009) Itraconazole vs caspofungin Study medications were dosed at the physician's discretion.	OBS Neutropenic patients with cancer and invasive fungal disease (IFD)	N=77 Variable duration	Primary: Evidence of IFD and mortality Secondary: Not reported	Primary: The incidence of breakthrough IFD after secondary prophylaxis was similar in both groups (32.1 and 31.9%). A trend towards fewer proven or probable breakthrough IFD events in the itraconazole group was not significant (29 and 17%). Overall survival favored the itraconazole group, but this trend was not significant (75 and 89%). Death was attributed to IFD in 3.6% of patients receiving caspofungin and 4.3% of patients in the itraconazole group. Secondary: Not reported
Sánchez-Ortega et al.[128]	OBS	N=49	Primary: Incidence of	Primary: The cumulative incidence of breakthrough proven or probable IFD during

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2011) Itraconazole 200 mg IV/PO BID for 2 days, then 200 mg daily vs posaconazole 200 mg PO TID	Adult patients receiving antifungal prophylaxis for a first allogeneic bone marrow transplant	100 days	probable or proven breakthrough invasive fungal disease (IFD) Secondary: Probabilities of FFS and OS	the 100-day study period was significantly lower in patients receiving posaconazole prophylaxis than in patients receiving itraconazole (0 vs 12%; P=0.04). Secondary: Patients receiving posaconazole had a significantly higher FFS (91 vs 56%; P=0.003) and OS (91 vs 63%; P=0.011) than patients who received itraconazole.
Cornely et al.[129] (2007) Posaconazole 200 mg orally three times daily vs fluconazole 400 mg orally once daily or itraconazole 200 mg orally twice daily Patients unable to tolerate the oral study drug could receive IV prophylaxis at the same dose for ≤3 days per chemotherapy cycle.	MC, RCT Patients ≥13 years of age with acute myelogenous leukemia or the myelodysplastic syndrome and anticipated neutropenia resulting from remission-induction chemotherapy	N=602 12 weeks	Primary: Incidence of proven or probable invasive fungal infections during the prophylactic treatment phase Secondary: Incidence of invasive aspergillosis, incidence of invasive fungal infection within 100 days after randomization, survival, and adverse events	Primary: Invasive fungal infections were reported in 2% of patients in the posaconazole group and 8% of patients in the fluconazole or itraconazole groups (95% CI, –9.7 to –2.5; P<0.001). Secondary: Significantly fewer patients in the posaconazole group had invasive aspergillosis as compared to patients receiving fluconazole or itraconazole (1 vs 7%, respectively; P<0.001). During the 100-day period after randomization, 14 of 304 patients (5%) in the posaconazole group had a proven or probable fungal infection, as compared to 33 of 298 patients (11%) in the fluconazole or itraconazole group (P=0.003). The mean (±SD) time to invasive fungal infection was 41±26 days in the posaconazole group and 25±26 days in the fluconazole or itraconazole group (P=0.003). Of the 304 patients in the posaconazole group, 49 (16%) died during the study period, as did 67 of 298 patients (22%) in the fluconazole or itraconazole group (P=0.048); 44 patients (14%) and 64 patients (21%), respectively, died within 100 days. Survival was significantly longer among recipients of posaconazole than among recipients of fluconazole or itraconazole (P=0.04).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Serious adverse events related to treatment were reported by 19 patients (6%) in the posaconazole group and 6 patients (2%) in the fluconazole or itraconazole group (P=0.01). The most common treatment-related adverse events in both groups were gastrointestinal disturbances.
Mandhaniya et al.[130] (2011) Voriconazole 6 mg/kg/dose for 2 doses, then 4 mg/kg/dose BID vs amphotericin B 0.5 mg/kg/day 3 times per week	RCT, OL, SC Pediatric patients with acute lymphocytic leukemia or acute myeloid leukemia undergoing induction chemotherapy	N=100 Variable duration	Primary: Failure of antifungal prophylaxis and completion of antifungal protocol Secondary: Not reported	Primary: In the voriconazole arm, 28% of patients failed antifungal prophylaxis compared to 34% of patients in the amphotericin arm (P=0.66). There was no significant difference in the proven, possible, or probable fungal infections in the two study arms. There was a significant increase in adverse events in the amphotericin arm (P<0.01). Secondary: Not reported
Wingard et al.[131] (2010) Voriconazole was 200 mg twice daily vs fluconazole 400 mg once daily	RCT, DB, MC Patients ≥2 years of age undergoing allogeneic hematopoietic cell transplantation after a myeloablative conditioning regimen receiving human leukocyte antigen-matched hematopoietic grafts	N=600 180 days	Primary: Fungal-free survival (FFS) at 180 days posttransplant Secondary: Incidence of IFIs, time to IFI, 6-month and 1-year relapse-free survival (RFS) and OS, frequency, time to, and duration of empiric antifungal therapy, frequency of severe adverse events, and	Primary: FFS rates were similar at 180 days: 75 and 78% for fluconazole and voriconazole, respectively (P=0.49). FFS rates were similar at 12 months: 65 and 64% for fluconazole and voriconazole, respectively (P=0.95). Secondary: The cumulative incidence rates of IFIs (proven, probable, and presumptive) were 11.2 and 7.3% for fluconazole and voriconazole, respectively at 180 days (P=0.12). The cumulative incidence rates of IFIs were 13.7 and 12.7% for fluconazole and voriconazole, respectively at 12 months (P=0.59). There was no difference in other outcomes between the two treatments.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			incidence of acute and chronic GVHD	
Mattiuzzi et al.[132] (2011) Voriconazole 400 mg IV every 12 hours for 2 doses, followed by 300 mg every 12 hours vs itraconazole 200 mg IV BID for 2 days, followed by 200 mg IV daily	OL, RCT, SC Adults with newly diagnosed acute myeloid leukemia or high-risk myelodysplastic syndrome undergoing first-line induction therapy or first salvage therapy	N=127 Up to 42 days	Primary: Completion of prophylaxis without the development of invasive fungal infection (IFI); mortality Secondary: Not reported	Primary: None of the patients receiving voriconazole developed proven or probable IFI, whereas two (4%) of the patients receiving itraconazole developed IFI (P=0.17). Six patients (8.4%) in the voriconazole group and 6 patients (11.5%) in the itraconazole group died during the study period (P=0.792). Secondary: Not reported
Marks et al.[133] (2011) Voriconazole 6 mg/kg IV every 12 hours for 1 day, then 200 mg orally twice daily vs itraconazole 200 mg IV every 12 hours for 2 days, then 200 mg orally twice daily Study medications were given for 100 to 180 days.	OL, MC, RCT Patients ≥12 years of age and received sibling or unrelated donor allogeneic hematopoietic cell transplantation for acute leukemia, myelodysplasia, transformed chronic myeloid leukemia, or failed lymphoma therapy	N=489 1 year	Primary: Success of prophylaxis, tolerability, survival to day 180 without proven/probable invasive fungal infections (IFI) Secondary: Not reported	Primary: Success of antifungal prophylaxis at day 180 was demonstrated in 48.7% of voriconazole patients and 33.2% of itraconazole patients (95% CI, 7.7 to 25; P=0.0002). At day 100, the adjusted difference in success of prophylaxis was 15.4% (95% CI, 6.6 to 24.2; P<0.01) favoring voriconazole (54.0 vs 39.8%, respectively). The difference in success rates between treatments did not vary across randomization strata (day 100, P=0.29; day 180, P=0.41). The proportion of patients who completed ≥100 days of study drug prophylaxis was 53.6% for voriconazole vs 39.0% for itraconazole (95% CI of difference, 5.6 to 23.5; P<0.01). Median total durations of study drug treatment were 96 and 68 days respectively (P<0.01). The most common treatment-related adverse events were vomiting (16.6%), nausea (15.8%) and diarrhea (10.4%) for itraconazole, and hepatotoxicity/liver function abnormality (12.9%) for voriconazole. More itraconazole patients received other systemic antifungals (41.9 vs 29.9%; P<0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Kaplan–Meier estimates of survival at day 100 (91.9% for voriconazole, 92.3% for itraconazole) and day 180 (81.9% for voriconazole, 80.9% for itraconazole) were similar. One-year survival rates were 73.5% and 67.0% for voriconazole and itraconazole respectively (P=0.17; log-rank test). The hazard ratio for death in the voriconazole group compared to the itraconazole group was 0.79 (95% CI, 0.56 to 1.11). A total of 1.3% of voriconazole patients developed a proven or probable IFI during the study period, compared to 2.1% of itraconazole patients (95% CI, 3.1 to 1.6; P=0.54). Secondary: Not reported
Huang et al.[134] (2012) Itraconazole 5 mg/kg/day PO vs micafungin 50 mg/day IV	MC, OL, PG, RCT Adult neutropenic patients undergoing hematopoietic stem cell transplants	N=287 10 weeks	Primary: Treatment success (proven, probable, or suspected invasive fungal infection through therapy and the absence of proven or probable invasive fungal infection through the end of four weeks after therapy) Secondary: Invasive fungal invasions throughout the study period and safety measures	Primary: There were no statistically significant or clinically meaningful differences between treatments in the rate of patients without proven, probable, or suspected invasive fungal infection during prophylactic antifungal treatment and without proven or probable invasive fungal infection after completion of prophylactic treatment (P=0.48). This demonstrates the noninferiority of micafungin over itraconazole. Secondary: Tolerability of treatment was better in the micafungin group, with more patients in that group completing the study (82.9 vs 67.3%) and a significantly lower incidence of premature study withdrawal due to an unacceptable toxicity (0.7 vs 19.7%; P=0.00, chi-square test) occurring in micafungin treated vs itraconazole-treated patients. Adverse events were reported in significantly fewer patients in the micafungin than in the itraconazole group. There was also a significant difference in the rate of investigator-identified, drug-related adverse events, which was 8.0% in micafungin treated patients (11 of 137 patients) and 26.5% in itraconazole-treated patients (39 of 147 patients; P=0.000, chi-square test).
Chaftari et al.[135] (2012)	OL, PRO, RCT Hematopoietic	N=40 6 weeks	Primary: incidence of invasive fungal	Primary: For the efficacy analysis, one patient in the ABLC arm and none in the posaconazole arm developed a definite invasive fungal infection (5 vs 0%;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Posaconazole 200 mg PO 3 times daily vs amphotericin B lipid complex (ABLC) 7.5 mg/kg IV once weekly	Stem cell transplant patients		infections and drug-related toxicities Secondary: Not reported	P=0.48). The rate of adverse event that led to the discontinuation of the drug was significantly higher in the ABLC arm compared with the posaconazole arm: 15 of 19 in ABLC vs 8 of 20 in posaconazole (P=0.009). There was a significantly lower creatinine clearance reached during the study in the ABLC group compared with the posaconazole group (46 mL/min [range, 33 to 81 mL/min] vs. 74 mL/min [range, 34 to 129 mL/min]; P=0.006). More patients in the ABLC arm doubled their serum creatinine level to abnormal ranges (10 vs one; P=0.001), which necessitated the discontinuation of the study drug according to the protocol. The study was stopped earlier because of the results of the interim data analysis suggesting that there was more than a 70% chance that the nephrotoxicity rate of the ABLC group was higher than 50%. Secondary: Not reported
Chabrol et al.[136] (2010) Voriconazole or caspofungin as primary prophylaxis vs no prophylaxis	RETRO Patients receiving first induction chemotherapy for AML of ALL	N=257 Variable duration	Primary: Cumulative incidence of invasive aspergillosis (IA) Secondary: Overall survival, survival at 100 days after chemotherapy, IA-specific survival, mean duration of hospitalization, cumulative incidence of adverse events	Primary: The cumulative incidence of IA was significantly lower in the prophylaxis group than in the non-prophylaxis group (4.5 and 12.4%, respectively; P=0.04). Secondary: The 3-month mortality rate was 28%. The median overall survival of patients with IA was significantly shorter than in patients without IA (215 vs 782 days; P=0.0008). There was no significant difference in 100-day survival between the two groups (83% in the prophylaxis group and 82% in the non-prophylaxis group). The 1-year survival rate was 53% in the prophylaxis group and 65% in the non-prophylaxis group (P=NS).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Shang et al.[137] (2012) Voriconazole loading dose of 6 mg/kg every 12 hours on the first day and maintenance dose of 4 mg/kg every 12 hours from the second day IV vs micafungin 100 or 150 mg/day IV	MC, OL, PRO, RCT Renal transplant recipients with invasive fungal infections	N=65 Variable duration	Primary: Efficacy and adverse events of the two treatments Secondary: Not reported	Primary: Fungal infection within one to three months after transplant was 83.6% (26/31) and 85.3% (29/34) in the micafungin and voriconazole groups, respectively. There was no significant difference between the two groups in terms of efficacy, survival beyond 10 days, and discontinuation of treatment because of lack of efficacy (P>0.05). Mortality rates in the micafungin and voriconazole groups were 9.7% (3/31) and 12.1% (4/33), respectively. Rates of adverse effects in the two groups were 41.9% and 51.6% (P>0.05), respectively. Secondary: Not reported
Clarkson et al.[138] (2007) Medications absorbed from the gastrointestinal (GI) tract (fluconazole, ketoconazole, itraconazole) vs medications partially absorbed from the GI tract (miconazole, clotrimazole)	MA Patients with cancer receiving chemotherapy, radiation, or both	N=4,226 (28 trials) Variable duration	Primary: Prevention of oral candidiasis Secondary: (If available) relief of pain, amount of analgesia, relief of dysphagia, incidence of systemic infection, duration of hospital stay, cost of oral care, patient quality of life, death, use of empirical antifungal therapy, toxicity,	Primary: Drugs absorbed or partially absorbed from the GI tract were found to significantly decrease the incidence of oral candidiasis compared to non-absorbed drugs (P<0.016). Drugs absorbed or partially absorbed from the GI tract were found to significantly decrease the incidence of oral candidiasis compared to placebo or no treatment (P<0.004). Secondary: Significantly fewer patients who were treated with drugs absorbed from the GI tract required empiric antifungal therapy compared to placebo or no treatment (P=0.04). This effect was not seen in patients treated with drugs which are partially absorbed (P=0.4). This outcome was not analyzed in any study on non-absorbable drugs. No significant differences were observed between groups in any other secondary endpoint.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs medications not absorbed from the GI tract (amphotericin B, nystatin, chlorhexidine, thymostimulin, natamycin, norfloxacin) vs placebo or no treatment			compliance	
Tinea Capitis				
González et al.[139] (2007) Terbinafine, itraconazole, fluconazole, ketoconazole, griseofulvin	MA Children <18 years of age with tinea capitis confirmed by microscopy or growth of dermatophytes in culture or both	N=1,812 (21 trials) 6 to 26 weeks	Primary: The proportion of participants with complete cure (clinical and mycological) Secondary: Not reported	Primary: <u>Terbinafine vs griseofulvin:</u> A pooled analysis of the five trials found that the difference in the cure rates between four weeks of terbinafine and eight weeks griseofulvin was not statistically significant (RR, 1.11; 95% CI, 0.96 to 1.29). <u>Itraconazole vs griseofulvin:</u> In the pooled analysis, there was no significant difference in cure rates between itraconazole and griseofulvin (RR, 0.94; 95% CI, 0.80 to 1.09). <u>Itraconazole vs terbinafine:</u> In the pooled analysis, there was no significant difference in cure rates between itraconazole and terbinafine (as treatment of *Trichophyton* species) when used for periods of two to three weeks (RR, 0.93; 95% CI, 0.72 to 1.19). <u>Ketoconazole vs griseofulvin:</u> In the pooled analysis, there was no significant difference in cure rates between ketoconazole and griseofulvin (RR, 0.72; 95% CI, 0.50 to 1.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Fluconazole vs griseofulvin: In the pooled analysis, there was no significant difference in cure rates between fluconazole and griseofulvin (RR, 0.92; 95% CI, 0.80 to 1.05). Fluconazole vs terbinafine: In one study, the cure rates were found to be similar between fluconazole and terbinafine (RR, 0.87; 95% CI, 0.75 to 1.01). Fluconazole vs itraconazole: In one study, the cure rates were found to be similar between fluconazole and itraconazole (RR, 1.00; 95% CI, 0.83 to 1.20). Secondary: Not reported
Grover et al.[140] (2012) Fluconazole 6 to 8 mg/kg administered weekly for 6 weeks vs griseofulvin 15 to 20 mg/kg/day administered in two doses per day for 6 weeks vs terbinafine 3 to 5 mg/kg/day for two weeks	OL, PRO Children aged ≤12 years with tinea capitis confirmed on microscopic examination	N=75 Variable duration	Primary: Clinical cure Secondary: Not reported	Primary: Cure rates of 96, 88, and 84% were achieved with griseofulvin, terbinafine, and fluconazole, respectively. Overall, seven patients required prolonged therapy. No side effects to therapy were seen. Griseofulvin remains the drug of choice in the treatment of tinea capitis. Terbinafine was the second best agent and offered the advantage of a shorter course of therapy. Fluconazole had comparatively low cure rates but was easier to administer than the other two medications. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Treatment in each group could be prolonged				
Shemer et al.[141] (2013) fluconazole 4 mg/kg/day vs fluconazole 6 mg/kg/day vs griseofulvin 15 mg/kg/day vs griseofulvin 25 mg/kg/day	CS Children with tinea capitis with positive fungal cultures (average age 4.2 years)	N=113 Up to 12 weeks	Primary: Efficacy and safety Secondary: Not reported	Primary: The lower doses for both griseofulvin and fluconazole required significantly longer treatment duration until mycological cure than the higher doses, independent of the fungus type. Both drugs were well tolerated, although patients treated with the high dose of fluconazole had minor gastrointestinal complaints. No significant abnormal routine laboratory tests were noted during the study.
Miscellaneous Infections				
Anaissie et al.[142] (1996) Fluconazole 400 mg daily IV for 5 days, then orally thereafter vs amphotericin B 25 to 50 mg daily IV	MC, PRO, RCT Patients 13 years of age and older with documented or presumed fungal infections	N=164 End of therapy	Primary: Response rates (response= disappearance of all clinical and laboratory indicators of infection), survival rates, adverse events Secondary:	Primary: Overall response rates were not significantly different between groups (P>0.26). Median time to defervescence was 5 days in both groups. Median duration of therapy was not statistically different between groups (P=0.80). There were no significant differences in survival rates between groups The incidence of adverse events was significantly higher in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(non-neutropenic patients) or 0.67 mg/kg/day (neutropenic patients)			Not reported	amphotericin B group compared to the fluconazole group (P<0.0001). Secondary: Not reported
Violaris et al.[143] (2010) Fluconazole 4 mg/kg/day vs nystatin suspension 100,000 units every 6 hours	RCT Pre-term, very low birth weight infants 3 to 7 days old admitted to the neonatal intensive-care unit	N=80 Treatment started during first week of life and continued until full oral feedings attained	Primary: Incidence of systemic fungal infection (SFI) Secondary: Not reported	Primary: SFI developed in 2 infants (5.3%) in the fluconazole group and 6 infants (14.3%) in the nystatin group (RR, 0.37; 95% CI, 0.08 to 1.72). There was a significant difference in mortality between groups (fluconazole, 0 deaths; nystatin, 6 deaths; P=0.03). Secondary: Not reported
van't Wout et al.[144] (1991) Itraconazole 200 mg orally twice daily vs amphotericin B 0.6 mg/kg/day IV Some patients treated with amphotericin B also received flucytosine at 150 mg/kg/day. In these cases, the amphotericin B	MC, RCT Neutropenic patients with proven or highly suspected fungal infections	N=40 Duration of therapy (up to 104 days)	Primary: Response to therapy (at least 50% decrease in size of initial site or severity of infection or resolution of all signs of infection) Secondary: Not reported	Primary: Response to treatment was observed in 63% of itraconazole patients and 56% of amphotericin B patients (P>0.90). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
dose was 0.3 mg/kg/day.				
Shikanai-Yasuda et al.[145] (2002) Itraconazole 50 mg to 100 mg daily for 4 to 6 months vs ketoconazole 200 mg to 400 mg daily for 4 to 6 months vs sulfadiazine 100 mg to 150 mg/kg/day for 4 to 6 months	RCT Patients with active para-coccidioidomycosis	N=42 10 months	Primary: Clinical response to therapy, serologic response (lowering of antibody levels) Secondary: Not reported	Primary: Clinical responses were similar between groups. All three regimens lowered antibody levels compared to baseline (P=0.0001, 0.017, 0.0012 for itraconazole, ketoconazole, and sulfadiazine, respectively). Secondary: Not reported
Schuler et al.[146] (2007) Itraconazole 200 mg IV every 12 hours for 2 days, then 200 mg once daily vs amphotericin B (AMB) IV 0.7 to 1.5	RCT, OL Hospitalized adult patients with hematological malignancy treated with myelosuppressive therapy and/or who were stem cell transplant recipients with a neutrophil count of $<1.0\times10^9$ cells/l expected to	N=162 28 days	Primary: Permanent discontinuation of study medication due to any adverse event Secondary: Response and success rate for both treatment groups	Primary: Significantly fewer itraconazole patients discontinued treatment due to any adverse event (22.2 vs 56.8% AMB; P<0.0001). The main reason for discontinuation was a rise in serum creatinine (1.2% itraconazole vs 23.5% AMB). Renal toxicity was significantly higher and more drug-related adverse events occurred in the AMB group. Secondary: Intention-to-treat (ITT) analysis showed favorable efficacy for itraconazole; response and success rates were both significantly higher than for AMB (61.7 vs 42% and 70.4 vs 49.3%; both P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/kg/day	last for at least 7 days from the start of the study medication; fever ≥38°C not responding to at least 72 h of broad spectrum antibiotics and a life expectancy ≥14 days			Treatment failure was reduced in itraconazole patients (25.9 vs 43.2%), primarily due to better tolerability.
Francesconi et al.[147] (2011) Itraconazole 100 to 200 mg/day vs terbinafine 250 to 500 mg/day	Cohort Patients diagnosed with cutaneous sporotrichosis	N=304 12 months	Primary: Clinical cure rate (defined as complete healing of the lesions) Secondary: Frequency of recurrence	Primary: The clinical cure rate was similar with terbinafine (92.7%) and itraconazole (92.0%; RR, 1.01; 95% CI, 0.93 to 1.09). Secondary: The mean time until achieving clinical cure did not differ between the two groups (terbinafine: 11.5 weeks; itraconazole: 11.8 weeks). In the terbinafine group, the duration of treatment until cure ranged from 2 to 24 months. One patient presented recurrence 3 months after the end of treatment. In the itraconazole group, 92.0% of patients were cured within a period of time of 2 to 44 months. Three patients presented recurrence. No difference in the frequency of adverse events was observed between the two groups (terbinafine group: 7.3%; itraconazole group: 7.6%; RR, 0.91; 95% CI, 0.39 to 2.07).
Herbrecht et al.[148] (2010) Posaconazole 800 mg/day vs	RCT Patients with invasive fungal infections refractory to standard antifungal therapy	N=193 12-month follow-up after discharge	Primary: Survival estimates Secondary: Not reported	Primary: Significantly more patients treated with posaconazole were alive at every time point analyzed (days 28 to 365) than patients treated with standard antifungal medications (P<0.0001). The absolute difference in all-cause mortality ranged from 27.0% to 31.2%. At the last time point (day 365), 41% of patients treated with 800 mg/day of posaconazole remained alive compared to 14% of patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
standard antifungal therapy				treated with standard antifungal therapy (P<0.0001). Secondary: Not reported
Perfect et al.[149] (2003) Voriconazole 6 mg/kg IV every 12 hours as a loading dose, followed by 4 mg/kg every 12 hours for at least 3 days Patients could be switched to oral voriconazole at 200 to 300 mg twice daily or started on oral voriconazole at this dose.	RCT, OL Patients with documented invasive fungal infections and evidence of failure, intolerance or toxicity related to other approved therapies or infections with no currently approved therapies (including scedosporiosis and fusariosis)	N=273 End of therapy	Primary: Global response Secondary: Not reported	Primary: Satisfactory global responses were observed in 50% of the overall cohort, in 47% of patients who failed to respond to other therapies, and 68% of patients with infections with no approved antifungal therapy. In patients with aspergillosis, the efficacy rate was 43.7%. In patients with candidiasis, the efficacy rate was 57.5%. In patients with Cryptococcus, the efficacy rate was 38.9%. In patients with fusariosis, the efficacy rate was 45.5%. In patients with scedosporiosis, the efficacy rate was 30%. Secondary: Not reported

Drug regimen abbreviations: BID=twice daily, IV=intravenously, PO=by mouth, PV=intravaginally, QD=once daily
Study abbreviations: AC=active control, CI=confidence interval, CS=comparative study, DB=double blind, DD=double dummy, MA=meta-analysis, MC=multi-center, NC=non-comparative, NI=non-inferiority, OBS=observational, OL=open label, OR=odds ratio, PC=placebo controlled, PG=parallel group, PRO=prospective trial, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, SB=single blind

Additional Evidence

Dose Simplification:
Itraconazole is said to maintain therapeutic levels in fingernails and toenails for a considerable period of time after systemic therapy. Because of this, pulse dosing with higher daily doses of itraconazole has been used to treat onychomycosis.[100] Several studies have been conducted analyzing the clinical effects of pulse doses of itraconazole compared to continuous dosing of terbinafine for the treatment of this condition.[98,100,102-105,113] Results indicate that clinical and mycological outcomes are not enhanced as a result of less frequent dosing, and some studies show significantly better results with the use of continuous terbinafine therapy compared to the use of itraconazole in a pulse-dose regimen.[98,100,103-105]

Stable Therapy:
An evidence-based medicine literature search did not reveal data pertinent to this topic.

Impact on Physician Visits:
An evidence-based medicine literature search did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 12. Relative Cost of the Azoles

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Fluconazole	injection, suspension, tablet	Diflucan®*	$$-$$$$$	$$
Itraconazole	capsule, solution	Sporanox®*, Onmel®	$$$$$	$$$$$
Ketoconazole	tablet	N/A	N/A	$
Posaconazole	injection, suspension, tablet	Noxafil®	$$$$$	N/A
Voriconazole	injection, suspension, tablet	Vfend®*, Vfend IV®*	$$$$$	$$$$$

*Generic is available in at least one dosage form or strength.
N/A=Not available

X. Conclusions

The azoles are approved to treat a variety of fungal infections.[1-8] All of the products are available in a generic formulation, with the exception of posaconazole. There are many guidelines that define the appropriate place in therapy for the azoles.[10-24] The agent that is recommended is dependent upon the infectious organism being treated and the location of the infection. The azoles are recommended as specific therapy for the treatment of aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, cryptococcal disease, histoplasmosis, sporotrichosis, tinea capitis, as well as for prophylaxis in patients with chemotherapy-induced neutropenia and hematopoietic stem cell transplantation recipients.[9-16,18-20,23-24]

Clinical trials have demonstrated comparable efficacy among the azoles for the treatment of candidiasis (esophageal, oropharyngeal, and vaginal), cryptococcal disease, dermatophyte infections, as well as for prophylaxis.[39,42-47,58-59,71,77,81,93,123,131-133,145] There are relatively few studies that have demonstrated greater efficacy with one azole antifungal agent over another.[40-41,128-129] The azoles have also been shown to be comparable in efficacy to antifungal agents in other classes.[48-52,60-61,64-67,69-70,72-75,78-79,85,87,91-92,97,101-102,126-127,130]

The azoles are generally well tolerated with gastrointestinal symptoms being the most frequently reported adverse event. Treatment with an azole may lead to hepatic function abnormalities, which range from mild elevations in transaminases to severe hepatotoxicity. There are also numerous drug interactions reported with these agents due to oxidative drug metabolism via the cytochrome P450 enzyme system.

There is insufficient evidence to support that one brand azole is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand azoles within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand azole is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

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I. Overview

The echinocandins are approved for the treatment of *Candida* infections.[1-6] Caspofungin is also approved for the treatment of invasive aspergillosis in patients who are refractory to, or intolerant of, other therapies. The echinocandins inhibit the synthesis of β (1,3)-D-glucan, an enzyme responsible for the synthesis of an essential component of fungal cell walls.[1-6]

The echinocandins that are included in this review are listed in Table 1. This review encompasses all systemic dosage forms and strengths. The topical antifungals were previously reviewed with the skin and mucous membrane agents (AHFS 840408) and are not included in this review. There are no generic products available. This class was last reviewed in May 2012.

Table 1. Echinocandins Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Anidulafungin	injection	Eraxis®	none
Caspofungin	injection	Cancidas®	none
Micafungin	injection	Mycamine®	none

PDL=Preferred Drug List

The echinocandins have been shown to be active against the strains of microorganisms indicated in Table 2. This activity has been demonstrated in clinical infections and is represented by the Food and Drug Administration (FDA)-approved indications for the echinocandins that are noted in Table 4. These agents may also have been found to show activity to other microorganisms in vitro; however, the clinical significance of this is unknown since their safety and efficacy in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials. Although empiric anti-infective therapy may be initiated before culture and susceptibility test results are known, once results become available, appropriate therapy should be selected.

Table 2. Microorganisms Susceptible to the Echinocandins[1-6]

Organism	Anidulafungin	Caspofungin	Micafungin
Aspergillus species		✔	
Candida species	✔	✔	✔

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the echinocandins are summarized in Table 3.

Table 3. Treatment Guidelines Using the Echinocandins

Clinical Guideline	Recommendation(s)
American Thoracic Society: **Treatment of Fungal Infections in Adult Pulmonary and Critical Care Patients (2011)**[7]	<u>Aspergillomas</u> • In patients with aspergillomas, it is recommended that antifungal agents not be used. • Antifungals should only be used only in patients suspected of having a component of semi-invasive disease. <u>Invasive Aspergillosis</u> • When invasive disease is suspected or confirmed, prompt, aggressive antifungal treatment is essential.

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	• Although amphotericin B deoxycholate had historically been the "gold standard" for the treatment of invasive aspergillosis, most clinicians and the most recent Infectious Diseases Society of America guidelines recommend voriconazole as the primary treatment option.
	• There are no definitive data or consensus opinions indicating improved efficacy of any of the lipid amphotericin formulations over amphotericin B deoxycholate in the treatment of invasive aspergillosis. Thus, the best indication for using a lipid formulation appears to be for reducing renal toxicity to allow the administration of high doses of amphotericin for a prolonged time.
	• Voriconazole has recently emerged as a standard therapy for the treatment of invasive aspergillosis based on the results of a randomized trial comparing the outcomes to amphotericin B deoxycholate; however, whether outcomes are superior to lipid formulations of amphotericin B has not been determined. In many instances voriconazole may be considered the treatment of choice. The patient can be transitioned to oral formulations of this drug.
	• Oral itraconazole is not recommended for initial therapy for invasive aspergillosis. However, after disease progression is arrested with either voriconazole or amphotericin, the patient can be transitioned to oral itraconazole.
	• Caspofungin use in invasive aspergillosis is largely limited to salvage therapy, often in combination with other antifungal agents, after primary therapy with amphotericin-based regimens have failed.
	• There is currently insufficient clinical support to recommend combination therapy, although many clinicians are employing this approach as a "last option," or in settings of particularly advanced disease.
	
	<u>Chronic necrotizing aspergillosis</u>
	• In patients with chronic necrotizing aspergillosis, with mild to moderate disease, voriconazole (200 mg every 12 hours) or itraconazole (400 to 600 mg/day) is recommended until resolution or stabilization of all clinical and radiographic manifestations.
	• If clinically severe, consider beginning therapy of chronic necrotizing aspergillosis with either liposomal amphotericin B or intravenous voriconazole as described above for invasive disease.
	• In select patients at high risk of invasive fungal infection, some anti-*Aspergillus* prophylaxis is warranted. Data support the use of posaconazole 200 mg orally three times daily until recovery from neutropenia and clinical remission is established. Other prophylaxis approaches have utilized itraconazole, micafungin, and inhaled liposomal amphotericin B.
	
	<u>Invasive Pulmonary Aspergillosis</u>
	• In patients with invasive pulmonary aspergillosis, the following are recommended:
	  o Intravenous voriconazole six mg/kg every 12 hours for one day, followed by four mg/kg every 12 hours until improvement, followed by oral voriconazole 200 mg every 12 hours (preferred) or oral itraconazole 400 to 600 mg/day until resolution or stabilization of all clinical and radiographic manifestations OR
	  o Intravenous liposomal amphotericin B three to five mg/kg/day until improvement, followed by oral voriconazole 200 mg every 12 hours (preferred) or oral itraconazole 400 to 600

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	mg/day until resolution or stabilization of all clinical and radiographic manifestation.
	• In patients with invasive pulmonary aspergillosis who have failed front line therapy and are requiring salvage therapy, the following are recommended:
	  o Intravenous caspofungin 70 mg on day one and 50 mg/day intravenously thereafter, or intravenous micafungin 100 to 150 mg/day until improvement, followed by oral voriconazole 200 mg every 12 hours or oral itraconazole 400 to 600 mg/day until resolution of disease OR
	  o Posaconazole 200 mg four times per day initially, then 400 mg twice daily orally after stabilization of disease.
	
	<u>Hypersensitivity pneumonitis related to *Aspergillus*</u>
	• In patients with hypersensitivity pneumonitis, it is recommended that antifungal therapy not be used.
	
	<u>Blastomycosis (immunocompetent hosts)</u>
	• In patients with mild to moderate pulmonary blastomycosis, oral itraconazole 200 mg twice daily is recommended for six months.
	• In patients with severe pulmonary blastomycosis, amphotericin B 0.7 to 1.0 mg/kg/day daily is recommended until clinical improvement is observed, followed by continuation of amphotericin B 0.7 to 1.0 mg/kg three times weekly, until a cumulative dose of 1.5 to 2.5 grams is reached. Once clinical improvement is observed, oral itraconazole 200 mg twice daily is recommended for six months.
	• In patients with pulmonary blastomycosis and bone involvement, it is recommended to prolong treatment with itraconazole to 12 months.
	• In patients with pulmonary blastomycosis and concomitant central nervous system involvement, the following are recommended:
	  o Liposomal amphotericin B 0.7 mg/kg/day until a cumulative dose of two grams is reached.
	  o Triazoles should not be used as monotherapy for meningeal blastomycosis.
	  o High dose intravenous or oral fluconazole 400 to 800 mg daily may be provided as an add-on therapy to intravenous amphotericin B in patients with severe or refractory disease, with the total duration of fluconazole therapy extended for at least six months.
	
	<u>Blastomycosis (immunocompromised hosts)</u>
	• In patients with severe pulmonary blastomycosis without central nervous system involvement, amphotericin B 0.7 mg/kg/day is recommended until clinical improvement is observed. Once clinical improvement is observed, oral itraconazole 200 mg twice daily is recommended for at least 12 months.
	• In patients with mild to moderate pulmonary blastomycosis without central nervous system involvement, oral itraconazole 200 mg twice daily is recommended for at least 12 months.
	• When acquired immunodeficiency syndrome is involved, oral itraconazole 200 mg/day is recommended indefinitely or until immunity is fully restored.
	• In patients with pulmonary blastomycosis and concomitant central nervous system involvement, the following are recommended:
	  o Combined therapy with amphotericin B 0.7 mg/kg/day together with intravenous or oral fluconazole 400 to 800 mg

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	daily from the onset until clinical improvement is observed. o Use of fluconazole for at least 12 months total after discontinuation of combined intravenous treatment with amphotericin B and high-dose fluconazole. o Use of liposomal amphotericin B rather than amphotericin B deoxycholate should be considered due to theoretic better central nervous system penetration. o Triazoles are not used as monotherapy. o Patients with acquired immunodeficiency syndrome should continue to receive oral fluconazole 400 mg per day indefinitely or until immunity is restored. • In patients with pulmonary blastomycosis with new or progressing central nervous system involvement despite amphotericin B monotherapy, the following are recommended: o Combined therapy with liposomal amphotericin B five mg/kg/day until clinical improvement is observed, together with intravenous or oral fluconazole 800 mg/day. o Fluconazole is used for at least six months in immunocompetent patients, and at least 12 months in immunocompromised patients, after discontinuation of combined treatment with amphotericin B and fluconazole. o Patients with acquired immunodeficiency syndrome receive oral fluconazole 400 mg daily indefinitely or until immunity is restored. • In critically ill patients with pulmonary blastomycosis, the following are recommended: o Combined therapy with amphotericin B (0.7 to 1.0 mg/kg amphotericin B deoxycholate or five mg/kg daily liposomal amphotericin B) until clinical improvement is observed, together with oral itraconazole 200 mg/day. o Following the initial intravenous therapy, oral itraconazole is used for at least six months in immunocompetent patients, and at least 12 months in immunocompromised patients, after discontinuation of combined treatment with amphotericin B and itraconazole. o After initial therapy is complete, patients with acquired immunodeficiency syndrome should receive oral itraconazole 200 mg/day indefinitely, or until immunity is restored. Voriconazole 200 mg twice daily may be used as an alternative to itraconazole. • In patients with pulmonary blastomycosis with new or progressing central nervous system involvement despite amphotericin B monotherapy, the following are recommended: o Combined therapy with liposomal amphotericin B five mg/kg/day until clinical improvement is observed, together with intravenous or oral fluconazole 800 mg/day. o Fluconazole is used for at least six months in immunocompetent patients, and at least 12 months in immunocompromised patients, after discontinuation of combined treatment with amphotericin B and fluconazole. o Patients with acquired immunodeficiency syndrome receive oral fluconazole 400 mg daily indefinitely or until immunity is restored. o Voriconazole 200 mg twice daily may be considered as an alternative to fluconazole, though extensive disease-specific data are currently lacking.

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	• In critically ill patients with pulmonary blastomycosis, the following are recommended:
	  o Combined therapy with amphotericin B (0.7 to 1.0 mg/kg amphotericin B deoxycholate or five mg/kg daily liposomal amphotericin B) until clinical improvement is observed, together with oral itraconazole 200 mg/day.
	  o Following the initial intravenous therapy, oral itraconazole is used for at least six months in immunocompetent patients, and at least 12 months in immunocompromised patients, after discontinuation of combined treatment with amphotericin B and itraconazole.
	  o After initial therapy is complete, patients with AIDS should receive oral itraconazole 200 mg/day indefinitely, or until immunity is restored.
	  o Voriconazole 200 mg twice daily may be considered as an alternative to itraconazole, though this is based largely on in vitro sensitivities and limited case based data.
	
	<u>Coccidioidomycosis (immunocompetent hosts)</u>
	• In most immunocompetent patients with primary pulmonary coccidioidomycosis and no additional risk factors for dissemination, we suggest no antifungal treatment.
	• In immunocompetent patients with primary pulmonary coccidioidomycosis and moderate to severe symptoms, or those in whom symptoms persist for more than six weeks, treatment with triazole antifungal drugs are recommended for at least three to six months or longer if symptoms and radiographic abnormalities persist.
	
	<u>Coccidioidomycosis (immunocompromised hosts and others at risk for disseminated disease)</u>
	• In many patients with pulmonary coccidioidomycosis and pulmonary nodules only, observation is recommended for at least one year without antifungal treatment. However, fluconazole (400 mg/day) or itraconazole (400 mg/day) may be considered during periods of significant immune suppression (i.e., chemotherapy, systemic corticosteroid therapy, or CD4 counts <250/µL).
	• In patients with pulmonary coccidioidomycosis and pulmonary nodules who have additional risk factors for disseminated disease, patients with cavities, and those presenting with hemoptysis, treatment with triazole antifungal drugs are recommended, either fluconazole (400 mg/day) or itraconazole (400 mg/day).
	• For diffuse pulmonary coccidioidomycosis with significant impairment of gas exchange, initial liposomal amphotericin B (five mg/kg/day) or amphotericin B (0.7 to 1.0 mg/kg/day) is recommended until clinical improvement, followed by fluconazole (400 mg/day) or itraconazole (400 mg/day) for at least another year. In patients with ongoing immune suppression, azole therapy may be continued indefinitely.
	• All patients, whether immunocompetent or immunocompromised, with any form of disseminated coccidioidomycosis require treatment. For non-meningeal disseminated disease, treatment with fluconazole (400 mg/day) or itraconazole (400 mg/day) is recommended for at least a year and until clinical improvement and stabilization. Itraconazole is preferred in bone disease. In severe or refractory cases, liposomal amphotericin B (five mg/kg/day) or amphotericin B (0.7 to 1.0 mg/kg/day) may be initiated until clinical improvement, followed by fluconazole (400 mg/day) or itraconazole (400 mg/day) for at least

Clinical Guideline	Recommendation(s)
	another year. • In patients with meningitis, fluconazole (400 to 1,000 mg/day) or itraconazole (400 to 600 mg/day) for life. In patients with meningitis in whom treatment with triazole antifungal drugs failed, intrathecal amphotericin B is recommended in select cases. <u>Cryptococcosis (immunocompetent hosts)</u> • In asymptomatic immunocompetent patients with respiratory tract colonization by *Cryptococcus neoformans*, no antifungal treatment is recommended. • In immunocompetent patients with pulmonary cryptococcosis and no evidence of other organ involvement, fluconazole 400 mg/day initially is recommended, tapering to 200 mg/day after clinical improvement is assured and with total treatment for six months. Alternatively, itraconazole 400 mg/day may be considered for six months. Fluconazole treatment is recommended for longer than six months in patients with documented *Cryptococcus gattii* infection. <u>Cryptococcosis (immunocompromised hosts and immunocompetent hosts with disseminated or central nervous system involvement)</u> • In patients with disseminated cryptococcosis or central nervous system involvement, amphotericin B (0.7 to 1.0 mg/kg/day) plus flucytosine (100 mg/kg/day) is recommended for two weeks, then fluconazole or itraconazole (400 mg/day) for eight to 10 weeks. Alternatively, amphotericin B (0.7 to 1.0 mg/kg/day) plus flucytosine (100 mg/kg/day) may be administered for six to 10 weeks in patients in whom azoles cannot be used. • In patients with disseminated cryptococcosis or central nervous system involvement, it is recommended that azoles not be used as monotherapy. • In patients with refractory disease not responding to fluconazole and itraconazole, voriconazole or posaconazole can be considered as salvage therapy on a case by case basis. • In patients with acquired immunodeficiency syndrome and CD4+ T cell count < 200/µL who have disseminated cryptococcosis or central nervous system involvement, fluconazole 200 mg/day is recommended to be used indefinitely, after successful primary therapy as outlined above, or until CD4+ T cell count is greater than 200/µL, human immunodeficiency virus ribonucleic acid is undetectable and sustained for three months, and the patient is stable for one to two years. <u>Histoplasmosis (immunocompetent hosts with *Histoplasma*-related pulmonary nodules, broncholithiasis, or fibrosing mediastinitis)</u> • Among asymptomatic patients with pulmonary nodules in whom *Histoplasma* cannot be cultured, antifungal treatment is not recommended. • In most patients with broncholithiasis, antifungal treatment is not recommended. • In patients with fibrosing mediastinitis, some clinicians recommend itraconazole 200 mg twice daily for 12 weeks. In patients with radiographic or physiologic improvement after an initial 12 weeks of therapy, longer treatment, up to 12 months, is recommended. <u>Histoplasmosis (immunocompetent hosts with symptomatic, progressive, or severe pulmonary histoplasmosis)</u> • In asymptomatic patients, no antifungal treatment is recommended.

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	• In symptomatic patients with mild pulmonary histoplasmosis, who remain symptomatic after three weeks of observation, itraconazole 200 mg twice daily for up to 12 weeks is recommended.
	• In selected patients with mild to moderate pulmonary histoplasmosis, initiating treatment with itraconazole 200 mg twice daily rather than with amphotericin B is recommended.
	• In patients with severe pulmonary histoplasmosis, amphotericin B 0.7 mg/kg/day is recommended until clinical improvement is observed or until a cumulative dose of two grams of amphotericin B is reached. In patients who improve clinically after initial treatment with amphotericin B, maintenance itraconazole 200 mg twice daily for at least 12 weeks is recommended.
	
	<u>Histoplasmosis (immunocompromised hosts with pulmonary histoplasmosis or with progressive or disseminated disease, or with chronic pulmonary histoplasmosis)</u>
	• In patients with mild to moderate histoplasmosis, itraconazole 200 mg three times daily for three days is recommended, followed by 200 mg twice daily for 12 months.
	• In patients with severe progressive disseminated histoplasmosis requiring hospitalization, amphotericin B 0.7 to 1.0 mg/kg/day (or a lipid formulation of amphotericin three to five mg/kg/day) is recommended until clinical improvement is observed or until a cumulative dose of two grams of amphotericin B is reached. In patients who improve clinically after initial treatment with amphotericin B, itraconazole 200 mg twice daily for 12 months is recommended.
	• In patients with acquired immunodeficiency syndrome and progressive disseminated histoplasmosis who completed 12 months of initial itraconazole therapy, itraconazole 200 mg twice daily is recommended until effective immune reconstitution occurs.
	• In patients with chronic pulmonary histoplasmosis, itraconazole 200 mg twice daily for 12 to 24 months is recommended rather than no antifungal treatment.
	• In patients with severe chronic pulmonary histoplasmosis, initial treatment with amphotericin B is recommended over itraconazole.
	
	<u>Paracoccidioidomycosis</u>
	• In critically ill patients with disseminated paracoccidioidomycosis, initial amphotericin B (0.7 to 1.0 mg/kg/day) therapy is recommended until clinical stabilization or until two grams total dose administered. This may be followed by azole therapy as listed below.
	• In patients with disseminated paracoccidioidomycosis and mild to moderate or slowly progressive symptoms, one of the following options is recommended until clinical stabilization and resolution of symptoms. The total duration of therapy must be individualized to clinical response, but generally therapy for six to 12 months or longer is employed. Potential regimens include:
	  o Ketoconazole 200 to 400 mg daily
	  o Itraconazole 100 to 400 mg daily
	  o Sulfadiazine four to six grams daily
	
	<u>Sporotrichosis</u>
	• In patients with mild to moderately severe pulmonary sporotrichosis, itraconazole 200 mg twice daily is recommended, with a total duration of therapy generally of three to six months based upon overall clinical response.

Clinical Guideline	Recommendation(s)

	• In patients with severe pulmonary sporotrichosis, amphotericin B 0.7 mg/kg/day is recommended until clinical improvement is observed or until a cumulative dose of one to two grams of amphotericin B is reached, followed by itraconazole 200 mg twice daily, with total duration of therapy generally of three to six months based upon overall clinical response.
	
	<u>Candidemia</u>
	• Candidemia should be treated with antifungal agents, selecting one of the following agents: fluconazole, an amphotericin B formulation, an echinocandin, voriconazole, or the combination regimen of fluconazole and amphotericin B.
	• For patients who are clinically stable and have not recently received azole therapy, the following are recommended:
	  o Fluconazole (400 mg/day or ~6 mg/kg/day) OR
	  o Caspofungin (70 mg loading dose day one, then 50 mg/day) OR
	  o Micafungin (100 mg/day) OR
	  o Anidulafungin (200 mg on day one, then 100 mg/day).
	• For patients who are clinically unstable and for whom identification of the *Candida* species in the blood is unknown, there is no definitive recommendation. Several options are available and include:
	  o Amphotericin B deoxycholate (0.6 to 1.0 mg/kg/day) or a lipid formulation of amphotericin B (three to five mg/kg/day) OR
	  o High-dose fluconazole (800 mg/kg/day or ~12 mg/kg/day) OR
	  o Caspofungin (70 mg loading dose day one, then 50 mg/day) OR
	  o Micafungin (100 mg/day) OR
	  o Anidulafungin (200 mg on day one, then 100 mg/day) OR
	  o Voriconazole (six mg/kg every 12 hours for two doses, then three mg/kg every 12 hours) OR
	  o A combination regimen with fluconazole (800 mg/day) and amphotericin B (0.6 to 1.0 mg/kg/day, for the first five to six days)
	• For *Candida albicans* and also possibly *Candida tropicalis*, the drugs of choice are fluconazole (400 mg/day), amphotericin B (0.6 to 1.0 mg/kg/day), and an echinocandin.
	• For *Candida parapsilosis*, the drugs of choice are fluconazole (400 mg/day) or amphotericin B (0.6 to 1.0 mg/kg/day).
	• For *Candida glabrata*, the drugs of choice are an echinocandin or amphotericin B. High-dose fluconazole (800 mg/day) may be a suitable alternative.
	• For *Candida krusei*, the drugs of choice are an echinocandin or amphotericin B.
	• For *Candida lusitaniae*, fluconazole is the preferred therapy.
	• Lipid formulations of amphotericin B are usually indicated for patients intolerant of, or refractory to, conventional antifungal therapy.
	
	<u>Other Fungi</u>
	• In patients with zygomycosis, lipid formulations of amphotericin B are recommended at five mg/kg/day or amphotericin B deoxycholate at 0.7 to 1.0 mg/kg/day.
	• In patients who are intolerant of, or refractory to, amphotericin B,

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	posaconazole 200 mg orally four times per day is recommended.
Infectious Diseases Society of America: **Treatment of Aspergillosis (2008)**[8]	Invasive pulmonary aspergillosis • For primary treatment of invasive pulmonary aspergillosis, intravenous or oral voriconazole is recommended for most patients. For seriously ill patients, the parenteral formulation is recommended. • Liposomal amphotericin B may be considered as alternative primary therapy in some patients. For salvage therapy, agents include lipid formulations of amphotericin, posaconazole, itraconazole, caspofungin, or micafungin. • In the absence of a well-controlled, prospective clinical trial, routine administration of combination therapy for primary therapy is not routinely recommended. For salvage therapy, an additional antifungal agent might be added to current therapy, or combination antifungal drugs from different classes other than those in the initial regimen may be used. • For patients with successfully treated invasive aspergillosis who will require subsequent immunosuppression, resumption of antifungal therapy can prevent recurrent infection. Tracheobronchial aspergillosis • Voriconazole is recommended as initial therapy in the treatment of tracheobronchial aspergillosis. • Because the use of deoxycholate amphotericin B may result in increased nephrotoxicity in association with calcineurin inhibitors, a lipid formulation of amphotericin B is recommended if a polyene is considered in the patient (e.g., lung transplant recipient). Chronic necrotizing pulmonary aspergillosis • The greatest body of evidence regarding effective therapy supports the use of orally administered itraconazole. • Although voriconazole (and presumably posaconazole) is also likely to be effective, there is less published information available. Single-organ, extrapulmonary forms of invasive aspergillosis • Voriconazole is recommended for primary treatment of these uncommon manifestations of invasive aspergillosis. Aspergillosis of the central nervous system • The weight of evidence supports voriconazole as the primary recommendation for systemic antifungal therapy of central nervous system aspergillosis. • Itraconazole, posaconazole, or lipid formulations of amphotericin are recommended for patients who are intolerant or refractory to voriconazole. Invasive sinonasal aspergillosis • If the infection is known to be due to *Aspergillus* species, voriconazole should be initiated. • If the etiological organism is not known or histopathologic examination is still pending, an amphotericin B formulation should be initiated in anticipation of possible sinus zygomycosis. Aspergillus endocarditis, pericarditis, and myocarditis • Voriconazole has been successfully used in case reports and may be the preferred agent.

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	• Because of the potential for recurrent infections following replacement of an infected prosthetic valve, strong consideration should be given to lifelong antifungal therapy with an antifungal triazole, such as oral voriconazole or posaconazole. *Aspergillus* osteomyelitis and septic arthritis • Combined medical and surgical intervention is recommended, where feasible, for management of *Aspergillus* osteomyelitis and arthritis. • Although there is currently limited experience with voriconazole for treatment of *Aspergillus* osteomyelitis, voriconazole appears to be effective for this indication. • Historically, amphotericin B has been used and would be appropriate therapy. *Aspergillus* endophthalmitis and *Aspergillus* keratitis • Following a diagnostic vitreal tap, intravenous amphotericin B and, where appropriate, intravitreal amphotericin B plus pars plana vitrectomy may be sight saving in *Aspergillus* endophthalmitis. • Voriconazole administered intravitreally or systemically is an alternative regimen. Management of *Aspergillus* keratitis requires emergency ophthalmologic intervention with ophthalmologic examination, topical antifungal therapy, and systemic antifungal therapy with amphotericin B, voriconazole, or itraconazole. Cutaneous aspergillosis • Therapy for secondary cutaneous lesions reflects that of disseminated infection, with systemic voriconazole recommended as primary therapy. • Alternative agents include liposomal amphotericin B, posaconazole, itraconazole, or an echinocandin. *Aspergillus* peritonitis • Removal of peritoneal dialysis catheter and intraperitoneal dialysis with amphotericin B, in addition to intravenous administration of amphotericin B, are recommended. • Itraconazole or an extended-spectrum azole (voriconazole or posaconazole) may be used as a salvage therapy. Esophageal and gastrointestinal aspergillosis • Once a diagnosis is established, medical and, where appropriate, surgical therapy is needed to prevent the complications of potentially fatal hemorrhage, perforation, obstruction, and infarction. • Systemic antifungal therapy, as used for disseminated invasive aspergillosis, is appropriate. Hepatic aspergillosis • Medical therapy of hepatic aspergillosis should be considered as initial therapy. • For extrahepatic or perihepatic biliary obstruction, surgical intervention is warranted. Empirical antifungal therapy of neutropenic patients • Empirical antifungal therapy with amphotericin B, lipid formulations of amphotericin, itraconazole, voriconazole, or caspofungin is recommended for high-risk patients with prolonged neutropenia who

Clinical Guideline	Recommendation(s)
	remain persistently febrile despite broad-spectrum antibiotic therapy. • Empirical antifungal therapy is not recommended for patients who are anticipated to have short durations of neutropenia (duration of neutropenia, <10 days), unless other findings indicate the presence of an invasive fungal infection. <u>Prophylaxis against invasive aspergillosis</u> • Antifungal prophylaxis with posaconazole can be recommended in hematopoietic stem cell transplantation recipients with graft-vs-host disease who are at high risk for invasive aspergillosis and in patients with acute myelogenous leukemia or myelodysplastic syndrome who are at high risk for invasive aspergillosis. • Itraconazole may be effective, but tolerability limits its use. <u>Aspergilloma and chronic pulmonary aspergillosis</u> • Antifungal chemotherapy with itraconazole, voriconazole, or presumably, posaconazole provides some potential for therapeutic benefit with comparatively minimal risk. <u>*Aspergillus* otomycosis (otic aspergillosis)</u> • Topical therapy with irrigating solutions of boric acid, acetic acid, or azole cream may be effective in eradicating *Aspergillus* otomycosis. • For refractory cases and in contexts of perforated tympanic membranes, use of voriconazole, posaconazole, or itraconazole may be appropriate. <u>Allergic bronchopulmonary aspergillosis</u> • Treatment of allergic bronchopulmonary aspergillosis should consist of a combination of corticosteroids and itraconazole. <u>Allergic *Aspergillus* sinusitis</u> • Itraconazole is recommended for consideration in allergic *Aspergillus* sinusitis. <u>Renal aspergillosis</u> • Because none of the available antifungal agents are excreted primarily into the pelvis of the kidney or urine, the management of pelvicaliceal and ureteral infection may require nephrostomy with instillation of amphotericin B.
Infectious Diseases Society of America: **Clinical Practice Guidelines for the Management of Candidiasis (2009)**[9]	<u>Candidemia in non-neutropenic patients</u> • Fluconazole or an echinocandin (caspofungin, micafungin, or anidulafungin) is recommended as initial therapy for most adult patients. An echinocandin is recommended for patients with moderately severe to severe illness or for patients who have had recent azole exposure. Fluconazole is recommended for patients who are less critically ill and who have had no recent azole exposure. The same therapeutic approach is advised for children, with attention to differences in dosing regimens. • Transition from an echinocandin to fluconazole is recommended for patients who have isolates that are likely to be susceptible to fluconazole (e.g., *Candida albicans*) and who are clinically stable. • For infection due to *Candida glabrata,* an echinocandin is preferred. Transition to fluconazole or voriconazole therapy is not recommended without confirmation of isolate susceptibility. For patients who have

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	initially received fluconazole or voriconazole, are clinically improved, and whose follow-up culture results are negative, continuing use of an azole to completion of therapy is reasonable. • For infection due to *Candida parapsilosis,* treatment with fluconazole is recommended. For patients who have initially received an echinocandin, are clinically improved, and whose follow-up culture results are negative, continuing use of an echinocandin is reasonable. • Amphotericin B deoxycholate or a lipid formulation of amphotericin B are alternatives if there is intolerance to or limited availability of other antifungals. Transition from amphotericin B deoxycholate or lipid formulation of amphotericin B to fluconazole is recommended for patients who have isolates that are likely to be susceptible to fluconazole (e.g., *Candida albicans*) and who are clinically stable. • Voriconazole is effective for candidemia, but it offers little advantage over fluconazole and is recommended as step-down oral therapy for selected cases of candidiasis due to *Candida krusei* or voriconazole-susceptible *Candida glabrata*. <u>Candidemia in neutropenic patients</u> • An echinocandin (caspofungin, micafungin, or anidulafungin) or lipid formulation of amphotericin B is recommended for most patients. • For patients who are less critically ill and who have no recent azole exposure, fluconazole is a reasonable alternative. Voriconazole can be used in situations in which additional mold coverage is desired. • For infections due to *Candida glabrata,* an echinocandin is preferred. Lipid formulations of amphotericin B are an alternative treatment option. For patients who were already receiving voriconazole or fluconazole, are clinically improved, and whose follow-up culture results are negative, continuing use of the azole to completion of therapy is reasonable. • For infections due to *Candida parapsilosis*, fluconazole or lipid formulation of amphotericin B is preferred as initial therapy. If the patient is receiving an echinocandin, is clinically stable, and follow-up culture results are negative, continuing the echinocandin until completion of therapy is reasonable. For infections due to *Candida krusei*, an echinocandin, lipid formulation of amphotericin B, or voriconazole is recommended. <u>Empirical treatment for suspected invasive candidiasis in non-neutropenic patients</u> • Empirical therapy for suspected candidiasis in non-neutropenic patients is similar to that for proven candidiasis. Fluconazole, caspofungin, anidulafungin, or micafungin is recommended as initial therapy. An echinocandin is preferred for patients who have had recent azole exposure, whose illness is moderately severe or severe, or who are at high risk of infection due to *Candida glabrata* or *Candida krusei*. • Amphotericin B deoxycholate or a lipid formulation of amphotericin B are alternatives if there is intolerance to other antifungals or limited availability of other antifungals. <u>Empirical treatment for suspected invasive candidiasis in neutropenic patients</u> • Lipid formulations of amphotericin B, caspofungin, or voriconazole are recommended. • Fluconazole and itraconazole are alternative agents.

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	• Azoles should not be used for empirical therapy in patients who have received an azole for prophylaxis. Chronic disseminated candidiasis • Fluconazole is recommended for clinically stable patients. Lipid formulation of amphotericin B or amphotericin B deoxycholate can be used to treat acutely ill patients or patients with refractory disease. Induction therapy with amphotericin B for one to two weeks, followed by oral fluconazole is also recommended. • Anidulafungin, micafungin, or caspofungin are alternatives for initial therapy, followed by oral fluconazole when clinically appropriate. • Therapy should be continued for weeks to months, until calcification occurs or lesions resolve. Premature discontinuation of antifungal therapy can lead to recurrent infection. • Patients with chronic disseminated candidiasis who require ongoing chemotherapy or undergo stem cell transplantation should continue to receive antifungal therapy throughout the period of high risk to prevent relapse. Treatment for neonatal candidiasis • Amphotericin B deoxycholate is recommended for neonates with disseminated candidiasis. If urinary tract involvement is excluded, lipid formulation of amphotericin B can be used. Fluconazole is a reasonable alternative. The recommended length of therapy is three weeks. • Echinocandins should be used with caution and are generally limited to situations in which resistance or toxicity precludes the use of fluconazole or amphotericin B deoxycholate. • In nurseries with high rates of invasive candidiasis, fluconazole prophylaxis may be considered in neonates whose birth weight is <1000 grams. Antifungal drug resistance, drug-related toxicity, and neurodevelopmental outcomes should be observed. Osteoarticular *Candida* infections • For osteomyelitis, fluconazole at a dosage of 400 mg daily for six to 12 months or lipid formulation of amphotericin B at a dosage of three to five mg/kg/day for at least two weeks, followed by fluconazole at a dosage of 400 mg daily for six to 12 months is recommended. Alternatives include an echinocandin or amphotericin B deoxycholate at a dosage of 0.5 to 1.0 mg/kg/day for at least two weeks, followed by fluconazole at a dosage of 400 mg daily for six to 12 months. • For septic arthritis, treatment for at least six weeks with fluconazole at a dosage of 400 mg daily or lipid formulation of amphotericin B at a dosage of three to five mg/kg/day for at least two weeks, followed by fluconazole at a dosage of 400 mg daily is recommended. Alternatives include an echinocandin or amphotericin B deoxycholate at a dosage of 0.5 to 1.0 mg/kg/day for at least two weeks, followed by fluconazole at a dosage of 400 mg daily for the remainder of therapy. • For infection involving a prosthetic device, device removal is recommended for most cases. Therapy for at least six weeks with the above dosages of fluconazole, lipid formulation of amphotericin B, an echinocandin, or amphotericin B deoxycholate is recommended. If the device cannot be removed, chronic suppression with fluconazole is recommended. Central nervous system candidiasis

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	• Lipid formulation of amphotericin B with or without flucytosine is recommended for the initial several weeks of treatment. • Fluconazole is recommended as step-down therapy after the patient responds to initial treatment with lipid formulation of amphotericin B and flucytosine. Therapy should continue until all signs and symptoms, cerebrospinal fluid abnormalities, and radiologic abnormalities have resolved. *Candida* endophthalmitis • Amphotericin B deoxycholate combined with flucytosine is recommended for advancing lesions or lesions threatening the macula. Fluconazole is an acceptable alternative for less severe endophthalmitis. Lipid formulation of amphotericin B, voriconazole, or an echinocandin can be used to treat patients who are intolerant of or experiencing treatment failure with amphotericin B deoxycholate in combination with flucytosine or fluconazole. • The recommended duration of therapy is at least four to six weeks and is determined by the stabilization or resolution of lesions as documented by repeated ophthalmological examinations. Cardiovascular *Candida* infections • For native valve endocarditis, lipid formulation of amphotericin B with or without flucytosine is recommended. Alternatives include amphotericin B deoxycholate with or without flucytosine or an echinocandin (caspofungin or anidulafungin). Step-down therapy to fluconazole should be considered among patients with susceptible *Candida* isolates who have demonstrated clinical stability and clearance of *Candida* from the bloodstream. Valve replacement is recommended, and treatment should continue for at least six weeks after valve replacement and should continue for a longer duration in patients with perivalvular abscesses and other complications. • For patients who cannot undergo valve replacement, long-term suppression with fluconazole is recommended. • For prosthetic valve endocarditis, the recommendations above apply, and suppressive therapy should be indefinite if valve replacement is not possible. • For pericarditis, lipid formulation of amphotericin B, amphotericin B deoxycholate, an echinocandin, or fluconazole for as long as several months, in combination with either a pericardial window or pericardiectomy, is recommended. Step-down therapy to fluconazole should be considered for patients who have initially responded to amphotericin B or an echinocandin and who are clinically stable. • For myocarditis, treatment as for endocarditis (as stated above) is recommended. • For suppurative thrombophlebitis, catheter removal and incision and drainage or resection of the vein, if feasible, is recommended. Lipid formulation of amphotericin B, amphotericin B deoxycholate, fluconazole, or an echinocandin for at least two weeks after candidemia has cleared is recommended. Step-down therapy to fluconazole should be considered for patients who have initially responded to amphotericin B or an echinocandin and who are clinically stable. Resolution of the thrombus can be used as evidence to discontinue antifungal therapy if clinical and culture data are supportive. • For pacemaker and implantable cardiac defibrillator wire infections, removal of the entire device and systemic antifungal therapy with lipid

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	formulation of amphotericin B with or without flucytosine, amphotericin B deoxycholate with or without flucytosine, or an echinocandin is recommended. Step-down therapy to fluconazole should be considered for patients with susceptible *Candida* isolates who have demonstrated clinical stability and clearance of *Candida* from the bloodstream. For infections limited to generators and/or pockets, four weeks of antifungal therapy after removal of the device is recommended. For pacemaker and implantable cardiac defibrillator wire infections, at least six weeks of antifungal therapy after wire removal is recommended. • For ventricular assist devices that cannot be removed, treatment with lipid formulation of amphotericin B, amphotericin B deoxycholate, or an echinocandin is recommended. After candidemia has cleared and the patient has responded clinically, fluconazole is recommended as step-down therapy. Chronic suppressive therapy with fluconazole is warranted until the device is removed. <u>Esophageal candidiasis</u> • Systemic antifungal therapy is always required. Oral fluconazole for 14 to 21 days is recommended. Intravenous fluconazole, amphotericin B deoxycholate, or an echinocandin should be used for patients who cannot tolerate oral therapy. A diagnostic trial of antifungal therapy is appropriate before performing an endoscopic examination. • For fluconazole-refractory disease, itraconazole solution, posaconazole suspension, or voriconazole (administered intravenously or orally) for 14 to 21 days is recommended. Micafungin, anidulafungin or amphotericin B deoxycholate are acceptable alternatives. • Suppressive therapy with fluconazole is recommended for recurrent infections. • In patients with acquired immunodeficiency syndrome, treatment with highly active antiretroviral therapy is recommended to reduce recurrent infections. <u>Oropharyngeal candidiasis</u> • For mild disease, clotrimazole troches, nystatin suspension, or nystatin pastilles for seven to 14 days is recommended. • For moderate to severe disease, oral fluconazole for seven to 14 days is recommended. • For fluconazole-refractory disease, either itraconazole solution or posaconazole suspension for up to 28 days is recommended. Voriconazole or amphotericin B deoxycholate is recommended when treatment with other agents has failed. Intravenous echinocandin or amphotericin B deoxycholate can be used in treating patients with refractory disease. • Chronic suppressive therapy is usually unnecessary for patients with human immunodeficiency virus infection. If suppressive therapy is required, fluconazole three times weekly is recommended. Treatment with highly active antiretroviral therapy is recommended to reduce recurrent infections. • For denture-related candidiasis, disinfection of the denture, in addition to antifungal therapy, is recommended. <u>Antifungal prophylaxis for solid-organ transplant recipients, patients hospitalized in intensive care units, neutropenic patients receiving chemotherapy, and stem cell transplant recipients at risk of candidiasis</u> • For solid-organ transplant recipients, fluconazole or liposomal

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	amphotericin B is recommended as postoperative antifungal prophylaxis for liver, pancreas, and small bowel transplant recipients at high risk of candidiasis. • For patients hospitalized in the intensive care unit, fluconazole is recommended for high-risk patients in adult units that have a high incidence of invasive candidiasis. • For patients with chemotherapy-induced neutropenia, fluconazole, posaconazole, or caspofungin is recommended during induction chemotherapy for the duration of neutropenia. Oral itraconazole is an effective alternative, but it offers little advantage over other agents and is less well tolerated. • For stem cell transplant recipients with neutropenia, fluconazole, posaconazole, or micafungin is recommended during the period of risk of neutropenia. <u>Urinary tract infections – asymptomatic candiduria</u> • Treatment is not recommended unless the patient belongs to a group at high risk of dissemination. Elimination of predisposing factors often results in resolution of candiduria. • High-risk patients include neutropenic patients, infants with low birth weight, and patients who will undergo urologic manipulations. Neutropenic patients and neonates should be managed as described for invasive candidiasis. For those patients undergoing urologic procedures, fluconazole or amphotericin B deoxycholate for several days before and after the procedure is recommended. <u>Urinary tract infections – symptomatic candiduria</u> • For candiduria with suspected disseminated candidiasis, treatment as described for candidemia is recommended. • For cystitis due to a fluconazole-susceptible *Candida* species, oral fluconazole for two weeks is recommended. For fluconazole-resistant organisms, amphotericin B deoxycholate for one to seven days or oral flucytosine for seven to 10 days are alternatives. Amphotericin B deoxycholate bladder irrigation is generally not recommended but may be useful for treatment of patients with fluconazole-resistant *Candida* species, especially *Candida glabrata.* • For pyelonephritis due to fluconazole-susceptible organisms, oral fluconazole daily for two weeks is recommended. For patients with fluconazole-resistant *Candida* strains, especially *Candida glabrata*, alternatives include amphotericin B deoxycholate with or without flucytosine or flucytosine alone for two weeks. • For fungus balls, surgical intervention is strongly recommended in non-neonates. Fluconazole is recommended. Amphotericin B deoxycholate with or without flucytosine is an alternative. If access to the renal collecting system is available, an adjunct to systemic therapy is irrigation with amphotericin B deoxycholate. Treatment duration should be until symptoms have resolved and urine cultures no longer yield *Candida* species. <u>Vulvovaginal candidiasis</u> • Several topical antifungal agents are effective therapy for vulvovaginal candidiasis, and no agent is clearly more effective than another. • A single 150 mg dose of fluconazole is recommended for the treatment of uncomplicated *Candida* vulvovaginal candidiasis. • For recurring *Candida* vulvovaginal candidiasis, 10 to 14 days of

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	induction therapy with a topical or oral azole, followed by fluconazole once per week for six months, is recommended.
National Institutes of Health, the Centers for Disease Control and Prevention, and the Human Immunodeficiency Virus Medicine Association of the Infectious Diseases Society of America: **Guidelines for Prevention and Treatment of Opportunistic Infections in Human Immunodeficiency Virus-Infected Adults and Adolescents (2013)**[10]	Aspergillosis • Voriconazole is the drug of choice but should be used cautiously with human immunodeficiency virus protease inhibitors and efavirenz. Amphotericin B deoxycholate at 1 mg/kg daily or lipid-formulation amphotericin B at 5 mg/kg daily are alternatives, as is caspofungin at 50 mg daily and posaconazole. • Other echinocandins, such as micafungin and anidulafungin, are reasonable alternatives. • For treatment failure (if voriconazole was used initially) substitution with amphotericin B, posaconazole, or echinocandins might be considered; the amphotericin B or echinocandins would be rational for those who began therapy with voriconazole or posaconazole. Candidiasis (mucocutaneous) • Oral fluconazole is as effective as topical therapy for oropharyngeal candidiasis and is considered the drug of choice. Initial episodes of oropharyngeal candidiasis can be adequately treated with topical therapy, including clotrimazole troches, nystatin suspension or pastilles, or miconazole mucoadhesive tablets. Itraconazole oral solution for seven to 14 days is as effective as oral fluconazole but less well tolerated. Posaconazole oral solution is also as effective as fluconazole and is generally better tolerated than itraconazole. Intravenous amphotericin B is usually effective and can be used among patients with refractory disease. Both conventional amphotericin B and lipid complex and liposomal amphotericin B have been used. • Systemic antifungals are required for effective treatment of esophageal candidiasis. A 14 to 21-day course of either fluconazole (oral or intravenous) or oral itraconazole solution is highly effective. Oral ketoconazole or itraconazole capsules are less effective than fluconazole because of variable absorption. Although intravenous caspofungin or intravenous voriconazole are effective in treating esophageal candidiasis among human immunodeficiency virus -infected patients, oral or intravenous fluconazole remain the preferred therapies. Azole-refractory esophageal candidiasis can be treated with posaconazole, amphotericin B, anidulafungin, caspofungin, micafungin, or voriconazole. • Vulvovaginal candidiasis in human immunodeficiency virus -infected women is usually uncomplicated (90%) and responds readily to short-course oral or topical treatment with any of several therapies, including oral fluconazole, topical azoles, and itraconazole oral solution. Severe or recurrent episodes of vaginitis require oral fluconazole or topical antifungal therapy for ≥7 days. Coccidioidomycosis • For patients with clinically mild infection, such as focal pneumonia or a positive coccidioidal serologic test alone, initial therapy with a triazole antifungal is appropriate. • For patients with either diffuse pulmonary involvement or severely ill patients with extrathoracic disseminated disease, amphotericin B is the preferred initial therapy. Therapy with amphotericin B should continue until clinical improvement is observed. Some specialists would use a triazole antifungal concurrently with amphotericin B and continue the triazole once amphotericin B is stopped.

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	Cryptococcosis • The recommended initial standard treatment is amphotericin B combined with flucytosine for ≥2 weeks for those with normal renal function. • The combination of amphotericin B with fluconazole is less effective than amphotericin B combined with flucytosine in terms of clearing *Cryptococcus* from the cerebrospinal fluid but is better than amphotericin B alone. • Fluconazole combined with flucytosine is an alternative to amphotericin B plus flucytosine, but is less effective than amphotericin B and is recommended only for persons unable to tolerate or unresponsive to standard treatment. • After at least a two-week period of successful induction therapy, amphotericin B and flucytosine may be discontinued and follow-up therapy initiated with fluconazole. This should continue for eight weeks. Itraconazole is an acceptable though less effective alternative. • The optimal therapy for those with treatment failure is not established. For those initially treated with fluconazole, therapy should be changed to amphotericin B, with or without flucytosine, and continued until a clinical response occurs. Liposomal amphotericin B may have improved efficacy over the deoxycholate formulation and should be considered in treatment failures. Higher doses of fluconazole in combination with flucytosine might also be useful. Cryptosporidiosis • In the setting of severe immunosuppression, antiretroviral therapy with immune restoration to a CD4+ count >100 cells/µL leads to resolution of clinical cryptosporidiosis and is the mainstay of treatment. • All patients with cryptosporidiosis should be offered antiretroviral therapy as part of the initial management of their infection. • Management should include symptomatic treatment of diarrhea. Rehydration and repletion of electrolyte losses by either the oral or intravenous route are important. Severe diarrhea can exceed >10 L/day among patients with acquired immunodeficiency syndrome, often requiring intensive support. Aggressive efforts at oral rehydration should be made with oral rehydration solutions. Prevention of Cytomegalovirus • Cytomegalovirus end-organ disease is best prevented by using antiretroviral therapy to maintain the CD4+ count >100 cells/µL. • Although oral valganciclovir would likely prevent the occurrence of cytomegalovirus retinitis in patients with CD4+ counts <50 cells/µL, such therapy is not generally recommended because of the potential to induce cytomegalovirus resistance, the utility of treating disease when it occurs, and the lack of demonstrated survival advantage. Treatment of Cytomegalovirus disease • Oral valganciclovir, intravenous ganciclovir, intravenous ganciclovir followed by oral valganciclovir, intravenous foscarnet, and intravenous cidofovir are all effective treatments for cytomegalovirus retinitis. • The ganciclovir implant, a surgically-implanted reservoir of ganciclovir, which lasts approximately six months, also is very effective but it no longer is being manufactured. In its absence, some clinicians will use intravitreal injections of ganciclovir or foscarnet in conjunction with oral valganciclovir, at least initially, to provide

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	immediate high intraocular levels of drug and presumably faster control of the retinitis. • Systemic therapy has been shown to reduce morbidity in the contralateral eye. This should be considered when choosing between the oral, intravenous, and local options. • The choice of initial therapy for cytomegalovirus retinitis should be individualized based on the location and severity of the lesion(s), the level of underlying immune suppression, and other factors such as concomitant medications and ability to adhere to treatment. • No one regimen has been proven in a clinical trial to have greater efficacy in terms of protecting vision, and thus clinical judgment must be used when choosing a regimen. • In studies conducted in the pre-antiretroviral therapy era, ganciclovir intraocular implant plus oral ganciclovir was superior to once-daily intravenous ganciclovir for treatment of cytomegalovirus retinitis; however, the implant is no longer manufactured. Assuming that this observation can be extended to other combinations of systemically and locally administered drugs, human immunodeficiency virus-specialists often recommend intravitreal ganciclovir or foscarnet injections plus oral valganciclovir as the preferred initial therapy for patients with immediate sight-threatening lesions. Intravitreal injections deliver high concentrations of the drug to the target organ immediately while steady-state concentrations in the eye are achieved with systemically delivered medications. For patients with small peripheral lesions, oral valganciclovir alone often is adequate. • After induction therapy, secondary prophylaxis (i.e., chronic maintenance therapy) should be continued until immune reconstitution occurs as a result of antiretroviral therapy. Regimens demonstrated to be effective for chronic suppression in randomized, controlled clinical trials include parenteral ganciclovir, oral valganciclovir, parenteral foscarnet, combined parenteral ganciclovir and foscarnet, and parenteral cidofovir. <u>Management of Cytomegalovirus retinitis treatment failures</u> • When patients relapse while receiving maintenance therapy, induction with the same drug followed by reinstitution of maintenance therapy can control the retinitis, although for progressively shorter periods of time with each relapse. • Ganciclovir and foscarnet in combination appear to be superior in efficacy to either agent alone and should be considered for patients whose disease does not respond to single-drug therapy, and for patients with multiple relapses of retinitis. This drug combination, however, is associated with substantial toxicity. <u>Treatment of Hepatitis B Virus coinfection in patients not receiving antiretroviral therapy</u> • For patients with CD4+ counts >350 cells/µL who are not receiving antiretroviral therapy but meet criteria for hepatitis B virus treatment, adefovir or peginterferon alfa-2a monotherapy for 48 weeks might be considered, with close monitoring of hepatitis B virus deoxyribonucleic acid levels and follow-up to evaluate for hepatitis B e antigen seroconversion. However, early initiation of antiretroviral therapy should also be considered for human immunodeficiency virus/hepatitis B virus -coinfected persons with CD4+ counts >350 cells/µL.

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	Treatment of Hepatitis B Virus coinfection in patients who require antiretroviral therapy
	• For human immunodeficiency virus-infected persons, some experts recommend combination therapy with two agents active against hepatitis B virus to reduce the risk of hepatitis B virus drug resistance; although, there are no results from controlled trials as yet to support this strategy.
	• Among patients infected with hepatitis B virus, hepatitis C virus, and human immunodeficiency virus, consideration of the need for antiretroviral therapy should be the first priority. If antiretroviral therapy is not required, interferon-based therapy, which suppresses both hepatitis C virus and hepatitis B virus, should be considered. If interferon-based therapy for hepatitis C virus has failed, treatment of chronic hepatitis B with nucleoside or nucleotide analogs is recommended.
	
	Treatment of Hepatitis C coinfection
	• Antiviral treatment for hepatitis C virus infection should be considered for all human immunodeficiency virus-infected persons with acute or chronic hepatitis C virus infection.
	• The combination of peginterferon alfa (PegIFN) plus ribavirin is the recommended backbone of therapy for HIV/HCV-co-infected patients regardless of HCV genotype.
	• Antiviral treatment with PegIFN is not recommended in patients with decompensated liver disease.
	• For HCV-genotype-1-infected patients who are not co-infected with HIV, a HCV NS3/4A protease inhibitor (PI), either boceprevir or telaprevir, in combination with PegIFN/ribavirin is recommended on the basis of large clinical trials demonstrating significantly higher SVR rates with an acceptable safety/tolerability profile compared to PegIFN/ribavirin alone.
	• For HIV/HCV co-infected patients, preliminary data from small, ongoing clinical trials of boceprevir or telaprevir plus PegIFN/ribavirin for the treatment of HCV genotype 1 infection in HIV/HCV co-infected patients demonstrate greater efficacy than PegIFN/ribavirin alone, with a safety and tolerability profile similar to that observed in HCV monoinfected patients treated with boceprevir or telaprevir plus PegIFN/ribavirin. Preliminary recommendations are as follows:
	  o PegIFN is recommended for use for all HCV genotypes
	  o Ribavirin is recommended for use with PegIFN for all HCV genotypes.
	  o Boceprevir is approved for use in combination with PegIFN/ribavirin in HCV-genotype-1-monoinfected-patients. For HIV/HCV-co-infected patients, the regimen being evaluated is PegIFN/ribavirin administered for four weeks (lead-in phase) followed by boceprevir 800 mg orally every 7 to 9 hours (with a light snack) added to PegIFN/ribavirin for an additional 44 weeks.
	  o Telaprevir is approved for use in combination with PegIFN/ribavirin in HCV-genotype-1-monoinfected-patients. Dosing regimens lasting 48 weeks are being evaluated.
	• Patients with contraindications to the use of ribavirin can be treated with peginterferon alfa (2a or 2b) monotherapy. However, substantially lower sustained viral response rates are expected in persons not receiving ribavirin. HCV PIs should not be administered without ribavirin because of the high likelihood of virologic failure.

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	Treatment of herpes simplex virus disease • Orolabial lesions can be treated with oral valacyclovir, famciclovir, or acyclovir for five to 10 days. • Severe mucocutaneous herpes simplex virus lesions are best treated initially with intravenous acyclovir. Patients may be switched to oral therapy after the lesions have begun to regress. Therapy should be continued until the lesions have completely healed. • Genital herpes simplex virus infection should be treated with oral valacyclovir, famciclovir, or acyclovir for five to 14 days. Short-course therapy (one, two, or three days) should not be used in patients with human immunodeficiency virus infection. • Most recurrences of genital herpes can be prevented by use of daily anti- herpes simplex virus therapy, and this is recommended for persons who have frequent or severe recurrences. • Suppressive therapy with oral acyclovir, valacyclovir, or famciclovir is effective in preventing recurrences. Suppressive therapy with valacyclovir should be 500 mg twice daily in human immunodeficiency virus -infected persons or twice-daily regimens with acyclovir or famciclovir should be used. Management of herpes simplex virus treatment failure • The treatment of choice for acyclovir-resistant herpes simplex virus is intravenous foscarnet. Topical trifluridine, cidofovir, and imiquimod also have been used successfully for lesions on external surfaces, although prolonged application for 21 to 28 days or longer might be required. Histoplasmosis • Patients with moderately severe to severe disseminated histoplasmosis should be treated with an intravenous lipid formulation of amphotericin B for ≥2 weeks or until they clinically improve followed by oral itraconazole (200 mg three times daily for three days and then 200 mg twice daily for a total of ≥12 months). • In patients with less severe disseminated histoplasmosis, oral itraconazole at 200 mg three times daily for three days followed by 200 mg twice daily is appropriate initial therapy. Treatment of Isosporiasis (also known as Cystoisosporiasis) • Sulfamethoxazole-trimethoprim is the antimicrobial agent of choice for treatment of isosporiasis. It is the only agent whose use is supported by substantial published data and clinical experience. Therefore, potential alternative therapies should be reserved for patients with documented sulfa intolerance or in whom treatment fails. The traditional treatment regimen has been a 10-day course of Sulfamethoxazole-trimethoprim (800-160 mg) administered orally four times daily. • Intravenous administration of Sulfamethoxazole-trimethoprim should be considered for patients with potential or documented malabsorption. • Single-agent therapy with pyrimethamine has been used, with anecdotal success for treatment and prevention of isosporiasis. Pyrimethamine (50 to 75 mg/day) plus leucovorin (10 to 25 mg/day) to prevent myelosuppression may be an effective treatment alternative; it is the option for sulfa-intolerant patients.

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	Leishmaniasis • Due to similar efficacy and a better toxicity profile, clinicians consider liposomal amphotericin B as the drug of choice for visceral leishmaniasis in human immunodeficiency virus-coinfected patients. The optimal amphotericin B dosage has not been determined. • Regimens with efficacy include conventional amphotericin B 0.5 to 1.0 mg/kg body weight/day intravenous to achieve a total dose of 1.5 to 2.0 g, or liposomal or lipid complex preparations of two to four mg/kg body weight administered on consecutive days or in an interrupted schedule (e.g., 4 mg/kg on Days 1 to 5, 10, 17, 24, 31, and 38) to achieve a total cumulative dose of 20 to 60 mg/kg body weight. A higher daily dosage is recommended for liposomal or lipid complex preparations than for conventional amphotericin B. Preventing disseminated *Mycobacterium avium* complex disease • Human immunodeficiency virus-infected adults and adolescents should receive chemoprophylaxis against disseminated *Mycobacterium avium* complex disease if they have a CD4+ count <50 cells/µL. • Azithromycin or clarithromycin are the preferred prophylactic agents. • The combination of clarithromycin and rifabutin is no more effective than clarithromycin alone for chemoprophylaxis, is associated with a higher rate of adverse effects than either drug alone, and should not be used. • The combination of azithromycin with rifabutin is more effective than azithromycin alone; however, the additional cost, increased occurrence of adverse effects, potential for drug interactions, and absence of a survival difference compared to azithromycin alone do not warrant a routine recommendation for this regimen. • Azithromycin and clarithromycin also each confer protection against respiratory bacterial infections. • If azithromycin or clarithromycin cannot be tolerated, rifabutin is an alternative prophylactic agent for *Mycobacterium avium* complex disease, although drug interactions may make this agent difficult to use. • Primary *Mycobacterium avium* complex disease prophylaxis should be discontinued among adult and adolescent patients who have responded to antiretroviral therapy with an increase in CD4+ counts to >100 cells/µL for ≥3 months. Primary prophylaxis should be reintroduced if the CD4+ count decreases to <50 cells/µL. Treatment of disseminated *Mycobacterium avium* Complex Disease • Initial treatment of *Mycobacterium avium* complex disease should consist of two or more antimycobacterial drugs to prevent or delay the emergence of resistance. • Clarithromycin is the preferred first agent; however, azithromycin can be substituted for clarithromycin when drug interactions or clarithromycin intolerance preclude the use of clarithromycin. • Testing of *Mycobacterium avium* complex disease isolates for susceptibility to clarithromycin or azithromycin is recommended for all patients. Treatment of Penicilliosis marneffei • Penicilliosis is caused by the dimorphic fungus *Penicillium marneffei*, which is known to be endemic in Southeast Asia (especially Northern Thailand and Vietnam) and southern China.

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	• The recommended treatment is liposomal amphotericin B, three to five mg/kg body weight/day intravenously for two weeks, followed by oral itraconazole, 400 mg/day for a subsequent duration of 10 weeks, followed by secondary prophylaxis. • Patients with mild disease can be initially treated with oral itraconazole 400 mg/day for eight weeks, followed by 200 mg/day for prevention of recurrence. • The alternative drug for primary treatment in the hospital is intravenous voriconazole, 6 mg/kg every 12 hours on day one and then 4 mg/kg every 12 hours for at least three days, followed by oral voriconazole, 200 mg twice daily for a maximum of 12 weeks. • Patients with mild disease can be initially treated with oral voriconazole 400 mg twice a day on day one, and then 200 mg twice daily for 12 weeks. The optimal dose of voriconazole for secondary prophylaxis after 12 weeks has not been studied. Primary prophylaxis of *Pneumocystis (carinii) jiroveci* pneumonia • Sulfamethoxazole-trimethoprim is the recommended prophylactic agent. One double-strength tablet daily is the preferred regimen. However, one single-strength tablet daily is also effective and might be better tolerated than one double-strength tablet daily. One double-strength tablet three times weekly is also effective. Sulfamethoxazole-trimethoprim at a dose of one double-strength tablet daily confers cross-protection against toxoplasmosis and selected common respiratory bacterial infections. Lower doses of sulfamethoxazole-trimethoprim likely also confer such protection. • For patients who have an adverse reaction that is not life threatening, chemoprophylaxis with sulfamethoxazole-trimethoprim should be continued if clinically feasible; for those who have discontinued such therapy because of an adverse reaction, reinstituting sulfamethoxazole-trimethoprim should be strongly considered after the adverse event has resolved. Patients who have experienced adverse events, including fever and rash, might better tolerate reintroduction of the drug with a gradual increase in dose (i.e., desensitization), according to published regimens or reintroduction of sulfamethoxazole-trimethoprim at a reduced dose or frequency; as many as 70% of patients can tolerate such reinstitution of therapy. • If sulfamethoxazole-trimethoprim cannot be tolerated, alternative prophylactic regimens include dapsone, dapsone/pyrimethamine plus leucovorin, aerosolized pentamidine and atovaquone. • Primary *Pneumocystis (carinii) jiroveci* pneumonia prophylaxis should be discontinued for adult and adolescent patients who have responded to antiretroviral therapy with an increase in CD4+ counts to >200 cells/µL for >3 months. Prophylaxis should be reintroduced if the CD4+ count decreases to <200 cells/µL. Treatment of *Pneumocystis (carinii) jiroveci* pneumonia • Sulfamethoxazole-trimethoprim is the treatment of choice. The dose must be adjusted for abnormal renal function. Multiple randomized clinical trials indicate that sulfamethoxazole-trimethoprim is as effective as parenteral pentamidine and more effective than other regimens. Adding leucovorin to prevent myelosuppression during acute treatment is not recommended because of questionable efficacy and some evidence for a higher failure rate. Oral outpatient therapy of sulfamethoxazole-trimethoprim is highly effective among patients with

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	mild-to-moderate disease. • Patients who have *Pneumocystis (carinii) jiroveci* despite sulfamethoxazole-trimethoprim prophylaxis are usually effectively treated with standard doses of sulfamethoxazole-trimethoprim. • Patients with documented or suspected *Pneumocystis (carinii) jiroveci* and moderate-to-severe disease, as defined by room air pO_2 <70 mm Hg or arterial-alveolar O_2 gradient >35 mm Hg, should receive adjunctive corticosteroids as early as possible, and certainly within 72 hours after starting specific *Pneumocystis (carinii) jiroveci* therapy. • The recommended duration of therapy for *Pneumocystis (carinii) jiroveci* is 21 days. • Patients who have a history of *Pneumocystis (carinii) jiroveci* should be administered chemoprophylaxis for life (i.e., secondary prophylaxis or chronic maintenance therapy) with sulfamethoxazole-trimethoprim unless immune reconstitution occurs as a result of antiretroviral therapy. • Secondary prophylaxis should be discontinued for adult and adolescent patients whose CD4+ count has increased from <200 cells/µL to >200 cells/µL for >3 months as a result of antiretroviral therapy. Prophylaxis should be reintroduced if the CD4+ count decreases to <200 cells/µL. If *Pneumocystis (carinii) jiroveci* recurs at a CD4+ count of ≥200 cells/µL, lifelong prophylaxis should be administered. <u>Primary prophylaxis of *Toxoplasma* encephalitis</u> • The double-strength tablet daily dose of sulfamethoxazole-trimethoprim recommended as the preferred regimen for *Pneumocystis (carinii) jiroveci* prophylaxis is effective against *Toxoplasma* encephalitis as well and is therefore recommended. Sulfamethoxazole-trimethoprim, one double-strength tablet three times weekly, is an alternative. • If patients cannot tolerate sulfamethoxazole-trimethoprim, the recommended alternative is dapsone-pyrimethamine plus leucovorin, which is also effective against *Pneumocystis (carinii) jiroveci* pneumonia. • Atovaquone with or without pyrimethamine/leucovorin can also be considered. • Prophylactic monotherapy with dapsone, pyrimethamine, azithromycin, or clarithromycin cannot be recommended on the basis of available data. Aerosolized pentamidine does not protect against *Toxoplasma* encephalitis and is not recommended. • Prophylaxis against *Toxoplasma* encephalitis should be discontinued among adult and adolescent patients who have responded to antiretroviral therapy with an increase in CD4+ counts to >200 cells/µL for >3 months. Prophylaxis for *Toxoplasma* encephalitis should be reintroduced if the CD4+ count decreases to <100–200 cells/µL. <u>Treatment of *Toxoplasma* encephalitis</u> • The initial therapy of choice for *Toxoplasma* encephalitis consists of the combination of pyrimethamine plus sulfadiazine plus leucovorin. • The preferred alternative regimen for patients with *Toxoplasma* encephalitis who are unable to tolerate or who fail to respond to first-line therapy is pyrimethamine plus clindamycin plus leucovorin. • Sulfamethoxazole-trimethoprim was reported in a small randomized trial to be effective and better tolerated than pyrimethamine-

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	sulfadiazine. On the basis of less in vitro activity and less experience with sulfamethoxazole-trimethoprim, treatment with this drug may be considered an option.
	• Acute therapy for *Toxoplasma* encephalitis should be continued for at least six weeks, if there is clinical and radiologic improvement.
	
	<u>Treatment of latent tuberculosis infection</u>
	• Human immunodeficiency virus-infected persons, regardless of age, should be treated for latent tuberculosis infection if they have no evidence of active tuberculosis and:
	  o A positive diagnostic test for latent tuberculosis infection and no prior history of treatment for active or latent tuberculosis.
	  o A negative diagnostic test for latent tuberculosis infection but are close contacts of persons with infectious pulmonary tuberculosis.
	  o A history of untreated or inadequately treated healed tuberculosis (i.e., old fibrotic lesions on chest radiography) regardless of diagnostic tests for latent tuberculosis infection.
	• Treatment options for latent tuberculosis infection include isoniazid daily or twice weekly for nine months.
	• Due to an increased risk of fatal and severe hepatotoxicity, a two-month regimen of daily rifampin and pyrazinamide is not recommended for latent tuberculosis infection treatment regardless of human immunodeficiency virus status.
	• Human immunodeficiency virus-infected persons receiving isoniazid should receive pyridoxine to minimize the risk of developing peripheral neuropathy. Alternatives for individuals who cannot take isoniazid or who have been exposed to a known isoniazid-resistant index case include either rifampin or rifabutin alone for four months.
	• For persons exposed to isoniazid- and/or rifampin-resistant tuberculosis, decisions to treat with one or two drugs other than isoniazid, rifampin, or rifabutin should be based on the relative risk of exposure to organisms broadly resistant to other antimycobacterial drugs and should be made in consultation with public health authorities.
	• Directly observed therapy should be used with intermittent dosing regimens when otherwise feasible to maximize regimen completion rates.
	• There is no evidence to suggest that latent tuberculosis infection treatment should be continued beyond the recommended duration in persons with human immunodeficiency virus infection. Therefore, latent tuberculosis infection treatment should be discontinued after completing the appropriate number of doses.
	
	<u>Treatment of active tuberculosis disease</u>
	• Recommendations for anti-tuberculosis treatment regimens in human immunodeficiency virus -infected adults follow the same principles as for adults without human immunodeficiency virus -infection.
	• Treatment of drug susceptible tuberculosis disease should include a six-month regimen with an initial phase of isoniazid, rifampin or rifabutin, pyrazinamide, and ethambutol administered for two months followed by isoniazid and rifampin (or rifabutin) for four additional months.
	• When drug-susceptibility testing confirms the absence of resistance to isoniazid, rifampin, and pyrazinamide, ethambutol may be discontinued before two months of treatment have been completed.

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	• For patients with cavitary lung disease and cultures positive for *Mycobacterium tuberculosis* after completion of two months of therapy, treatment should be extended with isoniazid and rifampin for an additional three months for a total of nine months. • All human immunodeficiency virus-infected patients treated with isoniazid should receive pyridoxine supplementation. • For patients with extrapulmonary tuberculosis, a six- to nine-month regimen (two months of isoniazid, rifampin, pyrazinamide, and ethambutol followed by four to seven months of isoniazid and rifampin) is recommended. • Exceptions to the recommendation for a six- to nine-month regimen for extrapulmonary tuberculosis include central nervous system disease (tuberculoma or meningitis) and bone and joint tuberculosis, for which many experts recommend nine to 12 months. • Adjuvant corticosteroids should be added when treating central nervous system and pericardial disease. • Treatment with corticosteroids should be started intravenously as early as possible with change to oral therapy individualized according to clinical improvement. • Recommended corticosteroid regimens are dexamethasone 0.3 to 0.4 mg/kg tapered over six to eight weeks or prednisone 1 mg/kg for three weeks, then tapered for three to five weeks. <u>Treatment of varicella zoster virus disease</u> • For uncomplicated varicella, the preferred treatment options are valacyclovir (1 gram orally three times daily), or famciclovir (500 mg orally three times daily) for five to seven days. Oral acyclovir (20 mg/kg body weight up to a maximum dose of 800 mg five times daily) can be an alternative. • Prompt antiviral therapy should be instituted in all human immunodeficiency virus-seropositive patients whose herpes zoster is diagnosed within one week of rash onset (or any time before full crusting of lesions). The recommended treatment options for acute localized dermatomal herpes zoster in human immunodeficiency virus-infected patients are oral valacyclovir, famciclovir, or acyclovir (doses as above) for seven to 10 days, although longer durations of therapy should be considered if lesions resolve slowly. Valacyclovir or famciclovir are preferred because of their improved pharmacokinetic properties and simplified dosing schedule. • If cutaneous lesions are extensive or if visceral involvement is suspected, intravenous acyclovir should be initiated and continued until clinical improvement is evident. A switch from intravenous acyclovir to oral antiviral therapy (to complete a 10 to 14 day treatment course) is reasonable when formation of new cutaneous lesions has ceased and the signs and symptoms of visceral varicella zoster virus infection are clearly improving. • Optimal antiviral therapy for progressive outer retinal necrosis remains undefined. Specific treatment should include systemic therapy with at least one intravenous drug (selected from acyclovir, ganciclovir, foscarnet, and cidofovir) coupled with injections of at least one intravitreal drug (selected from ganciclovir and foscarnet). Treatment regimens for progressive outer retinal necrosis recommended by certain specialists include a combination of intravenous ganciclovir and/or foscarnet plus intravitreal injections of ganciclovir and/or foscarnet. The prognosis for visual preservation in involved eyes is poor, despite aggressive antiviral therapy.

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	• Other infectious disease states mentioned within these guidelines note that the treatment guidelines for that disease state should be utilized. • The guideline specifies that detailed recommendations for the treatment of human herpesvirus-8 and associated malignancies are beyond the scope of these guidelines. • Other excluded infectious disease states offer no specific therapy or utilize medications not licensed in the United States.
Center for International Blood and Marrow Transplant Research/National Marrow Donor Program/European Blood and Marrow Transplant Group/American Society of Blood and Marrow Transplantation/ Canadian Blood and Marrow Transplant Group/ Infectious Diseases Society of America/Society for Healthcare Epidemiology of America/Association of Medical Microbiology and Infectious Diseases Canada/Centers for Disease Control and Prevention: **Guidelines for Preventing Infectious Complications Among Hematopoietic Stem Cell Transplantation Recipients: A Global Perspective (2009)**[11]	<u>Cytomegalovirus (CMV) recommendations</u> • Hematopoietic cell transplantation (HCT) candidates should be tested for CMV antibodies prior to transplant to determine their risk for primary CMV infection and reactivation after HCT. • CMV-seropositive HCT recipients and CMV-seronegative recipients with CMV-seropositive donors should be placed on CMV preventative therapy from time of engraftment until at least 100 days after HCT. • A prophylaxis strategy against early CMV replication for allogeneic recipients involves administering prophylaxis to all allogeneic recipients at risk throughout the period from engraftment to 100 days after HCT. Ganciclovir, high-dose acyclovir, and valacyclovir are all effective at reducing the risk for CMV infection after HCT. • Ganciclovir is often used as a first-line drug for preemptive therapy. Although foscarnet is as effective as ganciclovir, it is currently more commonly used as a second-line drug, because of the requirement for pre-hydration and electrolyte monitoring. Preemptive therapy should be given for a minimum of two weeks. Patients who are ganciclovir-intolerant should be treated with foscarnet. <u>Fungal infection recommendations</u> • Fluconazole is the drug of choice for the prophylaxis of invasive candidiasis before engraftment in allogeneic hematopoietic cell transplant recipients, and may be started from the beginning or just after the end of the conditioning regimen. • The optimal duration of fluconazole prophylaxis is not defined. • Fluconazole is not effective against *Candida krusei* and *Candida glabrata* and should not be used for prophylaxis against these strains. • Micafungin is an alternative prophylactic agent. • Itraconazole oral solution has been shown to prevent invasive fungal infections, but use of this drug is limited by poor tolerability and toxicities. • Voriconazole and posaconazole may be used for prevention of candidiasis post-engraftment. • Oral amphotericin B, nystatin, and clotrimazole troches may control superficial infection and control local candidiasis but have not been shown to prevent invasive candidiasis. • Transplant patients with candidemia or candidiasis may still receive transplants if their infection is diagnosed early and treated aggressively with amphotericin B or appropriate doses of fluconazole. • Autologous recipients have a lower risk of infection compared to allogeneic recipients and may not require prophylaxis, though it is still recommended in patients who have underlying hematologic malignancies, those who will have prolonged neutropenia and mucosal damage, or have recently received fludarabine. Itraconazole oral solution has been shown to prevent mold infections. • In patients with graft-vs-host disease, posaconazole has been reported

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	to prevent invasive mold infections. • Patients with prior invasive aspergillosis should receive secondary prophylaxis with a mold-active drug. The optimal drug has not been determined, but voriconazole has been shown to have benefit for this indication. <u>Hepatitis B virus (HBV) recommendations</u> • Limited data suggests HCT donors with detectable HBV DNA should receive antiviral therapy for four weeks or until viral load is undetectable. Expert opinion suggests entecavir for this use. • HCT recipients with active HBV posttransplant should be treated with lamivudine for at least six months in autologous HCT recipients and for six months after immunosuppressive therapy has stopped in allogenic HCT recipients. <u>Hepatitis C virus (HCV) recommendations</u> • Treatment for chronic HCV should be considered in all HCV-infected HCT recipients. • The patient must be in complete remission from the original disease, be >2 years posttransplant without evidence of either protracted GVHD, have been off immunosuppression for 6 months, and have normal blood counts and serum creatinine. • Treatment should consist of full-dose peginterferon and ribavirin and should be continued for 24 to 48 weeks, depending on response. <u>Herpes simplex virus (HSV) recommendations</u> • Acyclovir prophylaxis should be offered to all HSV-seropositive allogenic recipients to prevent HSV reactivation during the early transplant period for up to 30 days. • Routine acyclovir prophylaxis is not indicated for HSV-seronegative allogenic recipients. • Use of ganciclovir for CMV prophylaxis will provide sufficient prophylaxis for HSV. • Foscarnet is the treatment of choice for acyclovir-resistant HSV. • Valacyclovir is equally effective at HSV prophylaxis when compared to acyclovir. • Foscarnet is not recommended for routine HSV prophylaxis among HCT recipients due to renal and infusion-related toxicity. Patients who receive foscarnet for other reasons (e.g., CMV prophylaxis) do not require additional acyclovir prophylaxis. • There is inadequate data to make recommendations regarding the use of famciclovir for HSV prophylaxis. • HSV prophylaxis lasting >30 days after HCT might be considered for persons with frequent recurrences of HSV infection. Acyclovir or valacyclovir can be used during phase I (pre-engraftment) for administration to HSV-seropositive autologous recipients who are likely to experience substantial mucositis from the conditioning regimen. <u>Respiratory syncytial virus (RSV) recommendations</u> • Some researchers recommend preemptive aerosolized ribavirin for patients with RSV upper respiratory infection (URI), especially those with lymphopenia (during the first three months after HCT) and preexisting obstructive lung disease (late after HCT). • Although a definitive, uniformly effective preemptive therapy for RSV

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	infection among HCT recipients has not been identified, certain other strategies have been proposed, including systemic ribavirin, RSV antibodies (i.e., passive immunization with high-RSV-titer IVIG, RSV immunoglobulin) in combination with aerosolized ribavirin, and RSV monoclonal antibody. • No randomized trial has been completed to test the efficacy of these strategies; therefore, no specific recommendation regarding any of these strategies can be given at this time. <u>Varicella zoster virus (VZV) recommendations</u> • Long-term acyclovir prophylaxis to prevent recurrent VZV infection is recommended for the first year after HCT for VZV-seropositive allogenic and autologous HCT recipients. Acyclovir prophylaxis may be continued beyond one year in allogenic HCT recipients who have graft-vs-host disease or require systemic immunosuppression. • Valacyclovir may be used in place of acyclovir when oral medications are tolerated. • There is not enough data to recommend use of famciclovir in place of valacyclovir or acyclovir for VZV prophylaxis. • Any HCT recipient with VZV-like rash should receive preemptive intravenous acyclovir therapy until two days after the lesions have crusted • Acyclovir or valacyclovir may be used in place of VZV immunoglobulin for post-exposure therapy.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the echinocandins are noted in Table 4. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 4. FDA-Approved Indications for the Echinocandins[1-6]

Indication	Anidulafungin	Caspofungin	Micafungin
Candidemia and other forms of *Candida* infections (intra-abdominal abscesses and peritonitis)	✔		
Candidemia and other forms of *Candida* infections (intra-abdominal abscesses, peritonitis, and pleural space infections)		✔	
Candidemia, acute disseminated candidiasis, *Candida* peritonitis and abscesses			✔
Esophageal candidiasis	✔	✔	✔
Prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation			✔
Empirical therapy for presumed fungal infections in febrile, neutropenic patients		✔	
Treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies (e.g., amphotericin B, lipid formulations of amphotericin B, itraconazole)		✔	

IV. Pharmacokinetics

The pharmacokinetic parameters of the echinocandins are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Echinocandins[1-6]

Generic Name(s)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Anidulafungin	>99	Chemical degradation	Renal (<1) Feces (30)	26.5
Caspofungin	97	Liver	Renal (41) Feces (35)	8 to 13
Micafungin	99	Liver	Renal (<15) Feces (70)	5 to 17

V. Drug Interactions

Significant drug interactions with the echinocandins are listed in Table 6.

Table 6. Significant Drug Interactions with the Echinocandins[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Caspofungin, micafungin	2	Cyclosporine	The pharmacologic effects of caspofungin may be increased by cyclosporine. Transient increases of liver function tests up to 3 times normal may occur when caspofungin and cyclosporine are taken concomitantly.

Significance level 1 = major severity; significance level 2 = moderate severity

VI. Adverse Drug Events

The most common adverse drug events reported with the echinocandins are listed in Table 7.

Table 7. Adverse Drug Events (%) Reported with the Echinocandins[1-6]

Adverse Events	Anidulafungin	Caspofungin	Micafungin
Cardiovascular System			
Arrhythmia	-	<5	<1
Atrial fibrillation	<2	<5	3 to 5
Bradycardia	-	<5	3 to 5
Bundle branch block (right)	<2	-	-
Cardiac arrest	-	<5	<1
Cyanosis	-	-	<1
Electrocardiogram abnormality	<2	-	-
Edema	-	<5	5
Hypertension	<2	5 to 10	3 to 5
Hypotension	<2	3 to 20	6 to 10
Myocardial infarction	-	<5	<1
Peripheral edema	<2	6 to 11	7
QT prolongation	<2	-	-
Shock	-	-	<1
Sinus arrhythmia	<2	-	-
Tachycardia	-	4 to 11	3 to 8
Ventricular extrasystoles	<2	-	-
Central Nervous System			

Adverse Events	Anidulafungin	Caspofungin	Micafungin
Anxiety	-	<5	6
Chills	-	9 to 23	-
Confusion	-	<5	-
Delirium	-	-	<1
Depression	-	<5	-
Dizziness	<2	<5	-
Encephalopathy	-	-	<1
Fatigue	-	<5	6
Fever	<2	6 to 30	7 to 20
Headache	<2	5 to 15	2 to 16
Insomnia	-	<5	4 to 10
Intracranial hemorrhage	-	-	<1
Seizure	<2	<5	<1
Somnolence	-	<5	-
Tremor	-	<5	-
Dermatological			
Erythema	<2	4 to 9	-
Erythema multiforme	-	<5	<1
Flushing	<2	<5	-
Petechiae	-	<5	-
Pruritus	<2	6 to 7	6
Rash	<2	4 to 23	2 to 9
Skin exfoliation	-	<5	-
Skin lesion	-	<5	-
Skin necrosis	-	-	<1
Stevens-Johnson syndrome	-	<5	<1
Toxic epidermal necrolysis	-	-	<1
Urticaria	<2	<5	<1
Endocrine and metabolic			
Acidosis	-	-	<1
Cholestasis	<2	-	-
Hot flushes	<2	-	-
Jaundice	-	<5	-
Gastrointestinal			
Abdominal distension	-	<5	-
Abdominal pain	<2	4 to 9	2 to 10
Anorexia	-	<5	6
Appetite decreased	-	<5	-
Constipation	<2	<5	11
Diarrhea	3	6 to 27	8 to 23
Dyspepsia	-	-	6
Dyspepsia	<2	-	-
Fecal incontinence	<2	-	-
Hiccups	-	-	<1
Mucosal inflammation	-	4 to 10	14
Nausea	<2	4 to 15	7 to 22
Pancreatitis	-	<5	-
Vomiting	<2	6 to 17	7 to 22
Genitourinary			
Anuria	-	-	<1
Hematuria	-	10	-
Hemoglobinuria	-	-	<1
Nephrotoxicity	-	<5	-
Oliguria	-	-	<1

Adverse Events	Anidulafungin	Caspofungin	Micafungin
Renal failure/insufficiency	-	<5	<1
Renal tubular necrosis	-	-	<1
Urinary tract infection	-	<5	-
Hematological			
Anemia	-	2 to 11	3 to 10
Coagulopathy	<2	-	<1
Febrile neutropenia	-	-	6
Hematocrit decreased	-	13 to 18	-
Hemoglobin decreased	-	18 to 21	-
Hemolysis	-	-	<1
Hemolytic anemia	-	-	<1
Leukopenia	<1	-	-
Neutropenia	1	-	14
Pancytopenia	-	-	<1
Thrombocytopenia	<2	<5	4 to 15
Thrombotic thrombocytopenia purpura	-	-	<1
White blood cell decreases	-	12	<1
Hepatic			
Hepatic dysfunction	<2	-	<1
Hepatic failure	-	<5	<1
Hepatic necrosis	<2	<5	-
Hepatitis	<2	-	-
Hepatocellular damage	-	-	<1
Hepatomegaly	-	<5	<1
Hepatotoxicity	-	<5	-
Jaundice	-	-	<1
Laboratory Test Abnormalities			
Albumin decreased	-	7	-
Alkaline phosphatase increased	<2	9 to 22	6 to 8
Alanine aminotransferase increased	-	-	5
Amylase increased	<2	-	-
Aspartate aminotransferase increased	-	-	6
Bilirubin increased	<2	5 to 13	-
Blood urea nitrogen increased	-	4 to 9	<1
Creatine phosphokinase increased	<2	-	-
Gamma-glutamyl transpeptidase increased	<2	-	-
Hyperbilirubinemia	-	-	<1
Hypercalcemia	<2	<5	-
Hyperglycemia	<2	6	6
Hyperkalemia	<2	<5	4 to 5
Hypernatremia	<2	-	4 to 6
Hypocalcemia	-	-	7
Hypoglycemia	-	-	6 to 7
Hypokalemia	3	5 to 23	14 to 18
Hypomagnesemia	<2	7	6 to 13
Hyponatremia	-	-	<1
Lipase increased	<2	-	-
Platelet count increased	<2	-	-
Prothrombin time prolonged	<2	-	-
Serum creatinine increased	<2	3 to 11	<1
Transaminases increased	<1 to 2	2 to 18	-
Urea increased	<2	-	-
Musculoskeletal			

Adverse Events	Anidulafungin	Caspofungin	Micafungin
Arthralgia	-	<5	<1
Back pain	<2	<5	5
Rigors	<2	-	9
Weakness	-	<5	-
Respiratory			
Apnea	-	-	<1
Cough	<2	6 to 11	8
Dyspnea	-	9	6
Epistaxis	-	<5	6
Hypoxia	-	<5	<1
Pleural effusion	-	9	-
Pneumonia	-	4 to 11	<1
Pulmonary edema	-	<5	-
Pulmonary embolism	-	-	<1
Rales	-	7	-
Respiratory distress	-	≤8	-
Stridor	-	<5	-
Tachypnea	-	<5	-
Other			
Anaphylaxis	-	<5	-
Angioneurotic edema	<2	-	-
Bacteremia	-	<5	5 to 9
Blurred vision	<2	-	-
Candidiasis	<2	-	-
Clostridial infection	<2	-	-
Coagulopathy	-	<5	-
Deep vein thrombosis	<2	-	<1
Disseminated intravascular coagulation	-	-	<1
Dystonia	-	<5	-
Eye pain	<2	-	-
Facial edema	-	-	<1
Febrile neutropenia	-	<5	-
Fluid overload	-	<5	5
Fungemia	<2	-	-
Infection	-	1 to 9	<1
Infusion-related reaction	<2	20 to 35	-
Injection site necrosis	-	-	<1
Injection site thrombosis	-	-	<1
Pain (extremities)	-	<5	-
Phlebitis	<2	18	5 to 19
Sepsis	-	5 to 7	5 to 6
Septic shock	-	11 to 14	-
Sweating	<2	-	-
Thrombophlebitis	<2	18	<1
Vasodilation	-	-	<1
Visual disturbance	<2	-	-

✓ Percent not specified
- Event not reported

VII. Dosing and Administration

The usual dosing regimens for the echinocandins are listed in Table 8.

Table 8. Usual Dosing Regimens for the Echinocandins[1-6]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Anidulafungin	Candidemia and other forms of *Candida* infections (intra-abdominal abscesses and peritonitis): Injection: 200 mg loading dose on day one, followed by 100 mg daily thereafter. Treatment should continue for at least 14 days after the last positive culture Esophageal candidiasis: Injection: 100 mg loading dose on day one, followed by 50 mg daily thereafter. Patients should be treated for a minimum of 14 days and at least 7 days following resolution of symptoms	Safety and efficacy in children have not been established	Injection: 50 mg 100 mg
Caspofungin	Candidemia and other forms of *Candida* infections (intra-abdominal abscesses, peritonitis, and pleural space infections): Injection: 70 mg loading dose on day one, followed by 50 mg daily thereafter. Treatment should continue for at least 14 days after the last positive culture Empirical therapy for presumed fungal infections in febrile, neutropenic patients: Injection: 70 mg loading dose on day one, followed by 50 mg daily thereafter. Empirical therapy should be continued until resolution of neutropenia. Patients found to have a fungal infection should be treated for at least 14 days; treatment should continue for at least 7 days after resolution of neutropenia and clinical symptoms Esophageal candidiasis: Injection: 50 mg daily for 7 to 14 days after symptom resolution	Unspecified Infections: Injection, patients three months to 17 years of age, 70 mg/m^2 loading dose on day one, followed by 50 mg/m^2 daily thereafter. The maximum loading dose and the daily maintenance dose should not exceed 70 mg, regardless of the patient's calculated dose	Injection: 50 mg 70 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Treatment of invasive aspergillosis in patients who are refractory to or intolerant of other therapies (e.g., amphotericin B, lipid formulations of amphotericin B, itraconazole): Injection: 70 mg loading dose on day one, followed by 50 mg daily thereafter. Total duration of therapy depends on severity of underlying disease, recovery from immunosuppression, and clinical response		
Micafungin	Candidemia, Acute Disseminated Candidiasis, *Candida* Peritonitis and Abscesses: Injection:100 mg once daily Esophageal candidiasis: Injection:150 mg once daily Prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation: Injection:50 mg once daily	Candidemia, Acute Disseminated Candidiasis, *Candida* Peritonitis and Abscesses: Injection, patients 4 months and older: Two mg/kg once daily, maximum daily dose 100 mg Esophageal candidiasis: Injection, patients 4 months and older: ≤30 kg: Three mg/kg once daily >30 mg: 2.5 mg/kg once daily, maximum daily dose 150 mg Prophylaxis of *Candida* infections in patients undergoing hematopoietic stem cell transplantation: Injection, patients 4 months and older: 1 mg/kg once daily, maximum daily dose 50 mg	Injection: 50 mg 100 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the echinocandins are summarized in Table 9.

Table 9. Comparative Clinical Trials with the Echinocandins

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Aspergillosis				
Kartsonis et al.[12] (2005) Caspofungin 70 mg loading dose, followed by 50 mg daily for 28 to 90 days	OL Patients 18 to 80 years of age with definite or probable invasive aspergillosis who were refractory or intolerant to amphotericin B or a lipid preparation of amphotericin B	N=48 14 days posttreatment follow-up	Primary: Clinical response (favorable= complete or partial response; complete= resolution of signs, symptoms, radiographic findings, and bronchoscopic findings; partial= clinically meaningful improvement in above criteria) Secondary: Not reported	Primary: A favorable response was seen in 44% of patients treated with caspofungin. A complete response was seen in 20% of patients treated with caspofungin. A partial response was seen in 24% of patients treated with caspofungin. Secondary: Not reported
Maertens et al.[13] (2004) Caspofungin 70 mg loading dose, followed by 50 mg daily for an average of 28 days	OL, MC Patients with proven or probable invasive aspergillosis who were refractory or intolerant to amphotericin B, lipid formulations of amphotericin B, and itraconazole	N=83 28 day posttreatment follow-up	Primary: Clinical response (favorable= complete or partial response; complete response= resolution of all signs, symptoms, radiologic and/or bronchoscopic evidence; partial response=	Primary: Favorable response was seen in 44.6% of patients treated with caspofungin. Relapse was observed in 9.7% of patients, though only 1 case was confirmed microbiologically. Significantly more patients with hematological malignancies had a favorable response compared to patients who had undergone allogeneic hematopoietic stem cell transplant (P<0.01). Significantly more patients who were intolerant to standard therapy

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			clinically meaningful improvement in the above measures) Secondary: Eradication	(amphotericin B formulations, itraconazole) had a favorable response compared to patients who were refractory to standard therapy (P=0.03). Secondary: Eradication or presumptive eradication was observed in 33.8% of patients. Eradication was observed in 28% of patients infected with *Aspergillus fumigatus*, 54% infected with *Aspergillus flavus*, and 25% infected with *Aspergillus niger*.
Maertens et al.[14] (2006) Caspofungin 70 mg daily in combination with either an azole (itraconazole or voriconazole) or a polyene (amphotericin B deoxycholate or an amphotericin B lipid preparation) All patients received active treatment with combination therapy.	OL, MC Patients 16 years of age and older with definite or probable invasive aspergillosis who were refractory or intolerant to standard antifungal therapy	N=53 12 months posttreatment follow-up	Primary: Clinical response (favorable= complete or partial response; complete response= resolution of all signs, symptoms, radiologic and/or bronchoscopic evidence; partial response= clinically meaningful improvement in the above measures) Secondary: Not reported	Primary: At the end of combination therapy, 55% of patients had a favorable response. Of the patients with a favorable response (29), four showed a complete response and 25 showed a partial response. At day 84, 49% of patients had a favorable response. Success at the end of combination therapy ranged from 43% in the caspofungin plus itraconazole group to 60% in the caspofungin plus voriconazole group. In the caspofungin plus polyene group, success rates were 80, 29, and 50% for amphotericin B deoxycholate, amphotericin B lipid complex, and liposomal amphotericin B, respectively. Of 46 refractory patients, the addition of caspofungin to the initially refractory antifungal agent demonstrated a favorable response in 66% of patients. Success was observed in 20% of patients who were initially refractory to caspofungin and had a non-echinocandin antifungal agent added. Of the patients who were refractory to voriconazole therapy, 73% had a favorable response when caspofungin was added to voriconazole compared to a 40% favorable response rate in patients who discontinued voriconazole and switched to two new antifungal agents.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Caillot et al.[15] (2007) Caspofungin 70 mg on day 1, followed by 50 mg daily thereafter plus liposomal amphotericin B 3 mg/kg per day vs liposomal amphotericin B 10 mg/kg per day	RCT, MC Immuno-compromised patients ≥10 years of age with proven or probable invasive aspergillosis	N=30 12 week posttreatment follow-up	Primary: Percentage of patients who had favorable overall responses (partial or complete responses) at the end of therapy (EOT). Secondary: Time to favorable overall response, time to complete response, survival at EOT, percentage of patients with recurrent infection (defined as failure for overall response), and survival during the 4-week posttreatment follow-up	Primary: The overall response at EOT was significantly more favorable for patients in the combination group (67%) compared to patients in the high-dose monotherapy group (27%; P=0.028). Secondary: At week 12, a favorable response was obtained by 10 of 15 patients in the high-dose monotherapy group (67%; eight patients had a partial response and two patients had a complete response) and by 12 of 15 patients in the combination group (80%; nine patients had a partial response and three patients had a complete response). A favorable or unfavorable response at EOT was independent of hematologic status at EOT (recurrence, remission, or stable; P=0.442). The survival rate at EOT was 97% (one death had occurred in the high-dose monotherapy group). At week 12, all 15 patients in the combination group were alive, whereas three of 15 patients had died in the high-dose monotherapy group. Those three patients died due to progression of the underlying hematologic condition; and, in one patient, fungal infection contributed to the death. Study drug-related adverse events were less frequent in the combination group than in the high-dose monotherapy group.
Kontoyiannis et al.[16] (2009) Micafungin 75 mg/day IV daily (1.5 mg/kg/day for patients <40 kg)	OL Adult and pediatric hematopoietic stem cell transplant patients with proven or probable invasive aspergillosis	N=98 2 to 425 days	Primary: Global response to treatment, based on clinical, radiological, and mycological assessment at the end of therapy	Primary: The overall response rate was 26%. An additional 12 patients had stable infections. A response to treatment was seen in 22% of the patients in the *de novo* treatment group, 24% in the refractory IA group, 100% in the toxicity failure group, 24% in the combination therapy group, and 38% in the micafungin-alone group. There were no significant differences in response according to the type of transplant, site of infection, or infecting *Aspergillus* species.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
alone or in addition to the patient's current systemic antifungal regimen for up to 90 days			Secondary: Not reported	Adverse events that occurred in >2% of patients included nausea, increased alanine aminotransferase, vomiting, hyperbilirubinemia, and arthralgia. Secondary: Not reported
Candidiasis (Mucosal)				
Krause et al.[17] (2004) Anidulafungin 100 mg loading dose on day 1, then 50 mg daily for 14-21 days vs fluconazole 200 mg oral loading dose, then 100 mg orally daily for 14 to 21 days	RCT, DB, PC, MC Patients 18 to 65 years of age with esophageal candidiasis and a predisposing risk factor for fungal infection	N=601 Up to 35 weeks	Primary: Endoscopic response at the end of therapy (cure=complete resolution of lesions, improvement= decrease of ≥1 grade from baseline) Secondary: Clinical response (absence or improvement in symptoms), myco-logical response (eradication)	Primary: Endoscopic success was observed in 97.2% of patients in the anidulafungin group and 98.8% of patients in the fluconazole group. No significant difference was observed. Secondary: Clinical success was observed in 97.2% of patients in the anidulafungin group and in 98% in the fluconazole group. No significant difference was observed. Mycological success was observed in 86.7% of patients in the anidulafungin group and in 90.9% in the fluconazole group.
Kartsonis et al.[18] (2004) Caspofungin 50 mg daily (esophageal or oropharyngeal candidiasis) or 70 mg loading dose, then 50 mg daily	OL Patients 18 to 80 years of age with mucosal or invasive candidiasis who were intolerant or refractory to amphotericin B therapy	N=37 7 to 14 days after last positive culture	Primary: Clinical response Secondary: Not reported	Primary: Favorable outcomes were observed in 86% of patients who had mucosal candidiasis. Favorable outcomes were observed in 87% of patients with invasive candidiasis. Ten of 11 patients with previously failed fluconazole therapy responded to caspofungin.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(invasive candidiasis)				Thirteen of 14 patients who were refractory to multiple antifungals responded favorably to caspofungin. Eighty-three percent of patients with invasive disease who failed multiple antifungals responded favorably. Secondary: Not reported
Arathoon et al.[19] (2002) Caspofungin 35 to 70 mg daily for 7 to 14 days vs amphotericin B 0.5 mg/kg/day for 7 to 14 days	RCT, DB, DR Patients 18 to 65 years of age with a diagnosis of oropharyngeal and/or esophageal candidiasis	N=140 10 to 18 days	Primary: Clinical response Secondary: Microbiological eradication	Primary: A higher portion of patients in the caspofungin groups achieved a favorable clinical response (74 to 91%) compared to the amphotericin B treatment group (63%), however this was not statistically significant. More patients with oropharyngeal disease had a favorable response (85%) compared to those with esophageal involvement (73%). Secondary: Microbiological eradication was observed in a larger portion of patients in the caspofungin groups compared to the amphotericin B group. There was no significant difference in the clearance of *Candida albicans* vs non-*albicans* species.
Villanueva et al.[20] (2001) Caspofungin 50 mg for 14 days vs caspofungin 70 mg for 14 days vs amphotericin B 0.5 mg/kg/day for	RCT, DB, MC Patients 21 to 65 years of age with endoscopically and microbiologically documented *Candida* esophagitis	N=128 28 days	Primary: Combined clinical and endoscopic response and microbiological response	Primary: The highest response rate was observed in the caspofungin 70 mg group and the lowest was observed in the amphotericin B group. The mean differences in response rates for caspofungin vs amphotericin B were 11% (95% CI, -9 to 32%) and 26% (95% CI, 4 to 50%) for those receiving 50 and 70 mg, respectively, at the primary end point 2 weeks after discontinuation of therapy. Analysis of all evaluable patients (per protocol) were similar to the modified intention-to-treat analysis for combined response rates: 88, 96, and 78% at the end of therapy and 77, 89, and 68% two weeks after discontinuation of therapy for patients receiving caspofungin 50 mg, caspofungin 70 mg and amphotericin B, respectively. Time to resolution of symptoms was not different for any of the treatment

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
14 days				groups. More than half the patients in each treatment arm had resolution of all symptoms by day 4 of therapy. Symptoms persisted in 7, 0, and 13% of patients at the end of therapy in the groups receiving caspofungin 50 mg, caspofungin 70 mg, and amphotericin B, respectively. Endoscopic improvement was slightly higher in the caspofungin groups compared to the amphotericin B groups. Marked reduction in endoscopic grade was observed in 74, 89, and 63% of patients in the caspofungin 50 mg group, 70 mg group, and amphotericin B group, respectively. Caspofungin had slightly higher fungal eradication rates compared to amphotericin B. *Candida albicans* was not isolated from 71, 85, and 60% of patients taking caspofungin 50 mg, 70 mg, and amphotericin B, respectively. Eradication rates for non-*albicans* species were 64, 71, and 40% for caspofungin 50 mg, 70 mg, and amphotericin B, respectively.
Villanueva et al.[21] (2002) Caspofungin 50 mg daily for 7 to 21 days vs fluconazole 200 mg daily for 7 to 21 days	RCT, DB, MC Patients with symptomatic, endoscopically and microbiologically documented *Candida* esophagitis	N=177 5 to 7 day posttreatment follow-up	Primary: Combined clinical and endoscopic response and microbiological response Secondary: Not reported	Primary: Combined response rates in patients receiving caspofungin and fluconazole were 81 and 85%, respectively. No significant difference was seen between the treatment groups. Microbiological response was observed in 59% of patients in the caspofungin group and 76% of patients in the fluconazole group. Secondary: Not reported
Kartsonis et al.[22] (2002) Caspofungin 35 mg, 50 mg, or 70 mg daily	RETRO Symptomatic patients with endoscopically confirmed *Candida*	N=32 3 to 14 days posttreatment follow-up	Primary: Clinical outcomes Secondary: Not reported	Primary: Favorable response was seen in 64% of patients with infections which were clinically refractory to fluconazole and subsequently treated with caspofungin. Favorable response to caspofungin was seen in 79% of patients with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs amphotericin B 0.5 mg/kg/day vs fluconazole 200 mg IV daily	esophagitis and decreased susceptibility to fluconazole			infections that had decreased susceptibility to fluconazole. Secondary: Not reported
Pettengell et al.[23] (2004) Micafungin 12.5 to 100 mg daily for up to 14 to 21 days	MC, OL Patients 18 years of age and older with human immunodeficiency virus infection and endoscopically confirmed esophageal candidiasis	N=120 2-week posttreatment follow-up	Primary: Investigators' evaluation of clinical response at the end of therapy (success= cure or improvement in signs and symptoms) Secondary: Improvement in esophageal lesions	Primary: A positive clinical response was observed in all patients in all dose categories except for the 12.5 mg dose group, where all but one patient had a positive clinical response. A statistically significant dose-response relationship was observed in the proportion of patients cleared in each group: 33.3, 53.8, 86.7, 84.2, and 94.7% for the 12.5, 25, 50, 75, and 100 mg groups, respectively (P<0.001). Secondary: Based on endoscopy, the 75 and 100 mg doses were more effective in reducing mucosal lesions compared to the lower dose groups (P<0.001).
de Wet et al.[24] (2005) Micafungin 150 mg daily for up to 42 days vs fluconazole 200 mg IV for up to 42 days	RCT, DB, MC, PG Patients 16 years of age and older with endoscopically confirmed esophageal candidiasis	N=523 4-week posttreatment follow-up	Primary: Treatment success at the end of therapy Secondary: Clinical and mucosal response at the end of therapy, therapeutic response at the end of therapy, relapse at 2 and 4 weeks	Primary: Endoscopic cure rate was 87.7% at the end of therapy in the micafungin group compared to 88.0% for fluconazole patients and no significant differences were observed. Secondary: The clinical success rates (cleared or improved) for micafungin and fluconazole were 94.2 and 94.6%, respectively. Overall therapeutic success rates for micafungin and fluconazole were 87.3 and 87.2%, respectively. The overall incidence of relapse at two and four weeks post-therapy was 15.2 and 11.3% in the micafungin and fluconazole groups, respectively

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			post-treatment	(P>0.313).
de Wet et al.[25] (2004) Micafungin 50 mg, to 150 mg daily for up to 14 to 21 days vs fluconazole 200 mg IV daily for up to 14 to 21 days	RCT, DB, MC, PG Patients 18 years of age or older with human immunodeficiency virus infection and endoscopically confirmed esophageal candidiasis (EC)	N=245 2-week posttreatment follow-up	Primary: Endoscopic cure rate and eradication rates Secondary: Change in endoscopic cure rate compared to baseline at day 14, clinical response at end of treatment, EC severity score, overall therapeutic success, incidence of relapse	Primary: Comparisons of micafungin groups showed a dose-response relationship for endoscopic cure. Cure rates were 68.8, 77.4, and 89.9% for the 50, 100, and 150 mg dose groups, respectively (P=0.024 for comparison between the three groups; P=0.007 for the comparison of the 50 mg and 150 mg groups). There was no significant difference seen between the fluconazole group and either the 100 mg or 150 mg micafungin groups (P=0.136 and P=0.606, respectively). Fluconazole had a lower endoscopic cure rate than micafungin 150 mg in patients with an endoscopic grade 3 at baseline (77.8 and 100% respectively). Eradication rates were 35.1, 78.3, 57.1, and 67.3% for the micafungin 50, 100, and 150 mg groups and the fluconazole group, respectively. Eradication rates for micafungin 100 mg were higher than for micafungin 150 mg (P=0.031). No significant difference was observed between micafungin 100 mg and fluconazole or micafungin 150 mg and fluconazole (P=0.263 and P=0.312, respectively). Secondary: All treatment groups showed an improvement in endoscopic findings at the end of treatment compared to baseline (P=0.003 for the micafungin groups). Endoscopic cure rate at day 14 and clinical response at the end of treatment were dose-dependent in the micafungin groups, and comparable in the 100 mg and 150 mg micafungin group and the fluconazole group (P=0.574). Therapeutic success was comparable between the 100 mg and 150 mg micafungin groups and the fluconazole group (P=0.463).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The rates of improvement in EC severity scores were comparable in the 100 mg and 150 mg micafungin groups and the fluconazole group. Worsening EC severity or use of non-prophylactic antifungal therapy was observed in nine patients in the micafungin group during follow-up and in no patients in the fluconazole group.
Candidiasis (Systemic)				
Pfaller et al.[26] (2005) Anidulafungin 50 to 100 mg IV daily	OL, DR Patients 18 years of age and older with candidemia and/or candidiasis	N=68 2-week posttreatment follow-up	Primary: Clinical response (eradication of pathogen) Secondary: Not reported	Primary: Eradication rates were 74, 85, and 89% for the 50, 75, and 100 mg groups, respectively. Secondary: Not reported
Krause et al.[27] (2004) Anidulafungin 50 mg, 75 mg, or 100 mg IV daily	DR, OL Patients 18 years of age and older with invasive candidiasis and an expected survival of >72 hours	N=116 2-week posttreatment follow-up	Primary: Global response at the follow-up visit defined as both and microbiological response Secondary: Global response at end of treatment, clinical and micro-biological response at end of treatment and follow-up	Primary: Global response rates at follow-up were 72, 85, and 83% for the 50, 75, and 100 mg groups, respectively. Secondary: Global response rates at the end of treatment were 84, 90, and 89% for the 50, 75, and 100 mg groups, respectively. Microbiological response rates at the end of treatment were 84, 93, and 89% for the 50, 75, and 100 mg groups, respectively. Clinical response rates at the end of treatment were 88, 90, and 89% for the 50, 75, and 100 mg groups, respectively. Microbiological response rates at the follow-up visit were 78, 85, and 88% for the 50, 75, and 100 mg groups, respectively. Clinical response rates at the follow-up visit were 72, 85, and 83% for the 50, 75, and 100 mg groups, respectively.
Nucci et al.[28] (2014) Anidulafungin 100	MC, NC, OL Patients aged ≥18 years, with one or	N=54 14 to 42 days	Primary: Global response rate at the end of treatment (EOT)	Primary: The primary endpoint of global response rate at EOT for the MITT population was 59.1% (95% CI, 44.6 to 73.6), when 13 patients with missing responses were counted as failures.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg daily IV for a minimum of 5 days	more signs and symptoms of acute fungal infection within 48 h prior to initiation of study of treatment, acute physiological assessment and chronic health evaluation (APACHE) II score <25		based on the modified intent-to-treat (MITT) population, which included patients who received any dose of study medication with confirmed candidemia or invasive candidiasis Secondary: Global response rate at the end of IV therapy and at a week 2 followup assessment; all-cause mortality; incidence of adverse events and discontinuations from the study; and change from baseline in clinical and laboratory parameters.	Secondary: At day 30, the all-cause mortality rate in the MITT population was 43.1% (N=19). Four of those deaths were considered by the investigator to be attributable to candidemia. The most commonly reported adverse events (in >10% of patients) were septic shock (11/54 patients, 20.4%) and hypokalemia (10/54 patients, 18.5%) There were 26 deaths in the safety population, encompassing 48 adverse effects with a fatal outcome. Two patients experienced fatal serious adverse events that were considered to be related to study treatment (anidulafungin) by both investigator and sponsor; hyperkaliemia, and study drug ineffective. No clinically relevant changes in laboratory parameters or vital signs were reported.
Reboli et al.[29] (2007) Anidulafungin 200 mg IV on day one, then 100 mg daily for 14 to 42 days vs	RCT, DB, MC Patients ≥16 years of age with candidemia or other forms of invasive candidiasis	N=261 6-week posttreatment follow-up	Primary: Global response at the end of IV therapy (success= resolution of signs and symptoms and no need for additional antifungal therapy	Primary: Significantly more patients in the anidulafungin group achieved a successful global response compared to the fluconazole group (75.6 and 60.2% respectively; P=0.01). Secondary: Significantly more patients in the anidulafungin group had a successful global response at the end of all therapy compared to the fluconazole group (74 and 56.8%, respectively; P<0.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fluconazole 800 mg IV on day 1 then 400 mg daily for 14 to 42 days All patients could receive oral fluconazole after 10 days of IV therapy.			and eradication of *Candida* species) Secondary: Global response at the end of all therapy and at 2 and 6 weeks follow-up, per-patient and per-pathogen microbiological response at all time points, death from all causes	Significantly more patients in the anidulafungin group had a successful global response at the 2-week follow-up compared to the fluconazole group (64.6 and 49.2%, respectively; P<0.02). There was no significant difference in the proportion of patients in either group who had a successful global response at the 6-week follow-up (55.9 and 44.1%; respectively). Microbiological success was observed for 88.1% of all pathogens in the anidulafungin group compared to 76.2% in the fluconazole group (P=0.02). There was no significant difference in all-cause mortality between the two treatment groups (P=0.13).
Reboli et al.[30] (2011) Anidulafungin 200 mg IV on day 1, then 100 mg daily for 14 to 42 days vs fluconazole 800 mg IV on day 1 then 400 mg daily for 14 to 42 days All patients could receive oral fluconazole after 10 days of IV therapy.	RCT, DB, MC (Post-hoc analysis) Patients ≥16 years of age with candidemia or other forms of invasive candidiasis. The study database was reviewed to identify all patients with systemic candidiasis caused by *Candida albicans* only. Patients with nonalbicans *Candida* infections and mixed infections (*Candida albicans* and another concurrent pathogen) at	N=261 6-week posttreatment follow-up	Primary: Global response at the end of IV therapy Secondary: Global response at the end of all therapy and at 2 and 6 weeks follow-up, microbiological response, death	Primary: The investigator-assessed global response rate at end of IV study treatment was higher in patients with *Candida albicans* infections treated with anidulafungin compared to fluconazole: 81.1 vs 62.3% (95% CI, 3.7 to 33.9; P=0.02). Secondary: Significantly more patients in the anidulafungin group had a successful global response at the end of all therapy and 2-week follow-up compared to the fluconazole group. The time to negative blood culture was significantly shorter for anidulafungin compared to fluconazole (P<0.05); median times to negative blood culture were 2 and 5 days, respectively. Persistent infection was reported in 2.7% of patients in the anidulafungin group compared to 13.1% of patients in the fluconazole group (P<0.05). The proportion of patients who died during the 6-week period from study entry was 20.3% in the anidulafungin arm and 21.3% in the fluconazole arm (P=0.842). Fewer deaths occurred within 24 hours of end of treatment with anidulafungin than with fluconazole (4 vs 13; P=0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	baseline were excluded.			Both study drugs were well tolerated and the respective safety profiles in patients with *Candida albicans* infection only were similar to those in the overall study populations.
Mora-Duarte et al.[31] (2002) Caspofungin 70 mg loading dose followed by 50 mg daily thereafter vs amphotericin B 0.6 to 0.7 mg/kg/day (non-neutropenic patients) or 0.7 to 1.0 mg/kg/day (neutropenic patients) After 10 days of IV therapy, non-neutropenic patients could be switched to oral fluconazole 400 mg daily.	RCT, DB, DD Patients 18 years of age and older with one or more positive *Candida* cultures in the previous 4 days	N=239 8-week posttreatment follow-up	Primary: Overall response to treatment (favorable= resolution of signs and symptoms of infection and negative culture) at the end of IV therapy	Primary: At the end of IV therapy, favorable response was observed in 73.4% of patients in the caspofungin group and 61.7% in the amphotericin B group. After adjusting for neutropenic status, the difference in percentage with a favorable response was 12.7% (P=0.09). Among patients meeting the prespecified criteria for evaluation, 80.7% of caspofungin patients and 64.9% of amphotericin B patients had a favorable response (P=0.03). A larger portion of patients in the amphotericin B group had toxicities requiring a change in therapy compared to the caspofungin group (P=0.03).
DiNubile et al.[32] (2005) Caspofungin 70 mg loading dose followed by 50 mg daily thereafter	RETRO Adult patients with proven invasive candidiasis	N=239 14 days following last positive culture	Primary: Clinical outcome (favorable= complete resolution of signs and symptoms of disease and	Primary: Favorable responses were slightly lower in patients with cancer compared to those without cancer (62% and 70%, respectively). Favorable responses were seen in 61% of caspofungin patients and 50% of amphotericin B patients with hematological malignancies, and in 80 and 59%, respectively, in patients with solid organ malignancies.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs amphotericin B 0.6 to 1.0 mg/kg/day All patients could be switched to oral fluconazole therapy after 10 days of IV therapy.			negative cultures) Secondary: Not reported	Of patients who were neutropenic at baseline, 46% responded favorably to treatment compared to 70% of non-neutropenic patients. Of neutropenic patients, 50% in the caspofungin group responded favorably compared to 40% in the amphotericin B group. The response rate for non-*albicans Candida* species was 76% compared to 48% for *albicans* species. Favorable response rates for *Candida albicans* and *Candida tropicalis* infections were 56 and 71%, respectively, in the caspofungin group and 45 and 43%, respectively, in the amphotericin B group. Secondary: Not reported
Wahab Mohamed and Ismail[33] (2012) Caspofungin (2 mg/kg/day) IV vs amphotericin B (1 mg/kg/day) IV	DB, PRO, RCT Neonates with confirmed invasive candidiasis who had at least one positive blood culture and/or positive cerebrospinal fluid culture or positive urine culture obtained by suprapubic aspiration	N=32 Patients received study drug for at least 14 days and were monitored for 14 days post-treatment	Primary: Efficacy (overall response to treatment) and safety (clinical and laboratory adverse events) Secondary: Not reported	Primary: The efficacy of caspofungin was significantly higher than that of amphotericin B group, with successful outcomes in 86.7% of patients treated with caspofungin and in 41.7% of those treated with amphotericin B (P=0.04). The overall drug-related clinical and laboratory adverse events were significantly lower in neonates who received caspofungin than in those who received amphotericin B (P<0.05). None of these adverse events led to caspofungin discontinuation; however, amphotericin B was withdrawn in five (29.4%) neonates. Secondary: Not reported
Betts et al.[34] (2009) Caspofungin 70 mg loading dose followed by 50 mg	RCT, MC, DB Adult patients ≥18 years of age with both clinical and microbiological	N=204 8-week posttreatment follow-up	Primary: Proportion of patients who developed a significant drug-related adverse	Primary: Significant drug-related adverse events were reported for 2 patients (1.9%) in the 70/50 mg treatment group and 3 patients (3.0%) in the 150 mg treatment group (95% CI, -4.1 to 6.8). The incidences of drug-related clinical adverse events (13.5 vs 14.0%),

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
daily thereafter vs caspofungin 150 mg daily After ≥10 days of caspofungin therapy, patients either continued to receive caspofungin therapy or were switched to oral fluconazole.	evidence of invasive candidiasis at a sterile site		event Secondary: Overall response (clinical and microbiological) at the end of therapy	serious drug-related clinical adverse events (0 vs 3.0%), and discontinuations of caspofungin therapy because of drug-related clinical adverse events (1.9 vs 2.0%) were similar between the 70/50 mg and 150 mg treatment groups, respectively. Secondary: At the end of caspofungin therapy, 71.6% of patients in the 70/50 mg treatment group and 77.9% of patients in the 150 mg treatment group had a favorable overall response. A favorable clinical response occurred for 71.6% of the 70/50 mg treatment group and 80.0% of patients in the 150 mg treatment group. A favorable microbiological response occurred for 82.4% of patients in the 70/50 mg treatment group and 88.4% of patients in the 150 mg treatment group. For each response category, there were no statistically significant differences between the treatment groups.
Pappas et al.[35] (2007) Caspofungin 70 mg loading dose followed by 50 mg daily thereafter vs micafungin 100 mg daily vs micafungin 150 mg daily	RCT, DB Patients ≥18 years of age with candidemia or invasive candidiasis	N=595 6-week posttreatment follow-up	Primary: Treatment success (defined as clinical and mycological success at the end of blinded intravenous therapy) Secondary: Not reported	Primary: A successful outcome at the end of treatment was achieved by 76.4% of patients in the micafungin 100 mg group, 71.4% of patients in the micafungin 150 mg group, and 72.3% of patients in the caspofungin group. Both micafungin 100 mg and micafungin 150 mg were non-inferior to the caspofungin (95% CI, -4.4 to 12.3% and 95% CI, -9.3 to 7.8%, respectively). The overall response rates for patients with *Candida albicans* were similar to those for patients with non-*albicans Candida* species across treatment arms. For patients with baseline APACHE II scores of ≤20 and >20, treatment success at the end of blinded intravenous therapy was similar across treatment arms. Success at the end of therapy, based on management of intravascular catheters, did not vary significantly between treatment arms. However, in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
After ≥10 days of IV therapy, patients were allowed to be switched to oral fluconazole 400 mg daily				each arm, patients who underwent intravascular catheter removal or replacement more often achieved treatment success, compared to patients who did not undergo catheter removal. In aggregate, 77.9% of patients whose intravascular catheter was removed or replaced achieved treatment success, compared to 63.2% of patients whose catheter was not removed or replaced (P=0.001). Persistently positive culture results as a cause of treatment failure were seen more frequently in micafungin 150 mg group (11.6%) and the caspofungin group (9.6%), compared to the micafungin 100 mg group (5.8%). Five percent of patients who received caspofungin had a culture-confirmed relapsed infection, compared to 4.5% who received micafungin 100 mg and 2.9% who received micafungin 150 mg. A total of 29.6% of patients who received one of the study drugs died. More patients died in the micafungin 100 mg arm (29%) and the micafungin 150 mg arm (33.2%) than in the caspofungin arm (26.4%). No deaths were related to the study drugs. Secondary: Not reported
Cornely et al.[36] (2007) Caspofungin 70 mg loading dose followed by 50 mg daily thereafter or 100 mg daily without the loading dose (in patients with endocarditis, meningitis and osteomyelitis/	MC, OL Patients ≥18 years of age with proven invasive candidiasis	N=48 12-week posttreatment follow-up	Primary: Overall clinical and microbiological response Secondary: Not reported	Primary: In the modified intention-to-treat population, 39 patients (81%) had a favorable overall response at the end of caspofungin therapy. Among the nine patients with an unfavorable response, four had persistently positive *Candida* cultures and three patients had an indeterminate efficacy assessment. The remaining two patients with unfavorable responses had persistent signs/symptoms of endocarditis (despite negative follow-up cultures) or developed metastatic *Candida* lesions while on caspofungin. Among the 42 patients included in the evaluable-patients population, 37 (88%) demonstrated a favorable overall response at the end of caspofungin therapy. Efficacy was also assessed at day 10 of caspofungin and at the end of all

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
septic arthritis) After ≥10 days of caspofungin therapy, patients either continued to receive caspofungin therapy or were switched to oral fluconazole.				antifungal therapy. Seventy-nine percent (38/48) responded favorably at the end of all antifungal therapy. Sixty-nine percent (22/32) also had a successful outcome at the day 10 assessment. Eleven patients (23%) died while on caspofungin therapy or during the 12 week posttreatment period. None of the deaths was attributed to caspofungin. In five patients, mortality was directly attributed to the underlying *Candida* infection. The remaining deaths were the result of other co-morbidities. Among the 48 patients, 43 (90%) developed ≥1 adverse event. Secondary: Not reported
DiNubile et al.[37] (2008) Caspofungin 70 mg loading dose, followed by 50 mg daily thereafter	RETRO Invasive Candidiasis Protocol 014: Patients ≥18 years old with clinically and microbiologically documented invasive candidiasis Invasive Aspergillosis Protocol 019: Patients ≥18 years old with definite or probable invasive aspergillosis refractory to or intolerant of amphotericin or itraconazole	N=159 Variable duration	Primary: Clinical outcomes and safety Secondary: Not reported	Primary: A favorable response to caspofungin was observed in more elderly than non-elderly patients with invasive candidiasis (83 vs 68%) or invasive aspergillosis (64 vs 44%). Fewer elderly than non-elderly patients with invasive candidiasis had a favorable response to amphotericin B (42 vs 70%). In the Empirical Therapy Study, an overall favorable response occurred in similar proportions of elderly and non-elderly patients in both treatment groups. Both treatment groups also had similar proportions of elderly and non-elderly patients with a favorable response on the individual outcome components, except that survival to seven days posttreatment was lower in elderly patients vs non-elderly patients receiving liposomal amphotericin B (78 vs 91%). In all three studies, clinical and laboratory adverse events related to caspofungin occurred in similar proportions of elderly and non-elderly patients. The all-cause mortality rate was higher in elderly patients vs non-elderly patients in both treatment groups in the Invasive Candidiasis Study and the Empirical Therapy Study, but was lower in elderly vs non-elderly patients in the Invasive Aspergillosis Study. Nephrotoxicity and systemic infusion-related events occurred in similar

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	Empirical Therapy Protocol 026: Patients ≥16 years old with persistent fever and neutropenia after 96 hours of parenteral systemic antibacterial therapy			proportions of elderly and non-elderly patients in all treatment groups in all three studies. Infusion-site tolerability was also similar in elderly and non-elderly patients: caspofungin infusion was well-tolerated in over 95% of both age groups; amphotericin B infusion was well tolerated in 100% of elderly patients and 89% of non-elderly patients. Secondary: Not reported
Queiroz-Telles et al.[38] (2008) Micafungin 2 mg/kg/day (≤40 kg) or 100 mg/day (>40 kg) vs liposomal amphotericin B 3 mg/kg/day	RCT, DB Pediatric patients <16 years old with clinical signs of systemic *Candida* infection and one or more positive *Candida* cultures from blood or another sterile site within the previous 4 days	N=106 12-week posttreatment follow-up	Primary: Response rate based on the assessment of overall treatment success (clinical and mycological response at the end of therapy) Secondary: Not reported	Primary: In the modified intent-to-treat (MITT) population, the rate of overall treatment success was similar for micafungin (72.9%) compared to liposomal amphotericin B (76%; 95% CI, -20.1 to 15.3). Consistent findings were observed for the per protocol population, which showed success rates of 85.4% and 88.1% in the micafungin and liposomal amphotericin B groups, respectively (95% CI, -16.4 to 12.7). Mycologic persistence at the end of therapy was observed for 15.6% patients in both the micafungin and liposomal amphotericin B groups in the MITT population. Three patients in the micafungin group and none in the liposomal amphotericin B group had a proven recurrent fungal infection during the posttreatment phase. The mortality rate during the treatment phase was 1.9% for micafungin and 11.1% for liposomal amphotericin B in the ITT population. During the entire study, including the 12-week follow-up, the mortality rates were 25.0 and 24.1% of patients, respectively. The fungal infection was considered by the investigator to have contributed to the cause of death for 7.7 and 5.6% of patients, respectively. The incidence of adverse events was similar between the treatment groups. Secondary: Not reported
Kuse et al.[39] (2007)	RCT, DB	N=531	Primary: Response rate	Primary: In the modified intention-to-treat population (MITT), 74.1% of patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Micafungin 2 mg/kg/day (≤40 kg) or 100 mg/day (>40 kg) vs liposomal amphotericin B 3 mg/kg/day	Patients ≥16 years old with clinical signs of systemic *Candida* infection and one or more positive *Candida* cultures from blood or another sterile site within the previous 4 days	12-week posttreatment follow-up	based on the assessment of overall treatment success (clinical and mycological response at the end of therapy) Secondary: Not reported	were treated successfully with micafungin vs 69.6% of those treated with lipo somal amphotericin B (95% CI, –3.0 to 12.8). In the intention-to-treat population (ITT), success rates were 71.6% with micafungin and 68.2% with liposomal amphotericin B (95% CI, -3.9 to 11.6). In the per-protocol population, treatment success rates were 81.4% for micafungin and 80.4% for liposomal amphotericin B (95% CI, -6.1 to 9.6). Mycological persistence at the end of therapy was observed in 9% of patients in the micafungin group and 9% of patients in the liposomal amphotericin B group in the per-protocol population. Species specificity for mycological persistence was similar between treatment groups. A recurrent *Candida* infection during the 12-week posttreatment period was seen in seven patients who had received micafungin and six patients who had received liposomal amphotericin B; the minimum inhibitory concentration (MIC) values showed no marked changes relative to the baseline MIC values for these patients. In the ITT population, 18% of patients died in the micafungin group and 17% of patients died in the liposomal amphotericin B group during the treatment phase. During the study, including the 12-week follow-up period, 40% of patients in the micafungin group and 40% of patients in the liposomal amphotericin B group died. The fungal infection was considered by the investigator to have contributed to the cause of death for 13% patients in the micafungin group and 9% patients in the liposomal amphotericin B group (P=0.22). There were fewer treatment-related adverse events in the micafungin group than in the liposomal amphotericin B group. There were fewer cases of hypokalemia, rigors, increased serum creatinine, and back pain in the micafungin group than in the liposomal amphotericin B group, as well as fewer infusion-related reactions. Secondary: Not reported
Gafter-Gvili et al.[40]	MA	N=3,265 (15 trials)	Primary: 30-day all-cause	Primary: <u>Fluconazole vs other antifungal agents (nine studies)</u>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2008) Group 1 Echinocandins vs other antifungal agents Group 2 Fluconazole vs other antifungal agents	Patients with confirmed invasive candidiasis	Variable duration	mortality Secondary: Treatment failure, microbiological failure, adverse events	No difference in mortality was observed with fluconazole vs amphotericin B (RR, 0.92; 95% CI, 0.72 to 1.17). No difference in mortality was observed between fluconazole and itraconazole (RR, 1.91; 95% CI, 0.39 to 9.35) or between fluconazole and a combination of fluconazole and amphotericin B (RR, 0.98; 95% CI, 0.70 to 1.35). Echinocandins vs other antifungal agents (four studies) There was no difference in mortality with anidulafungin vs fluconazole (RR, 0.73; 95% CI, 0.48 to 1.10). There was no difference in mortality with caspofungin vs amphotericin B (RR, 1.08; 95% CI, 0.75 to 1.55) or with micafungin vs liposomal amphotericin B (RR, 1.04; 95% CI, 0.75 to 1.43). Other comparisons (two studies) There was no difference in mortality with micafungin vs caspofungin (100 mg/day: RR, 1.10; 95% CI, 0.80 to 1.51; 150 mg/day: RR, 1.27; 95% CI, 0.93 to 1.72). There was no difference in mortality with amphotericin B plus fluconazole vs voriconazole (RR, 1.18; 95% CI, 0.90 to 1.54). Secondary: Fluconazole vs other antifungal agents (nine studies) No significant difference in treatment failure was found with fluconazole and amphotericin B (RR, 1.22; 95% CI, 0.97 to 1.54) or with fluconazole vs a combination of fluconazole and amphotericin B (RR, 1.41; 95% CI, 0.99 to 1.99). Microbiological failure was higher in patients treated with fluconazole compared to amphotericin B (RR, 1.52; 95% CI, 1.12 to 2.07) or with fluconazole vs a combination of fluconazole and amphotericin B (RR, 2.69; 95% CI, 1.17 to 6.18). No difference in adverse events requiring discontinuation was noted with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				fluconazole vs amphotericin B (RR, 0.45; 95% CI, 0.13 to 1.56), itraconazole (RR, 0.32; 95% CI, 0.04 to 2.82) or with fluconazole vs a combination of fluconazole and amphotericin B (RR, 1.16; 95% CI, 0.49 to 2.75). Fluconazole caused less nephrotoxicity than amphotericin B (RR, 0.11; 95% CI, 0.03 to 0.48) or the combination of amphotericin B and fluconazole (RR, 0.12; 95% CI, 0.04 to 0.39). <u>Echinocandins vs other antifungal agents (four studies)</u> Treatment failure significantly decreased with anidulafungin vs fluconazole (RR, 0.61; 95% CI, 0.42 to 0.89). There was no difference in treatment failure with caspofungin vs amphotericin B (RR, 0.70; 95% CI, 0.47 to 1.03) or with micafungin vs liposomal amphotericin B (RR, 0.93; 95% CI, 0.74 to 1.19). Microbiological failure was significantly reduced with anidulafungin vs fluconazole (RR, 0.50; 95% CI, 0.29 to 0.86). No difference in microbiological failure was noted for caspofungin vs amphotericin B (RR, 0.95; 95% CI, 0.40 to 2.25) or with micafungin vs liposomal amphotericin B (RR, 1.01; 95% CI, 0.53 to 1.92). A significant decrease in adverse events requiring discontinuation was observed with anidulafungin vs fluconazole (RR, 0.52; 95% CI, 0.29 to 0.92). Caspofungin was associated with a significantly lower rate of adverse events requiring discontinuation when compared to amphotericin B (RR, 0.11; 95% CI, 0.04 to 0.36) or liposomal amphotericin B (RR, 0.45; 95% CI, 0.26 to 0.80). <u>Other comparisons (two studies)</u> There was no difference in treatment failure with micafungin and caspofungin (100 mg/day: RR, 0.85; 95% CI, 0.60 to 1.20; 150 mg/day: RR, 1.04; 95% CI, 0.74 to 1.42). There was no difference in treatment failure with amphotericin B plus fluconazole vs voriconazole (RR, 1.00; 95% CI, 0.83 to 1.19). There was no difference in microbiological failure with micafungin and caspofungin (100 mg/day: RR, 0.73; 95% CI, 0.41 to 1.22; 150 mg/day: RR, 1.10; 95% CI, 0.70 to 1.73).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was no difference in adverse events requiring discontinuation with micafungin and caspofungin. Adverse events requiring discontinuation were significantly lower (RR, 0.47; 95% CI, 0.23 to 0.93) and nephrotoxicity was significantly higher (RR, 2.64; 95% CI, 1.57 to 4.44) with the amphotericin B-fluconazole arm compared to voriconazole.
Empirical Therapy				
Kubiak et al.[41] (2010) Caspofungin70 mg for 1 dose, then 50 mg daily vs micafungin 100 mg daily	RETRO, OBS Patients who had received ≥2 doses on concurrent days of either caspofungin or micafungin for the empirical treatment of febrile neutropenia (FN)	N=149 Variable duration	Primary: Treatment success, survival to hospital discharge, breakthrough invasive fungal disease (IFD) during therapy or within seven days after completion of therapy, and discontinuation of therapy due to adverse events	Primary: Three IFDs were diagnosed at baseline in the caspofungin group and 6 in the micafungin cohort (2.0 vs 3.4%; P=NS). Treatment of baseline IFD was successful in 1.3% of patients receiving caspofungin and 2.3% of patients receiving micafungin. A total of 8.1% of patients in the caspofungin group and 7.5% of patients in the micafungin group died (RR, 0.93; 95% CI, 0.44 to 1.97; P=NS). The incidence of breakthrough IFD was similar between groups: 10.7% of patients receiving caspofungin and 12.1% of patients in the micafungin group (RR, 1.12; 95% CI, 0.61 to 2.07; P=NS). The probability of breakthrough IFD during echinocandin treatment at 7, 14, and 21 days of administration was 3, 8, and 14% when micafungin was used, and 6, 10, and 15% when caspofungin was used, respectively (P=NS for all time points). There were three adverse events related to caspofungin (2.0%) and there were two adverse events requiring discontinuation observed in patients receiving micafungin (1.1%). When the combination of successful treatment of baseline fungal infections, survival at hospital discharge, absence of breakthrough IFD, and no discontinuation of echinocandin treatment because of adverse effects was considered as a single outcome, a favorable response was observed in 81.9% of patients receiving caspofungin and in 81.0% of patients receiving micafungin (RR, 0.99; 95% CI, 0.89 to 1.10; P=NS).
Chabrol et al.[42] (2010)	RETRO	N=257	Primary: Cumulative	Primary: The cumulative incidence of IA was significantly lower in the prophylaxis

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Caspofungin or voriconazole as primary prophylaxis vs no prophylaxis	Patients receiving first induction chemotherapy for acute myeloid leukemia of acute lymphocytic leukemia	Variable duration	incidence of invasive aspergillosis (IA) Secondary: Overall survival, survival at 100 days after chemotherapy, IA-specific survival, mean duration of hospitalization, cumulative incidence of adverse events	group than in the non-prophylaxis group (4.5% and 12.4%, respectively; P=0.04). Secondary: The three month mortality rate was 28%. The median overall survival of patients with IA was significantly shorter than in patients without IA (215 vs 782 days; P=0.0008). There was no significant difference in 100-day survival between the two groups (83% in the prophylaxis group and 82% in the non-prophylaxis group). The 1-year survival rate was 53% in the prophylaxis group and 65% in the non-prophylaxis group (P=NS).
Ellis et al.[43] (2006) Caspofungin 70 mg loading dose, then 50 mg daily for at least 10 to 14 days vs liposomal amphotericin B 3 mg/kg/day for neutropenic fever (NF) or 5 mg/kg/day for invasive pulmonary aspergillosis (IPA) for at least 10 to 14 days	RETRO Patients with acute hematological malignancies with prolonged neutropenia or invasive fungal infections	N=73 7 day posttreatment follow-up	Primary: All cause mortality within 7 days of completion of antifungal therapy, response to treatment, toxicity Secondary: All antifungal drug administration during each hospital admission	Primary: Significantly more deaths were seen in patients following caspofungin therapy compared to liposomal amphotericin B therapy (P=0.013). Overall, response to therapy did not differ significantly between treatment groups (P>0.16). Significantly more patients experienced treatment failure due to a breakthrough invasive fungal infection in the caspofungin group compared to the amphotericin B group (P=0.047). The proportion of events treated with amphotericin B which were associated with at least one adverse event was significantly higher compared to the caspofungin group (P=0.02). Significantly more patients in the amphotericin B group experienced episodes of hypokalemia (P=0.01). A similar proportion of drug discontinuations was observed due to adverse effects between the groups (P=0.48). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There were a total of 97 episodes of treatment with either caspofungin or liposomal amphotericin B and results were similar to those seen in the primary efficacy endpoints.
Caselli et al.[44] (2012) High risk patients: liposomal amphotericin B (Arm B) vs caspofungin (Arm C) lower risk patients: liposomal amphotericin B (Arm B) vs caspofungin (Arm C) vs no antifungal treatment (Arm A)	MC, PRO, RCT Patients aged ≤18 years with neutropenia induced by chemotherapy or autologous hematopoietic stem cell transplant and persistent fever despite empirical IV antibiotic therapy	N=104 >30 days	Primary: Complete response to the treatment (fever <37.5°C for 48 hours, survival with no evidence of invasive fungal infection by day 30, and completion of the randomly assigned treatment) Secondary: Proportion of patients diagnosed with invasive fungal infection, duration of hospital stay, patient compliance (number of patients who completed the assigned treatment), and drug toxicity (the number of patients who developed renal or liver toxicity)	High risk group: Primary: A complete response was achieved in 48 of the 56 patients in the high-risk group (85.7%) with no difference between the two treatment arms. A complete response was achieved in 88.0% of the patients in Arm B and in 83.9% of the patients in Arm C (P=0.72). Secondary: Patients with a complete response in Arm B had a median hospital stay of 18 days (range, six to 51). Patients with a complete response in Arm C had a median hospital stay of 28 days (range, six to 52). Lower risk group: Primary: Within the low-risk group, a complete response was observed in 42 of 48 patients (87.5%). The proportion of patients achieving a complete response was comparable across the three arms: 87.5% in control Arm A, 80.0% in Arm B, and 94.1% in Arm C (P=0.41). Secondary: Patients with a complete response in Arm A had a median hospital stay of 8.5 days (range, four to 24). Patients with a complete response in Arm B had a median hospital stay of 11 days (range five to 29). Patients with a complete response in Arm C had a median hospital stay of 13 days (range, six to 31). Composite: Of the 110 patients at risk, nine were diagnosed with invasive fungal infections during the duration of the study for a global frequency of 8.2% (CI, 3.8 to 15.0). This study was terminated for futility when the number of randomized patients was still below the initial expected target. Nonetheless, the results show that, in terms of probability, none of the three experimental arms was superior to the others.
Maertens et al.[45]	DB, MC, RCT	N=83	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2010) Caspofungin 70 mg/m^2 loading dose on day 1, then 50 mg/m^2 daily vs liposomal amphotericin B (L-AmB) 3 mg/kg daily	Patients 2 to 17 years of age who had received chemotherapy for cancer or had undergone HSCT, had received parenteral broad-spectrum antibacterial therapy for ≥96 hours, and were neutropenic and febrile	Up to 28 days	Safety and tolerability Secondary: Efficacy	Serious clinical adverse events that were considered to be drug related were reported in one (1.8%) caspofungin recipient (hypotension) and three (11.5%) L-AmB recipients (hyperbilirubinemia; circumoral edema; and angioneurotic edema with dyspnea, laryngospasm, and tachycardia); all 4 patients discontinued the intended course of therapy. Three patients died during the study: two (3.6%) in the caspofungin group and one (3.8%) in the L-AmB group. Secondary: A favorable overall response was observed in 46.4% of patients who received caspofungin and 32.0% of those who received L-AmB; however, the 95% CIs for the treatment groups overlapped.
Döring et al.[46] (2012) Caspofungin (CAS) 1 or 3 mg/kg/day vs liposomal amphotericin B (L-AmB) 50 mg/m^2/day	OBS, RETRO Pediatric patients (<18 years of age) undergoing hematopoietic stem cell transplantation	N=120 9 to 49 days	Primary: Safety Secondary: Incidence of aspergillosis, candidiasis, and other mycoses	Primary: Clinical side effects directly related to intravenous treatment with L-AmB were observed in five (8.3%) and directly related to CAS in two (3.3%) pediatric patients. A total of 25% (15) of patients in the LAmB group required oral potassium supplementation and spironolactone upon discharge. This compares to only 11.7% (7) in the CAS group. Sodium bicarbonate substitution was required in five (8.33%) and calcium in three (5%) cases upon discharge in the L-AmB group. In the CAS group, calcium was given in two (3.3%) cases and sodium bicarbonate in one (1.7%) case. Secondary: Prophylaxis was effective with L-AmB as well as with CAS. There was no incidence of proven invasive aspergillosis or another invasive fungal infection in either group.
Vehreschild et al.[47] (2009) Caspofungin vs	OBS Neutropenic patients with cancer and invasive fungal disease (IFD)	N=77 Variable duration	Primary: Evidence of IFD and mortality Secondary: Not reported	Primary: The incidence of breakthrough IFD after secondary prophylaxis was similar in both groups (32.1 and 31.9%). A trend towards fewer proven or probable breakthrough IFD events in the itraconazole group was not significant (29 and 17%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
itraconazole Study medications were dosed at the physician's discretion.				Overall survival favored the itraconazole group, but this trend was not significant (75 and 89%). Death was attributed to IFD in 3.6% of patients receiving caspofungin and 4.3% of patients in the itraconazole group. Secondary: Not reported
Toubai et al.[48] (2007) Micafungin 50 to 300 mg IV daily for ≥5 days	OL Patients aged 27 to 82 years with febrile neutropenia for whom antibiotic therapy was not effective	N=23 5 to 43 days	Primary: Treatment success (based on clinical and mycological response at the end of therapy) Secondary: Not reported	Primary: The overall treatment success rate was 73.9%. None of the patients developed breakthrough fungal infections, discontinued the drug due to lack of efficacy, or died during the study period. The treatment success rates by primary diagnosis were 77.8% in patients with AML, 50.0% in patients with NHL, and 87.5% in patients with other diseases. The treatment success rate in patients who had previously received antifungal prophylaxis was not significantly different from those who had not received prophylaxis. The treatment success rate for patients with mild neutropenia (501 to 1000 cells/µL) was 100% (5 of 5 patients). Treatment success rate for patients with moderate neutropenia (101 to 500 cells/µL) and severe neutropenia (100 or less cells/µL) were both 66.7% (2 of 3 patients with moderate neutropenia and 10 of 15 patients with severe neutropenia). The treatment success rate in the severe neutropenia group and mild neutropenia group were not significantly different (P=0.266). The treatment success rate by maximum doses of micafungin were 0% in patients administered 50 mg and 75 mg (0/2 and 0/1, respectively), 100% in patients administered 100 mg (8/8), 70.0% in patients administered 150 mg (7/10) and 100% in patients administered 300 mg (2/2). Treatment was not discontinued because of an adverse event in any of the patients. One or more adverse events occurred in 21.7% of the patients during the study.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Park et al.[49] (2010) Micafungin 100 mg IV once daily for ≥5 days	PRO, MC Patients ≥18 years of age who were receiving chemotherapy for hematological diseases who had neutropenia and an unexplained high fever that was refractory to combined antimicrobial treatment for at least 72 hours	N=47 Variable duration	Primary: Response to therapy (success=no breakthrough fungal infection, survival for 7 days post-therapy, did not discontinue therapy prematurely, resolution of fever, and successfully treated for any baseline fungal infection) Secondary: Not reported	Primary: A total of 29 patients responded to micafungin therapy according to the composite score (61.7%), 89.4% of the patients did not show a spiking fever within seven days of the end of therapy, and 66% of the patients completed their micafungin treatment. About 77% of the patients experienced resolution of their fevers prior to their recovery from neutropenia. The median duration of neutropenia, fever and neutropenic fever was six days, three days, and two days, respectively. Grade 3 or 4 hyperbilirubinemia and aspartate aminotransferase elevation was observed in 6.4% and 21% of patients, respectively. On the first day of micafungin therapy, two patients presented with urticaria, which subsided after short-term steroid therapy without discontinuation of the study drug. A total of four patients died of septic shock during the study period, one additional patient died of septic shock and subsequent multiorgan failure including hyperbilirubinemia 54 days after discontinuation of the study drug. Secondary: Not reported
Yoshida et al.[50] (2012) Micafungin 50 to 150 mg IV for 5 days to 4 weeks, dose could be increased to 300 mg/day in severe cases	MC, OS, OL, PRO Patients with neutropenia with possible fungal infection or refractory fever	N=388 Mean treatment duration of 14 days	Primary: Efficacy (improvement in positive clinical symptoms/ findings, radiological imaging, and fungal serological testing) and safety (adverse events)	Primary: The overall clinical response rate, excluding four nonevaluable patients, was 63.3% (243/384). No difference in the response rate was observed between the main underlying hematological disorders. Excluding 19 patients who lacked follow-up radiological imaging after micafungin treatment, the improvement rate in the chest X-ray, or computed tomography was 51.8% (44/85). Among the 388 patients, 91 drug adverse events were observed in 56 patients (14.4%). The most common events were hepatic function abnormalities including elevation of alanine aminotransferase, aspartate

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: Not reported	aminotransferase, and serum bilirubin. The incidence of drug adverse events by maximum daily dose was 10.8% (8/74) for 100 mg or less, 16.5% (44/267) for 150 mg, and 8.5% (4/47) for 200 mg and higher. The incidence of drug adverse events by duration of micafungin treatment was 11.5% (28/243) for up to 14 days, 11.1% (8/72) for 15 to 21 days, and 27.4% (20/73) for 22 days and longer.
Huang et al.[51] (2012) Micafungin 50 mg/day IV vs itraconazole 5 mg/kg/day PO	MC, OL, PG, RCT Adult neutropenic patients undergoing hematopoietic stem cell transplants	N=287 10 weeks	Primary: Treatment success (proven, probable, or suspected invasive fungal infection through therapy and the absence of proven or probable invasive fungal infection through the end of four weeks after therapy) Secondary: Invasive fungal invasions throughout the study period and safety measures	Primary: There were no statistically significant or clinically meaningful differences between treatments in the rate of patients without proven, probable, or suspected invasive fungal infection during prophylactic antifungal treatment and without proven or probable invasive fungal infection after completion of prophylactic treatment (P=0.48). This demonstrates the noninferiority of micafungin over itraconazole. Secondary: Tolerability of treatment was better in the micafungin group, with more patients in that group completing the study (82.9 vs 67.3%) and a significantly lower incidence of premature study withdrawal due to an unacceptable toxicity (0.7 vs 19.7%; P=0.00, chi-square test) occurring in micafungin treated vs itraconazole-treated patients. Adverse events were reported in significantly fewer patients in the micafungin than in the itraconazole group. There was also a significant difference in the rate of investigator-identified, drug-related adverse events, which was 8.0% in micafungin treated patients (11 of 137 patients) and 26.5% in itraconazole-treated patients (39 of 147 patients; P=0.000, chi-square test).
Shang et al.[52] (2012) Micafungin 100 or 150 mg/day IV vs voriconazole	MC, OL, PRO, RCT Renal transplant recipients with invasive fungal infections	N=65 Variable duration	Primary: Efficacy and adverse events of the two treatments Secondary: Not reported	Primary: Fungal infection within one to three months after transplant was 83.6% (26/31) and 85.3% (29/34) in the micafungin and voriconazole groups, respectively. There was no significant difference between the two groups in terms of efficacy, survival beyond 10 days, and discontinuation of treatment because of lack of efficacy (P>0.05). Mortality rates in the micafungin and voriconazole groups were 9.7% (3/31) and 12.1% (4/33), respectively. Rates of adverse effects in the two groups were 41.9% and 51.6% (P>0.05), respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
loading dose of 6 mg/kg every 12 hours on the first day and maintenance dose of 4 mg/kg every 12 hours from the second day IV				Secondary: Not reported
Prophylaxis of Fungal Infections				
Cattaneo et al.[53] (2011) Caspofungin 50 to 70 mg/day vs standard prophylaxis regimens (SP) according to the physician's decision	RCT, MC Patients aged ≥18 years with acute lymphoblastic leukemia (ALL) or acute myeloid leukemia (AML) who were at the start of induction chemotherapy	N=175 Variable duration	Primary: Incidence of probable/proven invasive fungal infections (IFIs) Secondary: Death rate related to IFIs and safety	Primary: The incidence of IFIs was 16.1% with caspofungin prophylaxis and 20.7% with SP (RR, 0.78; 95% CI, 0.42 to 1.46). Probable/proven and possible IFIs were diagnosed in 7.5 and 8.6% of patients with caspofungin vs 3.7 and 17.1% of patients with SP (RR, 2.06; 95% CI, 0.55 to 7.7 and RR, 0.5; 95% CI, 0.22 to 1.14, respectively). In the SP subgroup there were no differences in the incidence of IFIs according to the different type of prophylaxis received. Secondary: A total of 8.6% of patients died (caspofungin: 9.7%; SP prophylaxis: 7.3%; RR, 1.32; 95% CI, 0.49 to 3.56). In only one case, death attributable to probable/proven IFI. None of the patients receiving caspofungin died of toxicity, whereas one patient receiving itraconazole died of hepato-renal failure, possibly due to prophylaxis-related toxicity. Five patients experienced WHO grade >2 toxicity, with three receiving caspofungin and two itraconazole.
de Fabritiis et al.[54] (2007) Caspofungin 70 mg loading dose, then 50 mg IV daily from the start of the conditioning regimen until a	OL, MC Patients ≥18 years of age who were undergoing allogeneic stem cell transplantation and had a previous probable or proven fungal infection	N=18 Up to 31 months from stem cell reinfusion	Primary: Success of secondary prophylaxis (defined as the absence of documented relapse of the fungal infection and the absence of	Primary: Of the 18 patients evaluable at day 30, four were considered stable, 12 improved and two progressed. Fifteen patients were evaluable at day 180 because three deaths occurred before day 30. Two patients were considered stable and 11 still improved at day 180, while 2 patients had their previous invasive fungal infection progress. Eleven patients were evaluable at one year of follow-up. No patient

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
stable engraftment of >1X10^9/l neutrophil cells Oral itraconazole 400 mg/day was given after caspofungin as maintenance therapy.			new proven, probable or possible invasive fungal infection) Secondary: Not reported	showed signs of previous invasive fungal infection progression. Two patients were stable and nine improved. At 31 months of follow-up, the probability of survival of the 18 patients submitted to allogeneic stem cell transplant with a previous invasive fungal infection was 45%. Three patients died due to leukemia relapse or progression; five patients died due to transplant-related complications with evidence of fungal infection in two patients. Transplant-related mortality of the 18 patients was 28.6%. Secondary: Not reported
Yuan et al.[55] (2012) Caspofungin vs other antifungal treatments	MA Patients at risk for or with proven fungal infections	N=2901 (Nine randomized controlled trials [RCTs]) Variable durations	Primary: Analyses of favorable response, microbiological response, mortality rate, survival rate, relapse rate, and adverse events Secondary: Not reported	Primary: Nine RCTs reported clinical favorable response rate in the modified intention-to-treat (MITT) population. Overall, the clinical favorable response rate in the caspofungin group [693 (55.3%) of 1253 MITT patients] was similar to that in the control group [670 (53.6%) of 1251 MITT patients], and no significant difference was found (RR, 1.07; 95% CI, 0.98 to 1.17). Three RCTs presented data on relapse rate. There was no significant difference in relapse rate between the caspofungin and control groups (571 patients; RR, 1.18; 95% CI, 0.81 to 1.73). Three RCTs showed data on mortality in clinically assessed patients. All-cause mortality in the caspofungin group was 97/413 (23.5%), and in the control group was 103/411 (25.1%), with no significant difference between the two groups (RR, 0.98; 95% CI, 0.78 to 1.24). In the total evaluable safety population, 372 (44.2%) of 841 patients in the caspofungin group and 513 (60.1%) of 853 patients in the control group experienced clinical adverse events, and there was a significant difference between the groups (RR, 0.66; 95% CI, 0.49 to 0.89). Secondary: Not reported
van Burik et al.[56]	RCT, DB, PRO	N=882	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2004) Micafungin 50 mg IV vs fluconazole 400 mg IV	Patients 6 months of age and older who were to undergo an allogeneic HSCT for any indication or an autologous HSCT for hematological malignancy and who were free from invasive fungal disease	4 week posttreatment follow-up	Treatment success (absence of proven, probable, or suspected fungal infection through the end of prophylaxis therapy and the absence of proven or probable fungal infection through the 4-week follow-up period) Secondary: Not reported	The treatment success rate was significantly higher in the micafungin group compared to the fluconazole group (80 and 73.5%, respectively; P=0.03). There were six breakthrough infections due to *Candida* species; four in the micafungin group and two in the fluconazole group. There was one case of probable breakthrough aspergillosis in patients treated with micafungin and seven cases in patients treated with fluconazole (P=0.071). There was one case of fusariosis in the micafungin group and two in the fluconazole group. There was one episode of zygomycosis in a micafungin-treated patient. Secondary: Not reported
Hiramatsu et al.[57] (2008) Micafungin 150 mg IV daily vs fluconazole 400 mg IV daily Patients received treatment within 48 hours of the transplant-related conditioning regimen.	RCT, OL Adult patients with a hematological malignancy who were undergoing high-dose combination chemotherapy with autologous or allogeneic hematopoietic stem cell transplantation (HSCT)	N=104 4-week posttreatment follow-up	Primary: Treatment success (defined as the absence of proven, probable, or suspected systemic fungal infection through the end of prophylaxis therapy and as the absence of a proven or probable systemic fungal infection through the end of the 4-week posttreatment period)	Primary: The overall treatment success rate for patients in the micafungin arm was comparable to that in the fluconazole arm (94.0 and 88.0%, respectively; 95% CI, -5.4 to 17.4; P=0.295). Suspected invasive fungal infections (IFIs) were reported to occur in 4% of patients in the micafungin arm and 12% of patients in the fluconazole arm (P=0.14). More fluconazole-treated patients received empirical antifungal therapy compared to micafungin-treated patients during the post-treatment period only (12.0 vs 4.0%; P=0.14), although there was no significant difference. In total, 4.0% of micafungin-treated patients and 1.0% of fluconazole-treated patients died during course of the study. None of the deaths were related to the study drug. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: Not reported	
Hashino et al.[58] (2008) Micafungin 100 mg IV daily beginning 14 days prior to allogenic STC vs fluconazole 400 mg IV/oral daily (historical control) Therapy was continued until hematological engraftment. Fluconazole 200 mg/day was given until the cessation of immuno-suppressants.	OL Adult patients with hematological and non-hematological malignancy undergoing allogeneic stem cell transplantation (STC)	N=44 11 to 80 days	Primary: Treatment success (defined as the absence of proven, probable, or possible invasive fungal infection [IFI] until day 21 after the SCT) Secondary: Not reported	Primary: Treatment success was achieved in 87.8% of patients in the micafungin group and in 65.5% of the patients) in the fluconazole group (P=0.038). None of the patients in the micafungin group were diagnosed with proven or probable IFI. In the patients treated with fluconazole, there was one with disseminated candidiasis (caused by *Candida* krusei) and one with invasive pulmonary aspergillosis. Five patients were diagnosed as having possible IFI. Seven patients in the fluconazole group were diagnosed as having possible IFI. Secondary: Not reported
Kusuki et al.[59] (2009) Micafungin 3 mg/kg once daily	RETRO Children with neutropenia during chemotherapy or hematopoietic stem cell transplant	N=40 Variable duration	Primary: Treatment success (defined as absence of proven, probable, possible, or suspected invasive fungal infection (IFI) during prophylaxis therapy), duration of neutropenia, time to IFI, and	Primary: Successful prophylaxis was achieved in 123 of 131 patient-cycles (93.9%) for chemotherapy and 12 of 15 hematopoietic stem cell transplants (80.0%), and in 32 of 39 patients (82.1%) for chemotherapy and 11 of 14 hematopoietic stem cell transplant patients (78.6%). A total of 75.0% of patients had successful prevention of IFI. The median duration of neutropenia was 13 days for chemotherapy and 23 days for hematopoietic stem cell transplants. The median duration of micafungin prophylaxis for these groups was 12 days and 21 days, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			adverse events Secondary: Not reported	Proven IFI was observed in one patient, who received micafungin prophylaxis for 62 days for prolonged neutropenia. No probable or possible IFI cases were observed. Suspected IFIs were observed in 10 cases: eight after chemotherapy and two after hematopoietic stem cell transplant. No adverse events were association with micafungin. Secondary: Not reported
Miscellaneous Infections				
Kohno et al.[60] (2013) Caspofungin vs micafungin	DB, MC, PRO, RCT Japanese patients aged 20 years and over with *Aspergillus* or *Candida* infection	N=121 7 to 84 days, depending on diagnosis	Primary: Proportion of patients who develop significant drug-related adverse events Secondary: Overall response by each of esophageal candidiasis, invasive candidiasis, and aspergillosis	Primary: The proportion of patients fulfilling the primary endpoint of this study was 5.0% (95% CI, 1.0 to 13.9) in the caspofungin group and 10.0% (95% CI, 3.8 to 20.5) in the micafungin group. The between-treatment difference was −5.0% (95% CI, −15.9 to 5.2), thereby, showing no significant difference between the two groups. Secondary: The overall response of caspofungin and micafungin in chronic pulmonary aspergillosis (other than aspergilloma) patients were 45.0% (9/20) and 46.7% (14/30), respectively. The overall response of caspofungin in aspergilloma patients was 50.0% (5/10), and there were no aspergilloma patients in the micafungin group. In general, the favorable overall responses were similar across the two treatment groups for each disease.
Zaoutis et al.[61] (2009) Caspofungin 70 mg/m^2 on day 1, followed by 50 mg/m^2 daily thereafter as primary or salvage monotherapy	OL, MC Children 3 months to 17 years of age with proven or probable invasive aspergillosis, proven invasive candidiasis, or proven esophageal	N=49 28-day posttreatment follow-up	Primary: Proportion of patients with a favorable response (complete or partial) at the end of caspofungin therapy Secondary:	Primary: Five of 10 patients (50%) with invasive aspergillosis had a favorable clinical response at the end of caspofungin therapy. All five of the patients continued to have a favorable clinical response at both the 14- and 28-day posttreatment follow-up visits, 30 of 37 with invasive candidiasis, and one of one with esophageal candidiasis. Thirty of 37 patients (81.8%) with invasive candidiasis had a favorable response at the end of caspofungin therapy. One patient with invasive candidiasis relapsed during the 28-day follow-up period.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	candidiasis		Not reported	One patient with esophageal candidiasis had complete resolution of esophageal and oropharyngeal lesions at the end of caspofungin therapy. All of the symptoms of infection had also resolved by day 32. This patient continued to have a favorable response at the 14- and 28-day posttreatment visits. Drug-related clinical or laboratory adverse events occurred in 27% and 35% of patients, respectively. There were no serious drug-related adverse events or discontinuations of caspofungin because of toxicity. Secondary: Not reported
Tamura et al.[62] (2009) Micafungin 50 to 150 mg IV daily for ≥5 days up to 8 weeks	OL, MC Patients ≥16 years of age with hematological diseases or hematopoietic stem cell transplantation (HSCT) and possible or proven fungal infections	N=197 8 weeks	Primary: Overall response rate Secondary: Not reported	Primary: The overall clinical response rate was 66.4% for patients with hematological diseases and 71.4% for those with HSCT, respectively. The total response rate was 68.0%. The subset analysis showed no significant difference among various underlying diseases except for chronic leukemia, in which the response rate was very low, although the number of patients was only eight. All other patients experienced over 50% of response. There were eight patients with proven invasive fungal infections (IFIs) consisting of candidemia or esophageal candidiasis, seven of whom had favorable responses. Seventeen of 38 patients with probable IFIs responded to micafungin. Sixty-three patients with possible fungal infections defined by clinical symptoms and physical findings, and positive serological tests or imaging study received micafungin and 39 had favorable response. In patients with febrile neutropenia, 86.3% of patients had a favorable response. For patients with persistent neutropenia (neutrophils <500 cells/mL), the efficacy rate was 69.2%. The efficacy rate by the duration of neutropenia was as follows: 1/1 (100%) for less than seven days, 4/7 (57.1%) for between eight and 14 days, 1/2 (50.0%) for between 15 and 28

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				days and 3/3 (100%) for more than 29 days. The response rate in patients with or without antifungal pre-treatment was 70.1% and 63.5%, respectively. Thirty-two patients were treated with a combination of micafungin and other antifungal agents. The overall response rate was 78.1%. For patients with micafungin treatment alone, the response rate was 66.1%. The most frequent drug-related adverse event was the elevation of serum aminotransferase, renal dysfunction and electrolyte imbalance. Secondary: Not reported
Mills et al.[63] (2009) Antifungal agents (azoles, amphotericin B, echinocandins)	MA Patients with invasive fungal infections	N=965 (11 trials) Variable duration	Primary: Global response rate Secondary: All-cause mortality, fungal-attributable mortality, and adverse events	Primary: For global response rate, the pooled estimate was 0.87 when azoles were compared to amphotericin B (95% CI, 0.78 to 0.96; P=0.007). When only fluconazole trials were compared to amphotericin B, there were similar effects (RR, 0.82; 95% CI, 0.74 to 0.92; P=0.0009). The itraconazole vs amphotericin B trial (RR, 0.90; 95% CI, 0.49 to 1.63; P=0.61) and voriconazole vs amphotericin B trial (RR, 0.99; 95% CI, 0.77 to 1.30; P=0.94) provided similar estimates. Two trials comparing echinocandins and amphotericin B demonstrated a pooled RR of 1.10 (95% CI, 0.99 to 1.23; P=0.08). The anidulafungin to fluconazole trial yielded a RR of 1.26 (95% CI, 1.06 to 1.51; P=0.001) in favor of anidulafungin; and micafungin to caspofungin (RR, 1.00; 95% CI, 0.94 to 1.08; P=0.21). Secondary: Seven trials comparing azoles and amphotericin B were pooled for all-cause mortality, which demonstrated a RR of 0.88 (95% CI, 0.74 to 1.05; P=0.17). Similar results were found when individual azoles were analyzed: fluconazole (five trials) RR 0.92 (95% CI, 0.73 to 1.17; P=0.51); itraconazole (one trial) RR 0.67 (95% CI, 0.74 to 1.05; P=0.20); voriconazole (one trial) RR 0.85 (95% CI, 0.65 to 1.12; P=0.67). When echinocandins were compared to amphotericin B (two trials), there was a pooled RR of 1.01 (95% CI, 0.84 to 1.20; P=0.93). Micafungin vs caspofungin resulted in a RR of 0.85 (95% CI, 0.96 to 1.11) in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				direction of favor of caspofungin. Anidulafungin vs fluconazole resulted in a RR of 0.73 (95% CI, 0.48 to 1.10; P=0.34) in the direction of anidulafungin. When five trials comparing azoles to amphotericin B were pooled, a RR of 0.84 was found (95% CI, 0.49 to 1.42; P=0.51). When the three echinocandin trials vs amphotericin B were pooled, the RR was 1.16 (95% CI, 0.75 to 1.79; P=0.50). Anidulafungin vs fluconazole yielded a RR of 0.84 (95% CI, 0.48 to 1.47; P=0.88). To assess serious adverse events, two trials were pooled comparing azoles and amphotericin B, which showed a RR of 0.67 (95% CI, 0.55 to 0.81; P≤0.0001) in favor of azoles. Two trials comparing echinocandins and amphotericin B were pooled, which showed a RR of 0.49 (95% CI, 0.37 to 0.66; P≤0.0001) in favor of the echinocandins. Micafungin and caspofungin had similar safety profiles (RR, 0.94; 95% CI, 0.70 to 1.29). There was no significant difference between anidulafungin vs fluconazole (RR, 0.90; 95% CI, 0.60 to 1.36; P=0.66).

Drug regimen abbreviations: IV=intravenously
Study abbreviations: AC=active control, CI=confidence interval, CS=comparative study, DB=double blind, DD=double dummy, DR=dose ranging, MA=meta-analysis, MC=multi-center, NC=non-comparative, NI=non-inferiority, OBS=observational, OL=open label, OR=odds ratio, OS=observational study, PC=placebo controlled, PG=parallel group, PRO=prospective trial, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, SB=single blind

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 10. Relative Cost of the Echinocandins

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Anidulafungin	injection	Eraxis®	$$$$$	N/A
Caspofungin	injection	Cancidas®	$$$$$	N/A
Micafungin	injection	Mycamine®	$$$$$	N/A

N/A=Not available

X. Conclusions

The echinocandins are approved for the treatment of *Candida* infections.[1-6] Caspofungin is also approved for the treatment of invasive aspergillosis, as well as empirical therapy for presumed fungal infections in febrile, neutropenic patients.[5] The echinocandins are only available in an injectable formulation and there are no generic products available.

The echinocandins are recommended as an alternative treatment option for patients with invasive aspergillosis and cutaneous aspergillosis.[7-8] However, empirical therapy with caspofungin is recommended for high-risk patients with prolonged neutropenia who remain persistently febrile despite broad-spectrum antibiotic therapy.[8] For the treatment of candidiasis, guidelines recommend the use of an echinocandin as initial therapy in patients with moderate-to-severe candidemia and for patients who have had recent azole exposure.[9] They are also recommended for the empirical treatment of suspected invasive candidiasis, as well as for prophylaxis in patients with chemotherapy-induced neutropenia and stem cell transplant patients with neutropenia.[9] They are considered an

alternative treatment option for patients with chronic disseminated candidiasis, osteoarticular *Candida* infections, *Candida* endophthalmitis, cardiovascular *Candida* infections, oropharyngeal candidiasis and esophageal candidiasis.[9]

Several non-comparative trials have demonstrated that the echinocandins are effective for both the empirical and targeted treatment of systemic *Candida* infections and aspergillosis.[12-14,18,23,26-27,34,36,48,54,58,61-62] However, there are relatively few studies that directly compare the efficacy and safety of the echinocandins. Caspofungin and micafungin demonstrated similar clinical outcomes in patients with systemic candidiasis, as well as for the empirical treatment of febrile neutropenia.[35,41] Studies have also demonstrated comparable efficacy when the echinocandins were compared to antifungal agents in other classes.[15,17,19-20,24-25,38-40,45,57,63] Relatively few studies have demonstrated greater efficacy with the echinocandins compared to treatment with amphotericin B or fluconazole.[15,20,29-31,56]

There is insufficient evidence to support that one brand echinocandin is safer or more efficacious than another. Since these agents are not indicated as first-line therapy for the management of common infectious diseases that would be seen in general use and due to concerns for the development of resistance, these agents should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand echinocandins within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand echinocandin is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Polyenes
AHFS Class 081428
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I. Overview

The polyenes include oral nystatin and parenteral amphotericin B. These agents bind to the sterol component of the cell membrane, which leads to alterations in cell permeability and cell death.[1-5] While amphotericin B has a higher affinity for the fungal cell membrane, it can also bind to the cholesterol component of the mammalian cell leading to cytotoxicity.

Conventional amphotericin B (deoxycholate) is a broad spectrum antifungal agent that has been available for several decades. However, its use is associated with a high incidence of infusion-related adverse events and nephrotoxicity. There are two lipid formulations of amphotericin B currently available, which were developed to minimize toxicity associated with conventional amphotericin B. These include amphotericin B lipid complex and amphotericin B liposome. Liposomal encapsulation, or incorporation in a lipid complex, can substantially affect a drug's functional properties relative to those of the unencapsulated or nonlipid-associated drug.[1-5] Different liposomal or lipid-complexed products with a common active ingredient may vary from one another in the chemical composition and physical form of the lipid component. Such differences may affect the functional properties of the various amphotericin B products.[1-5]

The polyenes that are included in this review are listed in Table 1. This review encompasses all systemic dosage forms and strengths. The topical antifungals were previously reviewed with the skin and mucous membrane agents (AHFS 840408) and are not included in this review. Amphotericin B (conventional) and nystatin are available in a generic formulation. This class was last reviewed in May 2012.

Table 1. Polyenes Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Amphotericin B	injection	N/A	amphotericin B
Amphotericin B lipid complex	injection	Abelcet®	none
Amphotericin B liposome	injection	AmBisome®	none
Nystatin	powder for suspension, suspension, tablet	N/A	nystatin

*Generic is available in at least one dosage form or strength.
N/A=Not available, PDL=Preferred Drug List

The polyenes have been shown to be active against the strains of microorganisms indicated in Table 2. This activity has been demonstrated in clinical infections and is represented by the Food and Drug Administration (FDA)-approved indications for the polyenes that are noted in Table 4. These agents may also have been found to show activity to other microorganisms in vitro; however, the clinical significance of this is unknown since their safety and efficacy in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials. Although empiric anti-infective therapy may be initiated before culture and susceptibility test results are known, once results become available, appropriate therapy should be selected.

Table 2. Organisms Susceptible to the Polyenes[1-5]

Organism	Amphotericin B	Amphotericin B Lipid Complex	Amphotericin B Liposome	Nystatin
Aspergillus species	✔	✔	✔	
Aspergillus fumigatus	✔	✔	✔	
Blastomyces dermatitidis	✔		✔	
Blastomyces species		✔		
Candida albicans		✔	✔	✔
Candida guilliermondii		✔		
Candida krusei			✔	
Candida lusitaniae			✔	
Candida species	✔	✔	✔	✔
Candida stellatoidea		✔		
Candida tropicalis		✔		
Coccidioides immitis	✔		✔	
Coccidioides species		✔		
Cryptococcus neoformans	✔		✔	
Cryptococcus species		✔		
Histoplasma capsulatum	✔		✔	
Histoplasma species		✔		
Leishmania donovani			✔	
Leishmania infantum			✔	
Leishmania species				
Mucor mucedo	✔			
Paracoccidioides brasiliensis			✔	
Rhodotorula	✔			
Sporothrix schenckii	✔			

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the polyenes are summarized in Table 3.

Table 3. Treatment Guidelines Using the Polyenes

Clinical Guideline	Recommendation(s)
American Thoracic Society: **Treatment of Fungal Infections in Adult Pulmonary and Critical Care Patients (2011)**[6]	Aspergillomas • In patients with aspergillomas, it is recommended that antifungal agents not be used. • Antifungals should only be used only in patients suspected of having a component of semi-invasive disease. Invasive Aspergillosis • When invasive disease is suspected or confirmed, prompt, aggressive antifungal treatment is essential. • Although amphotericin B deoxycholate had historically been the "gold standard" for the treatment of invasive aspergillosis, most clinicians and the most recent Infectious Diseases Society of America guidelines recommend voriconazole as the primary treatment option. • There are no definitive data or consensus opinions indicating improved efficacy of any of the lipid amphotericin formulations over amphotericin B deoxycholate in the treatment of invasive aspergillosis. Thus, the best indication for using a lipid formulation appears to be for reducing renal toxicity to allow the administration of high doses of amphotericin for a prolonged time. • Voriconazole has recently emerged as a standard therapy for the treatment of invasive aspergillosis based on the results of a randomized trial comparing the outcomes to amphotericin B deoxycholate; however, whether outcomes are superior to lipid formulations of amphotericin B has not been determined. In many instances voriconazole may be considered the treatment of choice. The patient can be transitioned to oral formulations of this drug. • Oral itraconazole is not recommended for initial therapy for invasive aspergillosis. However, after disease progression is arrested with either voriconazole or amphotericin, the patient can be transitioned to oral itraconazole. • Caspofungin use in invasive aspergillosis is largely limited to salvage therapy, often in combination with other antifungal agents, after primary therapy with amphotericin-based regimens have failed. • There is currently insufficient clinical support to recommend combination therapy, although many clinicians are employing this approach as a "last option," or in settings of particularly advanced disease. Chronic necrotizing aspergillosis • In patients with chronic necrotizing aspergillosis, with mild to moderate disease, voriconazole (200 mg every 12 hours) or itraconazole (400 to 600 mg/day) is recommended until resolution or stabilization of all clinical and radiographic manifestations. • If clinically severe, consider beginning therapy of chronic necrotizing aspergillosis with either liposomal amphotericin B or intravenous voriconazole as described above for invasive disease. • In select patients at high risk of invasive fungal infection, some anti-*Aspergillus* prophylaxis is warranted. Data support the use of posaconazole 200 mg orally three times daily until recovery from neutropenia and clinical remission is established. Other prophylaxis

Clinical Guideline	Recommendation(s)

	approaches have utilized itraconazole, micafungin, and inhaled liposomal amphotericin B.
	
	<u>Invasive Pulmonary Aspergillosis</u>
	• In patients with invasive pulmonary aspergillosis, the following are recommended:
	  o Intravenous voriconazole six mg/kg every 12 hours for one day, followed by four mg/kg every 12 hours until improvement, followed by oral voriconazole 200 mg every 12 hours (preferred) or oral itraconazole 400 to 600 mg/day until resolution or stabilization of all clinical and radiographic manifestations OR
	  o Intravenous liposomal amphotericin B three to five mg/kg/day until improvement, followed by oral voriconazole 200 mg every 12 hours (preferred) or oral itraconazole 400 to 600 mg/day until resolution or stabilization of all clinical and radiographic manifestation.
	• In patients with invasive pulmonary aspergillosis who have failed front line therapy and are requiring salvage therapy, the following are recommended:
	  o Intravenous caspofungin 70 mg on day one and 50 mg/day intravenously thereafter, or intravenous micafungin 100 to 150 mg/day until improvement, followed by oral voriconazole 200 mg every 12 hours or oral itraconazole 400 to 600 mg/day until resolution of disease OR
	  o Posaconazole 200 mg four times per day initially, then 400 mg twice daily orally after stabilization of disease.
	
	<u>Hypersensitivity pneumonitis related to *Aspergillus*</u>
	• In patients with hypersensitivity pneumonitis, it is recommended that antifungal therapy not be used.
	
	<u>Blastomycosis (immunocompetent hosts)</u>
	• In patients with mild to moderate pulmonary blastomycosis, oral itraconazole 200 mg twice daily is recommended for six months.
	• In patients with severe pulmonary blastomycosis, amphotericin B 0.7 to 1.0 mg/kg/day daily is recommended until clinical improvement is observed, followed by continuation of amphotericin B 0.7 to 1.0 mg/kg three times weekly, until a cumulative dose of 1.5 to 2.5 grams is reached. Once clinical improvement is observed, oral itraconazole 200 mg twice daily is recommended for six months.
	• In patients with pulmonary blastomycosis and bone involvement, it is recommended to prolong treatment with itraconazole to 12 months.
	• In patients with pulmonary blastomycosis and concomitant central nervous system involvement, the following are recommended:
	  o Liposomal amphotericin B 0.7 mg/kg/day until a cumulative dose of two grams is reached.
	  o Triazoles should not be used as monotherapy for meningeal blastomycosis.
	  o High dose intravenous or oral fluconazole 400 to 800 mg daily may be provided as an add-on therapy to intravenous amphotericin B in patients with severe or refractory disease, with the total duration of fluconazole therapy extended for at least six months.

Clinical Guideline	Recommendation(s)

	Blastomycosis (immunocompromised hosts)
	• In patients with severe pulmonary blastomycosis without central nervous system involvement, amphotericin B 0.7 mg/kg/day is recommended until clinical improvement is observed. Once clinical improvement is observed, oral itraconazole 200 mg twice daily is recommended for at least 12 months.
	• In patients with mild to moderate pulmonary blastomycosis without central nervous system involvement, oral itraconazole 200 mg twice daily is recommended for at least 12 months.
	• When acquired immunodeficiency syndrome is involved, oral itraconazole 200 mg/day is recommended indefinitely or until immunity is fully restored.
	• In patients with pulmonary blastomycosis and concomitant central nervous system involvement, the following are recommended:
	  o Combined therapy with amphotericin B 0.7 mg/kg/day together with intravenous or oral fluconazole 400 to 800 mg daily from the onset until clinical improvement is observed.
	  o Use of fluconazole for at least 12 months total after discontinuation of combined intravenous treatment with amphotericin B and high-dose fluconazole.
	  o Use of liposomal amphotericin B rather than amphotericin B deoxycholate should be considered due to theoretic better central nervous system penetration.
	  o Triazoles are not used as monotherapy.
	  o Patients with acquired immunodeficiency syndrome should continue to receive oral fluconazole 400 mg per day indefinitely or until immunity is restored.
	• In patients with pulmonary blastomycosis with new or progressing central nervous system involvement despite amphotericin B monotherapy, the following are recommended:
	  o Combined therapy with liposomal amphotericin B five mg/kg/day until clinical improvement is observed, together with intravenous or oral fluconazole 800 mg/day.
	  o Fluconazole is used for at least six months in immunocompetent patients, and at least 12 months in immunocompromised patients, after discontinuation of combined treatment with amphotericin B and fluconazole.
	  o Patients with acquired immunodeficiency syndrome receive oral fluconazole 400 mg daily indefinitely or until immunity is restored.
	• In critically ill patients with pulmonary blastomycosis, the following are recommended:
	  o Combined therapy with amphotericin B (0.7 to 1.0 mg/kg amphotericin B deoxycholate or five mg/kg daily liposomal amphotericin B) until clinical improvement is observed, together with oral itraconazole 200 mg/day.
	  o Following the initial intravenous therapy, oral itraconazole is used for at least six months in immunocompetent patients, and at least 12 months in immunocompromised patients, after discontinuation of combined treatment with amphotericin B and itraconazole.
	  o After initial therapy is complete, patients with acquired immunodeficiency syndrome should receive oral itraconazole 200 mg/day indefinitely, or until immunity is restored. Voriconazole 200 mg twice daily may be used as an

Clinical Guideline	Recommendation(s)

	alternative to itraconazole.
	• In patients with pulmonary blastomycosis with new or progressing central nervous system involvement despite amphotericin B monotherapy, the following are recommended:
	  o Combined therapy with liposomal amphotericin B five mg/kg/day until clinical improvement is observed, together with intravenous or oral fluconazole 800 mg/day.
	  o Fluconazole is used for at least six months in immunocompetent patients, and at least 12 months in immunocompromised patients, after discontinuation of combined treatment with amphotericin B and fluconazole.
	  o Patients with acquired immunodeficiency syndrome receive oral fluconazole 400 mg daily indefinitely or until immunity is restored.
	  o Voriconazole 200 mg twice daily may be considered as an alternative to fluconazole, though extensive disease-specific data are currently lacking.
	• In critically ill patients with pulmonary blastomycosis, the following are recommended:
	  o Combined therapy with amphotericin B (0.7 to 1.0 mg/kg amphotericin B deoxycholate or five mg/kg daily liposomal amphotericin B) until clinical improvement is observed, together with oral itraconazole 200 mg/day.
	  o Following the initial intravenous therapy, oral itraconazole is used for at least six months in immunocompetent patients, and at least 12 months in immunocompromised patients, after discontinuation of combined treatment with amphotericin B and itraconazole.
	  o After initial therapy is complete, patients with AIDS should receive oral itraconazole 200 mg/day indefinitely, or until immunity is restored.
	  o Voriconazole 200 mg twice daily may be considered as an alternative to itraconazole, though this is based largely on in vitro sensitivities and limited case based data.
	
	<u>Coccidioidomycosis (immunocompetent hosts)</u>
	• In most immunocompetent patients with primary pulmonary coccidioidomycosis and no additional risk factors for dissemination, we suggest no antifungal treatment.
	• In immunocompetent patients with primary pulmonary coccidioidomycosis and moderate to severe symptoms, or those in whom symptoms persist for more than six weeks, treatment with triazole antifungal drugs are recommended for at least three to six months or longer if symptoms and radiographic abnormalities persist.
	
	<u>Coccidioidomycosis (immunocompromised hosts and others at risk for disseminated disease)</u>
	• In many patients with pulmonary coccidioidomycosis and pulmonary nodules only, observation is recommended for at least one year without antifungal treatment. However, fluconazole (400 mg/day) or itraconazole (400 mg/day) may be considered during periods of significant immune suppression (i.e., chemotherapy, systemic corticosteroid therapy, or CD4 counts <250/µL).
	• In patients with pulmonary coccidioidomycosis and pulmonary nodules who have additional risk factors for disseminated disease,

Clinical Guideline	Recommendation(s)
	patients with cavities, and those presenting with hemoptysis, treatment with triazole antifungal drugs are recommended, either fluconazole (400 mg/day) or itraconazole (400 mg/day). • For diffuse pulmonary coccidioidomycosis with significant impairment of gas exchange, initial liposomal amphotericin B (five mg/kg/day) or amphotericin B (0.7 to 1.0 mg/kg/day) is recommended until clinical improvement, followed by fluconazole (400 mg/day) or itraconazole (400 mg/day) for at least another year. In patients with ongoing immune suppression, azole therapy may be continued indefinitely. • All patients, whether immunocompetent or immunocompromised, with any form of disseminated coccidioidomycosis require treatment. For non-meningeal disseminated disease, treatment with fluconazole (400 mg/day) or itraconazole (400 mg/day) is recommended for at least a year and until clinical improvement and stabilization. Itraconazole is preferred in bone disease. In severe or refractory cases, liposomal amphotericin B (five mg/kg/day) or amphotericin B (0.7 to 1.0 mg/kg/day) may be initiated until clinical improvement, followed by fluconazole (400 mg/day) or itraconazole (400 mg/day) for at least another year. • In patients with meningitis, fluconazole (400 to 1,000 mg/day) or itraconazole (400 to 600 mg/day) for life. In patients with meningitis in whom treatment with triazole antifungal drugs failed, intrathecal amphotericin B is recommended in select cases. <u>Cryptococcosis (immunocompetent hosts)</u> • In asymptomatic immunocompetent patients with respiratory tract colonization by *Cryptococcus neoformans*, no antifungal treatment is recommended. • In immunocompetent patients with pulmonary cryptococcosis and no evidence of other organ involvement, fluconazole 400 mg/day initially is recommended, tapering to 200 mg/day after clinical improvement is assured and with total treatment for six months. Alternatively, itraconazole 400 mg/day may be considered for six months. Fluconazole treatment is recommended for longer than six months in patients with documented *Cryptococcus gattii* infection. <u>Cryptococcosis (immunocompromised hosts and immunocompetent hosts with disseminated or central nervous system involvement)</u> • In patients with disseminated cryptococcosis or central nervous system involvement, amphotericin B (0.7 to 1.0 mg/kg/day) plus flucytosine (100 mg/kg/day) is recommended for two weeks, then fluconazole or itraconazole (400 mg/day) for eight to 10 weeks. Alternatively, amphotericin B (0.7 to 1.0 mg/kg/day) plus flucytosine (100 mg/kg/day) may be administered for six to 10 weeks in patients in whom azoles cannot be used. • In patients with disseminated cryptococcosis or central nervous system involvement, it is recommended that azoles not be used as monotherapy. • In patients with refractory disease not responding to fluconazole and itraconazole, voriconazole or posaconazole can be considered as salvage therapy on a case by case basis. • In patients with acquired immunodeficiency syndrome and CD4+ T cell count < 200/µL who have disseminated cryptococcosis or central nervous system involvement, fluconazole 200 mg/day is recommended to be used indefinitely, after successful primary therapy as outlined

Clinical Guideline	Recommendation(s)
	above, or until CD4+ T cell count is greater than 200/μL, human immunodeficiency virus ribonucleic acid is undetectable and sustained for three months, and the patient is stable for one to two years. <u>Histoplasmosis (immunocompetent hosts with *Histoplasma*-related pulmonary nodules, broncholithiasis, or fibrosing mediastinitis)</u> • Among asymptomatic patients with pulmonary nodules in whom *Histoplasma* cannot be cultured, antifungal treatment is not recommended. • In most patients with broncholithiasis, antifungal treatment is not recommended. • In patients with fibrosing mediastinitis, some clinicians recommend itraconazole 200 mg twice daily for 12 weeks. In patients with radiographic or physiologic improvement after an initial 12 weeks of therapy, longer treatment, up to 12 months, is recommended. <u>Histoplasmosis (immunocompetent hosts with symptomatic, progressive, or severe pulmonary histoplasmosis)</u> • In asymptomatic patients, no antifungal treatment is recommended. • In symptomatic patients with mild pulmonary histoplasmosis, who remain symptomatic after three weeks of observation, itraconazole 200 mg twice daily for up to 12 weeks is recommended. • In selected patients with mild to moderate pulmonary histoplasmosis, initiating treatment with itraconazole 200 mg twice daily rather than with amphotericin B is recommended. • In patients with severe pulmonary histoplasmosis, amphotericin B 0.7 mg/kg/day is recommended until clinical improvement is observed or until a cumulative dose of two grams of amphotericin B is reached. In patients who improve clinically after initial treatment with amphotericin B, maintenance itraconazole 200 mg twice daily for at least 12 weeks is recommended. <u>Histoplasmosis (immunocompromised hosts with pulmonary histoplasmosis or with progressive or disseminated disease, or with chronic pulmonary histoplasmosis)</u> • In patients with mild to moderate histoplasmosis, itraconazole 200 mg three times daily for three days is recommended, followed by 200 mg twice daily for 12 months. • In patients with severe progressive disseminated histoplasmosis requiring hospitalization, amphotericin B 0.7 to 1.0 mg/kg/day (or a lipid formulation of amphotericin three to five mg/kg/day) is recommended until clinical improvement is observed or until a cumulative dose of two grams of amphotericin B is reached. In patients who improve clinically after initial treatment with amphotericin B, itraconazole 200 mg twice daily for 12 months is recommended. • In patients with acquired immunodeficiency syndrome and progressive disseminated histoplasmosis who completed 12 months of initial itraconazole therapy, itraconazole 200 mg twice daily is recommended until effective immune reconstitution occurs. • In patients with chronic pulmonary histoplasmosis, itraconazole 200 mg twice daily for 12 to 24 months is recommended rather than no antifungal treatment. • In patients with severe chronic pulmonary histoplasmosis, initial treatment with amphotericin B is recommended over itraconazole.

Clinical Guideline	Recommendation(s)

	<u>Paracoccidioidomycosis</u>
	• In critically ill patients with disseminated paracoccidioidomycosis, initial amphotericin B (0.7 to 1.0 mg/kg/day) therapy is recommended until clinical stabilization or until two grams total dose administered. This may be followed by azole therapy as listed below.
	• In patients with disseminated paracoccidioidomycosis and mild to moderate or slowly progressive symptoms, one of the following options is recommended until clinical stabilization and resolution of symptoms. The total duration of therapy must be individualized to clinical response, but generally therapy for six to 12 months or longer is employed. Potential regimens include:
	  o Ketoconazole 200 to 400 mg daily
	  o Itraconazole 100 to 400 mg daily
	  o Sulfadiazine four to six grams daily
	
	<u>Sporotrichosis</u>
	• In patients with mild to moderately severe pulmonary sporotrichosis, itraconazole 200 mg twice daily is recommended, with a total duration of therapy generally of three to six months based upon overall clinical response.
	• In patients with severe pulmonary sporotrichosis, amphotericin B 0.7 mg/kg/day is recommended until clinical improvement is observed or until a cumulative dose of one to two grams of amphotericin B is reached, followed by itraconazole 200 mg twice daily, with total duration of therapy generally of three to six months based upon overall clinical response.
	
	<u>Candidemia</u>
	• Candidemia should be treated with antifungal agents, selecting one of the following agents: fluconazole, an amphotericin B formulation, an echinocandin, voriconazole, or the combination regimen of fluconazole and amphotericin B.
	• For patients who are clinically stable and have not recently received azole therapy, the following are recommended:
	  o Fluconazole (400 mg/day or ~6 mg/kg/day) OR
	  o Caspofungin (70 mg loading dose day one, then 50 mg/day) OR
	  o Micafungin (100 mg/day) OR
	  o Anidulafungin (200 mg on day one, then 100 mg/day).
	• For patients who are clinically unstable and for whom identification of the *Candida* species in the blood is unknown, there is no definitive recommendation. Several options are available and include:
	  o Amphotericin B deoxycholate (0.6 to 1.0 mg/kg/day) or a lipid formulation of amphotericin B (three to five mg/kg/day) OR
	  o High-dose fluconazole (800 mg/kg/day or ~12 mg/kg/day) OR
	  o Caspofungin (70 mg loading dose day one, then 50 mg/day) OR
	  o Micafungin (100 mg/day) OR
	  o Anidulafungin (200 mg on day one, then 100 mg/day) OR
	  o Voriconazole (six mg/kg every 12 hours for two doses, then three mg/kg every 12 hours) OR
	  o A combination regimen with fluconazole (800 mg/day) and amphotericin B (0.6 to 1.0 mg/kg/day, for the first five to six

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	days) • For *Candida albicans* and also possibly *Candida tropicalis*, the drugs of choice are fluconazole (400 mg/day), amphotericin B (0.6 to 1.0 mg/kg/day), and an echinocandin. • For *Candida parapsilosis*, the drugs of choice are fluconazole (400 mg/day) or amphotericin B (0.6 to 1.0 mg/kg/day). • For *Candida glabrata*, the drugs of choice are an echinocandin or amphotericin B. High-dose fluconazole (800 mg/day) may be a suitable alternative. • For *Candida krusei*, the drugs of choice are an echinocandin or amphotericin B. • For *Candida lusitaniae*, fluconazole is the preferred therapy. • Lipid formulations of amphotericin B are usually indicated for patients intolerant of, or refractory to, conventional antifungal therapy. Other Fungi • In patients with zygomycosis, lipid formulations of amphotericin B are recommended at five mg/kg/day or amphotericin B deoxycholate at 0.7 to 1.0 mg/kg/day. • In patients who are intolerant of, or refractory to, amphotericin B, posaconazole 200 mg orally four times per day is recommended.
Infectious Diseases Society of America: **Treatment of Aspergillosis (2008)**[7]	Invasive pulmonary aspergillosis • For primary treatment of invasive pulmonary aspergillosis, intravenous or oral voriconazole is recommended for most patients. For seriously ill patients, the parenteral formulation is recommended. • Liposomal amphotericin B may be considered as alternative primary therapy in some patients. For salvage therapy, agents include lipid formulations of amphotericin, posaconazole, itraconazole, caspofungin, or micafungin. • In the absence of a well-controlled, prospective clinical trial, routine administration of combination therapy for primary therapy is not routinely recommended. For salvage therapy, an additional antifungal agent might be added to current therapy, or combination antifungal drugs from different classes other than those in the initial regimen may be used. • For patients with successfully treated invasive aspergillosis who will require subsequent immunosuppression, resumption of antifungal therapy can prevent recurrent infection. Tracheobronchial aspergillosis • Voriconazole is recommended as initial therapy in the treatment of tracheobronchial aspergillosis. • Because the use of deoxycholate amphotericin B may result in increased nephrotoxicity in association with calcineurin inhibitors, a lipid formulation of amphotericin B is recommended if a polyene is considered in the patient (e.g., lung transplant recipient). Chronic necrotizing pulmonary aspergillosis • The greatest body of evidence regarding effective therapy supports the use of orally administered itraconazole. • Although voriconazole (and presumably posaconazole) is also likely to be effective, there is less published information available. Single-organ, extrapulmonary forms of invasive aspergillosis

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	• Voriconazole is recommended for primary treatment of these uncommon manifestations of invasive aspergillosis. <u>Aspergillosis of the central nervous system</u> • The weight of evidence supports voriconazole as the primary recommendation for systemic antifungal therapy of central nervous system aspergillosis. • Itraconazole, posaconazole, or lipid formulations of amphotericin are recommended for patients who are intolerant or refractory to voriconazole. <u>Invasive sinonasal aspergillosis</u> • If the infection is known to be due to *Aspergillus* species, voriconazole should be initiated. • If the etiological organism is not known or histopathologic examination is still pending, an amphotericin B formulation should be initiated in anticipation of possible sinus zygomycosis. <u>Aspergillus endocarditis, pericarditis, and myocarditis</u> • Voriconazole has been successfully used in case reports and may be the preferred agent. • Because of the potential for recurrent infections following replacement of an infected prosthetic valve, strong consideration should be given to lifelong antifungal therapy with an antifungal triazole, such as oral voriconazole or posaconazole. <u>*Aspergillus* osteomyelitis and septic arthritis</u> • Combined medical and surgical intervention is recommended, where feasible, for management of *Aspergillus* osteomyelitis and arthritis. • Although there is currently limited experience with voriconazole for treatment of *Aspergillus* osteomyelitis, voriconazole appears to be effective for this indication. • Historically, amphotericin B has been used and would be appropriate therapy. <u>*Aspergillus* endophthalmitis and *Aspergillus* keratitis</u> • Following a diagnostic vitreal tap, intravenous amphotericin B and, where appropriate, intravitreal amphotericin B plus pars plana vitrectomy may be sight saving in *Aspergillus* endophthalmitis. • Voriconazole administered intravitreally or systemically is an alternative regimen. Management of *Aspergillus* keratitis requires emergency ophthalmologic intervention with ophthalmologic examination, topical antifungal therapy, and systemic antifungal therapy with amphotericin B, voriconazole, or itraconazole. <u>Cutaneous aspergillosis</u> • Therapy for secondary cutaneous lesions reflects that of disseminated infection, with systemic voriconazole recommended as primary therapy. • Alternative agents include liposomal amphotericin B, posaconazole, itraconazole, or an echinocandin. <u>*Aspergillus* peritonitis</u> • Removal of peritoneal dialysis catheter and intraperitoneal dialysis with amphotericin B, in addition to intravenous administration of

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	amphotericin B, are recommended. • Itraconazole or an extended-spectrum azole (voriconazole or posaconazole) may be used as a salvage therapy. <u>Esophageal and gastrointestinal aspergillosis</u> • Once a diagnosis is established, medical and, where appropriate, surgical therapy is needed to prevent the complications of potentially fatal hemorrhage, perforation, obstruction, and infarction. • Systemic antifungal therapy, as used for disseminated invasive aspergillosis, is appropriate. <u>Hepatic aspergillosis</u> • Medical therapy of hepatic aspergillosis should be considered as initial therapy. • For extrahepatic or perihepatic biliary obstruction, surgical intervention is warranted. <u>Empirical antifungal therapy of neutropenic patients</u> • Empirical antifungal therapy with amphotericin B, lipid formulations of amphotericin, itraconazole, voriconazole, or caspofungin is recommended for high-risk patients with prolonged neutropenia who remain persistently febrile despite broad-spectrum antibiotic therapy. • Empirical antifungal therapy is not recommended for patients who are anticipated to have short durations of neutropenia (duration of neutropenia, <10 days), unless other findings indicate the presence of an invasive fungal infection. <u>Prophylaxis against invasive aspergillosis</u> • Antifungal prophylaxis with posaconazole can be recommended in hematopoietic stem cell transplantation recipients with graft-vs-host disease who are at high risk for invasive aspergillosis and in patients with acute myelogenous leukemia or myelodysplastic syndrome who are at high risk for invasive aspergillosis. • Itraconazole may be effective, but tolerability limits its use. <u>Aspergilloma and chronic pulmonary aspergillosis</u> • Antifungal chemotherapy with itraconazole, voriconazole, or presumably, posaconazole provides some potential for therapeutic benefit with comparatively minimal risk. <u>*Aspergillus* otomycosis (otic aspergillosis)</u> • Topical therapy with irrigating solutions of boric acid, acetic acid, or azole cream may be effective in eradicating *Aspergillus* otomycosis. • For refractory cases and in contexts of perforated tympanic membranes, use of voriconazole, posaconazole, or itraconazole may be appropriate. <u>Allergic bronchopulmonary aspergillosis</u> • Treatment of allergic bronchopulmonary aspergillosis should consist of a combination of corticosteroids and itraconazole. <u>Allergic *Aspergillus* sinusitis</u> • Itraconazole is recommended for consideration in allergic *Aspergillus* sinusitis.

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	Renal aspergillosis • Because none of the available antifungal agents are excreted primarily into the pelvis of the kidney or urine, the management of pelvicaliceal and ureteral infection may require nephrostomy with instillation of amphotericin B.
Infectious Diseases Society of America: **Clinical Practice Guidelines for the Management of Blastomycosis (2008)**[8] **Reviewed and deemed current as of April 2013**	Pulmonary blastomycosis • For moderately severe to severe disease, initial treatment with a lipid formulation of amphotericin B at a dosage of three to five mg/kg/day or amphotericin B deoxycholate at a dosage of 0.7 to 1.0 mg/kg/day for one to two weeks or until improvement is noted, followed by oral itraconazole, 200 mg three times per day for three days and then 200 mg twice per day, for a total of six to 12 months, is recommended. • For mild to moderate disease, oral itraconazole, 200 mg three times per day for three days and then once or twice per day for six to 12 months, is recommended. Disseminated extrapulmonary blastomycosis • For moderately severe to severe disease, lipid formulation amphotericin B, three to five mg/kg/day, or amphotericin B deoxycholate, 0.7 to 1.0 mg/kg/day, for one to two weeks or until improvement is noted, followed by oral itraconazole, 200 mg three times per day for three days and then 200 mg twice per day for a total of at least 12 months, is recommended. • For mild to moderate disease, oral itraconazole, 200 mg three times per day for three days and then once or twice per day for six to 12 months, is recommended. • Patients with osteoarticular blastomycosis should receive a total of at least 12 months of antifungal therapy. • Serum levels of itraconazole should be determined after the patient has received this agent for at least two weeks, to ensure adequate drug exposure. Central nervous system blastomycosis • Amphotericin B, given as a lipid formulation at a dosage of five mg/kg/day over four to six weeks followed by an oral azole, is recommended. Possible options for azole therapy include fluconazole, 800 mg per day, itraconazole, 200 mg two or three times per day, or voriconazole, 200 to 400 mg twice per day, for at least 12 months and until resolution of cerebrospinal fluid abnormalities. Treatment for immunosuppressed patients with blastomycosis • Amphotericin B, given as a lipid formulation, three to five mg/kg/day, or amphotericin B deoxycholate, 0.7 to 1.0 mg/kg/day, for one to two weeks or until improvement is noted, is recommended as initial therapy for patients who are immunosuppressed, including those with acquired immunodeficiency syndrome. • Itraconazole, 200 mg three times daily for three days and then twice daily, is recommended as step-down therapy after the patient has responded to initial treatment with amphotericin B and should be given to complete a total of at least 12 months of therapy. • Serum levels of itraconazole should be determined after the patient has received this agent for at least two weeks, to ensure adequate drug exposure. • Lifelong suppressive therapy with oral itraconazole, 200 mg per day, may be required for immunosuppressed patients if immunosuppression

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	cannot be reversed and in patients who experience relapse despite appropriate therapy. <u>Treatment for blastomycosis in pregnant women and in children</u> • During pregnancy, lipid formulation amphotericin B, three to five mg/kg/day, is recommended. Azoles should be avoided because of possible teratogenicity. • If the newborn shows evidence of infection, treatment is recommended with amphotericin B deoxycholate, 1.0 mg/kg/day. • For children with severe blastomycosis, amphotericin B deoxycholate, 0.7 to 1.0 mg/kg/day, or lipid formulation amphotericin B, at a dosage of three to five mg/kg/day, is recommended for initial therapy, followed by oral itraconazole, 10 mg/kg/day (up to 400 mg daily) as step-down therapy, for a total of 12 months. • For children with mild to moderate infection, oral itraconazole, at a dosage of 10 mg/kg/day (to a maximum of 400 mg orally daily) for six to 12 months, is recommended. • Serum levels of itraconazole should be determined after the patient has received this agent for at least two weeks, to ensure adequate drug exposure.
Infectious Diseases Society of America: **Clinical Practice Guidelines for the Management of Candidiasis (2009)**[9]	<u>Candidemia in non-neutropenic patients</u> • Fluconazole or an echinocandin (caspofungin, micafungin, or anidulafungin) is recommended as initial therapy for most adult patients. An echinocandin is recommended for patients with moderately severe to severe illness or for patients who have had recent azole exposure. Fluconazole is recommended for patients who are less critically ill and who have had no recent azole exposure. The same therapeutic approach is advised for children, with attention to differences in dosing regimens. • Transition from an echinocandin to fluconazole is recommended for patients who have isolates that are likely to be susceptible to fluconazole (e.g., *Candida albicans*) and who are clinically stable. • For infection due to *Candida glabrata,* an echinocandin is preferred. Transition to fluconazole or voriconazole therapy is not recommended without confirmation of isolate susceptibility. For patients who have initially received fluconazole or voriconazole, are clinically improved, and whose follow-up culture results are negative, continuing use of an azole to completion of therapy is reasonable. • For infection due to *Candida parapsilosis,* treatment with fluconazole is recommended. For patients who have initially received an echinocandin, are clinically improved, and whose follow-up culture results are negative, continuing use of an echinocandin is reasonable. • Amphotericin B deoxycholate or a lipid formulation of amphotericin B are alternatives if there is intolerance to or limited availability of other antifungals. Transition from amphotericin B deoxycholate or lipid formulation of amphotericin B to fluconazole is recommended for patients who have isolates that are likely to be susceptible to fluconazole (e.g., *Candida albicans*) and who are clinically stable. • Voriconazole is effective for candidemia, but it offers little advantage over fluconazole and is recommended as step-down oral therapy for selected cases of candidiasis due to *Candida krusei* or voriconazole-susceptible *Candida glabrata*. <u>Candidemia in neutropenic patients</u> • An echinocandin (caspofungin, micafungin, or anidulafungin) or lipid

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	formulation of amphotericin B is recommended for most patients. • For patients who are less critically ill and who have no recent azole exposure, fluconazole is a reasonable alternative. Voriconazole can be used in situations in which additional mold coverage is desired. • For infections due to *Candida glabrata,* an echinocandin is preferred. Lipid formulations of amphotericin B are an alternative treatment option. For patients who were already receiving voriconazole or fluconazole, are clinically improved, and whose follow-up culture results are negative, continuing use of the azole to completion of therapy is reasonable. • For infections due to *Candida parapsilosis*, fluconazole or lipid formulation of amphotericin B is preferred as initial therapy. If the patient is receiving an echinocandin, is clinically stable, and follow-up culture results are negative, continuing the echinocandin until completion of therapy is reasonable. For infections due to *Candida krusei*, an echinocandin, lipid formulation of amphotericin B, or voriconazole is recommended. <u>Empirical treatment for suspected invasive candidiasis in non-neutropenic patients</u> • Empirical therapy for suspected candidiasis in non-neutropenic patients is similar to that for proven candidiasis. Fluconazole, caspofungin, anidulafungin, or micafungin is recommended as initial therapy. An echinocandin is preferred for patients who have had recent azole exposure, whose illness is moderately severe or severe, or who are at high risk of infection due to *Candida glabrata* or *Candida krusei*. • Amphotericin B deoxycholate or a lipid formulation of amphotericin B are alternatives if there is intolerance to other antifungals or limited availability of other antifungals. <u>Empirical treatment for suspected invasive candidiasis in neutropenic patients</u> • Lipid formulations of amphotericin B, caspofungin, or voriconazole are recommended. • Fluconazole and itraconazole are alternative agents. • Azoles should not be used for empirical therapy in patients who have received an azole for prophylaxis. <u>Chronic disseminated candidiasis</u> • Fluconazole is recommended for clinically stable patients. Lipid formulation of amphotericin B or amphotericin B deoxycholate can be used to treat acutely ill patients or patients with refractory disease. Induction therapy with amphotericin B for one to two weeks, followed by oral fluconazole is also recommended. • Anidulafungin, micafungin, or caspofungin are alternatives for initial therapy, followed by oral fluconazole when clinically appropriate. • Therapy should be continued for weeks to months, until calcification occurs or lesions resolve. Premature discontinuation of antifungal therapy can lead to recurrent infection. • Patients with chronic disseminated candidiasis who require ongoing chemotherapy or undergo stem cell transplantation should continue to receive antifungal therapy throughout the period of high risk to prevent relapse.

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	Treatment for neonatal candidiasis • Amphotericin B deoxycholate is recommended for neonates with disseminated candidiasis. If urinary tract involvement is excluded, lipid formulation of amphotericin B can be used. Fluconazole is a reasonable alternative. The recommended length of therapy is three weeks. • Echinocandins should be used with caution and are generally limited to situations in which resistance or toxicity precludes the use of fluconazole or amphotericin B deoxycholate. • In nurseries with high rates of invasive candidiasis, fluconazole prophylaxis may be considered in neonates whose birth weight is <1000 grams. Antifungal drug resistance, drug-related toxicity, and neurodevelopmental outcomes should be observed. Osteoarticular *Candida* infections • For osteomyelitis, fluconazole at a dosage of 400 mg daily for six to 12 months or lipid formulation of amphotericin B at a dosage of three to five mg/kg/day for at least two weeks, followed by fluconazole at a dosage of 400 mg daily for six to 12 months is recommended. Alternatives include an echinocandin or amphotericin B deoxycholate at a dosage of 0.5 to 1.0 mg/kg/day for at least two weeks, followed by fluconazole at a dosage of 400 mg daily for six to 12 months. • For septic arthritis, treatment for at least six weeks with fluconazole at a dosage of 400 mg daily or lipid formulation of amphotericin B at a dosage of three to five mg/kg/day for at least two weeks, followed by fluconazole at a dosage of 400 mg daily is recommended. Alternatives include an echinocandin or amphotericin B deoxycholate at a dosage of 0.5 to 1.0 mg/kg/day for at least two weeks, followed by fluconazole at a dosage of 400 mg daily for the remainder of therapy. • For infection involving a prosthetic device, device removal is recommended for most cases. Therapy for at least six weeks with the above dosages of fluconazole, lipid formulation of amphotericin B, an echinocandin, or amphotericin B deoxycholate is recommended. If the device cannot be removed, chronic suppression with fluconazole is recommended. Central nervous system candidiasis • Lipid formulation of amphotericin B with or without flucytosine is recommended for the initial several weeks of treatment. • Fluconazole is recommended as step-down therapy after the patient responds to initial treatment with lipid formulation of amphotericin B and flucytosine. Therapy should continue until all signs and symptoms, cerebrospinal fluid abnormalities, and radiologic abnormalities have resolved. *Candida* endophthalmitis • Amphotericin B deoxycholate combined with flucytosine is recommended for advancing lesions or lesions threatening the macula. Fluconazole is an acceptable alternative for less severe endophthalmitis. Lipid formulation of amphotericin B, voriconazole, or an echinocandin can be used to treat patients who are intolerant of or experiencing treatment failure with amphotericin B deoxycholate in combination with flucytosine or fluconazole. • The recommended duration of therapy is at least four to six weeks and is determined by the stabilization or resolution of lesions as

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	documented by repeated ophthalmological examinations. <u>Cardiovascular *Candida* infections</u> • For native valve endocarditis, lipid formulation of amphotericin B with or without flucytosine is recommended. Alternatives include amphotericin B deoxycholate with or without flucytosine or an echinocandin (caspofungin or anidulafungin). Step-down therapy to fluconazole should be considered among patients with susceptible *Candida* isolates who have demonstrated clinical stability and clearance of *Candida* from the bloodstream. Valve replacement is recommended, and treatment should continue for at least six weeks after valve replacement and should continue for a longer duration in patients with perivalvular abscesses and other complications. • For patients who cannot undergo valve replacement, long-term suppression with fluconazole is recommended. • For prosthetic valve endocarditis, the recommendations above apply, and suppressive therapy should be indefinite if valve replacement is not possible. • For pericarditis, lipid formulation of amphotericin B, amphotericin B deoxycholate, an echinocandin, or fluconazole for as long as several months, in combination with either a pericardial window or pericardiectomy, is recommended. Step-down therapy to fluconazole should be considered for patients who have initially responded to amphotericin B or an echinocandin and who are clinically stable. • For myocarditis, treatment as for endocarditis (as stated above) is recommended. • For suppurative thrombophlebitis, catheter removal and incision and drainage or resection of the vein, if feasible, is recommended. Lipid formulation of amphotericin B, amphotericin B deoxycholate, fluconazole, or an echinocandin for at least two weeks after candidemia has cleared is recommended. Step-down therapy to fluconazole should be considered for patients who have initially responded to amphotericin B or an echinocandin and who are clinically stable. Resolution of the thrombus can be used as evidence to discontinue antifungal therapy if clinical and culture data are supportive. • For pacemaker and implantable cardiac defibrillator wire infections, removal of the entire device and systemic antifungal therapy with lipid formulation of amphotericin B with or without flucytosine, amphotericin B deoxycholate with or without flucytosine, or an echinocandin is recommended. Step-down therapy to fluconazole should be considered for patients with susceptible *Candida* isolates who have demonstrated clinical stability and clearance of *Candida* from the bloodstream. For infections limited to generators and/or pockets, four weeks of antifungal therapy after removal of the device is recommended. For pacemaker and implantable cardiac defibrillator wire infections, at least six weeks of antifungal therapy after wire removal is recommended. • For ventricular assist devices that cannot be removed, treatment with lipid formulation of amphotericin B, amphotericin B deoxycholate, or an echinocandin is recommended. After candidemia has cleared and the patient has responded clinically, fluconazole is recommended as step-down therapy. Chronic suppressive therapy with fluconazole is warranted until the device is removed.

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	Esophageal candidiasis • Systemic antifungal therapy is always required. Oral fluconazole for 14 to 21 days is recommended. Intravenous fluconazole, amphotericin B deoxycholate, or an echinocandin should be used for patients who cannot tolerate oral therapy. A diagnostic trial of antifungal therapy is appropriate before performing an endoscopic examination. • For fluconazole-refractory disease, itraconazole solution, posaconazole suspension, or voriconazole (administered intravenously or orally) for 14 to 21 days is recommended. Micafungin, anidulafungin or amphotericin B deoxycholate are acceptable alternatives. • Suppressive therapy with fluconazole is recommended for recurrent infections. • In patients with acquired immunodeficiency syndrome, treatment with highly active antiretroviral therapy is recommended to reduce recurrent infections. Oropharyngeal candidiasis • For mild disease, clotrimazole troches, nystatin suspension, or nystatin pastilles for seven to 14 days is recommended. • For moderate to severe disease, oral fluconazole for seven to 14 days is recommended. • For fluconazole-refractory disease, either itraconazole solution or posaconazole suspension for up to 28 days is recommended. Voriconazole or amphotericin B deoxycholate is recommended when treatment with other agents has failed. Intravenous echinocandin or amphotericin B deoxycholate can be used in treating patients with refractory disease. • Chronic suppressive therapy is usually unnecessary for patients with human immunodeficiency virus infection. If suppressive therapy is required, fluconazole three times weekly is recommended. Treatment with highly active antiretroviral therapy is recommended to reduce recurrent infections. • For denture-related candidiasis, disinfection of the denture, in addition to antifungal therapy, is recommended. Antifungal prophylaxis for solid-organ transplant recipients, patients hospitalized in intensive care units, neutropenic patients receiving chemotherapy, and stem cell transplant recipients at risk of candidiasis • For solid-organ transplant recipients, fluconazole or liposomal amphotericin B is recommended as postoperative antifungal prophylaxis for liver, pancreas, and small bowel transplant recipients at high risk of candidiasis. • For patients hospitalized in the intensive care unit, fluconazole is recommended for high-risk patients in adult units that have a high incidence of invasive candidiasis. • For patients with chemotherapy-induced neutropenia, fluconazole, posaconazole, or caspofungin is recommended during induction chemotherapy for the duration of neutropenia. Oral itraconazole is an effective alternative, but it offers little advantage over other agents and is less well tolerated. • For stem cell transplant recipients with neutropenia, fluconazole, posaconazole, or micafungin is recommended during the period of risk of neutropenia. Urinary tract infections – asymptomatic candiduria

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	• Treatment is not recommended unless the patient belongs to a group at high risk of dissemination. Elimination of predisposing factors often results in resolution of candiduria. • High-risk patients include neutropenic patients, infants with low birth weight, and patients who will undergo urologic manipulations. Neutropenic patients and neonates should be managed as described for invasive candidiasis. For those patients undergoing urologic procedures, fluconazole or amphotericin B deoxycholate for several days before and after the procedure is recommended. <u>Urinary tract infections – symptomatic candiduria</u> • For candiduria with suspected disseminated candidiasis, treatment as described for candidemia is recommended. • For cystitis due to a fluconazole-susceptible *Candida* species, oral fluconazole for two weeks is recommended. For fluconazole-resistant organisms, amphotericin B deoxycholate for one to seven days or oral flucytosine for seven to 10 days are alternatives. Amphotericin B deoxycholate bladder irrigation is generally not recommended but may be useful for treatment of patients with fluconazole-resistant *Candida* species, especially *Candida glabrata.* • For pyelonephritis due to fluconazole-susceptible organisms, oral fluconazole daily for two weeks is recommended. For patients with fluconazole-resistant *Candida* strains, especially *Candida glabrata*, alternatives include amphotericin B deoxycholate with or without flucytosine or flucytosine alone for two weeks. • For fungus balls, surgical intervention is strongly recommended in non-neonates. Fluconazole is recommended. Amphotericin B deoxycholate with or without flucytosine is an alternative. If access to the renal collecting system is available, an adjunct to systemic therapy is irrigation with amphotericin B deoxycholate. Treatment duration should be until symptoms have resolved and urine cultures no longer yield *Candida* species. <u>Vulvovaginal candidiasis</u> • Several topical antifungal agents are effective therapy for vulvovaginal candidiasis, and no agent is clearly more effective than another. • A single 150 mg dose of fluconazole is recommended for the treatment of uncomplicated *Candida* vulvovaginal candidiasis. • For recurring *Candida* vulvovaginal candidiasis, 10 to 14 days of induction therapy with a topical or oral azole, followed by fluconazole once per week for six months, is recommended.
Infectious Diseases Society of America: **Practice Guidelines for the Treatment of Coccidioidomycosis (2005)**[10]	<u>Uncomplicated acute coccidioidal pneumonia</u> • Commonly prescribed therapies include oral azole antifungal agents at dosages of 200 to 400 mg per day. Courses of therapy are typically administered for three to six months. • During pregnancy, amphotericin B is the treatment of choice because fluconazole (and likely other azole antifungals) are teratogenic. <u>Diffuse pneumonia</u> • Therapy is usually begun either with amphotericin B or high-dose fluconazole. • Amphotericin B is more frequently used as initial therapy if significant hypoxia is present or if deterioration is rapid. • Several weeks of therapy are often required to produce clear evidence of improvement. After this time, amphotericin B therapy may be

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	discontinued and replaced with treatment with an oral azole antifungal. • In combination, the total length of therapy should be at least one year, and for patients with severe immunodeficiency, oral azole therapy should be continued as secondary prophylaxis. <u>Symptomatic pulmonary cavity infections</u> • Complications of coccidioidal cavities include local discomfort, superinfection with other fungi or possibly bacteria, or hemoptysis. Should these complications occur, oral therapy with azole antifungals may result in improvement, although recurrence of symptoms may occur on cessation of therapy. • Rupture of a coccidioidal cavity into the pleural space, resulting in a pyopneumothorax, is an infrequent but serious complication of coccidioidal pneumonia. In young, otherwise-healthy patients, surgical closure by lobectomy with decortication is the preferred management. • Antifungal therapy is recommended for treatment, particularly in cases with delay of diagnosis and coexistent diseases. • For patients in whom the diagnosis was delayed a week or more, or for patients in whom there are coexistent diseases, management approaches are less uniform and may include courses of therapy with amphotericin B or oral azole antifungal drugs prior to surgery or chest tube drainage without surgery. <u>Chronic progressive fibrocavitary pneumonia</u> • Initial treatment with oral azole antifungal agents is recommended. • If the patient improves sufficiently, therapy should be continued for at least one year. If therapy is not satisfactory, switching to an alternative azole antifungal, raising the dosage of the azole, or therapy with amphotericin B are alternative strategies. • Surgical resection may be a useful option for refractory lesions that are well localized or in cases in which significant hemoptysis has occurred. <u>Non-meningeal disseminated infection (extrapulmonary)</u> • Initial therapy is usually initiated with oral azole antifungal agents. • Amphotericin B is recommended for alternative therapy, especially if lesions are appearing to worsen rapidly and are in particularly critical locations, such as the vertebral column. • In patients experiencing failure of conventional deoxycholate amphotericin B therapy, or experiencing intolerable drug-related toxicities, lipid amphotericin B formulations have been demonstrated to be safe and to cause less nephrotoxicity and may be considered. • Combination therapy with amphotericin B and an azole has been administered to some patients, especially when infection is widespread or in cases in which there has been disease progression during treatment with a single agent. Although combination therapy may improve responses, there is no evidence that such an approach is more effective than treatment with a single agent. <u>Meningeal disseminated infection (extrapulmonary)</u> • Therapy with oral fluconazole is preferred by most clinicians. Itraconazole, administered in dosages of 400 to 600 mg per day, has also been reported to be comparably effective. • Some physicians also initiate therapy with intrathecal amphotericin B in addition to an azole on the basis that responses are more prompt

Clinical Guideline	Recommendation(s)
	with this approach. Patients who respond to azole therapy should continue this treatment indefinitely. Patients who do not respond to fluconazole or itraconazole would be candidates for intrathecal amphotericin B therapy with or without continuation of azole treatment.

Infectious Diseases Society of America: **Clinical Practice Guidelines for the Management of Cryptococcal Disease (2010)**[11]
 	
Reviewed and deemed current as of April 2013
	<u>Cryptococcal meningoencephalitis (human immunodeficiency virus-infected individuals)</u>
	• Primary therapy: induction and consolidation:
	  o Amphotericin B deoxycholate (0.7 to 1.0 mg/kg per day IV) plus flucytosine (100 mg/kg/day orally in four divided doses; IV formulations may be used in severe cases and in those without oral intake where the preparation is available) for at least two weeks, followed by fluconazole (400 mg [six mg/kg] per day orally) for a minimum of eight weeks.
	  o Lipid formulations of amphotericin B, including liposomal amphotericin B (three to four mg/kg/day IV) and amphotericin B lipid complex (five mg/kg/day IV) for at least two weeks, could be substituted for amphotericin B deoxycholate among patients with or predisposed to renal dysfunction.
	• Alternative regimens for induction and consolidation (listed in order of highest recommendation top to bottom):
	  o Amphotericin B deoxycholate (0.7 to 1.0 mg/kg/day IV), liposomal amphotericin B (three to four mg/kg/day IV), or amphotericin B lipid complex (5 mg/kg/day IV) for four to six weeks. Liposomal amphotericin B has been given safely at six mg/kg/day IV in cryptococcal meningoencephalitis and could be considered in the event of treatment failure or high–fungal burden disease.
	  o Amphotericin B deoxycholate (0.7 mg/kg/day IV) plus fluconazole (800 mg/day orally) for two weeks, followed by fluconazole (800 mg/day orally) for a minimum of eight weeks.
	  o Fluconazole (≥800 mg/day orally; 1200 mg/day is favored) plus flucytosine (100 mg/kg/day orally) for six weeks.
	  o Fluconazole (800 to 2000 mg/day orally) for 10 to 12 weeks; a dosage of ≥1200 mg/day is encouraged if fluconazole alone is used.
	  o Itraconazole (200 mg twice/day orally) for 10 to 12 weeks, although use of this agent is discouraged.
	
	<u>Non-meningeal, pulmonary cryptococcosis (immunosuppressed):</u>
	• For mild-to-moderate symptoms, absence of diffuse pulmonary infiltrates, absence of severe immunosuppression, and negative results of a diagnostic evaluation for dissemination, use fluconazole (400 mg [six mg/kg] per day orally) for six to 12 months.
	• In human immunodeficiency virus-infected patients who are receiving highly active antiretroviral therapy with a CD4 cell count >100 cells/μL and a cryptococcal antigen titer that is ≤1:512 and/or not increasing, consider stopping maintenance fluconazole after one year of treatment.
	
	<u>Cryptococcal meningoencephalitis (non-human immunodeficiency virus-infected, non-transplant hosts)</u>
	• Amphotericin B deoxycholate (0.7 to 1.0 mg/kg/day IV) plus

Clinical Guideline	Recommendation(s)
	flucytosine (100 mg/kg/day orally in four divided doses) for at least four weeks for induction therapy. The four-week induction therapy is reserved for persons with meningoencephalitis without neurological complications and cerebrospinal fluid yeast culture results that are negative after two weeks of treatment. For amphotericin B deoxycholate toxicity issues, lipid formulations of amphotericin B may be substituted in the second two weeks. In patients with neurological complications, consider extending induction therapy for a total of six weeks, and lipid formulations of amphotericin B may be given for the last four weeks of the prolonged induction period. Then, start consolidation with fluconazole (400 mg per day) for eight weeks. • If patient is amphotericin B deoxycholate intolerant, substitute liposomal amphotericin B (three to four mg/kg/day IV) or amphotericin B lipid complex (five mg/kg/day IV). • If flucytosine is not given or treatment is interrupted, consider lengthening amphotericin B deoxycholate or lipid formulations of amphotericin B induction therapy for at least two weeks. • In patients at low risk for therapeutic failure, consider induction therapy with combination of amphotericin B deoxycholate plus flucytosine for only two weeks, followed by consolidation with fluconazole (800 mg [12 mg/kg] per day orally) for eight weeks. • After induction and consolidation therapy, use maintenance therapy with fluconazole (200 mg [three mg/kg] per day orally) for six to 12 months. <u>Non-meningeal, pulmonary cryptococcosis (non-immunosuppressed):</u> • For mild-to-moderate symptoms, administer fluconazole (400 mg per day orally) for six to 12 months; persistently positive serum cryptococcal antigen titers are not criteria for continuance of therapy. • For severe disease, treat similarly to central nervous system disease. • Itraconazole (200 mg twice/day orally), voriconazole (200 mg twice/day orally), and posaconazole (400 mg twice/day orally) are acceptable alternatives if fluconazole is unavailable or contraindicated. <u>Organ transplant recipients</u> • For central nervous system disease, liposomal amphotericin B (three to four mg/kg/day IV) or amphotericin B lipid complex (five mg/kg/day IV) plus flucytosine (100 mg/kg/day in four divided doses) for at least two weeks for the induction regimen, followed by fluconazole (400 to 800 mg [six to 12 mg/kg] per day orally) for eight weeks and by fluconazole (200 to 400 mg/day orally) for six to 12 months. If induction therapy does not include flucytosine, consider lipid formulations of amphotericin B for at least four to six weeks of induction therapy, and liposomal amphotericin B (six mg/kg/day) might be considered in high–fungal burden disease or relapse. • For mild-to-moderate non-central nervous system disease, fluconazole (400 mg [six mg/kg] per day) for six to 12 months. • For moderately severe–to-severe non-central nervous system or disseminated disease without central nervous system involvement, treat the same as central nervous system disease. • In the absence of any clinical evidence of extrapulmonary or disseminated cryptococcosis, severe pulmonary disease is treated the same as central nervous system disease. For mild-to-moderate symptoms without diffuse pulmonary infiltrates, use fluconazole (400 mg [six mg/kg] per day) for six to 12 months.

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	• Fluconazole maintenance therapy should be continued for at least six to 12 months. <u>Cryptococcal meningoencephalitis (management of complications-persistence)</u> • Reinstitute induction phase of primary therapy for longer course (four to 10 weeks). • Consider increasing the dose if the initial dosage of induction therapy was ≤0.7 mg/kg IV of amphotericin B deoxycholate per day or ≤3 mg/kg of lipid formulations of amphotericin B per day, up to one mg/kg IV of amphotericin B deoxycholate per day or six mg/kg of liposomal amphotericin B per day; in general, combination therapy is recommended. • If the patient is polyene intolerant, consider fluconazole (≥800 mg/day orally) plus flucytosine (100 mg/kg/day orally in four divided doses). • If patient is flucytosine intolerant, consider amphotericin B deoxycholate (0.7 mg/kg/day IV) plus fluconazole (800 mg [12 mg/kg] per day orally). • Use of intrathecal or intraventricular amphotericin B deoxycholate is generally discouraged and is rarely necessary. <u>Cerebral cryptococcomas</u> • Induction therapy with amphotericin B deoxycholate (0.7 to 1.0 mg/kg/day IV), liposomal amphotericin B (three to four mg/kg/day IV), or amphotericin B lipid complex (5 mg/kg/day IV) plus flucytosine (100 mg/kg/day orally in four divided doses) for at least six weeks. • Consolidation and maintenance therapy with fluconazole (400 to 800 mg/day orally) for 6 to 18 months. <u>Non-meningeal, non-pulmonary cryptococcosis</u> • If central nervous system disease is ruled out, fungemia is not present, infection occurs at single site, and there are no immunosuppressive risk factors, consider fluconazole (400 mg [six mg/kg] per day orally) for six to 12 months.
Infectious Diseases Society of America: **Clinical Practice Guidelines for the Management of Patients with Histoplasmosis (2007)**[12] **Reviewed and deemed current as of June 2011**	<u>Moderately severe to severe acute pulmonary histoplasmosis (adults)</u> • Lipid formulation of amphotericin B (3.0 to 5.0 mg/kg/day intravenously for one to two weeks) followed by itraconazole (200 mg three times daily for three days and then 200 mg twice daily, for a total of 12 weeks) is recommended. • The deoxycholate formulation of amphotericin B is an alternative to a lipid formulation in patients who are at a low risk for nephrotoxicity. <u>Mild-to-moderate acute pulmonary histoplasmosis (adults)</u> • Treatment is usually unnecessary. Itraconazole (200 mg three times daily for three days and then 200 mg once or twice daily for six to 12 weeks) is recommended for patients who continue to have symptoms for 11 month. <u>Acute pulmonary histoplasmosis (children)</u> • Treatment indications and regimens are similar to those for adults, except that amphotericin B deoxycholate (1.0 mg/kg/day) is usually well tolerated, and the lipid preparations are not preferred. • Itraconazole dosage in children is 5.0 to 10.0 mg/kg/day in two divided doses (not to exceed 400 mg daily), generally using the solution

Clinical Guideline	Recommendation(s)
	formulation. <u>Chronic cavitary pulmonary histoplasmosis</u> • Itraconazole (200 mg three times daily for three days and then once or twice daily for at least one year) is recommended, but some prefer 18 to 24 months in view of the risk for relapse. • Blood levels of itraconazole should be obtained after the patient has been receiving this agent for at least two weeks to ensure adequate drug exposure. <u>Pericarditis</u> • Nonsteroidal anti-inflammatory therapy is recommended in mild cases. • Prednisone (0.5 to 1.0 mg/kg daily [maximum, 80 mg daily] in tapering doses over one to two weeks) is recommended for patients with evidence of hemodynamic compromise or unremitting symptoms after several days of therapy with nonsteroidal anti-inflammatory therapy. • Pericardial fluid removal is indicated for patients with hemodynamic compromise. • Itraconazole (200 mg three times daily for three days and then once or twice daily for six to 12 weeks) is recommended if corticosteroids are administered. <u>Rheumatologic syndromes</u> • Nonsteroidal anti-inflammatory therapy is recommended in mild cases. • Prednisone (0.5 to 1.0 mg/kg/day [maximum, 80 mg daily] in tapering doses over one to two weeks) is recommended in severe cases. • Itraconazole (200 mg three times daily for three days and then once or twice daily for six to 12 weeks) is recommended only if corticosteroids are administered. <u>Mediastinal lymphadenitis</u> • Treatment is usually unnecessary. Itraconazole (200 mg three times daily for three days and then 200 mg once or twice daily for six to 12 weeks) is recommended in patients who have symptoms that warrant treatment with corticosteroids and in those who continue to have symptoms for 11 month. • Prednisone (0.5 to 1.0 mg/kg/day [maximum, 80 mg daily] in tapering doses over one to two weeks) is recommended in severe cases with obstruction or compression of contiguous structures. <u>Mediastinal granuloma</u> • Treatment is usually unnecessary. Itraconazole (200 mg three times daily for three days and then once or twice daily for six to 12 weeks) is recommended for symptomatic cases. <u>Mediastinal fibrosis</u> • Antifungal treatment is not recommended. The placement of intravascular stents is recommended for selected patients with pulmonary vessel obstruction. • Itraconazole (200 mg once or twice daily for 12 weeks) is recommended if clinical findings cannot differentiate mediastinal fibrosis from mediastinal granuloma. <u>Progressive disseminated histoplasmosis (adults)</u>

Clinical Guideline	Recommendation(s)
	• For moderately severe to severe disease, liposomal amphotericin B (3.0 mg/kg/day) is recommended for one to two weeks, followed by oral itraconazole (200 mg three times daily for three days and then 200 mg twice daily for a total of at least 12 months). • Substitution of another lipid formulation may be preferred in some patients because of tolerability. • The deoxycholate formulation of amphotericin B is an alternative to a lipid formulation in patients who are at a low risk for nephrotoxicity. • For mild-to-moderate disease, itraconazole (200 mg three times daily for three days and then twice daily for at least 12 months) is recommended. • Lifelong suppressive therapy with itraconazole (200 mg daily) may be required in immunosuppressed patients if immunosuppression cannot be reversed and in patients who relapse despite receipt of appropriate therapy. • Blood levels of itraconazole should be obtained to ensure adequate drug exposure. <u>Progressive disseminated histoplasmosis (children)</u> • Amphotericin B deoxycholate (1.0 mg/kg/day for four to six weeks) is recommended. • Amphotericin B deoxycholate (1.0 mg/kg/day for two to four weeks) followed by itraconazole (5.0 to 10.0 mg/kg/day in two divided doses) to complete three months of therapy is an alternative. • Longer therapy may be needed for patients with severe disease, immunosuppression, or primary immunodeficiency syndromes. • Lifelong suppressive therapy with itraconazole (5.0 mg/kg/day, up to 200 mg daily) may be required in immunosuppressed patients if immunosuppression cannot be reversed and in patients who experience relapse despite receipt of appropriate therapy. • Blood levels of itraconazole should be obtained to ensure adequate drug exposure. <u>Prophylaxis for immunosuppressed patients</u> • Prophylaxis with itraconazole (200 mg daily) is recommended in patients with human immunodeficiency virus with CD4 cell counts <150 cells/mm^3 in specific areas of endemicity where the incidence of histoplasmosis is 110 cases per 100 patient-years. • Prophylaxis with itraconazole (200 mg daily) may be appropriate in specific circumstances in other immunosuppressed patients. <u>Central nervous system histoplasmosis</u> • Liposomal amphotericin B (5.0 mg/kg/day for a total of 175 mg/kg given over four to six weeks) followed by itraconazole (200 mg two or three times daily) for at least one year and until resolution of cerebrospinal fluid abnormalities, including *Histoplasma* antigen levels, is recommended. • Blood levels of itraconazole should be obtained to ensure adequate drug exposure. <u>Histoplasmosis in Pregnancy</u> • Lipid formulation amphotericin B is recommended. The deoxycholate formulation of amphotericin B is an alternative to a lipid formulation in patients who are at a low risk for nephrotoxicity.

Clinical Guideline	Recommendation(s)
	• If the newborn shows evidence for infection, treatment is recommended with amphotericin B deoxycholate.
Infectious Diseases Society of America: **Clinical Practice Guidelines for the Management of Sporotrichosis (2007)**[13] **Reviewed and deemed current as of April 2013**	Lymphocutaneous and cutaneous sporotrichosis • For cutaneous and lymphocutaneous sporotrichosis, itraconazole 200 mg orally daily is recommended to be given for two to four weeks after all lesions have resolved, usually for a total of three to six months. • Patients who do not respond should be given a higher dosage of itraconazole (200 mg twice daily); terbinafine, administered at a dosage of 500 mg orally twice daily; or saturated solution of potassium iodide, initiated at a dosage of five drops (using a standard eye-dropper) three times daily and increasing, as tolerated, to 40 to 50 drops three times daily. • Fluconazole (400 to 800 mg daily) should be used only if the patient cannot tolerate these other agents. Osteoarticular sporotrichosis • Itraconazole, administered at 200 mg orally twice daily for at least 12 months, is recommended. • Amphotericin B, given as a lipid formulation at a dosage of three to five mg/kg/day, or amphotericin B deoxycholate, administered at a dosage of 0.7 to 1.0 mg/kg/day, can be used for initial therapy. After the patient has shown a favorable response, therapy can be changed to itraconazole administered at a dosage of 200 mg orally twice daily to complete a total of at least 12 months of therapy. • Serum levels of itraconazole should be determined after the patient has been receiving this agent for at least two weeks to ensure adequate drug exposure. Pulmonary sporotrichosis • For severe or life-threatening pulmonary sporotrichosis, amphotericin B, given as a lipid formulation at three to five mg/kg/day, is recommended. Amphotericin B deoxycholate, administered at a dosage of 0.7 to 1.0 mg/kg/day, could also be used. • After the patient has shown a favorable response to amphotericin B, therapy can be changed to itraconazole (200 mg orally twice daily) to complete a total of at least 12 months of therapy. • For less severe disease, itraconazole administered at 200 mg orally twice daily for at least 12 months is recommended. • Serum levels of itraconazole should be determined after the patient has been receiving this agent for at least two weeks to ensure adequate drug exposure. • Surgery combined with amphotericin B therapy is recommended for localized pulmonary disease. Meningeal sporotrichosis • Amphotericin B, given as a lipid formulation at a dosage of five mg/kg/day for four to six weeks, is recommended for the initial treatment of meningeal sporotrichosis. Amphotericin B deoxycholate, administered at a dosage of 0.7 to 1.0 mg/kg/day, could also be used but was not preferred by the panel. • Itraconazole (200 mg twice daily) is recommended as step-down therapy after the patient responds to initial treatment with amphotericin B and should be given to complete a total of at least 12 months of therapy.

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	• Serum levels of itraconazole should be determined after the patient has been receiving this agent for at least two weeks to ensure adequate drug exposure. • For patients with acquired immunodeficiency syndrome and other immunosuppressed patients, suppressive therapy with itraconazole at a dosage of 200 mg daily is recommended to prevent relapse. Disseminated (systemic) sporotrichosis • Amphotericin B, given as a lipid formulation at a dosage of three to five mg/kg/day, is recommended for disseminated sporotrichosis. Amphotericin B deoxycholate (0.7 to 1.0 mg/kg/day) could also be used but was not preferred by the panel. • Itraconazole (200 mg twice daily) is recommended as step-down therapy after the patient responds to initial treatment with amphotericin B and should be given to complete a total of at least 12 months of therapy. • Serum levels of itraconazole should be determined after the patient has been receiving this agent for at least two weeks to ensure adequate drug exposure. • Lifelong suppressive therapy with itraconazole (200 mg daily) may be required for patients with acquired immunodeficiency syndrome and other immunosuppressed patients if immunosuppression cannot be reversed. Sporotrichosis in pregnant women and in children • Amphotericin B, given as a lipid formulation at a dosage of three to five mg/kg/day, or amphotericin B deoxycholate, given at a dosage of 0.7 to 1.0 mg/kg/day, is recommended for severe sporotrichosis that must be treated during pregnancy; azoles should be avoided. • Itraconazole, administered at a dosage of six to 10 mg/kg to a maximum of 400 mg orally daily, is recommended for children with cutaneous or lymphocutaneous sporotrichosis. • For children with disseminated sporotrichosis, amphotericin B (0.7 mg/kg/day) should be the initial therapy, followed by itraconazole (six to 10 mg/kg, up to a maximum of 400 mg daily) as step-down therapy.
National Institutes of Health, the Centers for Disease Control and Prevention, and the Human Immunodeficiency Virus Medicine Association of the Infectious Diseases Society of America: **Guidelines for Prevention and Treatment of Opportunistic Infections in Human Immunodeficiency Virus-Infected Adults and Adolescents (2013)**[14]	Aspergillosis • Voriconazole is the drug of choice but should be used cautiously with human immunodeficiency virus protease inhibitors and efavirenz. Amphotericin B deoxycholate at 1 mg/kg daily or lipid-formulation amphotericin B at 5 mg/kg daily are alternatives, as is caspofungin at 50 mg daily and posaconazole. • Other echinocandins, such as micafungin and anidulafungin, are reasonable alternatives. • For treatment failure (if voriconazole was used initially) substitution with amphotericin B, posaconazole, or echinocandins might be considered; the amphotericin B or echinocandins would be rational for those who began therapy with voriconazole or posaconazole. Candidiasis (mucocutaneous) • Oral fluconazole is as effective as topical therapy for oropharyngeal candidiasis and is considered the drug of choice. Initial episodes of oropharyngeal candidiasis can be adequately treated with topical therapy, including clotrimazole troches, nystatin suspension or pastilles, or miconazole mucoadhesive tablets. Itraconazole oral solution for seven to 14 days is as effective as oral fluconazole but less

Clinical Guideline	Recommendation(s)
	well tolerated. Posaconazole oral solution is also as effective as fluconazole and is generally better tolerated than itraconazole. Intravenous amphotericin B is usually effective and can be used among patients with refractory disease. Both conventional amphotericin B and lipid complex and liposomal amphotericin B have been used. • Systemic antifungals are required for effective treatment of esophageal candidiasis. A 14 to 21-day course of either fluconazole (oral or intravenous) or oral itraconazole solution is highly effective. Oral ketoconazole or itraconazole capsules are less effective than fluconazole because of variable absorption. Although intravenous caspofungin or intravenous voriconazole are effective in treating esophageal candidiasis among human immunodeficiency virus -infected patients, oral or intravenous fluconazole remain the preferred therapies. Azole-refractory esophageal candidiasis can be treated with posaconazole, amphotericin B, anidulafungin, caspofungin, micafungin, or voriconazole. • Vulvovaginal candidiasis in human immunodeficiency virus -infected women is usually uncomplicated (90%) and responds readily to short-course oral or topical treatment with any of several therapies, including oral fluconazole, topical azoles, and itraconazole oral solution. Severe or recurrent episodes of vaginitis require oral fluconazole or topical antifungal therapy for ≥7 days. <u>Coccidioidomycosis</u> • For patients with clinically mild infection, such as focal pneumonia or a positive coccidioidal serologic test alone, initial therapy with a triazole antifungal is appropriate. • For patients with either diffuse pulmonary involvement or severely ill patients with extrathoracic disseminated disease, amphotericin B is the preferred initial therapy. Therapy with amphotericin B should continue until clinical improvement is observed. Some specialists would use a triazole antifungal concurrently with amphotericin B and continue the triazole once amphotericin B is stopped. <u>Cryptococcosis</u> • The recommended initial standard treatment is amphotericin B combined with flucytosine for ≥2 weeks for those with normal renal function. • The combination of amphotericin B with fluconazole is less effective than amphotericin B combined with flucytosine in terms of clearing *Cryptococcus* from the cerebrospinal fluid but is better than amphotericin B alone. • Fluconazole combined with flucytosine is an alternative to amphotericin B plus flucytosine, but is less effective than amphotericin B and is recommended only for persons unable to tolerate or unresponsive to standard treatment. • After at least a two-week period of successful induction therapy, amphotericin B and flucytosine may be discontinued and follow-up therapy initiated with fluconazole. This should continue for eight weeks. Itraconazole is an acceptable though less effective alternative. • The optimal therapy for those with treatment failure is not established. For those initially treated with fluconazole, therapy should be changed to amphotericin B, with or without flucytosine, and continued until a clinical response occurs. Liposomal amphotericin B may have improved efficacy over the deoxycholate formulation and should be

Clinical Guideline	Recommendation(s)
	considered in treatment failures. Higher doses of fluconazole in combination with flucytosine might also be useful. Cryptosporidiosis • In the setting of severe immunosuppression, antiretroviral therapy with immune restoration to a CD4+ count >100 cells/µL leads to resolution of clinical cryptosporidiosis and is the mainstay of treatment. • All patients with cryptosporidiosis should be offered antiretroviral therapy as part of the initial management of their infection. • Management should include symptomatic treatment of diarrhea. Rehydration and repletion of electrolyte losses by either the oral or intravenous route are important. Severe diarrhea can exceed >10 L/day among patients with acquired immunodeficiency syndrome, often requiring intensive support. Aggressive efforts at oral rehydration should be made with oral rehydration solutions. Prevention of Cytomegalovirus • Cytomegalovirus end-organ disease is best prevented by using antiretroviral therapy to maintain the CD4+ count >100 cells/µL. • Although oral valganciclovir would likely prevent the occurrence of cytomegalovirus retinitis in patients with CD4+ counts <50 cells/µL, such therapy is not generally recommended because of the potential to induce cytomegalovirus resistance, the utility of treating disease when it occurs, and the lack of demonstrated survival advantage. Treatment of Cytomegalovirus disease • Oral valganciclovir, intravenous ganciclovir, intravenous ganciclovir followed by oral valganciclovir, intravenous foscarnet, and intravenous cidofovir are all effective treatments for cytomegalovirus retinitis. • The ganciclovir implant, a surgically-implanted reservoir of ganciclovir, which lasts approximately six months, also is very effective but it no longer is being manufactured. In its absence, some clinicians will use intravitreal injections of ganciclovir or foscarnet in conjunction with oral valganciclovir, at least initially, to provide immediate high intraocular levels of drug and presumably faster control of the retinitis. • Systemic therapy has been shown to reduce morbidity in the contralateral eye. This should be considered when choosing between the oral, intravenous, and local options. • The choice of initial therapy for cytomegalovirus retinitis should be individualized based on the location and severity of the lesion(s), the level of underlying immune suppression, and other factors such as concomitant medications and ability to adhere to treatment. • No one regimen has been proven in a clinical trial to have greater efficacy in terms of protecting vision, and thus clinical judgment must be used when choosing a regimen. • In studies conducted in the pre-antiretroviral therapy era, ganciclovir intraocular implant plus oral ganciclovir was superior to once-daily intravenous ganciclovir for treatment of cytomegalovirus retinitis; however, the implant is no longer manufactured. Assuming that this observation can be extended to other combinations of systemically and locally administered drugs, human immunodeficiency virus-specialists often recommend intravitreal ganciclovir or foscarnet injections plus oral valganciclovir as the preferred initial therapy for patients with immediate sight-threatening lesions. Intravitreal injections deliver high

Clinical Guideline	Recommendation(s)
	concentrations of the drug to the target organ immediately while steady-state concentrations in the eye are achieved with systemically delivered medications. For patients with small peripheral lesions, oral valganciclovir alone often is adequate. • After induction therapy, secondary prophylaxis (i.e., chronic maintenance therapy) should be continued until immune reconstitution occurs as a result of antiretroviral therapy. Regimens demonstrated to be effective for chronic suppression in randomized, controlled clinical trials include parenteral ganciclovir, oral valganciclovir, parenteral foscarnet, combined parenteral ganciclovir and foscarnet, and parenteral cidofovir. Management of Cytomegalovirus retinitis treatment failures • When patients relapse while receiving maintenance therapy, induction with the same drug followed by reinstitution of maintenance therapy can control the retinitis, although for progressively shorter periods of time with each relapse. • Ganciclovir and foscarnet in combination appear to be superior in efficacy to either agent alone and should be considered for patients whose disease does not respond to single-drug therapy, and for patients with multiple relapses of retinitis. This drug combination, however, is associated with substantial toxicity. Treatment of Hepatitis B Virus coinfection in patients not receiving antiretroviral therapy • For patients with CD4+ counts >350 cells/µL who are not receiving antiretroviral therapy but meet criteria for hepatitis B virus treatment, adefovir or peginterferon alfa-2a monotherapy for 48 weeks might be considered, with close monitoring of hepatitis B virus deoxyribonucleic acid levels and follow-up to evaluate for hepatitis B e antigen seroconversion. However, early initiation of antiretroviral therapy should also be considered for human immunodeficiency virus/hepatitis B virus -coinfected persons with CD4+ counts >350 cells/µL. Treatment of Hepatitis B Virus coinfection in patients who require antiretroviral therapy • For human immunodeficiency virus-infected persons, some experts recommend combination therapy with two agents active against hepatitis B virus to reduce the risk of hepatitis B virus drug resistance; although, there are no results from controlled trials as yet to support this strategy. • Among patients infected with hepatitis B virus, hepatitis C virus, and human immunodeficiency virus, consideration of the need for antiretroviral therapy should be the first priority. If antiretroviral therapy is not required, interferon-based therapy, which suppresses both hepatitis C virus and hepatitis B virus, should be considered. If interferon-based therapy for hepatitis C virus has failed, treatment of chronic hepatitis B with nucleoside or nucleotide analogs is recommended. Treatment of Hepatitis C coinfection • Antiviral treatment for hepatitis C virus infection should be considered for all human immunodeficiency virus-infected persons with acute or chronic hepatitis C virus infection.

Clinical Guideline	Recommendation(s)

	• The combination of peginterferon alfa (PegIFN) plus ribavirin is the recommended backbone of therapy for HIV/HCV-co-infected patients regardless of HCV genotype.
	• Antiviral treatment with PegIFN is not recommended in patients with decompensated liver disease.
	• For HCV-genotype-1-infected patients who are not co-infected with HIV, a HCV NS3/4A protease inhibitor (PI), either boceprevir or telaprevir, in combination with PegIFN/ribavirin is recommended on the basis of large clinical trials demonstrating significantly higher SVR rates with an acceptable safety/tolerability profile compared to PegIFN/ribavirin alone.
	• For HIV/HCV co-infected patients, preliminary data from small, ongoing clinical trials of boceprevir or telaprevir plus PegIFN/ribavirin for the treatment of HCV genotype 1 infection in HIV/HCV co-infected patients demonstrate greater efficacy than PegIFN/ribavirin alone, with a safety and tolerability profile similar to that observed in HCV monoinfected patients treated with boceprevir or telaprevir plus PegIFN/ribavirin. Preliminary recommendations are as follows:
	  o PegIFN is recommended for use for all HCV genotypes
	  o Ribavirin is recommended for use with PegIFN for all HCV genotypes.
	  o Boceprevir is approved for use in combination with PegIFN/ribavirin in HCV-genotype-1-monoinfected-patients. For HIV/HCV-co-infected patients, the regimen being evaluated is PegIFN/ribavirin administered for four weeks (lead-in phase) followed by boceprevir 800 mg orally every 7 to 9 hours (with a light snack) added to PegIFN/ribavirin for an additional 44 weeks.
	  o Telaprevir is approved for use in combination with PegIFN/ribavirin in HCV-genotype-1-monoinfected-patients. Dosing regimens lasting 48 weeks are being evaluated.
	• Patients with contraindications to the use of ribavirin can be treated with peginterferon alfa (2a or 2b) monotherapy. However, substantially lower sustained viral response rates are expected in persons not receiving ribavirin. HCV PIs should not be administered without ribavirin because of the high likelihood of virologic failure.
	
	<u>Treatment of herpes simplex virus disease</u>
	• Orolabial lesions can be treated with oral valacyclovir, famciclovir, or acyclovir for five to 10 days.
	• Severe mucocutaneous herpes simplex virus lesions are best treated initially with intravenous acyclovir. Patients may be switched to oral therapy after the lesions have begun to regress. Therapy should be continued until the lesions have completely healed.
	• Genital herpes simplex virus infection should be treated with oral valacyclovir, famciclovir, or acyclovir for five to 14 days. Short-course therapy (one, two, or three days) should not be used in patients with human immunodeficiency virus infection.
	• Most recurrences of genital herpes can be prevented by use of daily anti- herpes simplex virus therapy, and this is recommended for persons who have frequent or severe recurrences.
	• Suppressive therapy with oral acyclovir, valacyclovir, or famciclovir is effective in preventing recurrences. Suppressive therapy with valacyclovir should be 500 mg twice daily in human immunodeficiency virus -infected persons or twice-daily regimens

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	with acyclovir or famciclovir should be used.
	
	Management of herpes simplex virus treatment failure
	• The treatment of choice for acyclovir-resistant herpes simplex virus is intravenous foscarnet. Topical trifluridine, cidofovir, and imiquimod also have been used successfully for lesions on external surfaces, although prolonged application for 21 to 28 days or longer might be required.
	
	Histoplasmosis
	• Patients with moderately severe to severe disseminated histoplasmosis should be treated with an intravenous lipid formulation of amphotericin B for ≥2 weeks or until they clinically improve followed by oral itraconazole (200 mg three times daily for three days and then 200 mg twice daily for a total of ≥12 months).
	• In patients with less severe disseminated histoplasmosis, oral itraconazole at 200 mg three times daily for three days followed by 200 mg twice daily is appropriate initial therapy.
	
	Treatment of Isosporiasis (also known as Cystoisosporiasis)
	  • Sulfamethoxazole-trimethoprim is the antimicrobial agent of choice for treatment of isosporiasis. It is the only agent whose use is supported by substantial published data and clinical experience. Therefore, potential alternative therapies should be reserved for patients with documented sulfa intolerance or in whom treatment fails. The traditional treatment regimen has been a 10-day course of Sulfamethoxazole-trimethoprim (800-160 mg) administered orally four times daily.
	  • Intravenous administration of Sulfamethoxazole-trimethoprim should be considered for patients with potential or documented malabsorption.
	  • Single-agent therapy with pyrimethamine has been used, with anecdotal success for treatment and prevention of isosporiasis. Pyrimethamine (50 to 75 mg/day) plus leucovorin (10 to 25 mg/day) to prevent myelosuppression may be an effective treatment alternative; it is the option for sulfa-intolerant patients.
	
	Leishmaniasis
	• Due to similar efficacy and a better toxicity profile, clinicians consider liposomal amphotericin B as the drug of choice for visceral leishmaniasis in human immunodeficiency virus-coinfected patients. The optimal amphotericin B dosage has not been determined.
	• Regimens with efficacy include conventional amphotericin B 0.5 to 1.0 mg/kg body weight/day intravenous to achieve a total dose of 1.5 to 2.0 g, or liposomal or lipid complex preparations of two to four mg/kg body weight administered on consecutive days or in an interrupted schedule (e.g., 4 mg/kg on Days 1 to 5, 10, 17, 24, 31, and 38) to achieve a total cumulative dose of 20 to 60 mg/kg body weight. A higher daily dosage is recommended for liposomal or lipid complex preparations than for conventional amphotericin B.
	
	Preventing disseminated *Mycobacterium avium* complex disease
	• Human immunodeficiency virus-infected adults and adolescents should receive chemoprophylaxis against disseminated *Mycobacterium avium* complex disease if they have a CD4+ count <50 cells/µL.

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	• Azithromycin or clarithromycin are the preferred prophylactic agents. • The combination of clarithromycin and rifabutin is no more effective than clarithromycin alone for chemoprophylaxis, is associated with a higher rate of adverse effects than either drug alone, and should not be used. • The combination of azithromycin with rifabutin is more effective than azithromycin alone; however, the additional cost, increased occurrence of adverse effects, potential for drug interactions, and absence of a survival difference compared to azithromycin alone do not warrant a routine recommendation for this regimen. • Azithromycin and clarithromycin also each confer protection against respiratory bacterial infections. • If azithromycin or clarithromycin cannot be tolerated, rifabutin is an alternative prophylactic agent for *Mycobacterium avium* complex disease, although drug interactions may make this agent difficult to use. • Primary *Mycobacterium avium* complex disease prophylaxis should be discontinued among adult and adolescent patients who have responded to antiretroviral therapy with an increase in CD4+ counts to >100 cells/µL for ≥3 months. Primary prophylaxis should be reintroduced if the CD4+ count decreases to <50 cells/µL. Treatment of disseminated *Mycobacterium avium* Complex Disease • Initial treatment of *Mycobacterium avium* complex disease should consist of two or more antimycobacterial drugs to prevent or delay the emergence of resistance. • Clarithromycin is the preferred first agent; however, azithromycin can be substituted for clarithromycin when drug interactions or clarithromycin intolerance preclude the use of clarithromycin. • Testing of *Mycobacterium avium* complex disease isolates for susceptibility to clarithromycin or azithromycin is recommended for all patients. Treatment of Penicilliosis marneffei • Penicilliosis is caused by the dimorphic fungus *Penicillium marneffei*, which is known to be endemic in Southeast Asia (especially Northern Thailand and Vietnam) and southern China. • The recommended treatment is liposomal amphotericin B, three to five mg/kg body weight/day intravenously for two weeks, followed by oral itraconazole, 400 mg/day for a subsequent duration of 10 weeks, followed by secondary prophylaxis. • Patients with mild disease can be initially treated with oral itraconazole 400 mg/day for eight weeks, followed by 200 mg/day for prevention of recurrence. • The alternative drug for primary treatment in the hospital is intravenous voriconazole, 6 mg/kg every 12 hours on day one and then 4 mg/kg every 12 hours for at least three days, followed by oral voriconazole, 200 mg twice daily for a maximum of 12 weeks. • Patients with mild disease can be initially treated with oral voriconazole 400 mg twice a day on day one, and then 200 mg twice daily for 12 weeks. The optimal dose of voriconazole for secondary prophylaxis after 12 weeks has not been studied. Primary prophylaxis of *Pneumocystis (carinii) jiroveci* pneumonia

Clinical Guideline	Recommendation(s)
	• Sulfamethoxazole-trimethoprim is the recommended prophylactic agent. One double-strength tablet daily is the preferred regimen. However, one single-strength tablet daily is also effective and might be better tolerated than one double-strength tablet daily. One double-strength tablet three times weekly is also effective. Sulfamethoxazole-trimethoprim at a dose of one double-strength tablet daily confers cross-protection against toxoplasmosis and selected common respiratory bacterial infections. Lower doses of sulfamethoxazole-trimethoprim likely also confer such protection. • For patients who have an adverse reaction that is not life threatening, chemoprophylaxis with sulfamethoxazole-trimethoprim should be continued if clinically feasible; for those who have discontinued such therapy because of an adverse reaction, reinstituting sulfamethoxazole-trimethoprim should be strongly considered after the adverse event has resolved. Patients who have experienced adverse events, including fever and rash, might better tolerate reintroduction of the drug with a gradual increase in dose (i.e., desensitization), according to published regimens or reintroduction of sulfamethoxazole-trimethoprim at a reduced dose or frequency; as many as 70% of patients can tolerate such reinstitution of therapy. • If sulfamethoxazole-trimethoprim cannot be tolerated, alternative prophylactic regimens include dapsone, dapsone/pyrimethamine plus leucovorin, aerosolized pentamidine and atovaquone. • Primary *Pneumocystis (carinii) jiroveci* pneumonia prophylaxis should be discontinued for adult and adolescent patients who have responded to antiretroviral therapy with an increase in CD4+ counts to >200 cells/µL for >3 months. Prophylaxis should be reintroduced if the CD4+ count decreases to <200 cells/µL. <u>Treatment of *Pneumocystis (carinii) jiroveci* pneumonia</u> • Sulfamethoxazole-trimethoprim is the treatment of choice. The dose must be adjusted for abnormal renal function. Multiple randomized clinical trials indicate that sulfamethoxazole-trimethoprim is as effective as parenteral pentamidine and more effective than other regimens. Adding leucovorin to prevent myelosuppression during acute treatment is not recommended because of questionable efficacy and some evidence for a higher failure rate. Oral outpatient therapy of sulfamethoxazole-trimethoprim is highly effective among patients with mild-to-moderate disease. • Patients who have *Pneumocystis (carinii) jiroveci* despite sulfamethoxazole-trimethoprim prophylaxis are usually effectively treated with standard doses of sulfamethoxazole-trimethoprim. • Patients with documented or suspected *Pneumocystis (carinii) jiroveci* and moderate-to-severe disease, as defined by room air pO_2 <70 mm Hg or arterial-alveolar O_2 gradient >35 mm Hg, should receive adjunctive corticosteroids as early as possible, and certainly within 72 hours after starting specific *Pneumocystis (carinii) jiroveci* therapy. • The recommended duration of therapy for *Pneumocystis (carinii) jiroveci* is 21 days. • Patients who have a history of *Pneumocystis (carinii) jiroveci* should be administered chemoprophylaxis for life (i.e., secondary prophylaxis or chronic maintenance therapy) with sulfamethoxazole-trimethoprim unless immune reconstitution occurs as a result of antiretroviral therapy. • Secondary prophylaxis should be discontinued for adult and adolescent

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	patients whose CD4+ count has increased from <200 cells/µL to >200 cells/µL for >3 months as a result of antiretroviral therapy. Prophylaxis should be reintroduced if the CD4+ count decreases to <200 cells/µL. If *Pneumocystis (carinii) jiroveci* recurs at a CD4+ count of ≥200 cells/µL, lifelong prophylaxis should be administered.
	
	Primary prophylaxis of *Toxoplasma* encephalitis
	• The double-strength tablet daily dose of sulfamethoxazole-trimethoprim recommended as the preferred regimen for *Pneumocystis (carinii) jiroveci* prophylaxis is effective against *Toxoplasma* encephalitis as well and is therefore recommended. Sulfamethoxazole-trimethoprim, one double-strength tablet three times weekly, is an alternative.
	• If patients cannot tolerate sulfamethoxazole-trimethoprim, the recommended alternative is dapsone-pyrimethamine plus leucovorin, which is also effective against *Pneumocystis (carinii) jiroveci* pneumonia.
	• Atovaquone with or without pyrimethamine/leucovorin can also be considered.
	• Prophylactic monotherapy with dapsone, pyrimethamine, azithromycin, or clarithromycin cannot be recommended on the basis of available data. Aerosolized pentamidine does not protect against *Toxoplasma* encephalitis and is not recommended.
	• Prophylaxis against *Toxoplasma* encephalitis should be discontinued among adult and adolescent patients who have responded to antiretroviral therapy with an increase in CD4+ counts to >200 cells/µL for >3 months. Prophylaxis for *Toxoplasma* encephalitis should be reintroduced if the CD4+ count decreases to <100–200 cells/µL.
	
	Treatment of *Toxoplasma* encephalitis
	• The initial therapy of choice for *Toxoplasma* encephalitis consists of the combination of pyrimethamine plus sulfadiazine plus leucovorin.
	• The preferred alternative regimen for patients with *Toxoplasma* encephalitis who are unable to tolerate or who fail to respond to first-line therapy is pyrimethamine plus clindamycin plus leucovorin.
	• Sulfamethoxazole-trimethoprim was reported in a small randomized trial to be effective and better tolerated than pyrimethamine-sulfadiazine. On the basis of less in vitro activity and less experience with sulfamethoxazole-trimethoprim, treatment with this drug may be considered an option.
	• Acute therapy for *Toxoplasma* encephalitis should be continued for at least six weeks, if there is clinical and radiologic improvement.
	
	Treatment of latent tuberculosis infection
	• Human immunodeficiency virus-infected persons, regardless of age, should be treated for latent tuberculosis infection if they have no evidence of active tuberculosis and:
	  o A positive diagnostic test for latent tuberculosis infection and no prior history of treatment for active or latent tuberculosis.
	  o A negative diagnostic test for latent tuberculosis infection but are close contacts of persons with infectious pulmonary tuberculosis.
	  o A history of untreated or inadequately treated healed tuberculosis (i.e., old fibrotic lesions on chest radiography)

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	regardless of diagnostic tests for latent tuberculosis infection. • Treatment options for latent tuberculosis infection include isoniazid daily or twice weekly for nine months. • Due to an increased risk of fatal and severe hepatotoxicity, a two-month regimen of daily rifampin and pyrazinamide is not recommended for latent tuberculosis infection treatment regardless of human immunodeficiency virus status. • Human immunodeficiency virus-infected persons receiving isoniazid should receive pyridoxine to minimize the risk of developing peripheral neuropathy. Alternatives for individuals who cannot take isoniazid or who have been exposed to a known isoniazid-resistant index case include either rifampin or rifabutin alone for four months. • For persons exposed to isoniazid- and/or rifampin-resistant tuberculosis, decisions to treat with one or two drugs other than isoniazid, rifampin, or rifabutin should be based on the relative risk of exposure to organisms broadly resistant to other antimycobacterial drugs and should be made in consultation with public health authorities. • Directly observed therapy should be used with intermittent dosing regimens when otherwise feasible to maximize regimen completion rates. • There is no evidence to suggest that latent tuberculosis infection treatment should be continued beyond the recommended duration in persons with human immunodeficiency virus infection. Therefore, latent tuberculosis infection treatment should be discontinued after completing the appropriate number of doses. <u>Treatment of active tuberculosis disease</u> • Recommendations for anti-tuberculosis treatment regimens in human immunodeficiency virus -infected adults follow the same principles as for adults without human immunodeficiency virus -infection. • Treatment of drug susceptible tuberculosis disease should include a six-month regimen with an initial phase of isoniazid, rifampin or rifabutin, pyrazinamide, and ethambutol administered for two months followed by isoniazid and rifampin (or rifabutin) for four additional months. • When drug-susceptibility testing confirms the absence of resistance to isoniazid, rifampin, and pyrazinamide, ethambutol may be discontinued before two months of treatment have been completed. • For patients with cavitary lung disease and cultures positive for *Mycobacterium tuberculosis* after completion of two months of therapy, treatment should be extended with isoniazid and rifampin for an additional three months for a total of nine months. • All human immunodeficiency virus-infected patients treated with isoniazid should receive pyridoxine supplementation. • For patients with extrapulmonary tuberculosis, a six- to nine-month regimen (two months of isoniazid, rifampin, pyrazinamide, and ethambutol followed by four to seven months of isoniazid and rifampin) is recommended. • Exceptions to the recommendation for a six- to nine-month regimen for extrapulmonary tuberculosis include central nervous system disease (tuberculoma or meningitis) and bone and joint tuberculosis, for which many experts recommend nine to 12 months. • Adjuvant corticosteroids should be added when treating central nervous system and pericardial disease.

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	• Treatment with corticosteroids should be started intravenously as early as possible with change to oral therapy individualized according to clinical improvement. • Recommended corticosteroid regimens are dexamethasone 0.3 to 0.4 mg/kg tapered over six to eight weeks or prednisone 1 mg/kg for three weeks, then tapered for three to five weeks. Treatment of varicella zoster virus disease • For uncomplicated varicella, the preferred treatment options are valacyclovir (1 gram orally three times daily), or famciclovir (500 mg orally three times daily) for five to seven days. Oral acyclovir (20 mg/kg body weight up to a maximum dose of 800 mg five times daily) can be an alternative. • Prompt antiviral therapy should be instituted in all human immunodeficiency virus-seropositive patients whose herpes zoster is diagnosed within one week of rash onset (or any time before full crusting of lesions). The recommended treatment options for acute localized dermatomal herpes zoster in human immunodeficiency virus-infected patients are oral valacyclovir, famciclovir, or acyclovir (doses as above) for seven to 10 days, although longer durations of therapy should be considered if lesions resolve slowly. Valacyclovir or famciclovir are preferred because of their improved pharmacokinetic properties and simplified dosing schedule. • If cutaneous lesions are extensive or if visceral involvement is suspected, intravenous acyclovir should be initiated and continued until clinical improvement is evident. A switch from intravenous acyclovir to oral antiviral therapy (to complete a 10 to 14 day treatment course) is reasonable when formation of new cutaneous lesions has ceased and the signs and symptoms of visceral varicella zoster virus infection are clearly improving. • Optimal antiviral therapy for progressive outer retinal necrosis remains undefined. Specific treatment should include systemic therapy with at least one intravenous drug (selected from acyclovir, ganciclovir, foscarnet, and cidofovir) coupled with injections of at least one intravitreal drug (selected from ganciclovir and foscarnet). Treatment regimens for progressive outer retinal necrosis recommended by certain specialists include a combination of intravenous ganciclovir and/or foscarnet plus intravitreal injections of ganciclovir and/or foscarnet. The prognosis for visual preservation in involved eyes is poor, despite aggressive antiviral therapy. • Other infectious disease states mentioned within these guidelines note that the treatment guidelines for that disease state should be utilized. • The guideline specifies that detailed recommendations for the treatment of human herpesvirus-8 and associated malignancies are beyond the scope of these guidelines. • Other excluded infectious disease states offer no specific therapy or utilize medications not licensed in the United States.
Infectious Diseases Society of America: **Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer**	Antifungal therapy in high risk patients • Empirical antifungal therapy and investigation for invasive fungal infections should be considered for patients with persistent or recurrent fever after four to seven days of antibiotics and whose overall duration of neutropenia is expected to be greater than seven days. • Data are insufficient to recommend a specific empirical antifungal

Clinical Guideline	Recommendation(s)
(2010)[15] **Reviewed and deemed current as of April 2013**	agent for a patient already receiving antifungal prophylaxis, but switching to a different class of antifungals that is given intravenously should be considered. • Preemptive antifungal management is acceptable as an alternative to empirical antifungal therapy in a subset of high-risk neutropenic patients. Those who remain febrile after four to seven days of broad-spectrum antibiotics but are clinically stable, have no clinical or chest and sinus computed tomography signs of fungal infection, have negative serologic assay results for evidence of invasive fungal infection, and have no recovery of fungi from any body site may have antifungal agents withheld. Antifungal therapy should be instituted if any of these indicators of possible invasive fungal infection are identified. • Prophylaxis against *Candida* infection is recommended in patient groups in whom the risk of invasive candidal infection is substantial, such as allogeneic hematopoietic stem cell transplant recipients or those undergoing intensive remission-induction or salvage-induction chemotherapy for acute leukemia. Fluconazole, itraconazole, voriconazole, posaconazole, micafungin, and caspofungin are all acceptable alternatives. • Prophylaxis against invasive *Aspergillus* infections with posaconazole should be considered for selected patients >13 years of age who are undergoing intensive chemotherapy for acute myeloid leukemia or myelodysplastic syndrome in whom the risk of invasive aspergillosis without prophylaxis is substantial. <u>Antifungal therapy in low risk patients</u> • In low-risk patients, the risk of invasive fungal infection is low, and therefore routine use of empirical antifungal therapy is not recommended. • Antifungal prophylaxis is not recommended for patients in whom the anticipated duration of neutropenia is less than seven days. <u>Antiviral prophylaxis</u> • Herpes simplex virus–seropositive patients undergoing allogeneic hematopoietic stem cell transplantation or leukemia induction therapy should receive acyclovir antiviral prophylaxis. • Antiviral treatment for herpes simplex or varicella-zoster virus infection is only indicated if there is clinical or laboratory evidence of active viral disease.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the polyenes are noted in Table 4. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 4. FDA-Approved Indications for the Polyenes[1-5]

Indication	Amphotericin B	Amphotericin B Lipid Complex	Amphotericin B Liposome	Nystatin
Aspergillosis	✔			
Blastomycosis (North American)	✔			
Candidiasis (systemic)	✔			
Coccidioidomycosis	✔			
Cryptococcosis	✔			
Empirical therapy for presumed fungal infection in febrile, neutropenic patients			✔	
Histoplasmosis	✔			
Leishmaniasis (mucocutaneous)	✔			
Leishmaniasis (visceral)			✔	
Mucormycosis	✔			
Sporotrichosis	✔			
Treatment of cryptococcal meningitis in HIV-infected patients			✔	
Treatment of invasive fungal infections in patients who are refractory to or intolerant of conventional amphotericin B therapy		✔		
Treatment of patients with *Aspergillus* species, *Candida* species and/or *Cryptococcus* species infections refractory to amphotericin B deoxycholate, or in patients where renal impairment or unacceptable toxicity precludes the use of amphotericin B deoxycholate			✔	
Treatment of intestinal and oral cavity infections caused by *Candida albicans*				✔ *
Treatment of candidiasis in the oral cavity				✔ †
Treatment of non-esophageal mucous membrane gastrointestinal candidiasis				✔ ‡
Zygomycosis	✔			

*Powder formulation only
†Suspension formulation only
‡Tablet formulation only

IV. Pharmacokinetics

The pharmacokinetic parameters of the polyenes are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Polyenes[1-5]

Generic Name(s)	Protein Binding (%)	Excretion (%)	Half-Life
Amphotericin B	>90	Renal (40)	15 days
Amphotericin B lipid complex	Not reported	Renal (1)	170 hours
Amphotericin B liposome	Not reported	Renal (10)	7 to 153 hours
Nystatin	Not reported	Feces	Not reported

V. Drug Interactions

Significant drug interactions with the polyenes are listed in Table 6.

Table 6. Significant Drug Interactions with the Polyenes[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
None			

Significance level 1 = major severity; significance level 2 = moderate severity

VI. Adverse Drug Events

The most common adverse drug events reported with the polyenes are listed in Table 7. The boxed warning for all amphotericin B products is listed in Table 8. Conventional amphotericin B causes acute infusion-related reactions and nephrotoxicity. Infusion-related reactions include fever, rigors, chills, myalgias, arthralgias, nausea, vomiting, headaches and bronchospasm. The lipid formulations of amphotericin B are associated with a lower risk of nephrotoxicity and infusion-related adverse events than conventional amphotericin B.

Table 7. Adverse Drug Events (%) Reported with the Polyenes[1-5]

Adverse Events	Amphotericin B	Amphotericin B Lipid Complex	Amphotericin B Liposome	Nystatin
Cardiovascular				
Arrhythmias	✔	✔	2 to 10	-
Atrial fibrillation	-	-	2 to 10	-
Bradycardia	-	-	2 to 10	-
Cardiac arrest	✔	6	2 to 10	-
Cardiac failure	✔	✔	-	-
Cardiomegaly	-	-	2 to 10	-
Cardiomyopathy	-	✔	-	-
Cardiovascular disorder	-	-	-	-
Chest pain	-	3	8 to 12	-
Congestive heart failure	-	-	-	-
Hypertension	✔	5	8 to 20	-
Hypotension	✔	8	7 to 14	-
Myocardial infarction	-	6	-	-
Orthostatic hypotension	-	-	2 to 10	-
Shock	✔	✔	-	-
Supraventricular tachycardia	-	-	-	-
Syncope	-	-	-	-
Tachycardia	-	-	9 to 19	✔
Valvular heart disease	-	-	2 to 10	-
Vascular disorder	-	-	2 to 10	-
Vasodilation	-	-	2 to 10	-
Ventricular fibrillation	✔	✔	-	-
Central Nervous System				
Agitation	-	-	2 to 10	-
Anxiety	-	-	7 to 14	-
Asthenia	-	-	6 to 8	-
Cerebrovascular accident	-	✔	-	-
Coma	-	-	2 to 10	-

Adverse Events	Amphotericin B	Amphotericin B Lipid Complex	Amphotericin B Liposome	Nystatin
Confusion	-	-	9 to 13	-
Convulsions	✔	✔	2 to 10	-
Depression	-	-	2 to 10	-
Dizziness	-	-	2 to 10	-
Dysesthesia	-	-	2 to 10	-
Hallucination	-	-	2 to 10	-
Headache	✔	6	9 to 20	-
Insomnia	-	-	17	-
Malaise	✔	✔	2 to 10	-
Nervousness	-	-	2 to 10	-
Neurologic symptoms	✔	✔	-	-
Paresthesia	-	-	2 to 10	-
Peripheral neuropathy	✔	✔	-	-
Psychosis	-	-	-	-
Somnolence	-	-	2 to 10	-
Tremor	-	-	2 to 10	-
Vertigo	✔	✔	2 to 10	-
Dermatological				
Alopecia	-	-	2 to 10	-
Dry skin	-	-	2 to 10	-
Ecchymosis	-	-	2 to 10	-
Erythema	-	-	✔	-
Erythema multiforme	-	✔	-	-
Exfoliative dermatitis	-	✔	-	-
Maculopapular rash	✔	✔	2 to 10	-
Pruritus	✔	✔	11	-
Purpura	-	-	2 to 10	-
Rash	✔	4	22 to 25	✔
Skin discoloration	-	-	2 to 10	-
Skin disorder	-	-	2 to 10	-
Skin ulceration	-	-	2 to 10	-
Stevens-Johnson syndrome	✔	-	-	✔
Urticaria	-	-	✔	✔
Vesiculobullous rash	-	-	2 to 10	-
Gastrointestinal				
Abdomen enlarged	-	-	2 to 10	-
Abdominal pain	-	4	10 to 20	-

Adverse Events	Amphotericin B	Amphotericin B Lipid Complex	Amphotericin B Liposome	Nystatin
Anorexia	✔	✔	2 to 10	-
Bloody diarrhea	-	-	-	✔
Cholangitis	-	✔	-	-
Cholecystitis	-	✔	-	-
Constipation	-	-	2 to 15	-
Cramping	✔	✔	-	-
Diarrhea	✔	6	15 to 30	✔
Dry mouth	-	-	2 to 10	-
Dyspepsia	✔	✔	2 to 10	-
Dysphagia	-	-	2 to 10	-
Epigastric pain	-	✔	-	-
Eructation	-	-	2 to 10	-
Fecal incontinence	-	-	2 to 10	-
Flatulence	-	-	2 to 10	-
Gastrointestinal hemorrhage	-	4	10	-
Gastrointestinal upset	-	-	-	✔
Gum/oral hemorrhage	-	-	2 to 10	-
Hematemesis	-	-	2 to 10	-
Hemorrhagic gastroenteritis	✔	-	-	-
Hemorrhoids	-	-	2 to 10	-
Ileus	-	-	2 to 10	-
Melena	✔	✔	-	-
Mucositis	-	-	2 to 10	-
Nausea	✔	9	26 to 40	✔
Nausea and vomiting	-	3	-	-
Stomatitis	-	-	2 to 10	-
Rectal disorder	-	-	2 to 10	-
Ulcerative stomatitis	-	-	2 to 10	-
Veno-occlusive liver disease	-	✔	2 to 10	-
Vomiting	✔	8	22 to 32	✔
Weight loss	✔	✔	-	-
Genitourinary				
Acute renal failure	✔	-	2 to 10	-
Albuminuria	-	-	-	-
Angioedema	-	-	2 to 10	-
Anuria	✔	✔	-	-
Azotemia	✔	-	-	-

Adverse Events	Amphotericin B	Amphotericin B Lipid Complex	Amphotericin B Liposome	Nystatin
Dysuria	-	✔	2 to 10	-
Glycosuria	-	-	-	-
Hematuria	-	-	14	-
Hemorrhagic cystitis	-	-	✔	-
Hyposthenuria	✔	-	-	-
Impotence	-	✔	-	-
Kidney failure	-	5	2 to 10	-
Nephrocalcinosis	✔	-	-	-
Oliguria	✔	✔	-	-
Renal function abnormalities	✔	-	2 to 10	-
Renal function decreased	✔	✔	-	-
Renal tubular acidosis	✔	✔	-	-
Toxic nephropathy	-	-	2 to 10	-
Urinary incontinence	-	-	2 to 10	-
Vaginal hemorrhage	-	-	2 to 10	-
Hematological				
Agranulocytosis	✔	-	✔	-
Anemia	✔	4	2 to 48	-
Blood dyscrasias	-	✔	-	-
Coagulation defects	✔	✔	2 to 10	-
Eosinophilia	✔	✔	-	-
Hypoproteinemia	-	-	2 to 10	-
Leukocytosis	✔	✔	-	-
Leukopenia	✔	4	15 to 17	-
Petechia	-	-	2 to 10	-
Prothrombin decreased	-	-	2 to 10	-
Prothrombin increased	-	-	2 to 10	-
Thrombocytopenia	✔	5	2 to 13	-
Hepatic				
Acute liver failure	✔	✔	-	-
Hepatitis	✔	✔	-	-
Hepatocellular damage	-	-	2 to 10	-
Hepatomegaly	-	✔	2 to 10	-
Jaundice	✔	✔	-	-
Laboratory Test Abnormalities				
Abnormal liver function tests	✔	-	7 to 11	-
Acidosis	✔	✔	2 to 10	-

Adverse Events	Amphotericin B	Amphotericin B Lipid Complex	Amphotericin B Liposome	Nystatin
Alkaline phosphatase increases	✔	-	7 to 22	-
Amylase increased	-	-	2 to 10	-
Bilirubin elevations	✔	4	11 to 18	-
Blood urea nitrogen elevations	✔	✔	19 to 21	-
Creatinine increased	-	11	19 to 22	-
Gamma-glutamyl transpeptidase increased	✔	-	-	-
Hyperamylasemia	-	✔	-	-
Hypercalcemia	-	✔	-	-
Hyperchloremia	-	-	2 to 10	-
Hyperglycemia	-	✔	8 to 23	-
Hyperkalemia	✔	✔	2 to 10	-
Hypermagnesemia	-	-	2 to 10	-
Hypernatremia	-	-	4	-
Hyperphosphatemia	-	-	2 to 10	-
Hyperuricemia	-	✔	-	-
Hypocalcemia	✔	✔	5 to 18	-
Hypoglycemia	-	✔	-	-
Hypokalemia	✔	5	38 to 43	-
Hypomagnesemia	✔	✔	15 to 26	-
Hyponatremia	-	-	2 to 12	-
Hypophosphatemia	-	✔	2 to 10	-
LDH increased	-	-	2 to 10	-
Liver enzyme elevations	✔	✔	4 to 15	-
Non-protein nitrogen increased	-	-	2 to 10	-
Serum creatinine elevations	✔	-	-	-
Musculoskeletal				
Arthralgia	✔	✔	2 to 10	-
Back pain	-	-	12	-
Bone pain	-	✔	2 to 10	-
Dystonia	-	-	2 to 10	-
Myalgia	✔	✔	2 to 10	✔
Myasthenia	-	✔	-	-
Neck pain	-	-	2 to 10	-
Respiratory				
Asthma	-	✔	2 to 10	-
Bronchospasm	✔	✔	-	✔

Adverse Events	Amphotericin B	Amphotericin B Lipid Complex	Amphotericin B Liposome	Nystatin
Cough increased	-	-	18	-
Cyanosis	-	-	✔	-
Dyspnea	✔	7	18 to 23	-
Epistaxis	-	-	9 to 15	-
Hemoptysis	-	✔	2 to 10	-
Hiccup	-	-	2 to 10	-
Hypersensitivity pneumonitis	✔	-	-	-
Hyperventilation	-	-	1 to 10	-
Hypoventilation	-	-	✔	-
Hypoxia	-	-	6 to 8	-
Lung disorder	-	-	14 to 18	-
Lung edema	-	-	2 to 10	-
Pharyngitis	-	-	2 to 10	-
Pleural effusion	-	✔	13	-
Pneumonia	-	-	2 to 10	-
Pulmonary edema	✔	✔	✔	-
Pulmonary embolism	-	✔	-	-
Respiratory alkalosis	-	-	2 to 10	-
Respiratory disorder	-	4	-	-
Respiratory failure	-	8	2 to 10	-
Respiratory insufficiency	-	-	2 to 10	-
Rhinitis	-	-	11	-
Sinusitis	-	-	2 to 10	-
Tachypnea	✔	✔	-	-
Wheezing	✔	✔	-	-
Special Senses				
Conjunctivitis	-	-	2 to 10	-
Deafness	-	✔	-	-
Diplopia	✔	✔	-	-
Dry eyes	-	-	2 to 10	-
Dry nose	-	-	2 to 10	-
Eye hemorrhage	-	-	2 to 10	-
Hearing loss	✔	✔	-	-
Tinnitus	✔	✔	-	-
Visual impairment	✔	✔	-	-
Other				
Allergic reactions	✔	✔	-	-

Adverse Events	Amphotericin B	Amphotericin B Lipid Complex	Amphotericin B Liposome	Nystatin
Anaphylactoid reactions	✔	✔	-	-
Angioedema	-	-	✔	-
Chills	✔	18	40 to 48	-
Edema	-	-	12 to 15	-
Facial swelling	-	-	2 to 10	✔
Fever	✔	14	7 to 47	-
Graft vs host disease	-	-	2 to 10	-
Hemorrhage	-	-	2 to 10	-
Herpes simplex	-	-	2 to 10	-
Hypervolemia	-	-	8 to 12	-
Infection	-	5	11 to 13	-
Influenza-like symptoms	-	-	2 to 10	-
Injection site inflammation	-	✔	2 to 10	-
Injection site pain	✔	-	-	-
Injection site reaction	✔	✔	-	-
Multiple organ failure	-	11	-	-
Pain	✔	5	14	-
Peripheral edema	-	-	15	-
Phlebitis	✔	-	9 to 11	-
Procedural complication	-	-	2 to 10	-
Sepsis	-	7	7 to 14	-
Shaking	✔	-	-	-
Sweating	-	-	7	-
Thrombophlebitis	✔	✔	-	-

✔ Percent not specified
- Event not reported

Table 8. Boxed Warning for Amphotericin B (All Formulations)[1]

WARNING
This drug should be used primarily for treatment of patients with progressive and potentially life-threatening fungal infections; it should not be used to treat noninvasive forms of fungal disease such as oral thrush, vaginal candidiasis, and esophageal candidiasis in patients with normal neutrophil counts. Exercise caution to prevent inadvertent overdose with amphotericin B. Verify the product name and dosage if dose exceeds 1.5 mg/kg.

VII. Dosing and Administration

The usual dosing regimens for the polyenes are listed in Table 9.

Table 9. Usual Dosing Regimens for the Polyenes[1-5]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Amphotericin B	Aspergillosis: Injection: Total dose up to 3.6 grams for a period up to 11 months Life-threatening fungal infections: Injection: Initial, 0.25 mg/kg/day IV; maintenance, depending on the patient's cardio-renal status, doses may gradually be increased by 5 to 10 mg/day to final daily dosage of 0.5 to 0.7 mg/kg; the optimal dose is unknown; total daily dosage may range up to 1 mg/kg/day or up to 1.5 mg/kg when given on alternate days Rhinocerebral phycomycosis: Injection: Cumulative dose of ≥3 grams Sporotrichosis: Injection: Total dose up to 2.5 grams for a period up to nine months	Safety and efficacy in children have not been established.	Injection: 50 mg
Amphotericin B lipid complex	Treatment of invasive fungal infections in patients who are refractory to or intolerant of conventional amphotericin B therapy: Injection: Five mg/kg IV as a single infusion daily	Treatment of invasive fungal infections in patients who are refractory to or intolerant of conventional amphotericin B therapy: Injection: Five mg/kg IV as a single infusion daily	Injection: 5 mg/mL
Amphotericin B liposome	Treatment of cryptococcal meningitis in HIV-infected patients: Injection: Six mg/kg/day Empirical therapy for presumed fungal infection in febrile,	Treatment of cryptococcal meningitis in HIV-infected patients: Injection: Six mg/kg/day Empirical therapy for presumed fungal infection in febrile,	Injection: 50 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	neutropenic patients: Injection: Three mg/kg/day Treatment of patients with *Aspergillus* species, *Candida* species and/or *Cryptococcus* species infections refractory to amphotericin B deoxycholate, or in patients where renal impairment or unacceptable toxicity precludes the use of amphotericin B deoxycholate: Injection: Three to five mg/kg/day Visceral Leishmaniasis: Injection: Immunocompetent patients, three mg/kg/day on days one through five, and three mg/kg/day on days 14 and 21; immunocompromised patients, four mg/kg/day on days one through five and four mg/kg/day on days 10, 17, 24, 31, and 38	neutropenic patients: Injection: Three mg/kg/day Treatment of patients with *Aspergillus* species, *Candida* species and/or *Cryptococcus* species infections refractory to amphotericin B deoxycholate, or in patients where renal impairment or unacceptable toxicity precludes the use of amphotericin B deoxycholate: Injection: Three to five mg/kg/day Visceral Leishmaniasis: Injection: Immunocompetent patients, three mg/kg/day on days one through five, and three mg/kg/day on days 14 and 21; immunocompromised patients, four mg/kg/day on days one through five and four mg/kg/day on days 10, 17, 24, 31, and 38	
Nystatin	Treatment of intestinal infections caused by *Candida albicans*: Powder: 500,000 to one million units three times daily Treatment of non-esophageal mucous membrane gastrointestinal candidiasis: Tablet: 500,000 to one million units three times daily Treatment of candidiasis in the oral cavity: Powder/Suspension: 400,000 to 600,000 units four times daily	Treatment of intestinal infections caused by *Candida albicans*: Powder: 500,000 to one million units three times daily Treatment of candidiasis in the oral cavity: Younger than one year of age: Powder/Suspension: 200,000 units four times daily One year of age and older: Powder/Suspension: 400,000 to 600,000 units four times daily	Powder: 50 million units 150 million units 500 million units Suspension: 100,000 units/mL Tablet: 500,000 units

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the polyenes are summarized in Table 10.

Table 10. Comparative Clinical Trials with the Polyenes

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Aspergillosis				
Barnes et al.[16] (1999) Amphotericin B colloidal dispersion (ABCD) 4 mg/kg/day for 12 to 36 days Oral itraconazole 600 mg/day was initiated as soon as oral therapy could be tolerated.	OL Neutropenic patients with proven or suspected invasive pulmonary aspergillosis	N=12 End of therapy	Primary: Survival at the end of the study period Secondary: Not reported	Primary: Eleven of 12 patients survived the acute episode of neutropenia. Secondary: Not reported
Bowden et al.[17] (2002) Amphotericin B colloidal dispersion (ABCD) 6 mg/kg/day vs amphotericin B deoxycholate (AmB) 1.0 to 1.5 mg/kg/day	RCT, DB, MC Immuno-compromised patients >2 years of age with newly diagnosed (proven or probable) invasive aspergillosis	N=174 End of therapy	Primary: Therapeutic response Secondary: Overall mortality, death due to fungal infection occurring by study day 84, nephrotoxicity, time to nephrotoxicity	Primary: Rates of therapeutic response were 35% in both groups (P=0.5). The study was underpowered to detect a difference. Rates of therapeutic response based on complete response, partial response and stable disease were similar between the treatment groups. Secondary: Overall mortality rate was 50% in the ABCD group and 55% in the AmB group. No significant differences were observed. The rate of death due to fungal infection was similar between the groups (P=0.6). Significantly fewer patients discontinued the study medication due to nephrotoxicity in the ABCD group compared to the AmB group (3% and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Patients were treated for 6 weeks or until 2 weeks after all signs and symptoms of infection disappeared, in addition to resolution of neutropenia.				16% respectively, P=0.001). The drug was discontinued due to overall toxicity in 22% of the patients receiving ABCD and in 24% of the patients receiving AmB. The ABCD group experienced significantly lower nephrotoxicity than in the AmB group (P=0.002). The mean increase in serum creatinine levels was significantly less in the ABCD group than in the AmB group (P=0.05). The median time to nephrotoxicity was 22 days in the AmB group and 301 days in the ABCD group (P<0.001).
White et al.[18] (1997) Amphotericin B colloidal dispersion (ABCD) 2 to 8 mg/kg/day vs amphotericin B deoxycholate 0.1 to 1.4 mg/kg/day	RETRO Patients with aspergillosis treated with amphotericin B or ABCD at 6 cancer or transplant centers	N=343 120 days	Primary: Therapeutic response, development of renal toxicity, mortality rates Secondary: Not reported	Primary: Complete or partial response was seen in 48.8% of ABCD patients and 23.4% of amphotericin B patients (P<0.001). Overall, 50% of patients in the ABCD group died compared to 71.6% of patients in the amphotericin B group (P<0.001). Renal toxicity developed in 43.1% of patients in the amphotericin B group compared to 8.2% in the ABCD group (P<0.001). Renal toxicity occurred significantly earlier in the amphotericin B group compared to the ABCD group (P<0.001). Secondary: Not reported
Herbrecht et al.[19] (2002) Amphotericin B deoxycholate 1.0 to 1.5 mg/kg/day vs	RCT, DB, MC Immuno-compromised patients ≥12 years of age with definite or probable invasive aspergillosis	N=277 12 weeks	Primary: Clinical response Secondary: Response at end of initial therapy, safety outcomes, survival up to week 12	Primary: Successful response at week 12 in patients receiving voriconazole and amphotericin B deoxycholate was 52.8 and 31.6%, respectively and was significantly better in the voriconazole group. Secondary: Successful response at end of initial therapy in patients receiving voriconazole and amphotericin B deoxycholate was 49.7 and 27.8%, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
voriconazole 6 mg/kg IV 2 times daily on day 1, 4 mg/kg IV 2 times daily for ≥7 days, then 200 mg orally 2 times daily				There were significantly fewer adverse events in the voriconazole group compared to the amphotericin B group (P=0.02). Visual disturbances (44.8 vs 4.3%; P<0.001), chills and/or fever (3.1 vs 24.9%; P<0.001) and severe adverse events (13.4 vs 24.3%; P=0.008), including renal impairment (1.0 vs 10.3%; P<0.001), hypokalemia (0 vs 3.2%; P=0.01) and systemic events (0.5 vs 3.8%; P=0.03) occurred in patients receiving voriconazole and amphotericin B deoxycholate, respectively. The survival rate for patients receiving voriconazole and amphotericin B deoxycholate was 70.8 and 57.9%, respectively.
Wingard et al.[20] (2007) Amphotericin B deoxycholate 1.0 to 1.5 mg/kg/day (CAB) vs voriconazole 6 mg/kg IV 2 times daily on day 1, 4 mg/kg IV 2 times daily for ≥7 days, then 200 mg orally 2 times daily	RCT, DB, MC (Post-hoc analysis) Immuno-compromised patients ≥12 years of age with definite or probable invasive aspergillosis	N=277 12 weeks	Primary: Resource utilization Secondary: Not reported	Primary: In the overall clinical trial population, total hospital days and intensive care unit days were similar for the voriconazole and CAB groups (total: 27.82 vs 27.71, P=0.97; and ICU: 5.59 vs 8.07; P=0.11). For survivors, voriconazole treatment was associated with a similar number of total hospital days (29.83 vs 32.01 days; P=0.54) compared to CAB, but significantly fewer intensive care unit days (3.86 vs 8.21; P=0.03). For non-survivors, those treated with voriconazole had a similar number of total (22.96 vs 21.77; P=0.73) and intensive care unit (9.76 vs 7.87; P=0.44) days in the hospital. Similar patterns of resource use across the treatment groups were observed for outpatient visits, specialist visits, and general practice physician visits. In the total population, days of IV therapy were fewer for voriconazole than for CAB (20.9 vs 30.0; P<0.01) and days of oral therapy were greater in the voriconazole arm (45.4 vs 16.5; P<0.01). For survivors, patients in the voriconazole treatment arm had fewer days on IV therapy than those in the CAB group (21.9 vs 38.9 days; P<0.01) but more days on oral therapy than CAB (58.8 vs 25.7, P<0.01). For non-survivors, the number of days on IV therapy was similar for voriconazole and CAB (18.3 vs 17.7 days; P=0.81) and higher for voriconazole for oral

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				therapy (13.3 vs 3.9; P<0.01). Patients in the voriconazole group had significantly more hospital-free survival days than those in the CAB group (P<0.001). Secondary: Not reported
Caillot et al.[21] (2007) Amphotericin B liposome 10 mg/kg/day vs caspofungin 70 mg on day 1, followed by 50 mg daily thereafter plus amphotericin B liposome 3 mg/kg per day	RCT, MC Immuno-compromised patients ≥10 years of age with proven or probable invasive aspergillosis	N=30 12 week posttreatment follow-up	Primary: Percentage of patients who had favorable overall responses (partial or complete responses) at the end of therapy (EOT). Secondary: Time to favorable overall response, time to complete response, survival at EOT, percentage of patients with recurrent infection (defined as failure for overall response), and survival during the 4-week posttreatment follow-up	Primary: The overall response at EOT was significantly more favorable for patients in the combination group (67%) compared to patients in the high-dose monotherapy group (27%; P=0.028). Secondary: At week 12, a favorable response was obtained by 10 of 15 patients in the high-dose monotherapy group (67%; eight patients had a partial response and two patients had a complete response) and by 12 of 15 patients in the combination group (80%; nine patients had a partial response and three patients had a complete response). A favorable or unfavorable response at EOT was independent of hematologic status at EOT (recurrence, remission, or stable; P=0.442). The survival rate at EOT was 97% (one death had occurred in the high-dose monotherapy group). At week 12, all 15 patients in the combination group were alive, whereas three of 15 patients had died in the high-dose monotherapy group. Those three patients died due to progression of the underlying hematologic condition; and, in one patient, fungal infection contributed to the death. Study drug-related adverse events were less frequent in the combination group than in the high-dose monotherapy group.
Cornely et al.[22] (2007) Amphotericin B liposome	RCT, DB Patients with a diagnosis of proven or probable invasive	N=339 1 to 60 days	Primary: Overall response (clinical, radiological, microbiological	Primary: There was no significant difference with regards to favorable overall responses between the treatment groups (50% in the standard-dose group vs 46% in the high-dose group; P=0.65).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
3 mg/kg/day for 14 days (standard dose arm) vs amphotericin B liposome 10 mg/kg/day for 14 days (high dose arm) After 14 days of treatment, all patients received the open-label drug at a dosage of 3 mg/kg/day	aspergillosis and other mold infections		findings) at the end of the study drug treatment Secondary: Survival (up to 12 weeks) and adverse events	Secondary: The rate of survival at the end of study drug treatment was 93% in the standard-dose group and 88% in the high-dose group (95% CI, -4 to 12%; P>0.05). At 12 weeks after study entry, the survival rates were 72% and 59% for the standard- and high-dose groups, respectively (95% CI, -0.2 to 26%; P>0.05). Nephrotoxicity occurred at a greater rate in the high-dose group (31% vs 14%; P<0.01). Grade 3 hypokalemia (blood potassium level, <3.0 mmol/L) was also more frequently found in the high-dose group (30% vs 16%; P=0.015). There was no difference between the groups with regard to the rates of grade 4 hypokalemia (blood potassium level, <2.5 mmol/L). No differences in the rates of drug-related reactions, including hypersensitivity/anaphylaxis, chills, or hypotension, were reported. There was a difference in the rates of study drug discontinuation resulting from adverse events (20% in the standard-dose group and 32% in the high-dose group; P=0.035). The most common events leading to study drug discontinuations in both groups were increases in the creatinine level, abnormal liver test results, and hypokalemia.
Raad et al.[23] (2008) Amphotericin B liposome 7.5 mg/kg/day (L-AMB) vs amphotericin B liposome 7.5 mg/kg/day plus caspofungin 70 mg on day 1, followed by 50 to 100 mg daily	RCT Patients with hematologic malignancies and invasive aspergillosis enrolled in a compassionate-use trial of antifungal salvage therapy	N=143 Up to 12 weeks	Primary: Response rate to salvage therapy Secondary: Deaths related to aspergillosis within 12 months after initiation of salvage therapy and adverse events	Primary: The overall response rate to salvage therapy was 40% for posaconazole, 8% for L-AMB (P≤0.001) and 11% for combination therapy (P<0.002). Secondary: Aspergillosis contributed to the death of 40% of posaconazole group, 65% of the L-AMB group and 68% of the combination group (P≤0.008). By multivariate analysis, posaconazole therapy independently improved response (95% CI, 2.8 to 32.5; P<0.001). L-AMB alone or in combination with caspofungin was associated with a significantly higher rate of nephrotoxicity (P≤0.02) and hepatotoxicity (P<0.03) than monotherapy with posaconazole.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs posaconazole 800 mg orally in divided doses daily				
Maertens et al.[24] (2006) Caspofungin 70 mg IV daily in combination with either an azole (itraconazole or voriconazole) or a polyene (amphotericin B deoxycholate or an amphotericin B lipid preparation) All patients received active treatment with combination therapy.	MC, OL Patients 16 years of age and older with definite or probable invasive aspergillosis refractory or intolerant to standard antifungal therapy (amphotericin B deoxycholate, lipid preparations of amphotericin B, caspofungin, itraconazole, voriconazole, or posaconazole)	N=53 12 months posttreatment follow-up	Primary: Clinical response (favorable= complete or partial response; complete response= resolution of all signs, symptoms, radiologic and/or bronchoscopic evidence; partial response= clinically meaningful improvement in the above measures) Secondary: Not reported	Primary: At the end of combination therapy, 55% of patients had a favorable response. Of the patients with a favorable response (29), four showed a complete response and 25 showed a partial response. At day 84, 49% of patients had a favorable response. Success at the end of combination therapy ranged from 43% in the caspofungin plus itraconazole group to 60% in the caspofungin plus voriconazole group. In the caspofungin plus polyene group, success rates were 80, 29, and 50% for amphotericin B deoxycholate, amphotericin B lipid complex, and liposomal amphotericin B, respectively. Of 46 refractory patients, the addition of caspofungin to the initially refractory antifungal agent demonstrated a favorable response in 66% of patients. Success was observed in 20% of patients who were initially refractory to caspofungin and had a non-echinocandin antifungal agent added. Of the patients who were refractory to voriconazole therapy, 73% had a favorable response when caspofungin was added to voriconazole compared to a 40% favorable response rate in patients who discontinued voriconazole and switched to two new antifungal agents. Secondary: Not reported
Candidiasis (Oropharyngeal/Esophageal)				
Villanueva et al.[25] (2001)	RCT, DB, MC Patients 21 to 65	N=128 28 days	Primary: Combined clinical and endoscopic	Primary: The highest response rate was observed in the caspofungin 70 mg group and the lowest was observed in the amphotericin B group. The mean

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Amphotericin B 0.5 mg/kg/day for 14 days vs caspofungin 50 mg for 14 days vs caspofungin 70 mg for 14 days	years of age with endoscopically and microbiologically documented *Candida* esophagitis		response and microbiological response Secondary: Not reported	differences in response rates for caspofungin vs amphotericin B were 11% (95% CI, -9 to 32%) and 26% (95% CI, 4 to 50%) for those receiving 50 and 70 mg, respectively, at the primary end point two weeks after discontinuation of therapy. Analysis of all evaluable patients (per protocol) were similar to the modified intention-to-treat analysis for combined response rates: 88, 96, and 78% at the end of therapy and 77, 89, and 68% two weeks after discontinuation of therapy for patients receiving caspofungin 50 mg, caspofungin 70 mg, and amphotericin B, respectively. Time to resolution of symptoms was not different for any of the treatment groups. More than half the patients in each treatment arm had resolution of all symptoms by day four of therapy. Symptoms persisted in seven, zero, and 13% of patients at the end of therapy in the groups receiving caspofungin 50 mg, caspofungin 70 mg, and amphotericin B, respectively. Endoscopic improvement was slightly higher in the caspofungin groups compared to the amphotericin B groups. Marked reduction in endoscopic grade was observed in 74, 89, and 63% of patients in the caspofungin 50 mg group, 70 mg group, and amphotericin B group, respectively. Caspofungin had slightly higher fungal eradication rates compared to amphotericin B. *Candida albicans* was not isolated from 71, 85, and 60% of patients taking caspofungin 50 mg, 70 mg, and amphotericin B, respectively. Eradication rates for non-*albicans* species were 64, 71, and 40% for caspofungin 50 mg, 70 mg, and amphotericin B, respectively. Secondary: Not reported
Arathoon et al.[26] (2002)	DB, DR, RCT Patients 18 to 65	N=140 10 to 18 days	Primary: Clinical response	Primary: A higher portion of patients in the caspofungin groups achieved a favorable clinical response (74 to 91%) compared to the amphotericin B

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Amphotericin B 0.5 mg/kg/day for 7 to 14 days vs caspofungin 35, 50, or 70 mg daily for 7 to 14 days	years of age with a diagnosis of oropharyngeal and/or esophageal candidiasis		Secondary: Microbiological eradication	treatment group (63%), however this was not statistically significant. More patients with oropharyngeal disease had a favorable response (85%) compared to those with esophageal involvement (73%). Secondary: Microbiological eradication was observed in a larger portion of patients in the caspofungin groups compared to the amphotericin B group. There was no significant difference in the clearance of *Candida albicans* vs non-*albicans* species.
Kartsonis et al.[27] (2002) Amphotericin B 0.5 mg/kg/day vs caspofungin 35 mg, 50 mg, or 70 mg daily vs fluconazole 200 mg IV daily	RETRO Symptomatic patients with endoscopically confirmed *Candida* esophagitis and decreased susceptibility to fluconazole	N=32 3 to 14 days posttreatment follow-up	Primary: Clinical outcomes Secondary: Not reported	Primary: Favorable response was seen in 64% of patients with infections which were clinically refractory to fluconazole and subsequently treated with amphotericin B. Favorable response to caspofungin was seen in 79% of patients with infections that had decreased susceptibility to fluconazole. Secondary: Not reported
Flynn et al.[28] (1995) Nystatin 400,000 units 4 times daily for 14 days (swish and swallow) vs	MC, RCT, SB Children 5 months to 14 years of age with oral thrush	N=182 42 days	Primary: Clinical and microbiologic response Secondary: Not reported	Primary: Significantly more patients treated with fluconazole were clinically cured (78 and 37%, respectively; P<0.001). Significantly more patients treated with fluconazole experienced mycological eradication (55 and 6%, respectively; P<0.001). At the end of therapy, significantly more patients taking the higher dose of fluconazole had mycological eradication compared to the lower dose (P<0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fluconazole suspension 4 mg/kg loading dose followed by 2 mg/kg daily for 14 days The dose of fluconazole was increased halfway through the study to 6 mg/kg loading dose followed by 3 mg/kg daily.				Secondary: Not reported
Goins et al.[29] (2002) Nystatin 100,000 units 4 times daily (applied with soaked cotton or washcloth) for 10 days vs fluconazole suspension 3 mg/kg/day for 7 days	OL, PRO, RCT Infants 1 to 12 months of age with signs of oral thrush	N=34 28 days	Primary: Clinical and microbiologic response Secondary: Not reported	Primary: At the end of therapy, 28.6% of nystatin patients and 100% of fluconazole patients were clinically cured (P<0.0001). At the end of therapy, 5.6% of nystatin patients and 73.3% of fluconazole patients were microbiologically cured (P<0.0001). By day 28, 23% of fluconazole patients had evidence of clinical relapse (relapse not evaluated in nystatin group). Secondary: Not reported
Pons et al.[30] (1997) Nystatin 500,000 units four times daily for 14 days (swish and	RCT, MC, PRO Patients with AIDS or HIV and typical signs and symptoms of oropharyngeal candidiasis	N=167 42 days	Primary: Clinical and mycological response Secondary: Not reported	Primary: Significantly more patients in the fluconazole group were considered clinically cured compared to patients in the nystatin group (87 and 52% respectively, P<0.001). Significantly more patients in the fluconazole group experienced mycological eradication compared to the nystatin group (60 and 6%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
swallow) vs fluconazole suspension 100 mg once daily (after 200 mg loading dose) for 14 days				respectively, P<0.001). Secondary: Not reported
Blomgren et al.[31] (1998) Nystatin rinse with 1 mL for 5 minutes 4 times daily for 3 weeks vs fluconazole 50 mg orally daily for 7 days	RCT Patients with a diagnosis of oral candidiasis	N=71 6 month posttreatment follow-up	Primary: Clinical response Secondary: Not reported	Primary: No significant differences were observed between groups in clinical response. Secondary: Not reported
Candidiasis (Systemic)				
Mora-Duarte et al.[32] (2002) Amphotericin B 0.6 to 0.7 mg/kg/day (non-neutropenic patients) or 0.7 to 1.0 mg/kg/day (neutropenic patients) vs	RCT, DB, DD Patients 18 years of age and older with one or more positive *Candida* cultures in the previous 4 days	N=239 8 weeks posttreatment follow-up	Primary: Overall response to treatment at the end of IV therapy Secondary: Not reported	Primary: At the end of IV therapy, favorable response was observed in 73.4% of patients in the caspofungin group and 61.7% in the amphotericin B group. After adjusting for neutropenic status, the difference in percentage with a favorable response was 12.7% (P=0.09). Among patients meeting the prespecified criteria for evaluation, 80.7% of caspofungin patients and 64.9% of amphotericin B patients had a favorable response (P=0.03). A larger portion of patients in the amphotericin B group had toxicities requiring a change in therapy compared to the caspofungin group (P=0.03).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
caspofungin 70 mg loading dose then 50 mg daily After 10 days of IV therapy, non-neutropenic patients could be switched to oral fluconazole 400 mg daily if appropriate.				Secondary: Not reported
Wahab Mohamed and Ismail[33] (2012) Caspofungin (2 mg/kg/day) IV vs amphotericin B (1 mg/kg/day) IV	DB, PRO, RCT Neonates with confirmed invasive candidiasis who had at least one positive blood culture and/or positive cerebrospinal fluid culture or positive urine culture obtained by suprapubic aspiration	N=32 Patients received study drug for at least 14 days and were monitored for 14 days post-treatment	Primary: Efficacy (overall response to treatment) and safety (clinical and laboratory adverse events) Secondary: Not reported	Primary: The efficacy of caspofungin was significantly higher than that of amphotericin B group, with successful outcomes in 86.7% of patients treated with caspofungin and in 41.7% of those treated with amphotericin B (P=0.04). The overall drug-related clinical and laboratory adverse events were significantly lower in neonates who received caspofungin than in those who received amphotericin B (P<0.05). None of these adverse events led to caspofungin discontinuation; however, amphotericin B was withdrawn in five (29.4%) neonates. Secondary: Not reported
DiNubile et al.[34] (2005) Amphotericin B 0.6 to 1.0 mg/kg/day vs	RETRO Adult patients with proven invasive candidiasis	N=239 14 days following last positive culture	Primary: Clinical outcomes Secondary: Not reported	Primary: Favorable responses were slightly lower in patients with cancer compared to those without cancer (62 and 70%, respectively). Favorable responses were seen in 61% of caspofungin patients and 50% of amphotericin B patients with hematological malignancies, and in 80% and 59%, respectively, in patients with solid organ malignancies. Of patients who were neutropenic at baseline, 46% responded favorably to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
caspofungin 70 mg loading dose followed by 50 mg daily thereafter All patients could be switched to oral fluconazole therapy after 10 days of IV therapy.				treatment compared to 70% of non-neutropenic patients. Of neutropenic patients, 50% in the caspofungin group responded favorably compared to 40% in the amphotericin B group. The response rate for non-*albicans Candida* species was 76% compared to 48% for *albicans* species. Favorable response rates for *Candida albicans* and *Candida tropicalis* infections were 56 and 71%, respectively, in the caspofungin group and 45 and 43%, respectively, in the amphotericin B group. Secondary: Not reported
Anaissie et al.[35] (1996) Amphotericin B 25 to 50 mg daily (non-neutropenic patients) or 0.67 mg/kg/day (neutropenic patients) vs fluconazole 400 mg daily IV for 5 days then orally thereafter	RCT, MC, PRO Patients 13 years of age and older with documented or presumed fungal infections	N=164 End of therapy	Primary: Response rates, survival rates, adverse events Secondary: Not reported	Primary: Overall response rates were not significantly different between the treatment groups (P>0.26). Median time to defervescence was five days in both groups. Median duration of therapy was not statistically different between groups (P=0.80). There were no significant differences in survival rates between groups. The incidence of adverse events was significantly higher in the amphotericin B group compared to the fluconazole group (P<0.0001). Secondary: Not reported
Phillips et al.[36] (1997) Amphotericin B 0.6 mg/kg/day	CS, RCT, SB Patients 18 years of age and older with one or more blood cultures positive for	N=106 6 months	Primary: Clinical response Secondary: Not reported	Primary: Successful response was seen in 50% of fluconazole patients and 58% of amphotericin B patients (P=0.39). Therapy failed in one amphotericin B patient during the 6th month of follow-up.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs fluconazole 800 mg IV loading dose on day 1 then 400 mg IV daily for 4 weeks Patients could be switched to oral fluconazole after 10 days of IV therapy if fungemia had cleared and patients could tolerate oral medication.	a yeast species			Secondary: Not reported
Rex et al.[37] (1994) Amphotericin B 0.5 to 0.6 mg/kg/day IV for the first 7 days then 3 times per week vs fluconazole 400 mg daily IV for 7 days then orally (or at 6 mg/kg if >90 kg or <50 kg)	MC, RCT Patients 13 years of age and older with at least 1 positive blood culture for *Candida* species	N=237 12 week posttreatment follow-up	Primary: Response rates Secondary: Response rates in the intent-to-treat population, outcome in patients who received at least 5 days of therapy	Primary: No significant difference was observed between fluconazole and amphotericin B in successful response to therapy (70 and 79% respectively; P=0.22). Secondary: No significant difference was observed in the intent-to-treat population between fluconazole and amphotericin B in successful response to therapy (72 and 80%, respectively; P=0.17). In patients who had received at least five days of treatment, 75% of fluconazole patients and 86% of amphotericin B patients had a successful outcome (P=0.05).
Kulberg et al.[38] (2005)	MC, RCT	N=370	Primary: Response to	Primary: No significant difference between groups was observed in successful

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Amphotericin B 0.7 to 1.0 mg/kg/day vs voriconazole 6 mg/kg IV every 12 hours for 1 day then 3 mg/kg every 12 hours Patients could be switched to oral voriconazole after 3 days, and patients in the amphotericin group were switched to IV or oral fluconazole after a minimum of 3 days.	Patients 12 years of age and older with candidemia	12 week posttreatment follow-up	treatment Secondary: Time to first negative blood culture, time from randomization to death	response to treatment (P=0.96). Significantly more patients in the voriconazole group infected with *Candida tropicalis* were considered to have a successful response compared to the amphotericin group (32 and 6%, respectively; P=0.032). Secondary: No significant difference between groups was observed in the time to first negative blood culture (two days in each group). No significant difference between groups was observed in the time from randomization to death (36% in the voriconazole group died in the first 14 days compared to 42% in the amphotericin B group).
Abele-Horn et al.[39] (1996) Amphotericin B 1.0 to 1.5 mg/kg/day every other day plus flucytosine 3×2.5 g as a total daily dose vs	MC, PRO, RCT Patients 18 to 80 years of age in the intensive care unit with evidence of systemic *Candida* infections	N=72 14 days	Primary: Clinical and microbiological response Secondary: Not reported	Primary: No significant differences were seen between the treatment groups in the treatment of pneumonia and sepsis/fungemia. In the treatment of peritonitis, amphotericin B plus flucytosine was more effective than fluconazole, as seen in clinical and microbiological response (P<0.05). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fluconazole 400 mg on day 1 then 200 mg daily IV				
Kujath et al.[40] (1993) Amphotericin B 0.5 mg/kg/day plus flucytosine 3×2.5 g as a total daily dose vs fluconazole 400 mg on day 1 then 300 mg daily IV	OL, PRO, RCT Patients 18 years of age and older with systemic candidiasis	N=40 Variable duration	Primary: Microbiological response, time to elimination of all fungi Secondary: Not reported	Primary: No statistical difference was observed between groups in microbiological elimination or improvement (P=0.44). Fungal elimination was observed significantly sooner in the amphotericin B plus flucytosine group compared to the fluconazole group (5.5 and 8.5 days, respectively; P=0.03). Secondary: Not reported
Queiroz-Telles et al.[41] (2008) Amphotericin B liposome 3 mg/kg/day vs micafungin 2 mg/kg/day (≤40 kg) or 100 mg/day (>40 kg)	RCT, DB Pediatric patients <16 years old with clinical signs of systemic *Candida* infection and one or more positive *Candida* cultures from blood or another sterile site within the previous 4 days	N=106 12-week posttreatment follow-up	Primary: Response rate based on the assessment of overall treatment success (clinical and mycological response at the end of therapy) Secondary: Not reported	Primary: In the modified intent-to-treat (MITT) population, the rate of overall treatment success was similar for micafungin (72.9%) compared to liposomal amphotericin B (76%; 95% CI, -20.1 to 15.3). Consistent findings were observed for the per protocol population, which showed success rates of 85.4 and 88.1% in the micafungin and liposomal amphotericin B groups, respectively (95% CI, -16.4 to 12.7). Mycologic persistence at the end of therapy was observed for 15.6% patients in both the micafungin and liposomal amphotericin B groups in the MITT population. Three patients in the micafungin group and none in the liposomal amphotericin B group had a proven recurrent fungal infection during the posttreatment phase. The mortality rate during the treatment phase was 1.9% for micafungin and 11.1% for liposomal amphotericin B in the ITT population. During the entire study, including the 12-week follow-up, the mortality rates were 25.0 and 24.1% of patients, respectively. The fungal infection was considered by the investigator to have contributed to the cause of death for 7.7 and 5.6% of patients, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The incidence of adverse events was similar between the treatment groups. Secondary: Not reported
Kuse et al.[42] (2007) Amphotericin B liposome 3 mg/kg/day vs micafungin 2 mg/kg/day (≤40 kg) or 100 mg/day (>40 kg)	RCT, DB Patients ≥16 years old with clinical signs of systemic *Candida* infection and one or more positive *Candida* cultures from blood or another sterile site within the previous 4 days	N=531 12-week posttreatment follow-up	Primary: Response rate based on the assessment of overall treatment success (clinical and mycological response at the end of therapy) Secondary: Not reported	Primary: In the modified intention-to-treat population (MITT), 74.1% of patients were treated successfully with micafungin vs 69.6% of those treated with lipo somal amphotericin B (95% CI, –3.0 to 12.8). In the intention-to-treat population (ITT), success rates were 71.6% with micafungin and 68.2% with liposomal amphotericin B (95% CI, -3.9 to 11.6). In the per-protocol population, treatment success rates were 81.4% for micafungin and 80.4% for liposomal amphotericin B (95% CI, -6.1 to 9.6). Mycological persistence at the end of therapy was observed in 9% of patients in the micafungin group and 9% of patients in the liposomal amphotericin B group in the per-protocol population. Species specificity for mycological persistence was similar between treatment groups. A recurrent *Candida* infection during the 12-week posttreatment period was seen in seven patients who had received micafungin and six patients who had received liposomal amphotericin B. In the ITT population, 18% of patients died in the micafungin group and 17% of patients died in the liposomal amphotericin B group during the treatment phase. During the study, including the 12-week follow-up period, 40% of patients in the micafungin group and 40% of patients in the liposomal amphotericin B group died. The fungal infection was considered by the investigator to have contributed to the cause of death for 13% patients in the micafungin group and 9% patients in the liposomal amphotericin B group (P=0.22). There were fewer treatment-related adverse events in the micafungin group than in the liposomal amphotericin B group. There were fewer cases of hypokalemia, rigors, increased serum creatinine, and back pain in the micafungin group than in the liposomal amphotericin B group, as well as fewer infusion-related reactions.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Gafter-Gvili et al.[43] (2008) <u>Group 1</u> Echinocandins vs other antifungal agents <u>Group 2</u> Fluconazole vs other antifungal agents	MA Trials that included patients with confirmed invasive candidiasis	N=3,265 (15 trials) Variable duration	Primary: 30-day all-cause mortality Secondary: Treatment failure, microbiological failure, adverse events	Primary: <u>Fluconazole vs other antifungal agents (nine studies)</u> No difference in mortality was observed with fluconazole vs amphotericin B (RR, 0.92; 95% CI, 0.72 to 1.17). No difference in mortality was observed between fluconazole and itraconazole (RR, 1.91; 95% CI, 0.39 to 9.35) or between fluconazole and a combination of fluconazole and amphotericin B (RR, 0.98; 95% CI, 0.70 to 1.35). <u>Echinocandins vs other antifungal agents (four studies)</u> There was no difference in mortality with anidulafungin vs fluconazole (RR, 0.73; 95% CI, 0.48 to 1.10). There was no difference in mortality with caspofungin vs amphotericin B (RR, 1.08; 95% CI, 0.75 to 1.55) or with micafungin vs liposomal amphotericin B (RR, 1.04; 95% CI, 0.75 to 1.43). <u>Other comparisons (two studies)</u> There was no difference in mortality with micafungin vs caspofungin (100 mg/day: RR, 1.10; 95% CI, 0.80 to 1.51; 150 mg/day: RR, 1.27; 95% CI, 0.93 to 1.72). There was no difference in mortality with amphotericin B plus fluconazole vs voriconazole (RR, 1.18; 95% CI, 0.90 to 1.54). Secondary: <u>Fluconazole vs other antifungal agents (nine studies)</u> No significant difference in treatment failure was found with fluconazole and amphotericin B (RR, 1.22; 95% CI, 0.97 to 1.54) or with fluconazole vs a combination of fluconazole and amphotericin B (RR, 1.41; 95% CI, 0.99 to 1.99). Microbiological failure was higher in patients treated with fluconazole

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				compared to amphotericin B (RR, 1.52; 95% CI, 1.12 to 2.07) or with fluconazole vs a combination of fluconazole and amphotericin B (RR, 2.69; 95% CI, 1.17 to 6.18). No difference in adverse events requiring discontinuation was noted with fluconazole vs amphotericin B (RR, 0.45; 95% CI, 0.13 to 1.56), itraconazole (RR, 0.32; 95% CI, 0.04 to 2.82) or with fluconazole vs a combination of fluconazole and amphotericin B (RR, 1.16; 95% CI, 0.49 to 2.75). Fluconazole caused less nephrotoxicity than amphotericin B (RR, 0.11; 95% CI, 0.03 to 0.48) or the combination of amphotericin B and fluconazole (RR, 0.12; 95% CI, 0.04 to 0.39). <u>Echinocandins vs other antifungal agents (four studies)</u> Treatment failure significantly decreased with anidulafungin vs fluconazole (RR, 0.61; 95% CI, 0.42 to 0.89). There was no difference in treatment failure with caspofungin vs amphotericin B (RR, 0.70; 95% CI, 0.47 to 1.03) or with micafungin vs liposomal amphotericin B (RR, 0.93; 95% CI, 0.74 to 1.19). Microbiological failure was significantly reduced with anidulafungin vs fluconazole (RR, 0.50; 95% CI, 0.29 to 0.86). No difference in microbiological failure was noted for caspofungin vs amphotericin B (RR, 0.95; 95% CI, 0.40 to 2.25) or with micafungin vs liposomal amphotericin B (RR, 1.01; 95% CI, 0.53 to 1.92). A significant decrease in adverse events requiring discontinuation was observed with anidulafungin vs fluconazole (RR, 0.52; 95% CI, 0.29 to 0.92). Caspofungin was associated with a significantly lower rate of adverse events requiring discontinuation when compared to amphotericin B (RR, 0.11; 95% CI, 0.04 to 0.36) or liposomal amphotericin B (RR, 0.45; 95% CI, 0.26 to 0.80). <u>Other comparisons (two studies)</u> There was no difference in treatment failure with micafungin and caspofungin (100 mg/day: RR, 0.85; 95% CI, 0.60 to 1.20; 150 mg/day: RR, 1.04; 95% CI, 0.74 to 1.42). There was no difference in treatment failure with amphotericin B plus fluconazole vs voriconazole (RR, 1.00;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				95% CI, 0.83 to 1.19). There was no difference in microbiological failure with micafungin and caspofungin (100 mg/day: RR, 0.73; 95% CI, 0.41 to 1.22; 150 mg/day: RR, 1.10; 95% CI, 0.70 to 1.73). There was no difference in adverse events requiring discontinuation with micafungin and caspofungin. Adverse events requiring discontinuation were significantly lower (RR, 0.47; 95% CI, 0.23 to 0.93) and nephrotoxicity was significantly higher (RR, 2.64; 95% CI, 1.57 to 4.44) with the amphotericin B-fluconazole arm compared to voriconazole.
Cryptococcal Meningitis				
Leenders et al.[44] (1997) Amphotericin B deoxycholate 0.7 mg/kg/day for 3 weeks (AMB-d) vs amphotericin B liposome 4 mg/kg/day for 3 weeks (L-AMB) Both treatments were followed by 7 weeks of fluconazole 400 mg daily.	RCT Hospitalized HIV-infected patients ≥18 years of age with a primary episode of cryptococcal meningitis	N=28 6 months posttreatment follow-up	Primary: Clinical response, mycological response, time to mycological response Secondary: Not reported	Primary: Clinical response rates after the first three weeks of treatment were 80% in the L-AMB group and 86% in the AMB-d group (P=1.0). The median time to clinical response was 15 days in both treatment groups. During the seven weeks of fluconazole treatment, one L-AMB patient died, and two patients in the AMB-d group died. At week 10, clinical response was observed in 87% of the L-AMB group and in 83% of the AMB-d group. No relapses were recorded during the 10 week study period or the six month follow-up. CSF culture conversion was observed in six of 15 L-AMB patients compared to one of 12 AMB-d patients within the first seven days of treatment (P=0.09). CSF culture conversion was observed in significantly more L-AMB patients compared to AMB-d patients within the first 14 days of treatment (P=0.01). CSF culture conversion was observed in 11 of 15 L-AMB patients compared to three of eight AMB-d patients within the first 21 days of treatment (P=0.18). Time to CSF culture conversion was significantly shorter in the L-AMB group compared to the AMB-d group (P<0.05) according to Kaplan-Meier estimates. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Techapornroong et al.[45] (2007) Amphotericin B deoxycholate 1 mg/kg once daily for 14 days (OD group) vs amphotericin B deoxycholate 2 mg/kg every other day for 14 days (AD group) After completion of the intensive phase, patients with a successful response were given fluconazole (400 mg/day). Patients without a successful response continued amphotericin B treatment.	RCT, DB HIV- infected patients ≥15 years old with cryptococcal meningitis	N=28 ≥3 months	Primary: Clinical outcomes, mycological outcomes, adverse events Secondary: Not reported	Primary: A clinical response was observed in 12 of 15 (80%) patients and 10 of 13 (76.9%) patients in the OD and AD groups, respectively (P=1.0). A mycological response was observed in three of nine (33.3%) patients and one of 10 (10%) patients in the OD and AD groups, respectively (P=0.3). At three months of treatment, there were nine and 12 patients in the OD and AD groups, respectively, for analysis. Nine of 21 (43%) patients (five and four in the OD and AD groups, respectively) had clinically relapsed. All nine patients had evidence of increased intracranial pressure, and five underwent continuous CSF drainage (two with lumbar drainage, one with ventriculostomy, one with lumboperitoneal shunt, and one with ventriculoperitoneal shunt). All 21 and five of nine patients had positive CSF cryptococcal antigen and culture for *Cryptococcus neoformans*, respectively. Four patients (one and three in the OD and AD groups, respectively) died due to no control of increased intracranial pressure including brain herniation, cerebral anoxia; one patient died due to bacterial sepsis. At two weeks of treatment, the median and mean creatinine levels as well as the percentage of patients with increased creatinine levels from the baseline levels between the two groups were not significantly different. Two (13.3%) and five (38.5%) patients in the OD and AD groups, respectively, had creatinine levels that were two times more than the baseline levels at two weeks of treatment (P=0.46). The percentage of patients who had anemia, hypokalemia, or hypomagnesaemia did not differ significantly between the two groups (P=1.0). Neutropenia was more commonly observed in the OD group than in the AD group (P=0.08). There was no difference in the incidence of infusion-related events between the two groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Hamill et al.[46] (2010) Amphotericin B deoxycholate (AMB-d) 0.7 mg/kg/day for 11 to 21 days vs amphotericin B liposome (L-AMB 3) 3 mg/kg/day for 11 to 21 days vs amphotericin B liposome (L-AMB 6) 6 mg/kg/day for 11 to 21 days At the end of induction, all patients received fluconazole 400 mg QD to complete 10 weeks of acute therapy.	MC, DB, RCT Patients with AIDS and acute cryptococcal meningitis	N=267 10 weeks	Primary: Incidence of mycological success (conversion of CSF culture results) at week 2 Secondary: Survival at week 10 among and adverse events	Primary: CSF culture results were negative at week two in 47.5% of patients who received AMB-d, in 58.3% of those who received L-AMB 3, and in 48.0% of those who received L-AMB 6. None of these differences among the groups were statistically significant (treatment difference for L-AMB 3 vs AMB-d, 10.8% [95% CI, -6.9 to 28.5%]; treatment difference for L-AMB 6 vs AMB-d, 0.5% [95% CI, -16.4 to 17.3%]). Secondary: Overall mortality at week 10 was 11.6%, with no significant differences among the treatment groups. The overall incidence of infusion–related reactions was significantly lower for both the 3 mg/kg/day and 6 mg/kg/day dosages of liposomal amphotericin B, compared to conventional amphotericin B (P<0.001). Significantly fewer patients who received the 3 mg/kg/day dosage of liposomal amphotericin B developed nephrotoxicity, indicated by a doubling of the serum creatinine value, compared to recipients of conventional amphotericin B (P=.004).
de Lalla et al.[47] (1995)	OL Patients with AIDS	N=31 2 months	Primary: Therapeutic response (success=	Primary: Therapeutic success was observed in 93.5% of all cases.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Amphotericin B 1 mg/kg/day for 14 days Some patients also received flucytosine 100-150 mg/kg in 4 doses IV or orally. At the end of primary therapy, patients received either itraconazole or fluconazole for suppressive therapy.	and either cryptococcal meningitis or extrameningeal disseminated cryptococcosis		resolution of symptoms and negative CSF cultures plus a fall in cryptococcal antigen titer after 2 months of therapy; favorable= clinical improvement and negative blood culture plus a decrease in antigen titer after 2 months of therapy) Secondary: Not reported	Nephrotoxicity developed in seven cases, requiring discontinuation in five patients and dosage adjustment in two patients. Secondary: Not reported
Sharkey et al.[48] (1996) Amphotericin B lipid complex (ABLC) 1.2 mg/kg/day for 2 weeks, followed by 2.5 mg/kg/day 3 times weekly for 4 weeks vs amphotericin B lipid complex (ABLC) 2.5 mg/kg/day for 2 weeks, followed by 5.0 mg/kg/day	MC, OL, RCT Patients with acquired immunodeficiency syndrome presenting with their first episode of cryptococcal meningitis	N=55 12 weeks posttreatment follow-up	Primary: Clinical response, mycological response, overall response Secondary: Not reported	Primary: No significant differences were observed in clinical, mycological, and overall responses between groups. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
3 times weekly for 4 weeks vs amphotericin B lipid complex (ABLC) 5.0 mg/kg/day for 2 weeks, followed by 5.0 mg/kg/day 3 times weekly for 4 weeks vs amphotericin B deoxycholate (AmB) 0.7 mg/kg/day for 2 weeks, followed by 1.2 mg/kg/day 3 times weekly for 4 weeks After primary treatment, patients were given oral fluconazole.				
Brouwer et al.[49] (2004) Amphotericin B 0.7 mg/kg/day plus fluconazole 400 mg daily	OL, RCT Adult patients with HIV and a first episode of cryptococcal meningitis	N=64 10 weeks	Primary: Rate of reduction of CSF cryptococcal colony-forming units Secondary:	Primary: Early fungicidal activity occurred faster for patients receiving amphotericin B plus flucytosine than amphotericin B alone (P=0.0006), amphotericin B plus fluconazole (P=0.03), or amphotericin B plus flucytosine plus fluconazole (P=0.01). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs amphotericin B 0.7 mg/kg/day plus fluconazole 400 mg daily plus flucytosine 100 mg/kg/day vs amphotericin B 0.7 mg/kg/day plus flucytosine 100 mg/kg/day vs amphotericin B 0.7 mg/kg/day After 2 weeks, all four arms were treated with fluconazole 400 mg daily for 8 weeks and 200 mg daily thereafter.			Not reported	
Saag et al.[50] (1992) Amphotericin B 0.3 mg/kg/day or an equivalent dose every other day vs	MC, RCT Patients 18 years of age and older with HIV and a positive CSF culture for *Cryptococcus neoformans*	N=194 10 weeks	Primary: Rate of treatment success (sterilization of CSF cultures) Secondary: Not reported	Primary: Treatment was successful in 40% of the amphotericin B patients and 34% of the fluconazole patients (P=0.40). Disease progression occurred more frequently in the fluconazole group while discontinuation of study drug occurred more frequently in the amphotericin B group though neither difference was statistically significant.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fluconazole 400 mg loading dose orally then 200 mg daily Patients in the amphotericin B group may also have been treated with flucytosine 150 mg/kg/day according to investigator discretion.				Secondary: Not reported
Pappas et al.[51] (2009) Amphotericin B deoxycholate 0.7 mg/kg/day for 14 days, followed by fluconazole 400 mg/day for 56 days (AmB) vs amphotericin B deoxycholate 0.7 mg/kg/day plus fluconazole 400 mg/day for 14 days, followed by fluconazole 400 mg/day for 56 days (AmB plus Fluc	RCT, OL, MC Patients ≥13 years of age who were experiencing a first episode of HIV-associated cryptococcal meningitis	N=143 Median 57 to 70 days	Primary: Safety and tolerability Secondary: Mortality and efficacy	Primary: More than 30% of patients in each arm experienced severe toxicities related to AmB or fluconazole. These events included hypomagnesemia, hypokalemia, anemia, AmB infusion intolerance, decreased renal function, psychosis, and subdural hematoma. Most of the toxicities were related to AmB. Neither of the combination therapy arms experienced a higher incidence of toxicities than the standard therapy arm. Except for nausea, the percentage of patients who experienced site-reported adverse events in the combination therapy arm was comparable to or less than the percentage in the standard arm who experienced site-reported adverse events. A greater percentage of patients experienced nausea in the combination therapy group compared to the standard therapy group (P=0.19). A greater percentage of patients in the AmB plus Fluc 800 arm than in the standard arm reported possible, probable, or definite treatment-associated adverse events that were dose limiting (14.3 vs 8.9%) or serious (12.2 vs 6.7%). The most frequent dose-limiting adverse events were related to a decrease in renal function. On average, all treatment arms experienced a decrease from baseline creatinine clearance level for days 7, 14, and 42.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
400) vs amphotericin B deoxycholate 0.7 mg/kg/day plus fluconazole 800 mg/day for 14 days, followed by fluconazole 800 mg/day for 56 days (AmB plus Fluc 800)				Secondary: Higher mortality was observed in the standard therapy arm than in the combination therapy arms (22.2, 17.0, and 18.4% for the AmB arm, the AmB plus Fluc 400 arm, and the AmB plus Fluc 800 arm, respectively). At day 14, a greater percentage of patients in the modified intention-to-treat population had experienced success in the AmB plus Fluc 800 arm than in the AmB arm; however, a smaller percentage of patients experienced success in the AmB plus Fluc 400 arm than in the AmB arm.
Chotmongkol et al.[52] (1997) Amphotericin B 0.3 mg/kg/day plus flucytosine 150 mg/kg/day plus itraconazole 400 mg/day (study group) vs amphotericin B 0.3 mg/kg/day plus flucytosine 150 mg/kg/day (control group)	OL, RCT Patients with AIDS and a diagnosis of cryptococcal meningitis	N=100 6 weeks	Primary: Clinical treatment outcomes, mean length of time until normalization of body temperature, mean time until negative CSF culture Secondary: Not reported	Primary: Successful treatment was significantly higher in the study group compared to the control group (100 and 90%, respectively; P=0.03). Mean length of time until normal body temperature was shorter in the study group compared to the control group (5.9 and 8.8 days, respectively; P=0.02). The mean length of time until the first negative CSF culture was 13.9 days in the study group and 13.3 days in the control group (P=0.66). Relapse rates were higher in the study group. Secondary: Not reported
Bennett et al.[53] (1979) Amphotericin B	PRO, RCT Patients with either positive CSF smear	N=78 10 weeks	Primary: Cure rates and mortality	Primary: Cure or improvement was observed in 66% of patients in the combination group and in 47% of patients in the amphotericin B group (P>0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
0.3 mg/kg/day plus flucytosine 150 mg/kg/day orally divided every 6 hours for 6 weeks vs amphotericin B 0.4 mg/kg/day for 42 days followed by 0.8 mg/kg every other day for 28 days	or culture or clinical features compatible with cryptococcal meningitis plus a positive culture from another site or positive cryptococcal antigen test or evidence of intracranial cryptococcosis		Secondary: Not reported	There were 15 deaths in the amphotericin B group (47%) compared to 8 deaths in the combination group (24%; P<0.05). Secondary: Not reported
Larsen et al.[54] (1990) Amphotericin B 0.7 mg/kg/day for 7 days then 3 times weekly for 9 weeks plus flucytosine 150 mg/kg/day orally in 4 doses for 10 weeks vs fluconazole 400 mg orally for 10 weeks	PRO, RCT Patients 18 years of age and older with evidence of cryptococcal meningitis, with or without AIDS	N=26 62 weeks	Primary: Clinical outcomes Secondary: Not reported	Primary: After 10 weeks of treatment, eight of 14 patients receiving fluconazole were considered failures while zero of six patients taking amphotericin B plus flucytosine were considered failures (P=0.04). Conversion from positive to negative blood and CSF cultures was significantly slower in patients taking fluconazole compared to amphotericin B and flucytosine for CSF cultures (P=0.02). No significant difference was seen in the time to achieve mycological success for blood cultures (P=0.19). Secondary: Not reported
de Gans et al.[55] (1992) Amphotericin B 0.3 mg/kg/day plus	OL, PRO, RCT Patients with suspected cryptococcal	N=28 6 weeks	Primary: Response to therapy, survival, relapse rates	Primary: Five of 14 patients in the itraconazole group showed a complete response and seven showed a partial response. Twelve of 14 patients in the itraconazole group survived for more than six

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
flucytosine 150 mg/kg orally daily in 4 divided doses for 6 weeks vs itraconazole 200 mg twice daily for 6 weeks All patients completing the study then received itraconazole 200 mg daily as maintenance therapy.	meningitis		Secondary: Not reported	weeks. Ten of 11 patients in the amphotericin B and flucytosine group had a complete response. Ten of 11 patients in the amphotericin B and flucytosine group survived for more than six weeks. The difference in complete response between groups was significant and favored the amphotericin B plus flucytosine group (P=0.009). Overall, no significant difference in relapse rates was observed between original groups during the maintenance period (P=0.22). No significant difference in mean survival was observed between original treatment groups (P=0.65). Secondary: Not reported
van der Horst et al.[56] (1997) Step 1 Amphotericin B 0.7 mg/kg/day plus flucytosine 100 mg/kg/day in 4 doses for 2 weeks vs amphotericin B 0.7 mg/kg/day for 2 weeks Step 2	DB, MC, RCT Patients were ≥13 years of age with a first episode of AIDS-associated cryptococcal meningitis	Step 1 N=381 Step 2 N=306 10 weeks	Primary: Mycological response at 2 and 10 weeks, clinical outcome at 2 and 10 weeks Secondary: Not reported	Primary: Mycological response rates at the end of step 1 in patients receiving amphotericin B plus flucytosine or amphotericin B alone were 60 and 51%, respectively (P=0.06). Clinical response rates at the end of step 1 in patients receiving amphotericin B plus flucytosine or amphotericin B alone were 78 and 83%, respectively (P=0.18). There was no significant difference between the treatments in combined mycological and clinical response (P=0.12). Mycological response rates at the end of step 2 in patients receiving fluconazole and itraconazole were 72 and 60%, respectively. Clinical response rates at the end of step 2 in patients receiving fluconazole and itraconazole were 68 and 70%, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fluconazole 800 mg daily for 2 days, then 400 mg daily for 8 weeks vs itraconazole 600 mg daily for 3 days, then 200 mg 2 times daily for 8 weeks				There was no significant difference between fluconazole and itraconazole in mycological or clinical response. Secondary: Not reported
Bicanic et al.[57] (2008) Amphotericin B deoxycholate 0.7 mg/kg/day plus flucytosine 25 mg/kg 4 times per day for 2 weeks (group 1) vs amphotericin B 1 mg/kg per day plus flucytosine 25 mg/kg 4 times per day for 2 weeks (group 2) After 2 weeks, patients received fluconazole 400 mg/day for 8 weeks and	RCT HIV-infected adults hospitalized with a first episode of cryptococcal meningitis	N=64 10 weeks	Primary: Mean rate of decrease in the number of *Cryptococcus* colony-forming units (cfu) in the CSF or early fungicidal activity (EFA) Secondary: Rates of renal impairment and anemia, mortality at two and 10 weeks, and long-term survival during antiretroviral therapy	Primary: The rate of clearance of infection during the first two weeks of therapy was more rapid for group 2 than for group 1. The mean EFA was -0.56 log cfu/mL of CSF per day for group 2 and -0.45 log cfu/mL of CSF per day for group 1. Secondary: The mortality rate was 6% at two weeks and 24% at 10 weeks, with no difference between groups. Sixty-eight percent and 60% of patients were alive at six months and one year, respectively, of follow-up. There was no difference in survival rates between the two groups at any time point. There were no significant differences between groups 1 and 2 in measurements of renal impairment. A decrease in the hemoglobin level 12 g/dL developed in 50 and 71% of patients in groups 1 and 2, respectively (P=0.2). The percentage decrease in the hemoglobin level was greater for group 2 (95% CI, 2 to 15%; P=0.01) and greater for women (95% CI, 4 to 17%; P=0.002).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
200 mg/day thereafter.				
Sloan et al.[58] (2008) Amphotericin B, flucytosine, and fluconazole given alone or in combination	MA HIV-infected adults with a first episode of cryptococcal meningitis	N=595 (5 trials) ≥2 weeks	Primary: Mortality, adverse events, proportion of patients with sterile CSF after two weeks of therapy Secondary: Not reported	Primary: <u>Fluconazole and flucytosine vs fluconazole</u> There was no difference in death rate at 14 days (RR, 0.4; 95% CI, 0.14 to 1.11) or at six months (RR, 0.77; 95% CI, 0.57 to 1.05). There were no major adverse events in either group. There was no difference in number of patients with sterile CSF at two months after treatment (RR, 0.4; 95% CI, 0.11 to 1.36). <u>Amphotericin B vs amphotericin B and flucytosine</u> There was no difference in the proportion deaths at 14 days (RR, 1.1; 95% CI, 0.51 to 2.4). There was no difference in major adverse events between the two treatment arms (RR, 0.94; 95% CI, 0.29 to 3.03).There was higher proportion of patients with sterile CSF cultures at 14 days in the group of patients receiving flucytosine (RR, 0.81; 95% CI, 0.68 to 0.98). <u>Amphotericin B vs amphotericin B, flucytosine and fluconazole</u> There was no difference in the proportion deaths at 14 days or 10 weeks (RR, 2.0; 95% CI, 0.20 to 19.91 and RR, 1.0; 95% CI, 0.24 to 4.23, respectively). There were no serious adverse events in either group. There was no difference in the proportion of patients with sterile CSF at 14 days (RR, 0.5; 95% CI, 0.11 to 2.35). <u>Amphotericin B and flucytosine vs amphotericin B, flucytosine and fluconazole</u> There was no difference in the proportion deaths at 14 days or 10 weeks (RR, 1.07; 95% CI, 0.07 to 15.57 and RR, 1.07; 95% CI, 0.07 to 15.57, respectively). There were no serious adverse events in either group. There was no difference in the proportion of patients with sterile CSF at 14 days (RR, 1.6; 95% CI, 0.56 to 4.58). <u>Amphotericin B and flucytosine vs amphotericin B and fluconazole</u> There was no difference in the proportion of deaths at 14 days or 10 weeks (RR, 0.21; 95% CI, 0.03 to 1.62 and RR, 0.15; 95% CI, 0.02 to 1.10). There were no serious adverse events in either group. There was no difference in the amount of patients with sterile CSF at 14 days (RR, 2.13

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				95% CI, 0.65 to 7.04). <u>Amphotericin B vs amphotericin B and fluconazole</u> There was no difference in the proportion deaths at 14 days or 10 weeks (RR, 0.4; 95% CI, 0.09 to 1.77 and RR, 0.43; 95% CI, 0.13 to 1.37). There were no serious adverse events in either group. There was no difference in the amount of patients with sterile CSF at 14 days (RR, 0.67; 95% CI, 0.13 to 3.47). <u>Amphotericin B and fluconazole vs amphotericin B, flucytosine and fluconazole</u> There was no difference in the proportion deaths at 14 days or 10 weeks (RR, 5.0; 95% CI, 0.66 to 38.15 and RR, 2.33; 95% CI, 0.73 to 7.45). There were no serious adverse events in either group. There was no difference in the amount of patients with sterile CSF at 14 days (RR, 0.75; 95% CI, 0.20 to 2.83). <u>Standard dose amphotericin B and flucytosine vs high dose amphotericin B and flucytosine</u> There was no difference in the proportion of deaths at 14 days or 10 weeks (RR, 0.34; 95% CI, 0.04 to 3.44 and RR, 0.76; 95% CI, 0.03 to 1.83, respectively). There was no difference in major adverse events defined as side effects of treatment leading to the study interventions being terminated (RR, 0.23; 95% CI, 0.03 to 1.83). The proportion of patients with sterile CSF at 14 days was not different between the two treatment groups (RR, 1.13; 95% CI, 0.43 to 2.94). <u>Amphotericin B vs liposomal amphotericin B</u> There was no difference in the proportion of patients who had a clinical response after 3 weeks of treatment in the liposomal amphotericin B group and the amphotericin B group (RR, 0.95; 95% CI, 0.67 to 1.33). There was no difference in the proportion of deaths at 14 days, 10 weeks or six months. At six months, 2/15 patients who received liposomal amphotericin B had died and 1/13 patients who received amphotericin B had died (RR, 1.73; 95% CI, 0.12 to 59.4). Major adverse events were less common in patients who received liposomal amphotericin B (RR, 0.19; 95% CI, 0.05 to 0.74). There was no difference in the patients with sterile

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				CSF at 14 days in either group (RR, 6.0; 95% CI, 0.91 to 39.41). Secondary: Not reported
Empirical Therapy				
Martino et al.[59] (2005) Amphotericin B lipid complex (ABLC) 3 mg/kg/day for minimum of 7 days and a maximum of 12 weeks	OL, PRO Patients with hematological malignancy and a documented or suspected invasive mycosis	N=74 Up to 12 weeks	Primary: Clinical response (overall response= complete and partial response; complete= resolution of signs and symptoms of infection and resolution of microbiological abnormalities; partial= substantial improvement) Secondary: Not reported	Primary: The overall response rate was 67% after a median of 18 days of therapy. The complete and partial response rates were 56 and 11%, respectively Patients with invasive aspergillosis had an overall response rate of 61% and patients with non-cultured invasive mold infections had an overall response rate of 67%. The overall response rate of patients who entered the study during neutropenia was 90%. Secondary: Not reported
Subria et al.[60] (2004) Amphotericin B lipid complex (ABLC) 1 mg/kg/day vs amphotericin B deoxycholate 0.6 mg/kg/day Therapy was	PRO, RCT Patients ≥18 years of age hospitalized with neutropenic fever due to chemotherapy for a hematological malignancy or after undergoing autologous hematopoietic stem cell transplantation	N=105 End of therapy	Primary: Toxicity and response to therapy Secondary: Not reported	Primary: The incidence of nephrotoxicity was significantly lower in the ABLC group compared to the amphotericin B group (P=0.003). A significantly higher proportion of patients in the amphotericin B group experienced increases in serum creatinine compared to the ABLC group (P=0.009). The mean absolute increase in serum creatinine from baseline was significantly lower in the ABLC group compared to the amphotericin B group (P=0.01). Hypokalemia was significantly more frequent in the amphotericin B group compared to the ABLC group (P=0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
continued until defervescence and recovery of neutrophil count to >0.5 × 10^9/L.				There were no statistically significant differences in infusion-related adverse events between groups (P>0.2). Significantly more patients in the ABLC group had a satisfactory response to therapy compared to those in the amphotericin group (P=0.018). Secondary: Not reported
Wingard et al.[61] (2000) Amphotericin B lipid complex (ABLC) 5 mg/kg/day vs amphotericin B liposome (L-AMB) 3 or 5 mg/kg/day Treatment was continued for up to 3 days after neutrophil recovery to a maximum of 42 days.	DB, MC, RCT Patients 2 years of age and older with neutropenia and a suspected fungal infection	N=244 7 day posttreatment follow-up	Primary: Frequency of infusion-related chills/rigors during infusion and for up to one hour after infusion on day one; clinical efficacy Secondary: Not reported	Primary: There was a lower frequency of chills/rigors on day one in the L-AMB group compared to the ABLC group (P<0.001). There was significantly less nephrotoxicity associated with L-AMB compared to ABLC (P<0.01). There was no significant difference observed in successful response between the groups. A lower portion of patients in the L-AMB group discontinued therapy due to an adverse event compared to the ABLC group (P<0.001). Secondary: Not reported
Fleming et al.[62] (2001) Amphotericin B lipid complex (ABLC) 3 to 5 mg/kg/day	RCT Patients with leukemia who developed suspected or documented fungal	N=75 End of treatment (mean 10 to 15 days)	Primary: Antifungal response Secondary: Safety	Primary: The overall response in patients treated for suspected or proven fungal infections was 70% in the ABLC group and 50% in the L-AMB group (P=0.15). Complete or partial response was observed in 63% of patients in the ABLC group and 39% of patients in the L-AMB group in the intent-to-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs amphotericin B liposome (L-AMB) 3 to 5 mg/kg/day	infections			treat population (P=0.03). Among patients receiving empiric therapy, resolution of fever and total or partial clearing of pulmonary infiltrates was observed in 94% of patients in the ABLC group and in 62% of patients in the L-AMB group (P=0.02). Secondary: Significantly more patients in the ABLC group experienced mild-to-moderate infusion-related adverse events compared to those in the L-AMB group (P=0.002). Significantly more patients in the L-AMB group experienced mild elevations in hepatic enzymes compared to the ABLC group (P=0.02). There were no significant differences between groups in any other safety parameter (P>0.05).
Day et al.[63] (2013) Amphotericin B IV (1 mg/kg/day) for 4 weeks (Group 1) vs amphotericin B deoxycholate (1 mg/kg/day) combined with oral flucytosine (100 mg/kg/day in 3 to 4 divided doses) for 2 weeks (Group 2) vs	OL, RCT Patients >14 years of age with HIV and signs and symptoms consistent with cryptococcal Meningitis, as well as a lab test indicative of *Cryptococcus*	N=299 6 months	Primary: All cause mortality in the first 14 and 70 days after randomization Secondary: Mortality at six months, disability status at 70 days and at six months, changes in CSF fungal counts in the first two weeks after randomization, time to CSF sterilization, and adverse events during the first 10	Primary: By day 70, a total of 44 patients treated with amphotericin B monotherapy had died, as compared with 30 patients treated with amphotericin B and flucytosine and 33 patients treated with amphotericin B and fluconazole. Treatment with amphotericin B and flucytosine was associated with a significantly reduced hazard of death by day 70 in the intention-to-treat analysis (HR, 0.61; 95% CI, 0.39 to 0.97; P=0.04); this benefit was maintained in the per-protocol analysis and after adjustment for predefined baseline covariates. Fewer patients receiving combination therapy with high-dose fluconazole died, as compared with those treated with amphotericin B monotherapy, but this finding was not significant (HR, 0.71; 95% CI, 0.45 to 1.11; P=0.13). Secondary: The survival benefit seen for patients receiving amphotericin B and flucytosine, as compared with those receiving amphotericin B monotherapy, was more marked at six months (HR, 0.56; 95% CI, 0.36 to 0.86; P=0.01). Treatment with amphotericin B and fluconazole did not confer a survival advantage, as compared with monotherapy. Patients receiving amphotericin B and flucytosine had a significantly

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
amphotericin B deoxycholate (1 mg/kg/day) combined with oral fluconazole (400 mg twice daily) for 2 weeks (Group 3) each treatment was followed by fluconazole (400 mg/day) to achieve a 10-week treatment course			weeks of the study	higher chance of being free of disability at six months, as compared with those receiving monotherapy (OR, 2.01; 95% CI, 1.04 to 3.88; P=0.04). The time to fungal clearance was significantly shorter in patients receiving amphotericin B plus flucytosine than in those receiving amphotericin B alone or in combination with fluconazole, with more rapid rates of decline in the colony count (P<0.001 for both comparisons). Adverse events occurred with similar frequency among all the treatment groups.
Cordonnier et al.[64] (2008) Amphotericin B liposome 10 mg/kg once per week as prophylaxis Treatment was received for 4 consecutive weeks for acute leukemia (AL) patients and 8 consecutive weeks for stem cell transplantation (SCT) patients.	OL, MC Patients ≥18 years old who underwent a standard myeloablative conditioning regimen and acute graft vs host disease cyclosporin prophylaxis for SCT or underwent first or second induction therapy after relapse or consolidation therapy for AL and had expected neutropenia $<0.5\times10^9$ neutrophils/L for at least 2 weeks	N=29 8 weeks	Primary: Rate of adverse events Secondary: Not reported	Primary: During the prophylaxis period, all patients reported at least one AE. The most frequent adverse events related to study drug were infusion-related reactions, 12 of which (from a total of 76 infusions) led to increased infusion duration for better tolerance. Because the rate of common toxicity criteria grade 3 and 4 adverse events was above the10% limit assigned by the protocol, it was decided by the independent data review committee to stop the inclusion of SCT subjects. In the AL group, 16 serious adverse events were reported for ten patients and eight serious adverse events were reported for four SCT patients. Two serious adverse events (anuria and anaphylactic shock), both in the SCT group, were considered to be related to the prophylactic antifungal treatment. Two episodes of hypokalemia were reported and were thought to be related to the study drug in the AL group. Renal and electrolyte disorders were frequent; however, they were frequently unrelated to the prophylactic treatment.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				All SCT patients received cyclosporin A. Analysis of serum creatinine values up to one month after the last infusion demonstrated an increase ≥2-fold the baseline value in 2/21 AL patients and 2/8 SCT patients. Discontinuation of prophylactic treatment occurred in three AL patients (14%) due to four AEs (fever, bronchopulmonary aspergillosis, *Escherichia coli* sepsis and positive *Candida* serology); none of these adverse events were related to study treatment. Discontinuation of prophylactic treatment occurred in eight SCT patients (100%) due to 11 adverse events: three were not related to study treatment (renal insufficiency, thrombotic microangiopathy and bronchopulmonary aspergillosis) and eight were reported to be related to study treatment (dyspnea, chest pain, abdominal pain, nausea, tubulointerstitial nephritis, renal insufficiency, anuria and anaphylactic shock). No adverse event related to the study drug led to discontinuation of prophylactic treatment in AL patients. In SCT patients, eight adverse events (in six patients) reported to be related to study treatment led to treatment discontinuation. Enrolment was discontinued in the SCT group as recommended by the independent data review committee in accordance with the 10% limit of adverse events (CTC grade 3 to 4) fixed by the protocol. Thirteen AL patients and four SCT patients received antifungal empirical treatment during the prophylaxis period. The median time to first empirical antifungal treatment was 17 days in AL patients and 7.5 days for SCT patients. Secondary: Not reported
Ellis et al.[65] (2006) Amphotericin B liposome	RETRO Patients with acute hematological malignancies with	N=73 7 day posttreatment follow-up	Primary: All-cause mortality within seven days of completion of antifungal therapy,	Primary: Significantly more deaths were seen in patients following caspofungin therapy compared to liposomal amphotericin B therapy (P=0.013). Overall, response to therapy did not differ significantly between treatment

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
3 to 5 mg/kg/day for at least 10 to 14 days vs caspofungin 70 mg loading dose then 50 mg daily for at least 10 to 14 days Treating physician could escalate amphotericin B dose to 10 mg/kg.	prolonged neutropenia or invasive fungal infections		response to treatment, toxicity Secondary: All antifungal drug administration during each hospital admission	groups (P>0.16). Significantly more patients experienced treatment failure due to a breakthrough invasive fungal infection in the caspofungin group compared to the amphotericin B group (P=0.047). The proportion of events treated with amphotericin B which had at least 1 adverse event was significantly higher compared to the caspofungin group (P=0.02). Significantly more patients in the amphotericin B group experienced episodes of hypokalemia (P=0.01). A similar proportion of drug discontinuations was observed due to adverse effects between the groups (P=0.48). Secondary: There were a total of 97 episodes of treatment with either caspofungin or liposomal amphotericin B and results were similar to those seen in the primary efficacy endpoints.
Maertens et al.[66] (2010) Amphotericin B liposome (L-AMB) 3 mg/kg daily vs caspofungin 70 mg/m^2 loading dose on day 1, then 50 mg/m^2 daily	MC, DB, RCT Patients 2 to 17 years of age who had received chemotherapy for cancer or had undergone hematopoietic stem cell transplantation, had received parenteral broad-spectrum antibacterial therapy for ≥96 hours, and were neutropenic and febrile	N=83 Up to 28 days	Primary: Safety and tolerability Secondary: Efficacy	Primary: Serious clinical adverse events that were considered to be drug related were reported in one (1.8%) caspofungin recipient (hypotension) and three (11.5%) L-AMB recipients (hyperbilirubinemia; circumoral edema; and angioneurotic edema with dyspnea, laryngospasm, and tachycardia); all four patients discontinued the intended course of therapy. Three patients died during the study: two (3.6%) in the caspofungin group and one (3.8%) in the L-AMB group. Secondary: A favorable overall response was observed in 46.4% of patients who received caspofungin and 32.0% of those who received L-AMB; however, the 95% CIs for the treatment groups overlapped.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Döring et al.[67] (2012) Caspofungin (CAS) 1 or 3 mg/kg/day vs liposomal amphotericin B (L-AmB) 50 mg/m^2/day	OBS, RETRO Pediatric patients (<18 years of age) undergoing hematopoietic stem cell transplantation	N=120 9 to 49 days	Primary: Safety Secondary: Incidence of aspergillosis, candidiasis, and other mycoses	Primary: Clinical side effects directly related to intravenous treatment with L-AmB were observed in five (8.3%) and directly related to CAS in two (3.3%) pediatric patients. A total of 25% (15) of patients in the LAmB group required oral potassium supplementation and spironolactone upon discharge. This compares to only 11.7% (7) in the CAS group. Sodium bicarbonate substitution was required in five (8.33%) and calcium in three (5%) cases upon discharge in the L-AmB group. In the CAS group, calcium was given in two (3.3%) cases and sodium bicarbonate in one (1.7%) case. Secondary: Prophylaxis was effective with L-AmB as well as with CAS. There was no incidence of proven invasive aspergillosis or another invasive fungal infection in either group.
Caselli et al.[68] (2012) High risk patients: liposomal amphotericin B (Arm B) vs caspofungin (Arm C) lower risk patients: liposomal amphotericin B (Arm B) vs caspofungin (Arm	MC, PRO, RCT Patients aged ≤18 years with neutropenia induced by chemotherapy or autologous hematopoietic stem cell transplant and persistent fever despite empirical IV antibiotic therapy	N=104 >30 days	Primary: Complete response to the treatment (fever <37.5°C for 48 hours, survival with no evidence of invasive fungal infection by day 30, and completion of the randomly assigned treatment) Secondary: Proportion of patients diagnosed with invasive fungal infection, duration of hospital stay, patient compliance (number of patients	High risk group: Primary: A complete response was achieved in 48 of the 56 patients in the high-risk group (85.7%) with no difference between the two treatment arms. A complete response was achieved in 88.0% of the patients in Arm B and in 83.9% of the patients in Arm C (P=0.72). Secondary: Patients with a complete response in Arm B had a median hospital stay of 18 days (range, six to 51). Patients with a complete response in Arm C had a median hospital stay of 28 days (range, six to 52). Lower risk group: Primary: Within the low-risk group, a complete response was observed in 42 of 48 patients (87.5%). The proportion of patients achieving a complete response was comparable across the three arms: 87.5% in control Arm A, 80.0% in Arm B, and 94.1% in Arm C (P=0.41). Secondary: Patients with a complete response in Arm A had a median hospital stay of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
C) vs no antifungal treatment (Arm A)			who completed the assigned treatment), and drug toxicity (the number of patients who developed renal or liver toxicity)	8.5 days (range, four to 24). Patients with a complete response in Arm B had a median hospital stay of 11 days (range five to 29). Patients with a complete response in Arm C had a median hospital stay of 13 days (range, six to 31). Composite: Of the 110 patients at risk, nine were diagnosed with invasive fungal infections during the duration of the study for a global frequency of 8.2% (CI, 3.8 to 15.0). This study was terminated for futility when the number of randomized patients was still below the initial expected target. Nonetheless, the results show that, in terms of probability, none of the three experimental arms was superior to the others.
Johansen et al.[69] (2002) Amphotericin B vs fluconazole	MA Patients with cancer complicated by neutropenia	N=3,798 (17 trials) Various durations	Primary: Mortality, invasive fungal infections, colonization, use of additional antifungal therapy, adverse effects leading to discontinuation Secondary: Not reported	Primary: No significant difference was observed between fluconazole and amphotericin B on mortality (P>0.1). No significant difference was observed between fluconazole and amphotericin B on the rate of invasive fungal infection (P>0.4). No significant difference was observed between fluconazole and amphotericin B on fungal colonization (P>0.3). No significant difference was observed overall between groups in the use of additional antifungal therapy (P>0.1). Significantly more patients receiving amphotericin B dropped out of the study due to adverse effects (P<0.009). Secondary: Not reported
van't Wout et al.[70] (1991) Amphotericin B 0.6 mg/kg/day IV vs	MC, RCT Neutropenic patients with proven or highly suspected fungal infections	N=40 End of therapy	Primary: Response to therapy (at least 50% decrease in size of initial site or severity of infection or	Primary: Response to treatment was observed in 63% of itraconazole patients and 56% of amphotericin B patients (P>0.90). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
itraconazole 200 mg orally 2 times daily Some patients treated with amphotericin B also received flucytosine at 150 mg/kg/day. In these cases, the amphotericin B dose was 0.3 mg/kg/day.			resolution of all signs of infection) Secondary: Not reported	
Schuler et al.[71] (2007) Amphotericin B (AMB) IV 0.7 to 1.5 mg/kg/day vs itraconazole 200 mg IV every 12 hours for 2 days, followed by 200 mg once daily	RCT, OL Hospitalized adult patients with hematological malignancy treated with myelosuppressive therapy and/or who were allogeneic/ autologous bone marrow or blood stem cell transplant recipients	N=162 28 days	Primary: Permanent discontinuation of study medication due to any adverse event Secondary: Response and success rate for both treatment groups	Primary: Significantly fewer itraconazole patients discontinued treatment due to any adverse event (22.2 vs 56.8% AMB; P<0.0001). The main reason for discontinuation was a rise in serum creatinine (1.2% itraconazole vs 23.5% AMB). Renal toxicity was significantly higher and more drug-related adverse events occurred in the AMB group. Secondary: Intention-to-treat analysis showed favorable efficacy for itraconazole; response and success rate were both significantly higher than for AMB (61.7 vs 42% and 70.4 vs 49.3%; both P<0.0001). Treatment failure was reduced in itraconazole patients (25.9 vs 43.2%), primarily due to better tolerability.
Chaftari et al.[72] (2012) Posaconazole 200 mg PO 3 times	OL, PRO, RCT Hematopoietic Stem cell transplant patients	N=40 6 weeks	Primary: incidence of invasive fungal infections and drug-related	Primary: For the efficacy analysis, one patient in the ABLC arm and none in the posaconazole arm developed a definite invasive fungal infection (5 vs 0%; P=0.48).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
daily vs amphotericin B lipid complex (ABLC) 7.5 mg/kg IV once weekly			toxicities Secondary: Not reported	The rate of adverse event that led to the discontinuation of the drug was significantly higher in the ABLC arm compared with the posaconazole arm: 15 of 19 in ABLC vs eight of 20 in posaconazole (P=0.009). There was a significantly lower creatinine clearance reached during the study in the ABLC group compared with the posaconazole group (46 mL/min [range, 33 to 81 mL/min] vs. 74 mL/min [range, 34 to 129 mL/min]; P=0.006). More patients in the ABLC arm doubled their serum creatinine level to abnormal ranges (10 vs one; P=0.001), which necessitated the discontinuation of the study drug according to the protocol. The study was stopped earlier because of the results of the interim data analysis suggesting that there was more than a 70% chance that the nephrotoxicity rate of the ABLC group was higher than 50%. Secondary: Not reported
Mandhaniya et al.[73] (2011) Amphotericin B 0.5 mg/kg/day 3 times per week vs voriconazole 6 mg/kg/dose for 2 doses, then 4 mg/kg/dose BID	RCT, OL, SC Pediatric patients <15 years of age with ALL or AML undergoing induction chemotherapy	N=100 Variable duration	Primary: Failure of prophylaxis indicated by proven/probable/ possible or suspected fungal infection or treatment discontinuation owing to side effects, adverse events Secondary: Not reported	Primary: In the voriconazole arm, 28% of patients failed antifungal prophylaxis compared to 34% of patients in the amphotericin arm (P=0.66). There was no significant difference in the proven, possible, or probable fungal infections in the two study arms. Drug related serious adverse events were six and 30% in voriconazole and amphotericin B treated patients, respectively (P<0.01). All patients on amphotericin B experienced infusion-related toxicity such as fever, chills, and/or rigors and almost half of them had hypokalemia. Abdominal pain, hyperbilirubinemia, and macular skin rashes were observed more in the voriconazole arm. Secondary: Not reported
Gotzsche et al.[74] (2002)	MA Patients with cancer	N=4,155 (31 trials)	Primary: Mortality	Primary: No significant differences were observed between the groups on mortality (P>0.08).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Amphotericin B, fluconazole, ketoconazole, itraconazole, miconazole, placebo	and neutropenia from chemotherapy or bone marrow transplants	Various study durations	Secondary: Invasive fungal infections, colonization, use of additional antifungal therapy	Secondary: Invasive fungal infections decreased significantly with amphotericin B, fluconazole, and itraconazole (P<0.04) but not with miconazole or ketoconazole (P>0.2). Definitions of fungal colonization differed greatly between studies, though the effect of prophylaxis on colonization was significant for amphotericin B, fluconazole, itraconazole, and ketoconazole (P<0.02) but not for miconazole (P=0.8) Significantly more patients who received placebo or no treatment required additional antifungal therapy.
Clarkson et al.[75] (2007) Medications not absorbed from the gastrointestinal (GI) tract (amphotericin B, nystatin, chlorhexidine, thymostimulin, natamycin, norfloxacin) vs medications absorbed from the GI tract (fluconazole, ketoconazole, itraconazole) vs	MA Patients with cancer receiving chemotherapy, radiation, or both	N=4,226 (28 trials) Variable duration	Primary: Prevention of oral candidiasis Secondary: (If available) relief of pain, amount of analgesia, relief of dysphagia, incidence of systemic infection, duration of hospital stay, cost of oral care, patient quality of life, death, use of empirical antifungal therapy, toxicity, compliance	Primary: Drugs absorbed or partially absorbed from the GI tract were found to significantly decrease the incidence of oral candidiasis compared to non-absorbed drugs (P<0.016). Drugs absorbed or partially absorbed from the GI tract were found to significantly decrease the incidence of oral candidiasis compared to placebo or no treatment (P<0.004). Secondary: Significantly fewer patients who were treated with drugs absorbed from the GI tract required empiric antifungal therapy compared to placebo or no treatment (P=0.04). This effect was not seen in patients treated with drugs which are partially absorbed (P=0.4). This outcome was not analyzed in any study on non-absorbable drugs. No significant differences were observed between groups in any other secondary endpoint.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
medications partially absorbed from the GI tract (miconazole, clotrimazole) vs placebo				
Violaris et al.[76] (2010) Nystatin 100,000 units divided in each side of the mouth every 6 hours vs fluconazole 4 mg/kg/day	RCT, OL Very low birth-weight neonates (<1.5 kg at birth)	N=80 Variable duration	Primary: Rate of systemic fungal infection Secondary: Mortality	Primary: Systemic fungal infection developed in two infants (5.3%) in the fluconazole group and six infants (14.3%) in the nystatin group (RR, 0.37; 95% CI, 0.08 to 1.72). Secondary: There were no deaths in the fluconazole group and six deaths in the nystatin group (P=0.03). Two infants died of neonatal sepsis, and four deaths were related to necrotizing enterocolitis and/or spontaneous intestinal perforation. No deaths were due to systemic fungal infection.
Aydemir et al.[77] (2011) Nystatin 100,000 units every 8 hours by orogastric tube vs fluconazole 3 mg/kg IV every third day vs	RCT, DB Very low birth-weight neonates (<1.5 kg at birth)	N=278 4-6 weeks	Primary: Prevention of fungal colonization and infection Secondary: Mortality, incidence of bacterial sepsis, necrotizing enterocolitis, threshold retinopathy of prematurity requiring surgery,	Primary: Fungal colonization occurred less frequently in the fluconazole (10.8%) and nystatin (11.7%) groups than in the placebo group (42.9%; P<0.001). Invasive fungal infection was less frequent in the fluconazole (3.2%) and nystatin groups (4.3%), as compared to in the placebo group (16.5%; P<0.001). Secondary: The overall mortality was similar among the three groups (8.6% in the fluconazole group and 8.5% in the nystatin group, as compared to 12.1% in the placebo group; P=0.64). There were no significant differences in other secondary outcomes.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo			severe intraventricular hemorrhage, and bronchopulmonary dysplasia	No serious adverse effects of the fluconazole or nystatin therapy were documented.
Histoplasmosis				
Johnson et al.[78] (2002) Amphotericin B liposome 3 mg/kg/day for 2 weeks (induction therapy) vs amphotericin B deoxycholate 0.7 mg/kg/day for 2 weeks (induction therapy) All patients in whom induction therapy was successful received itraconazole for 10 additional weeks.	DB, MC, RCT Patients with AIDS and disseminated histoplasmosis infection	N=81 12 weeks	Primary: Clinical success Secondary: Time to defervescence, mycological efficacy, change in *Histoplasma capsulatum* antigen levels in the urine and serum at week two, rates of infusion toxicity and nephrotoxicity	Primary: Clinical success following induction therapy was observed in 88% of liposomal amphotericin B patients compared to 64% of amphotericin B patients (P=0.014). Consolidation therapy was successful in 88% of patients in the liposomal amphotericin B group and in 93% of patients in the amphotericin B group (P>0.2). There was no significant difference in negative cultures between groups at the end of consolidation therapy. Clinical and mycological outcomes could not be assessed at week 12 due to limited data. Secondary: The median time to defervescence was three days for both therapies. There was no significant difference between groups in time to negative culture (P>0.2). *Histoplasma capsulatum* clearance was similar between groups. Significantly more patients treated with amphotericin B experienced infusion related toxicity compared to those in the liposomal amphotericin B group (P=0.002). Nephrotoxicity occurred in significantly more patients in the amphotericin B group compared to the liposomal amphotericin B group (P=0.003). Toxicities led to discontinuation of therapy in a similar number of patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				in both groups (P=0.19).
Wheat et al.[79] (2001) Amphotericin B liposome 3 mg/kg/day for 2 weeks, followed by itraconazole 200 mg 2 times daily for 10 weeks vs itraconazole 300 mg orally 2 times daily for 3 days then 200 mg 2 times daily for 12 weeks	OL, CS Patients 13 years of age and older with HIV infection and first episode of disseminated histoplasmosis	N=110 12 weeks	Primary: Mycological response (negative blood cultures), time to negative blood cultures Secondary: Not reported	Primary: By the end of the second week of therapy, blood cultures were negative in over 85% of amphotericin B patients compared to 53% of itraconazole patients (P=0.0008). By 12 weeks of therapy, cultures were negative in all patients in both groups. After two weeks of therapy, serum antigen levels fell by a significantly greater amount in the amphotericin B group compared to the itraconazole group (P=0.02). After two weeks of treatment, serum antigen levels were negative in 28% of the amphotericin B group and 20% of the itraconazole group (P=0.55). After two weeks of therapy, urine antigen levels were below the detection limit in 19% of amphotericin B patients and 3% of itraconazole patients (P=0.06). After two weeks of therapy, urine antigen levels fell by a significantly greater amount in the amphotericin B group compared to the itraconazole group (P<0.0005). By 12 weeks of therapy, there was no significant difference in the proportion of patients with undetectable serum and urine antigen levels in either group (P<0.80). Secondary: Not reported
Leishmaniasis				
Sundar et al.[80] (2004) Amphotericin B deoxycholate 1 mg/kg/day every	OL, RCT Patients with signs and symptoms of visceral leishmaniasis	N=153 6 month posttreatment follow-up	Primary: Apparent cure (day 19), definite cure (posttreatment follow-up)	Primary: On day 19, no significant differences in apparent cure were observed between the treatment groups. During the follow-up period, overall definite cure rates did not differ between groups (P>0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
other day for 15 infusions (Group A) vs amphotericin B liposome 2 mg/kg/day for 5 infusions (Group B) vs amphotericin B lipid complex 2 mg/kg/day for 5 infusions (Group C)	confirmed microscopically		Secondary: Not reported	On day seven, significantly fewer patients in Groups B and C had fever compared to Group A (P<0.05); however, only 4 infusions of amphotericin B deoxycholate had been given compared to all doses of the lipid formulations. Overall duration of fever was shorter in Group B compared to Group C (P<0.05) and both were shorter than Group A (P<0.05). Secondary: Not reported
Sundar et al.[81] (2002) Amphotericin B liposome 0.75 mg/kg/day for 5 days vs amphotericin B liposome 1.5 mg/kg/day for 5 days vs amphotericin B	DB, MC, RCT Patients of any age with visceral leishmaniasis	N=84 6 month posttreatment follow-up	Primary: Apparent cure (resolution of fever, regression of splenomegaly, absence of parasites in splenic or marrow smear at the end of two weeks of therapy), definite cure (absence of signs and symptoms of visceral leishmaniasis after six months of follow-up)	Primary: There were no significant differences between groups in apparent or definite cure. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
liposome 3 mg/kg/day for 5 days			Secondary: Not reported	
Miscellaneous				
Walsh et al.[82] (1999) Amphotericin B lipid complex (ABLC) 5 mg/kg/day	MC, OL Pediatric patients <18 years of age with an invasive fungal infection and one or more of the following: progression of infection despite antifungal treatment, onset of renal dysfunction secondary to amphotericin B or other nephrotoxic agents, intolerable infusion-related toxicity, or pre-established renal dysfunction	N=111 4 week posttreatment follow-up	Primary: Clinical response (complete=resolution of signs and symptoms of invasive mycosis; partial=substantial reduction in signs and symptoms), safety Secondary: Not reported	Primary: No significant differences were seen in renal function, serum creatinine, serum potassium, or serum magnesium compared to baseline values (P>0.054). The overall response rate (complete and partial responses) was 64% for filamentous fungi infections (including Zygomycetes and *Fusarium* species), and 56% for aspergillosis. The overall response rate for candidiasis was 81% and was similar for disseminated disease (82%), single organ disease (75%), and candidemia (83%) and no significant difference was observed between types of *Candida* infection. Secondary: Not reported
Cordonnier et al.[83] (2007) <u>Study 1</u> Amphotericin B liposome (L-AMB) 5 mg/kg/day vs amphotericin B	RETRO Patients with documented or suspected neutropenia-associated invasive fungal infections, or invasive aspergillosis	N=69 Variable duration	Primary: Favorable response (complete or partial response) and survival Secondary: Not reported	Primary: A favorable response with L-AMB was observed in 51% of cases: 55% of cases with proven invasive filamentous fungal infections (IFFI) and 49% of cases with probable IFFI. Treatment with L-AMB as the first-line therapy showed a higher favorable response (61%) compared to the administration of the second-line therapy (32%). Patients with severe neutropenia at baseline showed a response similar to that of patients without severe neutropenia, with 47% of patients and 54% of patients achieving a favorable response, respectively. In patients with hematological disease, a favorable response was observed

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
deoxycholate Study 2 Amphotericin B liposome (L-AMB) 1 mg/kg/day vs Amphotericin B liposome (L-AMB) 4 mg/kg/day Study 3 Amphotericin B liposome (L-AMB) 7.5 to 15 mg/kg/day				in 51% of patients. Of these, 44% who received allogeneic stem cell transplantation (SCT) and 57% who received autologous SCT showed a favorable response with L-AMB. Favorable response rates varied by the site of infection, ranging from 44% for pulmonary infections, 64% for sinus/nasal infections, 57% for disseminated infections and one of one case each for subcutaneous abscess, pericarditis, and mastoiditis. Of the patients with probable or proven IFFI, 51% treated with L-AMB survived to the last follow-up visit. Of these surviving patients, 23 of 35 patients had survival documented to ≥12 weeks after the initiation of treatment. For the remaining 12 patients whose last study visit was <12 weeks following the initiation of L-AMB treatment, Secondary: Not reported
Mills et al.[84] (2009) Antifungal agents (azoles, amphotericin B, echinocandins)	MA Patients with invasive fungal infections	N=965 (11 trials) Variable duration	Primary: Global response rate Secondary: All-cause mortality, fungal-attributable mortality, and adverse events	Primary: For global response rate, the pooled estimate was 0.87 when azoles were compared to amphotericin B (95% CI, 0.78 to 0.96; P=0.007). When only fluconazole trials were compared to amphotericin B, there were similar effects (RR, 0.82; 95% CI, 0.74 to 0.92; P=0.0009). The itraconazole vs amphotericin B trial (RR, 0.90; 95% CI, 0.49 to 1.63; P=0.61) and voriconazole vs amphotericin B trial (RR, 0.99; 95% CI, 0.77 to 1.30; P=0.94) provided similar estimates. Two trials comparing echinocandins and amphotericin B demonstrated a pooled RR of 1.10 (95% CI, 0.99 to 1.23; P=0.08). The anidulafungin to fluconazole trial yielded a RR of 1.26 (95% CI, 1.06 to 1.51; P=0.001) in favor of anidulafungin; and micafungin to caspofungin (RR, 1.00; 95% CI, 0.94 to 1.08; P=0.21). Secondary: Seven trials comparing azoles and amphotericin B were pooled for all-cause mortality, which demonstrated a RR of 0.88 (95% CI, 0.74 to 1.05;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				P=0.17). Similar results were found when individual azoles were analyzed: fluconazole (five trials) RR 0.92 (95% CI, 0.73 to 1.17; P=0.51); itraconazole (one trial) RR 0.67 (95% CI, 0.74 to 1.05; P=0.20); voriconazole (one trial) RR 0.85 (95% CI, 0.65 to 1.12; P=0.67). When echinocandins were compared to amphotericin B (two trials), there was a pooled RR of 1.01 (95% CI, 0.84 to 1.20; P=0.93). Micafungin vs caspofungin resulted in a RR of 0.85 (95% CI, 0.96 to 1.11) in the direction of favor of caspofungin. Anidulafungin vs fluconazole resulted in a RR of 0.73 (95% CI, 0.48 to 1.10; P=0.34) in the direction of anidulafungin. When five trials comparing azoles to amphotericin B were pooled, a RR of 0.84 was found (95% CI, 0.49 to 1.42; P=0.51). When the three echinocandin trials vs amphotericin B were pooled, the RR was 1.16 (95% CI, 0.75 to 1.79; P=0.50). Anidulafungin vs fluconazole yielded a RR of 0.84 (95% CI, 0.48 to 1.47; P=0.88). To assess serious adverse events, two trials were pooled comparing azoles and amphotericin B, which showed a RR of 0.67 (95% CI, 0.55 to 0.81; P≤0.0001) in favor of azoles. Two trials comparing echinocandins and amphotericin B were pooled, which showed a RR of 0.49 (95% CI, 0.37 to 0.66; P≤0.0001) in favor of the echinocandins. Micafungin and caspofungin had similar safety profiles (RR, 0.94; 95% CI, 0.70 to 1.29). There was no significant difference between anidulafungin vs fluconazole (RR, 0.90; 95% CI, 0.60 to 1.36; P=0.66).

Drug regimen abbreviations: IV=intravenously, PO=by mouth
Study abbreviations: CI=confidence interval, CS=comparative study, DB=double blind, DD=double dummy, DR=dose ranging, HR=hazard ration, MA=meta-analysis, MC=multi-center, OBS=observational, OL=open label, OR=odds ratio, PRO=prospective trial, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, SB=single blind
Miscellaneous abbreviations: AIDS=acquired immunodeficiency syndrome. CSF=cerebrospinal fluid, HIV=human immunodeficiency virus

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 11. Relative Cost of the Polyenes

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Amphotericin B	injection	N/A	N/A	$$$
Amphotericin B lipid complex	injection	Abelcet®	$$$$$	N/A
Amphotericin B liposome	injection	AmBisome®	$$$$$	N/A
Nystatin	powder for suspension, suspension, tablet	N/A	N/A	$-$$$

*Generic is available in at least one dosage form or strength.
N/A=Not available

X. Conclusions

The polyenes are approved for the treatment of numerous fungal infections. Conventional amphotericin B (deoxycholate) has been available for several decades; however, its use is associated with a high incidence of infusion-related adverse events and nephrotoxicity. There are two lipid formulations of amphotericin B currently available, including amphotericin B lipid complex and amphotericin B liposome. These agents were developed to minimize toxicity that is associated with conventional amphotericin B. Nystatin and conventional amphotericin B are both available in a generic formulation.

There are many guidelines that define the appropriate place in therapy for the polyenes.[6-15] Amphotericin B is recommended as specific therapy for the treatment of aspergillosis, blastomycosis, candidiasis, coccidioidomycosis, cryptococcal disease, histoplasmosis, sporotrichosis, as well as for prophylaxis in patients with chemotherapy-induced neutropenia.[6-15] The specific amphotericin B formulation that is recommended (conventional vs lipid) is dependent upon the location of the infection, pregnancy status, as well as the age of the patient (refer to Table 3 for further discussion). According to the prescribing information, the use of amphotericin B (all formulations) should be reserved for the treatment of patients with progressive and potentially life-threatening fungal infections. It should not be used to treat noninvasive forms of fungal disease, such as oral thrush, vaginal candidiasis, and esophageal candidiasis in patients with normal neutrophil counts.[1-5]

Several clinical trials have directly compared the efficacy and safety of the various amphotericin B formulations. Studies have demonstrated similar efficacy among the conventional and lipid formulations.[17,44,46,58,61-62,80] Rates of adverse events, including infusion-related reactions and nephrotoxicity, were higher with the conventional formulation than with the lipid formulations.[17-18,58,60,78] Amphotericin B lipid complex and amphotericin B liposome have also been shown to be comparable in efficacy.[61-62,80] Few studies have demonstrated greater clinical and/or mycological response rates with one amphotericin B formulation over another.[18,78,60] Studies have demonstrated similar efficacy when amphotericin B (all formulations) was compared to antifungal agents in other classes.[26,32,35-43,50,66,69-70,73-74]

Nystatin is approved for the treatment of gastrointestinal and oral cavity candidiasis.[1-3] Initial episodes of oropharyngeal candidiasis can be adequately treated with topical therapy, including clotrimazole troches or nystatin suspension.[9] For moderate-to-severe infections or refractory disease, oral and intravenous therapy with other antifungal agents is recommended.[9] Studies have demonstrated greater clinical and microbiologic response rates with fluconazole compared to nystatin.[28-30,76]

There is insufficient evidence to support that one brand polyene is more efficacious than another. Since amphotericin B is not indicated as first-line therapy for the management of common infectious diseases that would be seen in general use, formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand polyenes within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand polyene is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Pyrimidines
AHFS Class 081432
November 12, 2014

I. Overview

Flucytosine is approved for the treatment of serious infections caused by susceptible strains of *Candida* and/or *Cryptococcus*.[1-3] It should be used in combination with amphotericin B because of the emergence of resistance. Flucytosine is converted to fluorouracil inside the fungal cell.[1-3] Fluorouracil exerts its antifungal activity through the subsequent conversion to several active metabolites. These metabolites inhibit protein synthesis by being falsely incorporated into fungal ribonucleic acid (RNA), or interfere with the biosynthesis of fungal deoxyribonucleic acid (DNA) through the inhibition of the enzyme thymidylate synthetase.

The pyrimidines that are included in this review are listed in Table 1. This review encompasses all systemic dosage forms and strengths. The topical antifungals were previously reviewed with the skin and mucous membrane agents (AHFS 840408) and are not included in this review. Flucytosine is available in a generic formulation. This class was last reviewed in May 2012.

Table 1. Pyrimidines Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Flucytosine	capsule	Ancobon®*	flucytosine

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List

The pyrimidines have been shown to be active against the strains of microorganisms indicated in Table 2. This activity has been demonstrated in clinical infections and is represented by the Food and Drug Administration (FDA)-approved indications for the pyrimidines that are noted in Table 4. These agents may also have been found to show activity to other microorganisms in vitro; however, the clinical significance of this is unknown since their safety and efficacy in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials. Although empiric anti-infective therapy may be initiated before culture and susceptibility test results are known, once results become available, appropriate therapy should be selected.

Table 2. Microorganisms Susceptible to the Pyrimidines[1-3]

Organism	Flucytosine
Cryptococcus species	✔
Candida species	✔

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the pyrimidines are summarized in Table 3.

Table 3. Treatment Guidelines Using the Pyrimidines

Clinical Guideline	Recommendation(s)
American Thoracic Society: **Treatment of Fungal Infections in Adult Pulmonary and Critical Care Patients (2011)**[4]	Aspergillomas • In patients with aspergillomas, it is recommended that antifungal agents not be used. • Antifungals should only be used only in patients suspected of having a component of semi-invasive disease. Invasive Aspergillosis • When invasive disease is suspected or confirmed, prompt, aggressive antifungal treatment is essential.

Clinical Guideline	Recommendation(s)

	• Although amphotericin B deoxycholate had historically been the "gold standard" for the treatment of invasive aspergillosis, most clinicians and the most recent Infectious Diseases Society of America guidelines recommend voriconazole as the primary treatment option.
	• There are no definitive data or consensus opinions indicating improved efficacy of any of the lipid amphotericin formulations over amphotericin B deoxycholate in the treatment of invasive aspergillosis. Thus, the best indication for using a lipid formulation appears to be for reducing renal toxicity to allow the administration of high doses of amphotericin for a prolonged time.
	• Voriconazole has recently emerged as a standard therapy for the treatment of invasive aspergillosis based on the results of a randomized trial comparing the outcomes to amphotericin B deoxycholate; however, whether outcomes are superior to lipid formulations of amphotericin B has not been determined. In many instances voriconazole may be considered the treatment of choice. The patient can be transitioned to oral formulations of this drug.
	• Oral itraconazole is not recommended for initial therapy for invasive aspergillosis. However, after disease progression is arrested with either voriconazole or amphotericin, the patient can be transitioned to oral itraconazole.
	• Caspofungin use in invasive aspergillosis is largely limited to salvage therapy, often in combination with other antifungal agents, after primary therapy with amphotericin-based regimens have failed.
	• There is currently insufficient clinical support to recommend combination therapy, although many clinicians are employing this approach as a "last option," or in settings of particularly advanced disease.
	
	<u>Chronic necrotizing aspergillosis</u>
	• In patients with chronic necrotizing aspergillosis, with mild to moderate disease, voriconazole (200 mg every 12 hours) or itraconazole (400 to 600 mg/day) is recommended until resolution or stabilization of all clinical and radiographic manifestations.
	• If clinically severe, consider beginning therapy of chronic necrotizing aspergillosis with either liposomal amphotericin B or intravenous voriconazole as described above for invasive disease.
	• In select patients at high risk of invasive fungal infection, some anti-*Aspergillus* prophylaxis is warranted. Data support the use of posaconazole 200 mg orally three times daily until recovery from neutropenia and clinical remission is established. Other prophylaxis approaches have utilized itraconazole, micafungin, and inhaled liposomal amphotericin B.
	
	<u>Invasive Pulmonary Aspergillosis</u>
	• In patients with invasive pulmonary aspergillosis, the following are recommended:
	  o Intravenous voriconazole six mg/kg every 12 hours for one day, followed by four mg/kg every 12 hours until improvement, followed by oral voriconazole 200 mg every 12 hours (preferred) or oral itraconazole 400 to 600 mg/day until resolution or stabilization of all clinical and radiographic manifestations OR
	  o Intravenous liposomal amphotericin B three to five mg/kg/day until improvement, followed by oral voriconazole 200 mg every 12 hours (preferred) or oral itraconazole 400 to 600

Clinical Guideline	Recommendation(s)

	mg/day until resolution or stabilization of all clinical and radiographic manifestation.
	• In patients with invasive pulmonary aspergillosis who have failed front line therapy and are requiring salvage therapy, the following are recommended:
	  o Intravenous caspofungin 70 mg on day one and 50 mg/day intravenously thereafter, or intravenous micafungin 100 to 150 mg/day until improvement, followed by oral voriconazole 200 mg every 12 hours or oral itraconazole 400 to 600 mg/day until resolution of disease OR
	  o Posaconazole 200 mg four times per day initially, then 400 mg twice daily orally after stabilization of disease.
	
	<u>Hypersensitivity pneumonitis related to *Aspergillus*</u>
	• In patients with hypersensitivity pneumonitis, it is recommended that antifungal therapy not be used.
	
	<u>Blastomycosis (immunocompetent hosts)</u>
	• In patients with mild to moderate pulmonary blastomycosis, oral itraconazole 200 mg twice daily is recommended for six months.
	• In patients with severe pulmonary blastomycosis, amphotericin B 0.7 to 1.0 mg/kg/day daily is recommended until clinical improvement is observed, followed by continuation of amphotericin B 0.7 to 1.0 mg/kg three times weekly, until a cumulative dose of 1.5 to 2.5 grams is reached. Once clinical improvement is observed, oral itraconazole 200 mg twice daily is recommended for six months.
	• In patients with pulmonary blastomycosis and bone involvement, it is recommended to prolong treatment with itraconazole to 12 months.
	• In patients with pulmonary blastomycosis and concomitant central nervous system involvement, the following are recommended:
	  o Liposomal amphotericin B 0.7 mg/kg/day until a cumulative dose of two grams is reached.
	  o Triazoles should not be used as monotherapy for meningeal blastomycosis.
	  o High dose intravenous or oral fluconazole 400 to 800 mg daily may be provided as an add-on therapy to intravenous amphotericin B in patients with severe or refractory disease, with the total duration of fluconazole therapy extended for at least six months.
	
	<u>Blastomycosis (immunocompromised hosts)</u>
	• In patients with severe pulmonary blastomycosis without central nervous system involvement, amphotericin B 0.7 mg/kg/day is recommended until clinical improvement is observed. Once clinical improvement is observed, oral itraconazole 200 mg twice daily is recommended for at least 12 months.
	• In patients with mild to moderate pulmonary blastomycosis without central nervous system involvement, oral itraconazole 200 mg twice daily is recommended for at least 12 months.
	• When acquired immunodeficiency syndrome is involved, oral itraconazole 200 mg/day is recommended indefinitely or until immunity is fully restored.
	• In patients with pulmonary blastomycosis and concomitant central nervous system involvement, the following are recommended:
	  o Combined therapy with amphotericin B 0.7 mg/kg/day together with intravenous or oral fluconazole 400 to 800 mg

Clinical Guideline	Recommendation(s)
	daily from the onset until clinical improvement is observed. o Use of fluconazole for at least 12 months total after discontinuation of combined intravenous treatment with amphotericin B and high-dose fluconazole. o Use of liposomal amphotericin B rather than amphotericin B deoxycholate should be considered due to theoretic better central nervous system penetration. o Triazoles are not used as monotherapy. o Patients with acquired immunodeficiency syndrome should continue to receive oral fluconazole 400 mg per day indefinitely or until immunity is restored. • In patients with pulmonary blastomycosis with new or progressing central nervous system involvement despite amphotericin B monotherapy, the following are recommended: o Combined therapy with liposomal amphotericin B five mg/kg/day until clinical improvement is observed, together with intravenous or oral fluconazole 800 mg/day. o Fluconazole is used for at least six months in immunocompetent patients, and at least 12 months in immunocompromised patients, after discontinuation of combined treatment with amphotericin B and fluconazole. o Patients with acquired immunodeficiency syndrome receive oral fluconazole 400 mg daily indefinitely or until immunity is restored. • In critically ill patients with pulmonary blastomycosis, the following are recommended: o Combined therapy with amphotericin B (0.7 to 1.0 mg/kg amphotericin B deoxycholate or five mg/kg daily liposomal amphotericin B) until clinical improvement is observed, together with oral itraconazole 200 mg/day. o Following the initial intravenous therapy, oral itraconazole is used for at least six months in immunocompetent patients, and at least 12 months in immunocompromised patients, after discontinuation of combined treatment with amphotericin B and itraconazole. o After initial therapy is complete, patients with acquired immunodeficiency syndrome should receive oral itraconazole 200 mg/day indefinitely, or until immunity is restored. Voriconazole 200 mg twice daily may be used as an alternative to itraconazole. • In patients with pulmonary blastomycosis with new or progressing central nervous system involvement despite amphotericin B monotherapy, the following are recommended: o Combined therapy with liposomal amphotericin B five mg/kg/day until clinical improvement is observed, together with intravenous or oral fluconazole 800 mg/day. o Fluconazole is used for at least six months in immunocompetent patients, and at least 12 months in immunocompromised patients, after discontinuation of combined treatment with amphotericin B and fluconazole. o Patients with acquired immunodeficiency syndrome receive oral fluconazole 400 mg daily indefinitely or until immunity is restored. o Voriconazole 200 mg twice daily may be considered as an alternative to fluconazole, though extensive disease-specific data are currently lacking.

Clinical Guideline	Recommendation(s)

	• In critically ill patients with pulmonary blastomycosis, the following are recommended:
	  o Combined therapy with amphotericin B (0.7 to 1.0 mg/kg amphotericin B deoxycholate or five mg/kg daily liposomal amphotericin B) until clinical improvement is observed, together with oral itraconazole 200 mg/day.
	  o Following the initial intravenous therapy, oral itraconazole is used for at least six months in immunocompetent patients, and at least 12 months in immunocompromised patients, after discontinuation of combined treatment with amphotericin B and itraconazole.
	  o After initial therapy is complete, patients with AIDS should receive oral itraconazole 200 mg/day indefinitely, or until immunity is restored.
	  o Voriconazole 200 mg twice daily may be considered as an alternative to itraconazole, though this is based largely on in vitro sensitivities and limited case based data.
	
	<u>Coccidioidomycosis (immunocompetent hosts)</u>
	• In most immunocompetent patients with primary pulmonary coccidioidomycosis and no additional risk factors for dissemination, we suggest no antifungal treatment.
	• In immunocompetent patients with primary pulmonary coccidioidomycosis and moderate to severe symptoms, or those in whom symptoms persist for more than six weeks, treatment with triazole antifungal drugs are recommended for at least three to six months or longer if symptoms and radiographic abnormalities persist.
	
	<u>Coccidioidomycosis (immunocompromised hosts and others at risk for disseminated disease)</u>
	• In many patients with pulmonary coccidioidomycosis and pulmonary nodules only, observation is recommended for at least one year without antifungal treatment. However, fluconazole (400 mg/day) or itraconazole (400 mg/day) may be considered during periods of significant immune suppression (i.e., chemotherapy, systemic corticosteroid therapy, or CD4 counts <250/µL).
	• In patients with pulmonary coccidioidomycosis and pulmonary nodules who have additional risk factors for disseminated disease, patients with cavities, and those presenting with hemoptysis, treatment with triazole antifungal drugs are recommended, either fluconazole (400 mg/day) or itraconazole (400 mg/day).
	• For diffuse pulmonary coccidioidomycosis with significant impairment of gas exchange, initial liposomal amphotericin B (five mg/kg/day) or amphotericin B (0.7 to 1.0 mg/kg/day) is recommended until clinical improvement, followed by fluconazole (400 mg/day) or itraconazole (400 mg/day) for at least another year. In patients with ongoing immune suppression, azole therapy may be continued indefinitely.
	• All patients, whether immunocompetent or immunocompromised, with any form of disseminated coccidioidomycosis require treatment. For non-meningeal disseminated disease, treatment with fluconazole (400 mg/day) or itraconazole (400 mg/day) is recommended for at least a year and until clinical improvement and stabilization. Itraconazole is preferred in bone disease. In severe or refractory cases, liposomal amphotericin B (five mg/kg/day) or amphotericin B (0.7 to 1.0 mg/kg/day) may be initiated until clinical improvement, followed by fluconazole (400 mg/day) or itraconazole (400 mg/day) for at least

Clinical Guideline	Recommendation(s)
	another year. • In patients with meningitis, fluconazole (400 to 1,000 mg/day) or itraconazole (400 to 600 mg/day) for life. In patients with meningitis in whom treatment with triazole antifungal drugs failed, intrathecal amphotericin B is recommended in select cases. <u>Cryptococcosis (immunocompetent hosts)</u> • In asymptomatic immunocompetent patients with respiratory tract colonization by *Cryptococcus neoformans*, no antifungal treatment is recommended. • In immunocompetent patients with pulmonary cryptococcosis and no evidence of other organ involvement, fluconazole 400 mg/day initially is recommended, tapering to 200 mg/day after clinical improvement is assured and with total treatment for six months. Alternatively, itraconazole 400 mg/day may be considered for six months. Fluconazole treatment is recommended for longer than six months in patients with documented *Cryptococcus gattii* infection. <u>Cryptococcosis (immunocompromised hosts and immunocompetent hosts with disseminated or central nervous system involvement)</u> • In patients with disseminated cryptococcosis or central nervous system involvement, amphotericin B (0.7 to 1.0 mg/kg/day) plus flucytosine (100 mg/kg/day) is recommended for two weeks, then fluconazole or itraconazole (400 mg/day) for eight to 10 weeks. Alternatively, amphotericin B (0.7 to 1.0 mg/kg/day) plus flucytosine (100 mg/kg/day) may be administered for six to 10 weeks in patients in whom azoles cannot be used. • In patients with disseminated cryptococcosis or central nervous system involvement, it is recommended that azoles not be used as monotherapy. • In patients with refractory disease not responding to fluconazole and itraconazole, voriconazole or posaconazole can be considered as salvage therapy on a case by case basis. • In patients with acquired immunodeficiency syndrome and CD4+ T cell count < 200/µL who have disseminated cryptococcosis or central nervous system involvement, fluconazole 200 mg/day is recommended to be used indefinitely, after successful primary therapy as outlined above, or until CD4+ T cell count is greater than 200/µL, human immunodeficiency virus ribonucleic acid is undetectable and sustained for three months, and the patient is stable for one to two years. <u>Histoplasmosis (immunocompetent hosts with *Histoplasma*-related pulmonary nodules, broncholithiasis, or fibrosing mediastinitis)</u> • Among asymptomatic patients with pulmonary nodules in whom *Histoplasma* cannot be cultured, antifungal treatment is not recommended. • In most patients with broncholithiasis, antifungal treatment is not recommended. • In patients with fibrosing mediastinitis, some clinicians recommend itraconazole 200 mg twice daily for 12 weeks. In patients with radiographic or physiologic improvement after an initial 12 weeks of therapy, longer treatment, up to 12 months, is recommended. <u>Histoplasmosis (immunocompetent hosts with symptomatic, progressive, or severe pulmonary histoplasmosis)</u> • In asymptomatic patients, no antifungal treatment is recommended.

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	• In symptomatic patients with mild pulmonary histoplasmosis, who remain symptomatic after three weeks of observation, itraconazole 200 mg twice daily for up to 12 weeks is recommended.
	• In selected patients with mild to moderate pulmonary histoplasmosis, initiating treatment with itraconazole 200 mg twice daily rather than with amphotericin B is recommended.
	• In patients with severe pulmonary histoplasmosis, amphotericin B 0.7 mg/kg/day is recommended until clinical improvement is observed or until a cumulative dose of two grams of amphotericin B is reached. In patients who improve clinically after initial treatment with amphotericin B, maintenance itraconazole 200 mg twice daily for at least 12 weeks is recommended.
	
	<u>Histoplasmosis (immunocompromised hosts with pulmonary histoplasmosis or with progressive or disseminated disease, or with chronic pulmonary histoplasmosis)</u>
	• In patients with mild to moderate histoplasmosis, itraconazole 200 mg three times daily for three days is recommended, followed by 200 mg twice daily for 12 months.
	• In patients with severe progressive disseminated histoplasmosis requiring hospitalization, amphotericin B 0.7 to 1.0 mg/kg/day (or a lipid formulation of amphotericin three to five mg/kg/day) is recommended until clinical improvement is observed or until a cumulative dose of two grams of amphotericin B is reached. In patients who improve clinically after initial treatment with amphotericin B, itraconazole 200 mg twice daily for 12 months is recommended.
	• In patients with acquired immunodeficiency syndrome and progressive disseminated histoplasmosis who completed 12 months of initial itraconazole therapy, itraconazole 200 mg twice daily is recommended until effective immune reconstitution occurs.
	• In patients with chronic pulmonary histoplasmosis, itraconazole 200 mg twice daily for 12 to 24 months is recommended rather than no antifungal treatment.
	• In patients with severe chronic pulmonary histoplasmosis, initial treatment with amphotericin B is recommended over itraconazole.
	
	<u>Paracoccidioidomycosis</u>
	• In critically ill patients with disseminated paracoccidioidomycosis, initial amphotericin B (0.7 to 1.0 mg/kg/day) therapy is recommended until clinical stabilization or until two grams total dose administered. This may be followed by azole therapy as listed below.
	• In patients with disseminated paracoccidioidomycosis and mild to moderate or slowly progressive symptoms, one of the following options is recommended until clinical stabilization and resolution of symptoms. The total duration of therapy must be individualized to clinical response, but generally therapy for six to 12 months or longer is employed. Potential regimens include:
	  o Ketoconazole 200 to 400 mg daily
	  o Itraconazole 100 to 400 mg daily
	  o Sulfadiazine four to six grams daily
	
	<u>Sporotrichosis</u>
	• In patients with mild to moderately severe pulmonary sporotrichosis, itraconazole 200 mg twice daily is recommended, with a total duration of therapy generally of three to six months based upon overall clinical response.

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	• In patients with severe pulmonary sporotrichosis, amphotericin B 0.7 mg/kg/day is recommended until clinical improvement is observed or until a cumulative dose of one to two grams of amphotericin B is reached, followed by itraconazole 200 mg twice daily, with total duration of therapy generally of three to six months based upon overall clinical response.
	
	<u>Candidemia</u>
	• Candidemia should be treated with antifungal agents, selecting one of the following agents: fluconazole, an amphotericin B formulation, an echinocandin, voriconazole, or the combination regimen of fluconazole and amphotericin B.
	• For patients who are clinically stable and have not recently received azole therapy, the following are recommended:
	  o Fluconazole (400 mg/day or ~6 mg/kg/day) OR
	  o Caspofungin (70 mg loading dose day one, then 50 mg/day) OR
	  o Micafungin (100 mg/day) OR
	  o Anidulafungin (200 mg on day one, then 100 mg/day).
	• For patients who are clinically unstable and for whom identification of the *Candida* species in the blood is unknown, there is no definitive recommendation. Several options are available and include:
	  o Amphotericin B deoxycholate (0.6 to 1.0 mg/kg/day) or a lipid formulation of amphotericin B (three to five mg/kg/day) OR
	  o High-dose fluconazole (800 mg/kg/day or ~12 mg/kg/day) OR
	  o Caspofungin (70 mg loading dose day one, then 50 mg/day) OR
	  o Micafungin (100 mg/day) OR
	  o Anidulafungin (200 mg on day one, then 100 mg/day) OR
	  o Voriconazole (six mg/kg every 12 hours for two doses, then three mg/kg every 12 hours) OR
	  o A combination regimen with fluconazole (800 mg/day) and amphotericin B (0.6 to 1.0 mg/kg/day, for the first five to six days)
	• For *Candida albicans* and also possibly *Candida tropicalis*, the drugs of choice are fluconazole (400 mg/day), amphotericin B (0.6 to 1.0 mg/kg/day), and an echinocandin.
	• For *Candida parapsilosis*, the drugs of choice are fluconazole (400 mg/day) or amphotericin B (0.6 to 1.0 mg/kg/day).
	• For *Candida glabrata*, the drugs of choice are an echinocandin or amphotericin B. High-dose fluconazole (800 mg/day) may be a suitable alternative.
	• For *Candida krusei*, the drugs of choice are an echinocandin or amphotericin B.
	• For *Candida lusitaniae*, fluconazole is the preferred therapy.
	• Lipid formulations of amphotericin B are usually indicated for patients intolerant of, or refractory to, conventional antifungal therapy.
	
	<u>Other Fungi</u>
	• In patients with zygomycosis, lipid formulations of amphotericin B are recommended at five mg/kg/day or amphotericin B deoxycholate at 0.7 to 1.0 mg/kg/day.
	• In patients who are intolerant of, or refractory to, amphotericin B,

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	posaconazole 200 mg orally four times per day is recommended.
Infectious Diseases Society of America: **Clinical Practice Guidelines for the Management of Candidiasis (2009)**[5]	<u>Candidemia in non-neutropenic patients</u> • Fluconazole or an echinocandin (caspofungin, micafungin or anidulafungin) is recommended as initial therapy for most adult patients. An echinocandin is recommended for patients with moderately severe to severe illness or for patients who have had recent azole exposure. Fluconazole is recommended for patients who are less critically ill and who have had no recent azole exposure. The same therapeutic approach is advised for children, with attention to differences in dosing regimens. • Transition from an echinocandin to fluconazole is recommended for patients who have isolates that are likely to be susceptible to fluconazole (e.g., *Candida albicans*) and who are clinically stable. • For infection due to *Candida glabrata,* an echinocandin is preferred. Transition to fluconazole or voriconazole therapy is not recommended without confirmation of isolate susceptibility. For patients who have initially received fluconazole or voriconazole, are clinically improved, and whose follow-up culture results are negative, continuing use of an azole to completion of therapy is reasonable. • For infection due to *Candida parapsilosis,* treatment with fluconazole is recommended. For patients who have initially received an echinocandin, are clinically improved, and whose follow-up culture results are negative, continuing use of an echinocandin is reasonable. • Amphotericin B deoxycholate or a lipid formulation of amphotericin B are alternatives if there is intolerance to or limited availability of other antifungals. Transition from amphotericin B deoxycholate or lipid formulation of amphotericin B to fluconazole is recommended for patients who have isolates that are likely to be susceptible to fluconazole (e.g., *Candida albicans*) and who are clinically stable. • Voriconazole is effective for candidemia, but it offers little advantage over fluconazole and is recommended as step-down oral therapy for selected cases of candidiasis due to *Candida krusei* or voriconazole-susceptible *Candida glabrata*. <u>Candidemia in neutropenic patients</u> • An echinocandin (caspofungin, micafungin or anidulafungin) or lipid formulation of amphotericin B is recommended for most patients. • For patients who are less critically ill and who have no recent azole exposure, fluconazole is a reasonable alternative. Voriconazole can be used in situations in which additional mold coverage is desired. • For infections due to *Candida glabrata,* an echinocandin is preferred. Lipid formulations of amphotericin B are an alternative treatment option. For patients who were already receiving voriconazole or fluconazole, are clinically improved, and whose follow-up culture results are negative, continuing use of the azole to completion of therapy is reasonable. • For infections due to *Candida parapsilosis*, fluconazole or lipid formulation of amphotericin B is preferred as initial therapy. If the patient is receiving an echinocandin, is clinically stable, and follow-up culture results are negative, continuing the echinocandin until completion of therapy is reasonable. For infections due to *Candida krusei*, an echinocandin, lipid formulation of amphotericin B, or voriconazole is recommended. <u>Empirical treatment for suspected invasive candidiasis in non-neutropenic patients</u>

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	• Empirical therapy for suspected candidiasis in non-neutropenic patients is similar to that for proven candidiasis. Fluconazole, caspofungin, anidulafungin, or micafungin is recommended as initial therapy. An echinocandin is preferred for patients who have had recent azole exposure, whose illness is moderately severe or severe, or who are at high risk of infection due to *Candida glabrata* or *Candida krusei*. • Amphotericin B deoxycholate or a lipid formulation of amphotericin B are alternatives if there is intolerance to other antifungals or limited availability of other antifungals. <u>Empirical treatment for suspected invasive candidiasis in neutropenic patients</u> • Lipid formulations of amphotericin B, caspofungin, or voriconazole are recommended. • Fluconazole and itraconazole are alternative agents. • Azoles should not be used for empirical therapy in patients who have received an azole for prophylaxis. <u>Chronic disseminated candidiasis</u> • Fluconazole is recommended for clinically stable patients. Lipid formulation of amphotericin B or amphotericin B deoxycholate can be used to treat acutely ill patients or patients with refractory disease. Induction therapy with amphotericin B for one to two weeks, followed by oral fluconazole is also recommended. • Anidulafungin, micafungin, or caspofungin are alternatives for initial therapy, followed by oral fluconazole when clinically appropriate. • Therapy should be continued for weeks to months, until calcification occurs or lesions resolve. Premature discontinuation of antifungal therapy can lead to recurrent infection. • Patients with chronic disseminated candidiasis who require ongoing chemotherapy or undergo stem cell transplantation should continue to receive antifungal therapy throughout the period of high risk to prevent relapse. <u>Treatment for neonatal candidiasis</u> • Amphotericin B deoxycholate is recommended for neonates with disseminated candidiasis. If urinary tract involvement is excluded, lipid formulation of amphotericin B can be used. Fluconazole is a reasonable alternative. The recommended length of therapy is three weeks. • Echinocandins should be used with caution and are generally limited to situations in which resistance or toxicity precludes the use of fluconazole or amphotericin B deoxycholate. • In nurseries with high rates of invasive candidiasis, fluconazole prophylaxis may be considered in neonates whose birth weight is <1000 grams. Antifungal drug resistance, drug-related toxicity, and neurodevelopmental outcomes should be observed. <u>Osteoarticular *Candida* infections</u> • For osteomyelitis, fluconazole at a dosage of 400 mg daily for six to 12 months or lipid formulation of amphotericin B at a dosage of three to five mg/kg/day for at least two weeks, followed by fluconazole at a dosage of 400 mg daily for six to 12 months is recommended. Alternatives include an echinocandin or amphotericin B deoxycholate

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	at a dosage of 0.5 to 1.0 mg/kg/day for at least two weeks, followed by fluconazole at a dosage of 400 mg daily for six to 12 months. • For septic arthritis, treatment for at least six weeks with fluconazole at a dosage of 400 mg daily or lipid formulation of amphotericin B at a dosage of three to five mg/kg/day for at least two weeks, followed by fluconazole at a dosage of 400 mg daily is recommended. Alternatives include an echinocandin or amphotericin B deoxycholate at a dosage of 0.5 to 1.0 mg/kg/day for at least two weeks, followed by fluconazole at a dosage of 400 mg daily for the remainder of therapy. • For infection involving a prosthetic device, device removal is recommended for most cases. Therapy for at least six weeks with the above dosages of fluconazole, lipid formulation of amphotericin B, an echinocandin, or amphotericin B deoxycholate is recommended. If the device cannot be removed, chronic suppression with fluconazole is recommended. <u>Central nervous system candidiasis</u> • Lipid formulation of amphotericin B with or without flucytosine is recommended for the initial several weeks of treatment. • Fluconazole is recommended as step-down therapy after the patient responds to initial treatment with lipid formulation of amphotericin B and flucytosine. Therapy should continue until all signs and symptoms, cerebrospinal fluid abnormalities, and radiologic abnormalities have resolved. <u>*Candida* endophthalmitis</u> • Amphotericin B deoxycholate combined with flucytosine is recommended for advancing lesions or lesions threatening the macula. Fluconazole is an acceptable alternative for less severe endophthalmitis. Lipid formulation of amphotericin B, voriconazole, or an echinocandin can be used to treat patients who are intolerant of or experiencing treatment failure with amphotericin B deoxycholate in combination with flucytosine or fluconazole. • The recommended duration of therapy is at least four to six weeks and is determined by the stabilization or resolution of lesions as documented by repeated ophthalmological examinations. <u>Cardiovascular *Candida* infections</u> • For native valve endocarditis, lipid formulation of amphotericin B with or without flucytosine is recommended. Alternatives include amphotericin B deoxycholate with or without flucytosine or an echinocandin (caspofungin or anidulafungin). Step-down therapy to fluconazole should be considered among patients with susceptible *Candida* isolates who have demonstrated clinical stability and clearance of *Candida* from the bloodstream. Valve replacement is recommended, and treatment should continue for at least six weeks after valve replacement and should continue for a longer duration in patients with perivalvular abscesses and other complications. • For patients who cannot undergo valve replacement, long-term suppression with fluconazole is recommended. • For prosthetic valve endocarditis, the recommendations above apply, and suppressive therapy should be indefinite if valve replacement is not possible. • For pericarditis, lipid formulation of amphotericin B, amphotericin B deoxycholate, an echinocandin, or fluconazole for as long as several months, in combination with either a pericardial window or

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	pericardiectomy, is recommended. Step-down therapy to fluconazole should be considered for patients who have initially responded to amphotericin B or an echinocandin and who are clinically stable. • For myocarditis, treatment as for endocarditis (as stated above) is recommended. • For suppurative thrombophlebitis, catheter removal and incision and drainage or resection of the vein, if feasible, is recommended. Lipid formulation of amphotericin B, amphotericin B deoxycholate, fluconazole, or an echinocandin for at least two weeks after candidemia has cleared is recommended. Step-down therapy to fluconazole should be considered for patients who have initially responded to amphotericin B or an echinocandin and who are clinically stable. Resolution of the thrombus can be used as evidence to discontinue antifungal therapy if clinical and culture data are supportive. • For pacemaker and implantable cardiac defibrillator wire infections, removal of the entire device and systemic antifungal therapy with lipid formulation of amphotericin B with or without flucytosine, amphotericin B deoxycholate with or without flucytosine, or an echinocandin is recommended. Step-down therapy to fluconazole should be considered for patients with susceptible *Candida* isolates who have demonstrated clinical stability and clearance of *Candida* from the bloodstream. For infections limited to generators and/or pockets, four weeks of antifungal therapy after removal of the device is recommended. For pacemaker and implantable cardiac defibrillator wire infections, at least six weeks of antifungal therapy after wire removal is recommended. • For ventricular assist devices that cannot be removed, treatment with lipid formulation of amphotericin B, amphotericin B deoxycholate, or an echinocandin is recommended. After candidemia has cleared and the patient has responded clinically, fluconazole is recommended as step-down therapy. Chronic suppressive therapy with fluconazole is warranted until the device is removed. <u>Esophageal candidiasis</u> • Systemic antifungal therapy is always required. Oral fluconazole for 14 to 21 days is recommended. Intravenous fluconazole, amphotericin B deoxycholate, or an echinocandin should be used for patients who cannot tolerate oral therapy. A diagnostic trial of antifungal therapy is appropriate before performing an endoscopic examination. • For fluconazole-refractory disease, itraconazole solution, posaconazole suspension, or voriconazole (administered intravenously or orally) for 14 to 21 days is recommended. Micafungin, anidulafungin or amphotericin B deoxycholate are acceptable alternatives. • Suppressive therapy with fluconazole is recommended for recurrent infections. • In patients with acquired immunodeficiency syndrome, treatment with highly active antiretroviral therapy is recommended to reduce recurrent infections. <u>Oropharyngeal candidiasis</u> • For mild disease, clotrimazole troches, nystatin suspension, or nystatin pastilles for seven to 14 days is recommended. • For moderate to severe disease, oral fluconazole for seven to 14 days is recommended. • For fluconazole-refractory disease, either itraconazole solution or

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	posaconazole suspension for up to 28 days is recommended. Voriconazole or amphotericin B deoxycholate is recommended when treatment with other agents has failed. Intravenous echinocandin or amphotericin B deoxycholate can be used in treating patients with refractory disease. • Chronic suppressive therapy is usually unnecessary for patients with human immunodeficiency virus infection. If suppressive therapy is required, fluconazole three times weekly is recommended. Treatment with highly active antiretroviral therapy is recommended to reduce recurrent infections. • For denture-related candidiasis, disinfection of the denture, in addition to antifungal therapy, is recommended. <u>Antifungal prophylaxis for solid-organ transplant recipients, patients hospitalized in intensive care units, neutropenic patients receiving chemotherapy, and stem cell transplant recipients at risk of candidiasis</u> • For solid-organ transplant recipients, fluconazole or liposomal amphotericin B is recommended as postoperative antifungal prophylaxis for liver, pancreas, and small bowel transplant recipients at high risk of candidiasis. • For patients hospitalized in the intensive care unit, fluconazole is recommended for high-risk patients in adult units that have a high incidence of invasive candidiasis. • For patients with chemotherapy-induced neutropenia, fluconazole, posaconazole, or caspofungin is recommended during induction chemotherapy for the duration of neutropenia. Oral itraconazole is an effective alternative, but it offers little advantage over other agents and is less well tolerated. • For stem cell transplant recipients with neutropenia, fluconazole, posaconazole, or micafungin is recommended during the period of risk of neutropenia. <u>Urinary tract infections – asymptomatic candiduria</u> • Treatment is not recommended unless the patient belongs to a group at high risk of dissemination. Elimination of predisposing factors often results in resolution of candiduria. • High-risk patients include neutropenic patients, infants with low birth weight, and patients who will undergo urologic manipulations. Neutropenic patients and neonates should be managed as described for invasive candidiasis. For those patients undergoing urologic procedures, fluconazole or amphotericin B deoxycholate for several days before and after the procedure is recommended. <u>Urinary tract infections – symptomatic candiduria</u> • For candiduria with suspected disseminated candidiasis, treatment as described for candidemia is recommended. • For cystitis due to a fluconazole-susceptible *Candida* species, oral fluconazole for two weeks is recommended. For fluconazole-resistant organisms, amphotericin B deoxycholate for one to seven days or oral flucytosine for seven to 10 days are alternatives. Amphotericin B deoxycholate bladder irrigation is generally not recommended but may be useful for treatment of patients with fluconazole-resistant *Candida* species, especially *Candida glabrata.* • For pyelonephritis due to fluconazole-susceptible organisms, oral fluconazole daily for two weeks is recommended. For patients with fluconazole-resistant *Candida* strains, especially *Candida glabrata*,

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	alternatives include amphotericin B deoxycholate with or without flucytosine or flucytosine alone for two weeks. • For fungus balls, surgical intervention is strongly recommended in non-neonates. Fluconazole is recommended. Amphotericin B deoxycholate with or without flucytosine is an alternative. If access to the renal collecting system is available, an adjunct to systemic therapy is irrigation with amphotericin B deoxycholate. Treatment duration should be until symptoms have resolved and urine cultures no longer yield *Candida* species. <u>Vulvovaginal candidiasis</u> • Several topical antifungal agents are effective therapy for vulvovaginal candidiasis, and no agent is clearly more effective than another. • A single 150 mg dose of fluconazole is recommended for the treatment of uncomplicated *Candida* vulvovaginal candidiasis. • For recurring *Candida* vulvovaginal candidiasis, 10 to 14 days of induction therapy with a topical or oral azole, followed by fluconazole once per week for six months, is recommended.

Infectious Diseases Society of America: **Clinical Practice Guidelines for the Management of Cryptococcal Disease (2010)**[6]
 	
Reviewed and deemed current as of April 2013
	<u>Cryptococcal meningoencephalitis (human immunodeficiency virus-infected individuals)</u>
	• Primary therapy: induction and consolidation:
	  o Amphotericin B deoxycholate (0.7 to 1.0 mg/kg per day IV) plus flucytosine (100 mg/kg/day orally in four divided doses; IV formulations may be used in severe cases and in those without oral intake where the preparation is available) for at least two weeks, followed by fluconazole (400 mg [six mg/kg] per day orally) for a minimum of eight weeks.
	  o Lipid formulations of amphotericin B, including liposomal amphotericin B (three to four mg/kg/day IV) and amphotericin B lipid complex (five mg/kg/day IV) for at least two weeks, could be substituted for amphotericin B deoxycholate among patients with or predisposed to renal dysfunction.
	• Alternative regimens for induction and consolidation (listed in order of highest recommendation top to bottom):
	  o Amphotericin B deoxycholate (0.7 to 1.0 mg/kg/day IV), liposomal amphotericin B (three to four mg/kg/day IV), or amphotericin B lipid complex (5 mg/kg/day IV) for four to six weeks. Liposomal amphotericin B has been given safely at six mg/kg/day IV in cryptococcal meningoencephalitis and could be considered in the event of treatment failure or high–fungal burden disease.
	  o Amphotericin B deoxycholate (0.7 mg/kg/day IV) plus fluconazole (800 mg/day orally) for two weeks, followed by fluconazole (800 mg/day orally) for a minimum of eight weeks.
	  o Fluconazole (≥800 mg/day orally; 1200 mg/day is favored) plus flucytosine (100 mg/kg/day orally) for six weeks.
	  o Fluconazole (800 to 2000 mg/day orally) for 10 to 12 weeks; a dosage of ≥1200 mg/day is encouraged if fluconazole alone is used.
	  o Itraconazole (200 mg twice/day orally) for 10 to 12 weeks, although use of this agent is discouraged.
	
	<u>Non-meningeal, pulmonary cryptococcosis (immunosuppressed):</u>
	• For mild-to-moderate symptoms, absence of diffuse pulmonary

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	infiltrates, absence of severe immunosuppression, and negative results of a diagnostic evaluation for dissemination, use fluconazole (400 mg [six mg/kg] per day orally) for six to 12 months. • In human immunodeficiency virus-infected patients who are receiving highly active antiretroviral therapy with a CD4 cell count >100 cells/µL and a cryptococcal antigen titer that is ≤1:512 and/or not increasing, consider stopping maintenance fluconazole after one year of treatment. <u>Cryptococcal meningoencephalitis (non-human immunodeficiency virus-infected, non-transplant hosts)</u> • Amphotericin B deoxycholate (0.7 to 1.0 mg/kg/day IV) plus flucytosine (100 mg/kg/day orally in four divided doses) for at least four weeks for induction therapy. The four-week induction therapy is reserved for persons with meningoencephalitis without neurological complications and cerebrospinal fluid yeast culture results that are negative after two weeks of treatment. For amphotericin B deoxycholate toxicity issues, lipid formulations of amphotericin B may be substituted in the second two weeks. In patients with neurological complications, consider extending induction therapy for a total of six weeks, and lipid formulations of amphotericin B may be given for the last four weeks of the prolonged induction period. Then, start consolidation with fluconazole (400 mg per day) for eight weeks. • If patient is amphotericin B deoxycholate intolerant, substitute liposomal amphotericin B (three to four mg/kg/day IV) or amphotericin B lipid complex (five mg/kg/day IV). • If flucytosine is not given or treatment is interrupted, consider lengthening amphotericin B deoxycholate or lipid formulations of amphotericin B induction therapy for at least two weeks. • In patients at low risk for therapeutic failure, consider induction therapy with combination of amphotericin B deoxycholate plus flucytosine for only two weeks, followed by consolidation with fluconazole (800 mg [12 mg/kg] per day orally) for eight weeks. • After induction and consolidation therapy, use maintenance therapy with fluconazole (200 mg [three mg/kg] per day orally) for six to 12 months. <u>Non-meningeal, pulmonary cryptococcosis (non-immunosuppressed):</u> • For mild-to-moderate symptoms, administer fluconazole (400 mg per day orally) for six to 12 months; persistently positive serum cryptococcal antigen titers are not criteria for continuance of therapy. • For severe disease, treat similarly to central nervous system disease. • Itraconazole (200 mg twice/day orally), voriconazole (200 mg twice/day orally), and posaconazole (400 mg twice/day orally) are acceptable alternatives if fluconazole is unavailable or contraindicated. <u>Organ transplant recipients</u> • For central nervous system disease, liposomal amphotericin B (three to four mg/kg/day IV) or amphotericin B lipid complex (five mg/kg/day IV) plus flucytosine (100 mg/kg/day in four divided doses) for at least two weeks for the induction regimen, followed by fluconazole (400 to 800 mg [six to 12 mg/kg] per day orally) for eight weeks and by fluconazole (200 to 400 mg/day orally) for six to 12 months. If induction therapy does not include flucytosine, consider lipid formulations of amphotericin B for at least four to six weeks of induction therapy, and liposomal amphotericin B (six mg/kg/day)

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	might be considered in high–fungal burden disease or relapse. • For mild-to-moderate non-central nervous system disease, fluconazole (400 mg [six mg/kg] per day) for six to 12 months. • For moderately severe–to-severe non-central nervous system or disseminated disease without central nervous system involvement, treat the same as central nervous system disease. • In the absence of any clinical evidence of extrapulmonary or disseminated cryptococcosis, severe pulmonary disease is treated the same as central nervous system disease. For mild-to-moderate symptoms without diffuse pulmonary infiltrates, use fluconazole (400 mg [six mg/kg] per day) for six to 12 months. • Fluconazole maintenance therapy should be continued for at least six to 12 months. <u>Cryptococcal meningoencephalitis (management of complications-persistence)</u> • Reinstitute induction phase of primary therapy for longer course (four to 10 weeks). • Consider increasing the dose if the initial dosage of induction therapy was ≤0.7 mg/kg IV of amphotericin B deoxycholate per day or ≤3 mg/kg of lipid formulations of amphotericin B per day, up to one mg/kg IV of amphotericin B deoxycholate per day or six mg/kg of liposomal amphotericin B per day; in general, combination therapy is recommended. • If the patient is polyene intolerant, consider fluconazole (≥800 mg/day orally) plus flucytosine (100 mg/kg/day orally in four divided doses). • If patient is flucytosine intolerant, consider amphotericin B deoxycholate (0.7 mg/kg/day IV) plus fluconazole (800 mg [12 mg/kg] per day orally). • Use of intrathecal or intraventricular amphotericin B deoxycholate is generally discouraged and is rarely necessary. <u>Cerebral cryptococcomas</u> • Induction therapy with amphotericin B deoxycholate (0.7 to 1.0 mg/kg/day IV), liposomal amphotericin B (three to four mg/kg/day IV), or amphotericin B lipid complex (5 mg/kg/day IV) plus flucytosine (100 mg/kg/day orally in four divided doses) for at least six weeks. • Consolidation and maintenance therapy with fluconazole (400 to 800 mg/day orally) for 6 to 18 months. <u>Non-meningeal, non-pulmonary cryptococcosis</u> • If central nervous system disease is ruled out, fungemia is not present, infection occurs at single site, and there are no immunosuppressive risk factors, consider fluconazole (400 mg [six mg/kg] per day orally) for six to 12 months.
National Institutes of Health, the Centers for Disease Control and Prevention, and the Human Immunodeficiency Virus Medicine Association of the Infectious Diseases Society of America: **Guidelines for Prevention and Treatment of Opportunistic**	<u>Aspergillosis</u> • Voriconazole is the drug of choice but should be used cautiously with human immunodeficiency virus protease inhibitors and efavirenz. Amphotericin B deoxycholate at 1 mg/kg daily or lipid-formulation amphotericin B at 5 mg/kg daily are alternatives, as is caspofungin at 50 mg daily and posaconazole. • Other echinocandins, such as micafungin and anidulafungin, are reasonable alternatives. • For treatment failure (if voriconazole was used initially) substitution

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Infections in Human Immunodeficiency Virus - Infected Adults and Adolescents (2013)[7]	with amphotericin B, posaconazole, or echinocandins might be considered; the amphotericin B or echinocandins would be rational for those who began therapy with voriconazole or posaconazole. Candidiasis (mucocutaneous) • Oral fluconazole is as effective as topical therapy for oropharyngeal candidiasis and is considered the drug of choice. Initial episodes of oropharyngeal candidiasis can be adequately treated with topical therapy, including clotrimazole troches, nystatin suspension or pastilles, or miconazole mucoadhesive tablets. Itraconazole oral solution for seven to 14 days is as effective as oral fluconazole but less well tolerated. Posaconazole oral solution is also as effective as fluconazole and is generally better tolerated than itraconazole. Intravenous amphotericin B is usually effective and can be used among patients with refractory disease. Both conventional amphotericin B and lipid complex and liposomal amphotericin B have been used. • Systemic antifungals are required for effective treatment of esophageal candidiasis. A 14 to 21-day course of either fluconazole (oral or intravenous) or oral itraconazole solution is highly effective. Oral ketoconazole or itraconazole capsules are less effective than fluconazole because of variable absorption. Although intravenous caspofungin or intravenous voriconazole are effective in treating esophageal candidiasis among human immunodeficiency virus - infected patients, oral or intravenous fluconazole remain the preferred therapies. Azole-refractory esophageal candidiasis can be treated with posaconazole, amphotericin B, anidulafungin, caspofungin, micafungin, or voriconazole. • Vulvovaginal candidiasis in human immunodeficiency virus -infected women is usually uncomplicated (90%) and responds readily to short-course oral or topical treatment with any of several therapies, including oral fluconazole, topical azoles, and itraconazole oral solution. Severe or recurrent episodes of vaginitis require oral fluconazole or topical antifungal therapy for ≥7 days. Coccidioidomycosis • For patients with clinically mild infection, such as focal pneumonia or a positive coccidioidal serologic test alone, initial therapy with a triazole antifungal is appropriate. • For patients with either diffuse pulmonary involvement or severely ill patients with extrathoracic disseminated disease, amphotericin B is the preferred initial therapy. Therapy with amphotericin B should continue until clinical improvement is observed. Some specialists would use a triazole antifungal concurrently with amphotericin B and continue the triazole once amphotericin B is stopped. Cryptococcosis • The recommended initial standard treatment is amphotericin B combined with flucytosine for ≥2 weeks for those with normal renal function. • The combination of amphotericin B with fluconazole is less effective than amphotericin B combined with flucytosine in terms of clearing *Cryptococcus* from the cerebrospinal fluid but is better than amphotericin B alone. • Fluconazole combined with flucytosine is an alternative to amphotericin B plus flucytosine, but is less effective than amphotericin B and is recommended only for persons unable to tolerate or

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	unresponsive to standard treatment. • After at least a two-week period of successful induction therapy, amphotericin B and flucytosine may be discontinued and follow-up therapy initiated with fluconazole. This should continue for eight weeks. Itraconazole is an acceptable though less effective alternative. • The optimal therapy for those with treatment failure is not established. For those initially treated with fluconazole, therapy should be changed to amphotericin B, with or without flucytosine, and continued until a clinical response occurs. Liposomal amphotericin B may have improved efficacy over the deoxycholate formulation and should be considered in treatment failures. Higher doses of fluconazole in combination with flucytosine might also be useful. <u>Cryptosporidiosis</u> • In the setting of severe immunosuppression, antiretroviral therapy with immune restoration to a CD4+ count >100 cells/µL leads to resolution of clinical cryptosporidiosis and is the mainstay of treatment. • All patients with cryptosporidiosis should be offered antiretroviral therapy as part of the initial management of their infection. • Management should include symptomatic treatment of diarrhea. Rehydration and repletion of electrolyte losses by either the oral or intravenous route are important. Severe diarrhea can exceed >10 L/day among patients with acquired immunodeficiency syndrome, often requiring intensive support. Aggressive efforts at oral rehydration should be made with oral rehydration solutions. <u>Prevention of Cytomegalovirus</u> • Cytomegalovirus end-organ disease is best prevented by using antiretroviral therapy to maintain the CD4+ count >100 cells/µL. • Although oral valganciclovir would likely prevent the occurrence of cytomegalovirus retinitis in patients with CD4+ counts <50 cells/µL, such therapy is not generally recommended because of the potential to induce cytomegalovirus resistance, the utility of treating disease when it occurs, and the lack of demonstrated survival advantage. <u>Treatment of Cytomegalovirus disease</u> • Oral valganciclovir, intravenous ganciclovir, intravenous ganciclovir followed by oral valganciclovir, intravenous foscarnet, and intravenous cidofovir are all effective treatments for cytomegalovirus retinitis. • The ganciclovir implant, a surgically-implanted reservoir of ganciclovir, which lasts approximately six months, also is very effective but it no longer is being manufactured. In its absence, some clinicians will use intravitreal injections of ganciclovir or foscarnet in conjunction with oral valganciclovir, at least initially, to provide immediate high intraocular levels of drug and presumably faster control of the retinitis. • Systemic therapy has been shown to reduce morbidity in the contralateral eye. This should be considered when choosing between the oral, intravenous, and local options. • The choice of initial therapy for cytomegalovirus retinitis should be individualized based on the location and severity of the lesion(s), the level of underlying immune suppression, and other factors such as concomitant medications and ability to adhere to treatment. • No one regimen has been proven in a clinical trial to have greater efficacy in terms of protecting vision, and thus clinical judgment must

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	be used when choosing a regimen. • In studies conducted in the pre-antiretroviral therapy era, ganciclovir intraocular implant plus oral ganciclovir was superior to once-daily intravenous ganciclovir for treatment of cytomegalovirus retinitis; however, the implant is no longer manufactured. Assuming that this observation can be extended to other combinations of systemically and locally administered drugs, human immunodeficiency virus-specialists often recommend intravitreal ganciclovir or foscarnet injections plus oral valganciclovir as the preferred initial therapy for patients with immediate sight-threatening lesions. Intravitreal injections deliver high concentrations of the drug to the target organ immediately while steady-state concentrations in the eye are achieved with systemically delivered medications. For patients with small peripheral lesions, oral valganciclovir alone often is adequate. • After induction therapy, secondary prophylaxis (i.e., chronic maintenance therapy) should be continued until immune reconstitution occurs as a result of antiretroviral therapy. Regimens demonstrated to be effective for chronic suppression in randomized, controlled clinical trials include parenteral ganciclovir, oral valganciclovir, parenteral foscarnet, combined parenteral ganciclovir and foscarnet, and parenteral cidofovir. <u>Management of Cytomegalovirus retinitis treatment failures</u> • When patients relapse while receiving maintenance therapy, induction with the same drug followed by reinstitution of maintenance therapy can control the retinitis, although for progressively shorter periods of time with each relapse. • Ganciclovir and foscarnet in combination appear to be superior in efficacy to either agent alone and should be considered for patients whose disease does not respond to single-drug therapy, and for patients with multiple relapses of retinitis. This drug combination, however, is associated with substantial toxicity. <u>Treatment of Hepatitis B Virus coinfection in patients not receiving antiretroviral therapy</u> • For patients with CD4+ counts >350 cells/µL who are not receiving antiretroviral therapy but meet criteria for hepatitis B virus treatment, adefovir or peginterferon alfa-2a monotherapy for 48 weeks might be considered, with close monitoring of hepatitis B virus deoxyribonucleic acid levels and follow-up to evaluate for hepatitis B e antigen seroconversion. However, early initiation of antiretroviral therapy should also be considered for human immunodeficiency virus/hepatitis B virus -coinfected persons with CD4+ counts >350 cells/µL. <u>Treatment of Hepatitis B Virus coinfection in patients who require antiretroviral therapy</u> • For human immunodeficiency virus-infected persons, some experts recommend combination therapy with two agents active against hepatitis B virus to reduce the risk of hepatitis B virus drug resistance; although, there are no results from controlled trials as yet to support this strategy. • Among patients infected with hepatitis B virus, hepatitis C virus, and human immunodeficiency virus, consideration of the need for antiretroviral therapy should be the first priority. If antiretroviral therapy is not required, interferon-based therapy, which suppresses

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	both hepatitis C virus and hepatitis B virus, should be considered. If interferon-based therapy for hepatitis C virus has failed, treatment of chronic hepatitis B with nucleoside or nucleotide analogs is recommended.
	
	Treatment of Hepatitis C coinfection
	• Antiviral treatment for hepatitis C virus infection should be considered for all human immunodeficiency virus-infected persons with acute or chronic hepatitis C virus infection.
	• The combination of peginterferon alfa (PegIFN) plus ribavirin is the recommended backbone of therapy for HIV/HCV-co-infected patients regardless of HCV genotype.
	• Antiviral treatment with PegIFN is not recommended in patients with decompensated liver disease.
	• For HCV-genotype-1-infected patients who are not co-infected with HIV, a HCV NS3/4A protease inhibitor (PI), either boceprevir or telaprevir, in combination with PegIFN/ribavirin is recommended on the basis of large clinical trials demonstrating significantly higher SVR rates with an acceptable safety/tolerability profile compared to PegIFN/ribavirin alone.
	• For HIV/HCV co-infected patients, preliminary data from small, ongoing clinical trials of boceprevir or telaprevir plus PegIFN/ribavirin for the treatment of HCV genotype 1 infection in HIV/HCV co-infected patients demonstrate greater efficacy than PegIFN/ribavirin alone, with a safety and tolerability profile similar to that observed in HCV monoinfected patients treated with boceprevir or telaprevir plus PegIFN/ribavirin. Preliminary recommendations are as follows:
	  o PegIFN is recommended for use for all HCV genotypes
	  o Ribavirin is recommended for use with PegIFN for all HCV genotypes.
	  o Boceprevir is approved for use in combination with PegIFN/ribavirin in HCV-genotype-1-monoinfected-patients. For HIV/HCV-co-infected patients, the regimen being evaluated is PegIFN/ribavirin administered for four weeks (lead-in phase) followed by boceprevir 800 mg orally every 7 to 9 hours (with a light snack) added to PegIFN/ribavirin for an additional 44 weeks.
	  o Telaprevir is approved for use in combination with PegIFN/ribavirin in HCV-genotype-1-monoinfected-patients. Dosing regimens lasting 48 weeks are being evaluated.
	• Patients with contraindications to the use of ribavirin can be treated with peginterferon alfa (2a or 2b) monotherapy. However, substantially lower sustained viral response rates are expected in persons not receiving ribavirin. HCV PIs should not be administered without ribavirin because of the high likelihood of virologic failure.
	
	Treatment of herpes simplex virus disease
	• Orolabial lesions can be treated with oral valacyclovir, famciclovir, or acyclovir for five to 10 days.
	• Severe mucocutaneous herpes simplex virus lesions are best treated initially with intravenous acyclovir. Patients may be switched to oral therapy after the lesions have begun to regress. Therapy should be continued until the lesions have completely healed.
	• Genital herpes simplex virus infection should be treated with oral valacyclovir, famciclovir, or acyclovir for five to 14 days. Short-course therapy (one, two, or three days) should not be used in patients with

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	human immunodeficiency virus infection.
	• Most recurrences of genital herpes can be prevented by use of daily anti- herpes simplex virus therapy, and this is recommended for persons who have frequent or severe recurrences.
	• Suppressive therapy with oral acyclovir, valacyclovir, or famciclovir is effective in preventing recurrences. Suppressive therapy with valacyclovir should be 500 mg twice daily in human immunodeficiency virus -infected persons or twice-daily regimens with acyclovir or famciclovir should be used.
	
	<u>Management of herpes simplex virus treatment failure</u>
	• The treatment of choice for acyclovir-resistant herpes simplex virus is intravenous foscarnet. Topical trifluridine, cidofovir, and imiquimod also have been used successfully for lesions on external surfaces, although prolonged application for 21 to 28 days or longer might be required.
	
	<u>Histoplasmosis</u>
	• Patients with moderately severe to severe disseminated histoplasmosis should be treated with an intravenous lipid formulation of amphotericin B for ≥2 weeks or until they clinically improve followed by oral itraconazole (200 mg three times daily for three days and then 200 mg twice daily for a total of ≥12 months).
	• In patients with less severe disseminated histoplasmosis, oral itraconazole at 200 mg three times daily for three days followed by 200 mg twice daily is appropriate initial therapy.
	
	<u>Treatment of Isosporiasis (also known as Cystoisosporiasis)</u>
	  • Sulfamethoxazole-trimethoprim is the antimicrobial agent of choice for treatment of isosporiasis. It is the only agent whose use is supported by substantial published data and clinical experience. Therefore, potential alternative therapies should be reserved for patients with documented sulfa intolerance or in whom treatment fails. The traditional treatment regimen has been a 10-day course of Sulfamethoxazole-trimethoprim (800-160 mg) administered orally four times daily.
	  • Intravenous administration of Sulfamethoxazole-trimethoprim should be considered for patients with potential or documented malabsorption.
	  • Single-agent therapy with pyrimethamine has been used, with anecdotal success for treatment and prevention of isosporiasis. Pyrimethamine (50 to 75 mg/day) plus leucovorin (10 to 25 mg/day) to prevent myelosuppression may be an effective treatment alternative; it is the option for sulfa-intolerant patients.
	
	<u>Leishmaniasis</u>
	• Due to similar efficacy and a better toxicity profile, clinicians consider liposomal amphotericin B as the drug of choice for visceral leishmaniasis in human immunodeficiency virus-coinfected patients. The optimal amphotericin B dosage has not been determined.
	• Regimens with efficacy include conventional amphotericin B 0.5 to 1.0 mg/kg body weight/day intravenous to achieve a total dose of 1.5 to 2.0 g, or liposomal or lipid complex preparations of two to four mg/kg body weight administered on consecutive days or in an interrupted schedule (e.g., 4 mg/kg on Days 1 to 5, 10, 17, 24, 31, and 38) to achieve a total cumulative dose of 20 to 60 mg/kg body weight. A

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	higher daily dosage is recommended for liposomal or lipid complex preparations than for conventional amphotericin B. Preventing disseminated *Mycobacterium avium* complex disease • Human immunodeficiency virus-infected adults and adolescents should receive chemoprophylaxis against disseminated *Mycobacterium avium* complex disease if they have a CD4+ count <50 cells/µL. • Azithromycin or clarithromycin are the preferred prophylactic agents. • The combination of clarithromycin and rifabutin is no more effective than clarithromycin alone for chemoprophylaxis, is associated with a higher rate of adverse effects than either drug alone, and should not be used. • The combination of azithromycin with rifabutin is more effective than azithromycin alone; however, the additional cost, increased occurrence of adverse effects, potential for drug interactions, and absence of a survival difference compared to azithromycin alone do not warrant a routine recommendation for this regimen. • Azithromycin and clarithromycin also each confer protection against respiratory bacterial infections. • If azithromycin or clarithromycin cannot be tolerated, rifabutin is an alternative prophylactic agent for *Mycobacterium avium* complex disease, although drug interactions may make this agent difficult to use. • Primary *Mycobacterium avium* complex disease prophylaxis should be discontinued among adult and adolescent patients who have responded to antiretroviral therapy with an increase in CD4+ counts to >100 cells/µL for ≥3 months. Primary prophylaxis should be reintroduced if the CD4+ count decreases to <50 cells/µL. Treatment of disseminated *Mycobacterium avium* Complex Disease • Initial treatment of *Mycobacterium avium* complex disease should consist of two or more antimycobacterial drugs to prevent or delay the emergence of resistance. • Clarithromycin is the preferred first agent; however, azithromycin can be substituted for clarithromycin when drug interactions or clarithromycin intolerance preclude the use of clarithromycin. • Testing of *Mycobacterium avium* complex disease isolates for susceptibility to clarithromycin or azithromycin is recommended for all patients. Treatment of Penicilliosis marneffei • Penicilliosis is caused by the dimorphic fungus *Penicillium marneffei*, which is known to be endemic in Southeast Asia (especially Northern Thailand and Vietnam) and southern China. • The recommended treatment is liposomal amphotericin B, three to five mg/kg body weight/day intravenously for two weeks, followed by oral itraconazole, 400 mg/day for a subsequent duration of 10 weeks, followed by secondary prophylaxis. • Patients with mild disease can be initially treated with oral itraconazole 400 mg/day for eight weeks, followed by 200 mg/day for prevention of recurrence. • The alternative drug for primary treatment in the hospital is intravenous voriconazole, 6 mg/kg every 12 hours on day one and then 4 mg/kg every 12 hours for at least three days, followed by oral voriconazole, 200 mg twice daily for a maximum of 12

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	weeks. • Patients with mild disease can be initially treated with oral voriconazole 400 mg twice a day on day one, and then 200 mg twice daily for 12 weeks. The optimal dose of voriconazole for secondary prophylaxis after 12 weeks has not been studied. Primary prophylaxis of *Pneumocystis (carinii) jiroveci* pneumonia • Sulfamethoxazole-trimethoprim is the recommended prophylactic agent. One double-strength tablet daily is the preferred regimen. However, one single-strength tablet daily is also effective and might be better tolerated than one double-strength tablet daily. One double-strength tablet three times weekly is also effective. Sulfamethoxazole-trimethoprim at a dose of one double-strength tablet daily confers cross-protection against toxoplasmosis and selected common respiratory bacterial infections. Lower doses of sulfamethoxazole-trimethoprim likely also confer such protection. • For patients who have an adverse reaction that is not life threatening, chemoprophylaxis with sulfamethoxazole-trimethoprim should be continued if clinically feasible; for those who have discontinued such therapy because of an adverse reaction, reinstituting sulfamethoxazole-trimethoprim should be strongly considered after the adverse event has resolved. Patients who have experienced adverse events, including fever and rash, might better tolerate reintroduction of the drug with a gradual increase in dose (i.e., desensitization), according to published regimens or reintroduction of sulfamethoxazole-trimethoprim at a reduced dose or frequency; as many as 70% of patients can tolerate such reinstitution of therapy. • If sulfamethoxazole-trimethoprim cannot be tolerated, alternative prophylactic regimens include dapsone, dapsone/pyrimethamine plus leucovorin, aerosolized pentamidine and atovaquone. • Primary *Pneumocystis (carinii) jiroveci* pneumonia prophylaxis should be discontinued for adult and adolescent patients who have responded to antiretroviral therapy with an increase in CD4+ counts to >200 cells/µL for >3 months. Prophylaxis should be reintroduced if the CD4+ count decreases to <200 cells/µL. Treatment of *Pneumocystis (carinii) jiroveci* pneumonia • Sulfamethoxazole-trimethoprim is the treatment of choice. The dose must be adjusted for abnormal renal function. Multiple randomized clinical trials indicate that sulfamethoxazole-trimethoprim is as effective as parenteral pentamidine and more effective than other regimens. Adding leucovorin to prevent myelosuppression during acute treatment is not recommended because of questionable efficacy and some evidence for a higher failure rate. Oral outpatient therapy of sulfamethoxazole-trimethoprim is highly effective among patients with mild-to-moderate disease. • Patients who have *Pneumocystis (carinii) jiroveci* despite sulfamethoxazole-trimethoprim prophylaxis are usually effectively treated with standard doses of sulfamethoxazole-trimethoprim. • Patients with documented or suspected *Pneumocystis (carinii) jiroveci* and moderate-to-severe disease, as defined by room air pO_2 <70 mm Hg or arterial-alveolar O_2 gradient >35 mm Hg, should receive adjunctive corticosteroids as early as possible, and certainly within 72 hours after starting specific *Pneumocystis (carinii) jiroveci* therapy. • The recommended duration of therapy for *Pneumocystis (carinii) jiroveci* is 21 days.

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	• Patients who have a history of *Pneumocystis (carinii) jiroveci* should be administered chemoprophylaxis for life (i.e., secondary prophylaxis or chronic maintenance therapy) with sulfamethoxazole-trimethoprim unless immune reconstitution occurs as a result of antiretroviral therapy. • Secondary prophylaxis should be discontinued for adult and adolescent patients whose CD4+ count has increased from <200 cells/µL to >200 cells/µL for >3 months as a result of antiretroviral therapy. Prophylaxis should be reintroduced if the CD4+ count decreases to <200 cells/µL. If *Pneumocystis (carinii) jiroveci* recurs at a CD4+ count of ≥200 cells/µL, lifelong prophylaxis should be administered. <u>Primary prophylaxis of *Toxoplasma* encephalitis</u> • The double-strength tablet daily dose of sulfamethoxazole-trimethoprim recommended as the preferred regimen for *Pneumocystis (carinii) jiroveci* prophylaxis is effective against *Toxoplasma* encephalitis as well and is therefore recommended. Sulfamethoxazole-trimethoprim, one double-strength tablet three times weekly, is an alternative. • If patients cannot tolerate sulfamethoxazole-trimethoprim, the recommended alternative is dapsone-pyrimethamine plus leucovorin, which is also effective against *Pneumocystis (carinii) jiroveci* pneumonia. • Atovaquone with or without pyrimethamine/leucovorin can also be considered. • Prophylactic monotherapy with dapsone, pyrimethamine, azithromycin, or clarithromycin cannot be recommended on the basis of available data. Aerosolized pentamidine does not protect against *Toxoplasma* encephalitis and is not recommended. • Prophylaxis against *Toxoplasma* encephalitis should be discontinued among adult and adolescent patients who have responded to antiretroviral therapy with an increase in CD4+ counts to >200 cells/µL for >3 months. Prophylaxis for *Toxoplasma* encephalitis should be reintroduced if the CD4+ count decreases to <100–200 cells/µL. <u>Treatment of *Toxoplasma* encephalitis</u> • The initial therapy of choice for *Toxoplasma* encephalitis consists of the combination of pyrimethamine plus sulfadiazine plus leucovorin. • The preferred alternative regimen for patients with *Toxoplasma* encephalitis who are unable to tolerate or who fail to respond to first-line therapy is pyrimethamine plus clindamycin plus leucovorin. • Sulfamethoxazole-trimethoprim was reported in a small randomized trial to be effective and better tolerated than pyrimethamine-sulfadiazine. On the basis of less in vitro activity and less experience with sulfamethoxazole-trimethoprim, treatment with this drug may be considered an option. • Acute therapy for *Toxoplasma* encephalitis should be continued for at least six weeks, if there is clinical and radiologic improvement. <u>Treatment of latent tuberculosis infection</u> • Human immunodeficiency virus-infected persons, regardless of age, should be treated for latent tuberculosis infection if they have no evidence of active tuberculosis and: o A positive diagnostic test for latent tuberculosis infection and

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	no prior history of treatment for active or latent tuberculosis. o A negative diagnostic test for latent tuberculosis infection but are close contacts of persons with infectious pulmonary tuberculosis. o A history of untreated or inadequately treated healed tuberculosis (i.e., old fibrotic lesions on chest radiography) regardless of diagnostic tests for latent tuberculosis infection. • Treatment options for latent tuberculosis infection include isoniazid daily or twice weekly for nine months. • Due to an increased risk of fatal and severe hepatotoxicity, a two-month regimen of daily rifampin and pyrazinamide is not recommended for latent tuberculosis infection treatment regardless of human immunodeficiency virus status. • Human immunodeficiency virus-infected persons receiving isoniazid should receive pyridoxine to minimize the risk of developing peripheral neuropathy. Alternatives for individuals who cannot take isoniazid or who have been exposed to a known isoniazid-resistant index case include either rifampin or rifabutin alone for four months. • For persons exposed to isoniazid- and/or rifampin-resistant tuberculosis, decisions to treat with one or two drugs other than isoniazid, rifampin, or rifabutin should be based on the relative risk of exposure to organisms broadly resistant to other antimycobacterial drugs and should be made in consultation with public health authorities. • Directly observed therapy should be used with intermittent dosing regimens when otherwise feasible to maximize regimen completion rates. • There is no evidence to suggest that latent tuberculosis infection treatment should be continued beyond the recommended duration in persons with human immunodeficiency virus infection. Therefore, latent tuberculosis infection treatment should be discontinued after completing the appropriate number of doses. <u>Treatment of active tuberculosis disease</u> • Recommendations for anti-tuberculosis treatment regimens in human immunodeficiency virus -infected adults follow the same principles as for adults without human immunodeficiency virus -infection. • Treatment of drug susceptible tuberculosis disease should include a six-month regimen with an initial phase of isoniazid, rifampin or rifabutin, pyrazinamide, and ethambutol administered for two months followed by isoniazid and rifampin (or rifabutin) for four additional months. • When drug-susceptibility testing confirms the absence of resistance to isoniazid, rifampin, and pyrazinamide, ethambutol may be discontinued before two months of treatment have been completed. • For patients with cavitary lung disease and cultures positive for *Mycobacterium tuberculosis* after completion of two months of therapy, treatment should be extended with isoniazid and rifampin for an additional three months for a total of nine months. • All human immunodeficiency virus-infected patients treated with isoniazid should receive pyridoxine supplementation. • For patients with extrapulmonary tuberculosis, a six- to nine-month regimen (two months of isoniazid, rifampin, pyrazinamide, and ethambutol followed by four to seven months of isoniazid and rifampin) is recommended.

Clinical Guideline	Recommendation(s)
	• Exceptions to the recommendation for a six- to nine-month regimen for extrapulmonary tuberculosis include central nervous system disease (tuberculoma or meningitis) and bone and joint tuberculosis, for which many experts recommend nine to 12 months. • Adjuvant corticosteroids should be added when treating central nervous system and pericardial disease. • Treatment with corticosteroids should be started intravenously as early as possible with change to oral therapy individualized according to clinical improvement. • Recommended corticosteroid regimens are dexamethasone 0.3 to 0.4 mg/kg tapered over six to eight weeks or prednisone 1 mg/kg for three weeks, then tapered for three to five weeks. <u>Treatment of varicella zoster virus disease</u> • For uncomplicated varicella, the preferred treatment options are valacyclovir (1 gram orally three times daily), or famciclovir (500 mg orally three times daily) for five to seven days. Oral acyclovir (20 mg/kg body weight up to a maximum dose of 800 mg five times daily) can be an alternative. • Prompt antiviral therapy should be instituted in all human immunodeficiency virus-seropositive patients whose herpes zoster is diagnosed within one week of rash onset (or any time before full crusting of lesions). The recommended treatment options for acute localized dermatomal herpes zoster in human immunodeficiency virus-infected patients are oral valacyclovir, famciclovir, or acyclovir (doses as above) for seven to 10 days, although longer durations of therapy should be considered if lesions resolve slowly. Valacyclovir or famciclovir are preferred because of their improved pharmacokinetic properties and simplified dosing schedule. • If cutaneous lesions are extensive or if visceral involvement is suspected, intravenous acyclovir should be initiated and continued until clinical improvement is evident. A switch from intravenous acyclovir to oral antiviral therapy (to complete a 10 to 14 day treatment course) is reasonable when formation of new cutaneous lesions has ceased and the signs and symptoms of visceral varicella zoster virus infection are clearly improving. • Optimal antiviral therapy for progressive outer retinal necrosis remains undefined. Specific treatment should include systemic therapy with at least one intravenous drug (selected from acyclovir, ganciclovir, foscarnet, and cidofovir) coupled with injections of at least one intravitreal drug (selected from ganciclovir and foscarnet). Treatment regimens for progressive outer retinal necrosis recommended by certain specialists include a combination of intravenous ganciclovir and/or foscarnet plus intravitreal injections of ganciclovir and/or foscarnet. The prognosis for visual preservation in involved eyes is poor, despite aggressive antiviral therapy. • Other infectious disease states mentioned within these guidelines note that the treatment guidelines for that disease state should be utilized. • The guideline specifies that detailed recommendations for the treatment of human herpesvirus-8 and associated malignancies are beyond the scope of these guidelines. • Other excluded infectious disease states offer no specific therapy or utilize medications not licensed in the United States.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the pyrimidines are noted in Table 4. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 4. FDA-Approved Indications for the Pyrimidines[1-3]

Indication	Flucytosine
Treatment of serious infections caused by susceptible strains of *Candida* and/or *Cryptococcus* in combination with amphotericin B	✔

IV. Pharmacokinetics

The pharmacokinetic parameters of the pyrimidines are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Pyrimidines[1-3]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Flucytosine	80 to 90	<4	Not reported	Renal (65 to 90)	3 to 8

V. Drug Interactions

No significant drug interactions have been reported with the pyrimidines.[1]

VI. Adverse Drug Events

The most common adverse drug events reported with the pyrimidines are listed in Table 6. The boxed warning for flucytosine is listed in Table 7.

Table 6. Adverse Drug Events (%) Reported with the Pyrimidines[1-3]

Adverse Events	Flucytosine
Cardiovascular System	
Cardiac arrest	✔
Chest pain	✔
Myocardial toxicity	✔
Ventricular dysfunction	✔
Central Nervous System	
Ataxia	✔
Confusion	✔
Dizziness	✔
Drowsiness	✔
Fatigue	✔
Hallucinations	✔
Headache	✔
Paresthesia	✔
Parkinsonism	✔
Peripheral neuropathy	✔
Psychosis	✔

Adverse Events	Flucytosine
Pyrexia	✔
Sedation	✔
Seizure	✔
Vertigo	✔
Dermatological	
Photosensitivity	✔
Pruritus	✔
Rash	✔
Toxic epidermal necrolysis	✔
Urticaria	✔
Gastrointestinal	
Abdominal pain	✔
Anorexia	✔
Diarrhea	✔
Dry mouth	✔
Duodenal ulcer	✔
Gastrointestinal hemorrhage	✔
Nausea	✔
Ulcerative colitis	✔
Vomiting	✔
Genitourinary	
Azotemia	✔
Crystalluria	✔
Renal failure	✔
Hematological	
Agranulocytosis	✔
Anemia	✔
Aplastic anemia	✔
Eosinophilia	✔
Leukopenia	✔
Pancytopenia	✔
Thrombocytopenia	✔
Hepatic	
Acute hepatic injury	✔
Hepatic dysfunction	✔
Jaundice	✔
Laboratory Test Abnormalities	
Bilirubin increased	✔
BUN increased	✔
Hypoglycemia	✔
Hypokalemia	✔
Liver enzymes increased	✔
Serum creatinine increased	✔
Respiratory	
Dyspnea	✔
Respiratory arrest	✔
Other	
Allergic reactions	✔
Hearing loss	✔
Weakness	✔

✔ Percent not specified

Table 7. Boxed Warning for Flucytosine[1]

WARNING
Use with extreme caution in patients with impaired renal function. Close monitoring of hematologic, renal and hepatic status of all patients is essential.

VII. Dosing and Administration

The usual dosing regimens for the pyrimidines are listed in Table 8.

Table 8. Usual Dosing Regimens for the Pyrimidines[1-3]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Flucytosine	Treatment of serious infections caused by susceptible strains of *Candida* and/or *Cryptococcus* in combination with amphotericin B: Capsule: 50 to 150 mg/kg/day administered in divided doses every six hours	Safety and efficacy in children have not been established.	Capsule: 250 mg 500 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the pyrimidines are summarized in Table 9.

Table 9. Comparative Clinical Trials with the Pyrimidines

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Candidiasis				
Abele-Horn et al.[8] (1996) Flucytosine 3×2.5 g as a total daily dose plus amphotericin B 1 to 1.5 mg/kg/day every other day for 14 days vs fluconazole 400 mg IV on day 1, then 200 mg daily for 14 days	MC, PRO, RCT Patients 18 to 80 years of age in the intensive care unit with evidence of systemic *Candida* infection	N=72 14 days	Primary: Clinical response (cure=resolution of all symptoms and signs of infection), microbiological response (cure=eradication of *Candida* species) Secondary: Not reported	Primary: No significant differences were seen between the treatment groups in the treatment of pneumonia and sepsis/fungemia. In the treatment of peritonitis, amphotericin B plus flucytosine was more effective than fluconazole, as seen in clinical and microbiological response (P<0.05). Secondary: Not reported
Kujath et al.[9] (1993) Flucytosine 3×2.5 g as a total daily dose plus amphotericin B 0.5 mg/kg/day vs fluconazole 400 mg IV on day 1 then 300 mg daily	OL, PRO, RCT Patients ≥18 years of age with systemic candidiasis	N=40 Variable duration	Primary: Microbiological response (elimination or improvement [reduction of fungal density by two stages on a six-stage scale]), time to elimination of all fungi Secondary: Not reported	Primary: No statistical difference was observed between groups in microbiological elimination or improvement (P=0.44). Fungal elimination was observed significantly sooner in the amphotericin B plus flucytosine group compared to the fluconazole group (5.5 days and 8.5 days, respectively; P=0.03). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cryptococcal Disease				
van der Horst et al.[10] (1997) Step 1 Flucytosine 100 mg/kg/day plus amphotericin B (0.7 mg/kg/day) in four divided doses for 2 weeks vs amphotericin B (0.7 mg/kg/day) for 2 weeks Step 2 Fluconazole 800 mg oral loading dose, then 400 mg orally daily for 8 weeks vs itraconazole 600 mg oral loading dose daily for 3 days, followed by 200 mg 2 times daily for 8 weeks	DB, MC, RCT Patients ≥13 years of age with HIV infection and a first episode of cryptococcal meningitis confirmed by cerebrospinal fluid culture	Step 1 N=381 Step 2 N=306 10 weeks	Primary: Mycological outcome (CSF culture negative at weeks two and 10), clinical outcome (fever, headache, meningismus improved at week two and absent at week 10) Secondary: Not reported	Primary: Mycological response rates at the end of step 1 in patients receiving amphotericin B plus flucytosine or amphotericin B alone were 60 and 51%, respectively (P=0.06). Clinical response rates at the end of step 1 in patients receiving amphotericin B plus flucytosine or amphotericin B alone were 78 and 83%, respectively (P=0.18). There was no significant difference between the treatments in combined mycological and clinical response (P=0.12). Mycological response rates at the end of step 2 in patients receiving fluconazole and itraconazole were 72 and 60%, respectively. Clinical response rates at the end of step 2 in patients receiving fluconazole and itraconazole were 68 and 70%, respectively. There was no significant difference between fluconazole and itraconazole in mycological or clinical response. Secondary: Not reported
Brouwer et al.[11] (2004)	RCT Adult patients with	N=64 10 weeks	Primary: Fungicidal activity (rate of reduction	Primary: Early fungicidal activity occurred faster for patients receiving amphotericin B plus flucytosine than amphotericin B alone

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Flucytosine 100 mg/kg/day plus amphotericin B 0.7 mg/kg/day for 2 weeks vs flucytosine 100 mg/kg/day plus amphotericin B 0.7 mg/kg/day plus fluconazole 400 mg daily for 2 weeks vs amphotericin B 0.7 mg/kg/day for 2 weeks vs amphotericin B 0.7 mg/kg/day plus fluconazole 400 mg daily for 2 weeks After 2 weeks, all patients were treated with fluconazole 400 mg daily for 8 weeks, followed by 200 mg daily.	HIV infections and a first episode of cryptococcal meningitis		in CSF cryptococcal colony-forming units from sequential CSF cultures on days three, seven, and 14 of treatment) Secondary: Not reported	(P=0.0006), amphotericin B plus fluconazole (P=0.03), or amphotericin B plus flucytosine plus fluconazole (P=0.01). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Chotmongkol et al.[12] (1997) Flucytosine 150 mg/kg/day plus amphotericin B 0.3 mg/kg/day plus itraconazole 400 mg/day (study group) vs flucytosine 150 mg/kg/day plus amphotericin B 0.3 mg/kg/day (control group)	OL, RCT Patients with AIDS and a diagnosis of cryptococcal meningitis	N=100 6 weeks	Primary: Clinical treatment outcomes, mean length of time until normalization of body temperature, mean time until negative CSF culture Secondary: Not reported	Primary: Successful treatment was significantly higher in the study group compared to the control group (100 and 90%, respectively; P=0.03). Mean length of time until normal body temperature was shorter in the study group compared to the control group (5.9 and 8.8 days, respectively; P=0.02). The mean length of time until the first negative CSF culture was 13.9 days in the study group and 13.3 days in the control group (P=0.66). Relapse rates were higher in the study group. Secondary: Not reported
Bennett et al.[13] (1979) Flucytosine 150 mg/kg/day divided every 6 hours plus amphotericin B 0.3 mg/kg/day for 6 weeks vs amphotericin B 0.4 mg/kg/day for 42 days, then 0.8 mg/kg every other day for 28 days	PRO, RCT Patients with either positive CSF smear or culture or clinical features compatible with cryptococcal meningitis plus a positive culture from another site or positive cryptococcal antigen test or evidence of intracranial cryptococcosis	N=78 10 weeks	Primary: Cure rates and mortality Secondary: Not reported	Primary: Cure or improvement was observed in 66% of patients in the combination group and in 47% of patients in the amphotericin B group (P>0.05). There were 15 deaths in the amphotericin B group (47%) compared to 8 deaths in the combination group (24%; P<0.05). Secondary: Not reported
Larsen et al.[14]	PRO, RCT	N=26	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1990) Flucytosine 150 mg/kg/day in 4 divided doses for 10 weeks plus amphotericin B 0.7 mg/kg/day for 7 days, then 3 times weekly for 9 weeks vs fluconazole 400 mg orally for 10 weeks	Patients ≥18 years of age with evidence of cryptococcal meningitis (with or without AIDS)	62 weeks	Clinical outcomes (success=negative blood and CSF cultures) Secondary: Not reported	After 10 weeks of treatment, eight of 14 patients receiving fluconazole were considered failures, while zero of six patients taking amphotericin B plus flucytosine were considered failures (P=0.04). Conversion from positive to negative blood and CSF cultures was significantly slower in patients taking fluconazole compared to amphotericin B and flucytosine for CSF cultures (P=0.02). No significant difference was seen in the time to achieve mycological success for blood cultures (P=0.19). Secondary: Not reported
Day et al.[15] (2013) Amphotericin B IV (1 mg/kg/day) for 4 weeks (Group 1) vs amphotericin B deoxycholate (1 mg/kg/day) combined with oral flucytosine (100 mg/kg/day in 3 to 4 divided doses) for 2 weeks (Group 2)	OL, RCT Patients >14 years of age with HIV and signs and symptoms consistent with cryptococcal Meningitis, as well as a lab test indicative of *Cryptococcus*	N=299 6 months	Primary: All cause mortality in the first 14 and 70 days after randomization Secondary: Mortality at 6 months, disability status at 70 days and at 6 months, changes in CSF fungal counts in the first 2 weeks after randomization, time to CSF sterilization, and adverse events	Primary: By day 70, a total of 44 patients treated with amphotericin B monotherapy had died, as compared with 30 patients treated with amphotericin B and flucytosine and 33 patients treated with amphotericin B and fluconazole. Treatment with amphotericin B and flucytosine was associated with a significantly reduced hazard of death by day 70 in the intention-to-treat analysis (HR, 0.61; 95% CI, 0.39 to 0.97; P=0.04); this benefit was maintained in the per-protocol analysis and after adjustment for predefined baseline covariates. Fewer patients receiving combination therapy with high-dose fluconazole died, as compared with those treated with amphotericin B monotherapy, but this finding was not significant (HR, 0.71; 95% CI, 0.45 to 1.11; P=0.13). Secondary: The survival benefit seen for patients receiving amphotericin B and flucytosine, as compared with those receiving amphotericin B monotherapy, was more marked at six months (HR, 0.56; 95% CI, 0.36 to 0.86; P=0.01). Treatment with amphotericin B and fluconazole did not confer a survival advantage, as compared with monotherapy.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs amphotericin B deoxycholate (1 mg/kg/day) combined with oral fluconazole (400 mg twice daily) for 2 weeks (Group 3) each treatment was followed by fluconazole (400 mg/day) to achieve a 10-week treatment course			during the first 10 weeks of the study	Patients receiving amphotericin B and flucytosine had a significantly higher chance of being free of disability at six months, as compared with those receiving monotherapy (OR, 2.01; 95% CI, 1.04 to 3.88; P=0.04). The time to fungal clearance was significantly shorter in patients receiving amphotericin B plus flucytosine than in those receiving amphotericin B alone or in combination with fluconazole, with more rapid rates of decline in the colony count (P<0.001 for both comparisons). Adverse events occurred with similar frequency among all the treatment groups.
de Gans et al.[16] (1992) Flucytosine 150 mg/kg/day in 4 divided doses plus amphotericin B 0.3 mg/kg/day for 6 weeks vs itraconazole 200 mg twice daily for 6 weeks All patients received itraconazole 200 mg/day as	OL, PRO, RCT Patients with suspected cryptococcal meningitis	N=28 6 weeks	Primary: Response to therapy (complete= resolution of symptoms and negative CSF cultures, partial= resolution of symptoms with persistently positive cultures), survival, relapse rates Secondary: Not reported	Primary: Five of 14 patients in the itraconazole group showed a complete response and seven showed a partial response. Twelve of 14 patients in the itraconazole group survived for more than six weeks. Ten of 11 patients in the amphotericin B and flucytosine group had a complete response. Ten of 11 patients in the amphotericin B and flucytosine group survived for more than six weeks. The difference in complete response between groups was significant and favored the amphotericin B and flucytosine group (P=0.009). Overall, no significant difference in relapse rates was observed between original groups during the maintenance period (P=0.22). No significant difference in mean survival was observed between

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
maintenance therapy.				original treatment groups (P=0.65). Secondary: Not reported
Bicanic et al.[17] (2008) Group 1 Flucytosine 25 mg/kg divided 4 times daily plus amphotericin B deoxycholate 0.7 mg/kg/day for 2 weeks vs Group 2 Flucytosine 25 mg/kg divided 4 times daily plus amphotericin B 1 mg/kg per day for 2 weeks After 2 weeks, patients received fluconazole 400 mg/day for 8 weeks and 200 mg/day thereafter.	RCT HIV-infected adults hospitalized with a first episode of cryptococcal meningitis	N=64 10 weeks	Primary: Mean rate of decrease in the number of *Cryptococcus* colony-forming units (cfu) in the CSF or early fungicidal activity (EFA) Secondary: Rates of renal impairment and anemia, mortality at two and 10 weeks, and long-term survival during antiretroviral therapy	Primary: The rate of clearance of infection during the first two weeks of therapy was more rapid for group 2 than for group 1. The mean EFA was -0.56 log cfu/mL of CSF per day for group 2 and -0.45 log cfu/mL of CSF per day for group 1. Secondary: The mortality rate was 6% at two weeks and 24% at 10 weeks, with no difference between groups. Sixty-eight percent and 60% of patients were alive at six months and one year, respectively, of follow-up. There was no difference in survival rates between the two groups at any time point. There were no significant differences between groups 1 and 2 in measurements of renal impairment. A decrease in the hemoglobin level 12 g/dL developed in 50 and 71% of patients in groups 1 and 2, respectively (P=0.2). The percentage decrease in the hemoglobin level was greater for group 2 (95% CI, 2 to 15%; P=0.01) and greater for women (95% CI, 4 to 17%; P=0.002).
Milefchik et al.[18] (2008) Cohort 1	RCT HIV-infected adults with a first episode	N=89 10 weeks	Primary: Overall response rates (success defined as alive	Primary: Fluconazole alone at the highest doses (1,600 mg and 2,000 mg/day) had clinical success rates of 62%. As the dose level of fluconazole was increased, there was an incremental increase in response (P<0.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Fluconazole 800 mg for 10 weeks with or without flucytosine 100 mg/kg/day for 4 weeks Cohort 2 Fluconazole 1,200 mg for 10 weeks with or without flucytosine 100 mg/kg/day for 4 weeks Cohort 3 Fluconazole 1,600 mg for 10 weeks with or without flucytosine 100 mg/kg/day for 4 weeks Cohort 4 Fluconazole 2,000 mg for 10 weeks with or without flucytosine 100 mg/kg/day for 4 weeks	of cryptococcal meningitis		and CSF culture negative) Secondary: Not reported	At each dose level of fluconazole (except 1,600 mg dosing of fluconazole), the addition of flucytosine to the fluconazole improved the overall response rates (P<0.02). There was a two way interaction between the fluconazole and flucytosine with higher doses of fluconazole associated with an improved response and the addition of flucytosine to fluconazole improving response (P<0.05). The overall success was 75% for subjects that received the combination of fluconazole and flucytosine. No relapses were observed during follow-up among those subjects deemed successful at 10 weeks. Secondary: Not reported
Nussbaum et al.[19] (2010) Flucytosine 100 mg/kg/day plus fluconazole 1,200 mg daily, followed	OL, RCT HIV-positive adults with their first episode of cryptococcal meningitis	N=41 24 days	Primary: Rate of CSF infection clearance Secondary: Not reported	Primary: The rate of clearance of infection was more rapid in the combination arm compared to fluconazole alone. The difference in early fungicidal activity was 0.18 (95% CI, 0.085 to 0.270; P=0.0005). Four patients in the combination arm and one in the monotherapy arm had sterile CSF cultures by day 14.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
by fluconazole 800 mg/day vs fluconazole 1,200 mg daily for 14 days				Secondary: Not reported
Sloan et al.[20] (2008) Amphotericin B, flucytosine, and fluconazole given alone or in combination	MA HIV-infected adults with a first episode of cryptococcal meningitis	N=595 (5 trials) ≥2 weeks	Primary: Mortality, adverse events, and proportion of patients with sterile CSF after two weeks of therapy Secondary: Not reported	Primary: <u>Fluconazole and flucytosine vs fluconazole</u> There was no difference in death rate at two weeks (RR, 0.4; 95% CI, 0.14 to 1.11) or at six months (RR, 0.77; 95% CI, 0.57 to 1.05). There were no major adverse events in either group. There was no difference in number of patients with sterile CSF at two months after treatment (RR, 0.4; 95% CI, 0.11 to 1.36). <u>Amphotericin B vs amphotericin B and flucytosine</u> There was no difference in the proportion deaths at 14 days (RR, 1.1; 95% CI, 0.51 to 2.40). There was no difference in major adverse events between the two treatment arms (RR, 0.94; 95% CI, 0.29 to 3.03).There was higher proportion of patients with sterile CSF cultures at 14 days in the group of patients receiving flucytosine (RR, 0.81; 95% CI, 0.68 to 0.98). <u>Amphotericin B vs amphotericin B, flucytosine and fluconazole</u> There was no significant difference in the proportion of patients dying at two weeks or ten weeks (RR, 2.0; 95% CI, 0.20 to 19.91 and RR, 1.0; 95% CI, 0.24 to 4.23, respectively). There were no serious adverse events in either group. There was no difference in the proportion of patients with sterile CSF at 14 days (RR, 0.5; 95% CI, 0.11 to 2.35). <u>Amphotericin B and flucytosine vs amphotericin B, flucytosine and fluconazole</u> There was no difference in death at 14 days or 10 weeks between the groups (RR, 1.07; 95% CI, 0.07 to 15.57 and RR, 1.07; 95% CI, 0.07 to 15.57, respectively). There were no serious adverse events in either group. There was no difference in the proportion of patients with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				sterile CSF at 14 days (RR, 1.6; 95% CI, 0.56 to 4.58). <u>Amphotericin B and flucytosine vs amphotericin B and fluconazole</u> There was no difference in the proportion of deaths at 14 days or 10 weeks (RR, 0.21; 95% CI, 0.03 to 1.62 and RR, 0.15; 95% CI, 0.02 to 1.10). There were no serious adverse events in either group. There was no difference in the amount of patients with sterile CSF at 14 days (RR, 2.13; 95% CI 0.65 to 7.04). <u>Amphotericin B vs amphotericin B and fluconazole</u> There was no difference in the proportion deaths at 14 days or 10 weeks (RR, 0.4; 95% CI, 0.09 to 1.77 and RR, 0.43; 95% CI, 0.13 to 1.37). There were no serious adverse events in either group. There was no difference in the amount of patients with sterile CSF at 14 days (RR, 0.67; 95% CI, 0.13 to 3.47). <u>Amphotericin B and fluconazole vs amphotericin B, flucytosine and fluconazole</u> There was no difference in the proportion deaths at 14 days or 10 weeks (RR, 5.0; 95% CI, 0.66 to 38.15 and RR, 2.33; 95% CI, 0.73 to 7.45). There were no serious adverse events in either group. There was no difference in the amount of patients with sterile CSF at 14 days (RR, 0.75; 95% CI, 0.20 to 2.83). <u>Standard dose amphotericin B and flucytosine vs high dose amphotericin B and flucytosine</u> There was no difference in the proportion of deaths at 14 days or 10 weeks (RR, 0.34; 95% CI, 0.04 to 3.44 and RR, 0.76; 95% CI 0.03 to 1.83, respectively). There was no difference in major adverse events defined as side effects of treatment leading the study interventions being terminated (RR, 0.23; 95% CI, 0.03 to 1.83). The proportion of patients with sterile CSF at 14 days was not different between the two treatment groups (RR, 1.13; 95% CI, 0.43 to 2.94). <u>Amphotericin B vs liposomal amphotericin B</u> There was no difference in the proportion of patients who had a clinical response after three weeks treatment in the liposomal

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				amphotericin B group and the amphotericin B group (RR, 0.95; 95% CI, 0.67 to 1.33). There was no difference in the proportion of deaths at 14 days, 10 weeks or six months. At six months 2/15 patients who received liposomal amphotericin B had died and 1/13 patients who received amphotericin B (RR, 1.73; 95% CI, 0.12 to 59.4). Major adverse events were less common in patients who received liposomal amphotericin B (RR, 0.19; 95% CI, 0.05 to 0.74). There was no difference in the patients with sterile CSF at 14 days in either group (RR, 6.0; 95% CI, 0.91 to 39.41). Secondary: Not reported

Drug regimen abbreviations: IV=intravenous
Study abbreviations: CI=confidence interval, DB=double blind, HR=hazard ratio, MA=meta-analysis, MC=multi-center, OL=open label, OR=odds ratio, PRO=prospective trial, RCT=randomized controlled trial, RR=relative risk
Miscellaneous abbreviations: AIDS= acquired immunodeficiency syndrome. CSF=cerebrospinal fluid, HIV=human immunodeficiency virus

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 10. Relative Cost of the Pyrimidines

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Flucytosine	capsule	Ancobon®*	$$$$$	$$$$$

*Generic is available in at least one dosage form or strength.

X. Conclusions

Flucytosine is approved for the treatment of serious infections caused by susceptible strains of *Candida* and/or *Cryptococcus*.[1-3] It should be used in combination with amphotericin B because of the emergence of resistance. Flucytosine is available in a generic formulation.

Guidelines recommend the use of amphotericin B, with or without flucytosine, for the treatment of candida endophthalmitis, cardiovascular candidiasis, central nervous system candidiasis, and for the treatment of fluconazole-resistant urinary tract infections.[5] For the treatment of cryptococcal disease, guidelines recommend the combination of amphotericin B and flucytosine in immunocompetent individuals with severe pulmonary disease and central nervous system (CNS) infections.[6] The combination is recommended in organ transplant recipients with CNS infections, moderately severe-to-severe non-CNS or disseminated disease, as well as severe pulmonary disease. Amphotericin B and flucytosine are also recommended for the treatment of human immunodeficiency virus (HIV)-infected individuals with cryptococcal meningoencephalitis.[6-7]

Clinical trials have demonstrated similar efficacy with the combination of flucytosine and amphotericin B compared to fluconazole monotherapy in patients with systemic candidiasis.[8-9] Several trials have also evaluated the use of flucytosine for the treatment of cryptococcal infections with variable results. Two studies demonstrated similar efficacy with the combination of flucytosine and amphotericin B compared to amphotericin B monotherapy.[10,13] Whereas, three other studies demonstrated better clinical outcomes with the combination of flucytosine and amphotericin B compared to monotherapy with amphotericin B, fluconazole or itraconazole.[11,14,16] A meta-analysis of five studies found no difference in mortality with flucytosine treatment regimens compared to other antifungal treatment regimens in HIV-infected adults with cryptococcal meningitis.[20]

Therefore, all brand pyrimidines within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand pyrimidine is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Antifungals, Miscellaneous
AHFS Class 081492
November 12, 2014

I. Overview

Griseofulvin is approved for the treatment of tinea barbae, tinea capitis, tinea corporis, tinea cruris, tinea pedis, and tinea unguium.[1-4] It is fungistatic with activity against *Epidermophyton, Microsporum,* and *Trichophyton* species. Griseofulvin is supplied in two different formulations, including microsize and ultramicrosize. The gastrointestinal absorption of ultramicrosize griseofulvin is approximately one and one-half times that of microsize griseofulvin.[4] This allows for the administration of lower doses with the ultramicrosize product; however, there is currently no evidence that this lower dose confers any significant clinical differences with regard to efficacy or safety.[4]

The miscellaneous antifungals that are included in this review are listed in Table 1. This review encompasses all systemic dosage forms and strengths. The topical antifungals were previously reviewed with the skin and mucous membrane agents (AHFS 840408) and are not included in this review. All products are available in a generic formulation. This class was last reviewed in May 2012.

Table 1. Antifungals, Miscellaneous Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Griseofulvin microsize	suspension, tablet	Grifulvin V®*	griseofulvin microsize
Griseofulvin ultramicrosize	tablet	Gris-Peg®*	griseofulvin ultramicrosize

PDL=Preferred Drug List

The miscellaneous antifungals have been shown to be active against the strains of microorganisms indicated in Table 2. This activity has been demonstrated in clinical infections and is represented by the Food and Drug Administration (FDA)-approved indications for the miscellaneous antifungals that are noted in Table 4. These agents may also have been found to show activity to other microorganisms in vitro; however, the clinical significance of this is unknown since their safety and efficacy in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials. Although empiric anti-infective therapy may be initiated before culture and susceptibility test results are known, once results become available, appropriate therapy should be selected.

Table 2. Microorganisms Susceptible to the Antifungals, Miscellaneous[1-4]

Organism	Griseofulvin Microsize	Griseofulvin Ultramicrosize
Epidermophyton floccosum	✔	✔
Microsporum audouinii	✔	✔
Microsporum canis	✔	✔
Microsporum gypseum	✔	✔
Trichophyton crateriform	✔	✔
Trichophyton gallinae	✔	✔
Trichophyton interdigitalis	✔	✔
Trichophyton megninii	✔	✔
Trichophyton mentagrophytes	✔	✔
Trichophyton rubrum	✔	✔
Trichophyton schoenleinii	✔	✔
Trichophyton sulphureum	✔	✔
Trichophyton tonsurans	✔	✔
Trichophyton verrucosum	✔	✔

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the miscellaneous antifungals are summarized in Table 3.

Table 3. Treatment Guidelines Using the Antifungals, Miscellaneous

Clinical Guideline	Recommendation(s)
European Academy of Dermatology and Venereology: **Onychomycosis Treatment Guidelines (2005)**[5]	• Prior to initiating treatment, it is important that diagnosis be confirmed and the etiological agent identified. • Topical monotherapy is indicated when the matrix area is not involved. Topical treatment is also suitable for patients who are reluctant to take oral medications or have swallowing difficulties. The only case in which it is not recommended is if nail penetration may be suboptimal. • Oral antifungal drugs are generally considered to be more effective than topical treatments. However, they are accompanied by a higher risk of systemic adverse effects and drug interactions. • Oral monotherapy (terbinafine, itraconazole or fluconazole) or combined oral and topical (nail lacquer) is recommended when 1) at least 50% of the distal nail plate is involved; 2) the nail matrix area is involved; 3) mycological criteria such as the causative agent or agents are known and oral agents can target specific fungi; 4) topical drugs are not indicated when topical drug transport is suboptimal; and 5) oral or combined therapy is also recommended in cases of nail matrix area involvement. • Combination therapy with systemic and topical treatments may be considered when a large portion of the nail plate is affected (>50%), when the nail matrix is involved, and in cases of treatment failure. • Griseofulvin is associated with the poorest mycological cure rate (<30%) and is rarely used. Terbinafine is associated with the highest mycological cure rate (77 to 100%).
British Association of Dermatologists: **Guidelines for the Treatment of Onychomycosis (2003)**[6]	• Both topical and oral agents are available for the treatment of fungal nail infection. The primary aim of treatment is to eradicate the organism as demonstrated by microscopy and culture. • Systemic therapy is almost always more successful than topical treatment, which should only be used in superficial white onychomycosis, possibly very early distal and lateral subungual onychomycosis or when systemic therapy is contraindicated. • Both terbinafine and itraconazole have been shown to be more effective than griseofulvin in dermatophyte onychomycosis and therefore the optimum choice of treatment lies between terbinafine and itraconazole. • Terbinafine is more effective than itraconazole for dermatophyte infection of the nails and should be first-line treatment. Itraconazole may be considered a second-line treatment. • Expected cure rates vary and range from 80 to 90% for fingernail infections and 70 to 80% for toenail infections.
European Society for Pediatric Dermatology: **Guidelines for the Management of Tinea Capitis in Children (2010)**[7]	• Tinea capitis always requires systemic treatment because topical antifungal agents do not penetrate the hair follicle. • Topical treatment is only used as adjuvant therapy to systemic antifungals. • Griseofulvin has been the gold standard for systemic therapy of tinea capitis. The main disadvantage of griseofulvin is the long duration of treatment required (six to 12 weeks or longer) which may lead to reduced compliance. • The newer oral antifungal agents including terbinafine, itraconazole, and fluconazole appear to have efficacy rates and potential adverse effects similar to those of griseofulvin in children with tinea capitis due

Clinical Guideline	Recommendation(s)
	to *Trichophyton* species, while requiring much shorter duration of treatment. • Griseofulvin is still the treatment of choice for cases caused by *Microsporum* species. • Adjunctive topical therapies, such as selenium sulfide or ketoconazole shampoos, as well as fungicidal creams or lotions have been shown to decrease the carriage of viable spores responsible for the disease contagion and reinfection and may shorten the cure rate with oral antifungals. • The topical fungicidal cream/lotion should be applied to the lesions once daily for a week. The shampoo should be applied to the scalp and hair for five minutes twice weekly for two to four weeks or three times weekly until the patient is clinically and mycologically cured. The latter in conjunction with one week of topical fungicidal cream or lotion application is recommended.

British Association of Dermatologists: **Guidelines for the Management of Tinea Capitis (2000)**[8]	• The aim of treatment is to achieve a clinical and mycological cure as quickly as possible.
	• Oral antifungal therapy is generally needed. Topical treatment alone is not recommended for the management of tinea capitis.
	• Oral therapy options include griseofulvin, terbinafine, itraconazole, fluconazole, and ketoconazole.
	• If there has been no clinical response and signs persist at the end of the treatment period, then the options include:
	  o Increase the dose or duration of the original drug (both griseofulvin and terbinafine have been used successfully and safely at higher doses or for longer courses to clear resistant infections)
	  o Change to an alternative antifungal (e.g. switch from griseofulvin to terbinafine or itraconazole).
	• Symptom-free carriers with light growth/low spore count on culture may be treated with twice weekly selenium or povidone shampoo.
	• The definitive end-point for adequate treatment is not clinical response but mycological cure; therefore, follow-up with repeat mycology sampling is recommended at the end of the standard treatment period and then monthly until mycological clearance is documented. Treatment should, therefore, be tailored for each individual patient according to response.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the miscellaneous antifungals are noted in Table 4. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 4. FDA-Approved Indications for the Antifungals, Miscellaneous[1-4]

Indication	Griseofulvin Microsize	Griseofulvin Ultramicrosize
Tinea barbae	✔	✔
Tinea capitis	✔	✔
Tinea corporis	✔	✔
Tinea cruris	✔	✔
Tinea pedis	✔	✔
Tinea unguium	✔	✔

IV. Pharmacokinetics

The pharmacokinetic parameters of the miscellaneous antifungals are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Antifungals, Miscellaneous[1-4]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Griseofulvin	Variable	Not reported	Liver	Feces (36)	9 to 22

V. Drug Interactions

Significant drug interactions with the miscellaneous antifungals are listed in Table 6.

Table 6. Significant Drug Interactions with the Antifungals, Miscellaneous[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Griseofulvin	1	Dienogest	Griseofulvin may increase hepatic metabolism and decrease the pharmacologic effects of dienogest. Menstrual irregularities (spotting, breakthrough bleeding, and amenorrhea) and pregnancy may occur.
Griseofulvin	1	Oral contraceptives	Pharmacologic effects of oral contraceptives may be decreased by griseofulvin. Menstrual irregularities (spotting, breakthrough bleeding) and pregnancy may occur.
Griseofulvin	2	Anticoagulants	The hypoprothrombinemic effect of warfarin may be decreased. Suboptimal anticoagulation with possible exacerbation of the problem being treated can occur.
Griseofulvin	2	Cabazitaxel	Inhibition of CYP3A4 by griseofulvin may increase the metabolic elimination of cabazitaxel. Plasma concentrations and pharmacologic effects cabazitaxel may be decreased by griseofulvin.
Griseofulvin	2	Ulipristal	Induction of CYP3A4 enzymes by griseofulvin may increase the metabolic elimination of ulipristal. Plasma concentrations and pharmacologic effects of ulipristal may be decreased by griseofulvin.

Significance level 1 = major severity, significance level 2 = moderate severity

VI. Adverse Drug Events

The most common adverse drug events reported with the miscellaneous antifungals are listed in Table 7.

Table 7. Adverse Drug Events (%) Reported with the Antifungals, Miscellaneous[1-4]

Adverse Events	Griseofulvin
Central Nervous System	
Dizziness	✔
Fatigue	✔
Headache	✔
Insomnia	✔
Mental confusion	✔
Paresthesia	✔
Dermatological	
Erythema multiforme-like drug reaction	✔
Photosensitivity	✔
Rash	✔
Urticaria	✔
Gastrointestinal	
Diarrhea	✔
Epigastric distress	✔
Gastrointestinal bleeding	✔
Nausea	✔
Oral thrush	✔
Vomiting	✔
Genitourinary	
Nephrosis	✔
Proteinuria	✔
Hematological	
Granulocytopenia	✔
Leukopenia	✔
Other	
Angioneurotic edema	✔
Drug-induced lupus-like syndrome	✔
Hepatotoxicity	✔
Menstrual irregularities	✔

✔ Percent not specified

VII. Dosing and Administration

The usual dosing regimens for the miscellaneous antifungals are listed in Table 8.

Table 8. Usual Dosing Regimens for the Antifungals, Miscellaneous[1-4]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Griseofulvin microsize	Tinea Capitis, Tinea Corporis, Tinea Cruris: Suspension/tablet: 500 mg daily Tinea Pedis, Tinea Unguium: Suspension/tablet: 1 gram daily	Tinea Infections: Suspension/tablet: 30 to 50 pounds, 125 mg to 250 mg daily; >50 pounds, 250 mg to 500 mg daily	Suspension: 125 mg/5 mL Tablet: 500 mg
Griseofulvin ultramicrosize	Tinea Capitis, Tinea Corporis, Tinea Cruris: Tablet: 375 mg as a single	Tinea Infections: >2 years of age: Tablet: 35 to 60 pounds, 125	Tablet: 125 mg 250 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	dose or in divided doses Tinea Pedis, Tinea Unguium: Tablet: 750 mg as a single dose or in divided doses	mg to 187.5 mg daily; >60 pounds, 187.5 mg to 375 mg daily	

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the miscellaneous antifungals are summarized in Table 9.

Table 9. Comparative Clinical Trials with the Antifungals, Miscellaneous

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Tinea Capitis				
Dastghaib et al.[9] (2005) Griseofulvin 15 mg/kg/day for 6 weeks vs fluconazole 5 mg/kg/day for 4 weeks	PRO, RCT, SB Patients with a mycological diagnosis of non-inflammatory tinea capitis	N=40 8 weeks	Primary: Complete cure (negative culture and ≥50% decrease in clinical scores which are based on hair loss, erythema, pruritus, presence of crust and presence of scales), mycological cure Secondary: Not reported	Primary: No significant difference was observed in the proportion of patients infected with *Trichophyton* who experienced complete cure in the griseofulvin and fluconazole groups (76 and 93%, respectively; P=0.41). No significant difference was observed in the proportion of patients infected with *Microsporum* who experienced complete cure in the griseofulvin and fluconazole groups (P=0.27). No significant difference was observed between groups in mycological cure rate. Secondary: Not reported
Shemer et al.[10] (2013) Griseofulvin 15 mg/kg/day vs griseofulvin 25 mg/kg/day vs fluconazole 4 mg/kg/day vs	CS Children with tinea capitis with positive fungal cultures (average age 4.2 years)	N=113 Up to 12 weeks	Primary: Efficacy and safety Secondary: Not reported	Primary: The lower doses for both griseofulvin and fluconazole required significantly longer treatment duration until mycological cure than the higher doses, independent of the fungus type. Both drugs were well tolerated, although patients treated with the high dose of fluconazole had minor gastrointestinal complaints. No significant abnormal routine laboratory tests were noted during the study. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
fluconazole 6 mg/kg/day				
Gupta et al.[11] (2001) Griseofulvin 20 mg/kg/day for 6 weeks vs fluconazole 6 mg/kg/day for 2 weeks vs itraconazole 5 mg/kg/day for 2 weeks vs terbinafine 62.5 mg, 125 mg, or 250 mg daily for 2 weeks	CS, PRO, RCT, SB Patients 6 months of age and older with clinical symptoms and signs of tinea capitis confirmed mycologically	N=200 12 weeks	Primary: Complete clinical (negative culture and no signs and symptoms), mycological cure (negative culture and few residual signs and symptoms) Secondary: Not reported	Primary: Effective therapy (complete clinical and mycological cure or mycological cure) was observed in 92% of patients in the griseofulvin group, 94% in the terbinafine group, 86% in the itraconazole group, and 84% in the fluconazole group. No significant differences were noted at week 12 between treatment groups (P=0.33). Secondary: Not reported
Grover et al.[12] (2012) Griseofulvin 15 to 20 mg/kg/day administered in two doses per day for 6 weeks	OL, PRO Children aged ≤12 years with tinea capitis confirmed on microscopic examination	N=75 Variable duration	Primary: Clinical cure Secondary: Not reported	Primary: Cure rates of 96, 88, and 84% were achieved with griseofulvin, terbinafine, and fluconazole, respectively. Overall, seven patients required prolonged therapy. No side effects to therapy were seen. Griseofulvin remains the drug of choice in the treatment of tinea capitis. Terbinafine was the second best agent and offered the advantage of a shorter course of therapy. Fluconazole had comparatively low cure rates but was easier to administer than the other two medications.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs fluconazole 6 to 8 mg/kg administered weekly for 6 weeks vs terbinafine 3 to 5 mg/kg/day for two weeks Treatment in each group could be prolonged				Secondary: Not reported
Tanz et al.[13] (1988) Griseofulvin 10 to 20 mg/kg/day for 12 weeks vs ketoconazole 3.3 to 6.6 mg/kg/day for 12 weeks	DB, RCT Patients 2 to 16 years of age with tinea capitis or mycological evidence of dermatophyte infection of the scalp	N=79 12 weeks	Primary: Clinical response (success=clinical improvement and negative cultures), mycological response, symptom severity score Secondary: Not reported	Primary: Treatment success was observed in 73% of patients in the ketoconazole group and in 96% of patients in the griseofulvin group (P<0.10). There were no significant differences in symptom severity scores between groups (P>0.20). There were no significant differences between groups in mycological response (P<0.90). Secondary: Not reported
Tanz et al.[14] (1985) Griseofulvin 500 mg daily vs	DB, RCT Children 2 to 16 years of age with mycologically proven tinea capitis	N=22 6 weeks	Primary: Symptom severity score, mycological response (negative cultures) Secondary:	Primary: The total severity scores decreased in all patients during the course of the study (P<0.05 compared to baseline) and the decrease was similar between groups (P=0.62). After six weeks of therapy, 57% of patients in each group were culture negative.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ketoconazole 200 mg daily			Not reported	Secondary: Not reported
Gan et al.[15] (1987) Griseofulvin 15 mg/kg/day until clearance of lesions and negative culture or for 6 months vs ketoconazole 5 mg/kg/day until clearance of lesions and negative culture or for 6 months	RCT Patients 1 to 12 years of age with a diagnosis of tinea capitis	N=63 6 months	Primary: Negative cultures, relapse rates Secondary: Not reported	Primary: After one month of therapy, fungal cultures were negative in 69% of patients treated with griseofulvin and 29% of patients treated with ketoconazole (P<0.01). This statistical difference persisted throughout the follow-up period. At the end of 12 weeks of therapy, 4% of griseofulvin patients continued to have positive cultures compared to 26% in the ketoconazole group. Seven patients (one in the griseofulvin group and six in the ketoconazole group) reverted to negative samples between the 12th and 26th week of treatment. The median time from initiation of therapy to negative culture was significantly longer in the ketoconazole group compared to the griseofulvin group (eight and four weeks respectively; P<0.01). Three patients (one in the griseofulvin group and two in the ketoconazole group) had recurrence of tinea capitis at four weeks (two patients) and at four months (one patient) after discontinuation of therapy. Secondary: Not reported
Lipozencic et al.[16] (2002) Griseofulvin oral suspension 20 mg/kg/day for 12 weeks (open-label) vs terbinafine 125 mg	DB, MC, PG, RCT Patients 4 years of age and older diagnosed with tinea capitis clinically confirmed by positive culture for *Microsporum* species	N=134 16 weeks	Primary: Complete cure at the end of study (EOS) defined by negative culture and no residual signs and symptoms Secondary: Effective treatment	Primary: There was no significant difference between any of the terbinafine treatment groups in complete cure at EOS (P=0.12). Higher daily doses of terbinafine (>4.5 mg/kg/day) had a positive effect on complete cure rates at EOS compared to lower doses (<4.5 mg/kg/day) (P=0.048). Open-label, high-dose griseofulvin showed a high rate of complete cure at EOS of 84%.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
or 250 mg (based on weight) daily for 6, 8, 10, or 12 weeks (blinded as to study duration)			(negative culture and minimal signs and symptoms), clinical cure (no clinical signs and symptoms), mycological cure (negative microscopy and culture)	No comparisons were made between griseofulvin group and terbinafine groups. Secondary: At EOS, no significant differences were observed between any of the terbinafine treatment groups in any secondary endpoint (P>0.05). Open-label, high-dose griseofulvin produced effective treatment in 88% of patients, mycological cure in 76%, and clinical cure in 96%. No comparisons were made between the griseofulvin and terbinafine groups.
Fuller et al.[17] (2001) Griseofulvin suspension 10 mg/kg/day for 4 weeks vs terbinafine 62.5 mg or 125 mg daily for 4 weeks All patients were instructed to use selenium sulfide shampoo at least 2 times weekly for the first 2 weeks.	MC, OL, PG, RCT Patients 2 to 16 years of age with a diagnosis of tinea capitis confirmed by culture	N=210 24 weeks	Primary: Clinical response (complete cure= microscopy and culture negative, no residual signs and symptoms; cure= microscopy and culture negative and total symptom score ≤2)	Primary: No significant differences were observed between groups in clinical response (P>0.2). Graphical representation of cure rates shows a numerically higher response to terbinafine at earlier time points. Significantly more children weighing over 20 kg and infected with *Trichophyton* species were rated as cured at week four compared to children in the griseofulvin group (36 and 13% respectively, P=0.03).
Memisoglu et al.[18] (1999) Griseofulvin once daily for 8 weeks	DB, RCT Children with mycologically proven tinea capitis	N=78 12 weeks	Primary: Mycological cure, effective treatment (complete disappearance of	Primary: At week 12, a mycological cure was recorded in 88.0% of the terbinafine-treated group, compared to 91.0% of the griseofulvin-treated group. Effective treatment was recorded in 78% of patients in the terbinafine-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs terbinafine once daily for 4 weeks			signs/symptoms and negative mycology, or not >2 signs/symptoms of mild erythema, desquamation or pruritus) Secondary: Not reported	treated group compared to 74% of patients in the griseofulvin-treated group. *Trichophyton* species and *Microsporum canis* showed similar responsiveness to terbinafine treatment. Secondary: Not reported
Fleece et al.[19] (2004) Griseofulvin administered for 6 to 8 weeks vs terbinafine administered for 2 to 4 weeks	MA Patients with tinea capitis	N=603 (6 trials) 12 to 16 weeks	Primary: Clinical outcomes Secondary: Not reported	Primary: Three separate meta-analyses were performed. Analysis I included all six studies using culture status at least 12 weeks after enrollment in the study as the outcome. The OR was 0.86 (95% CI, 0.57 to 1.27; P=0.444). Analysis II included only the five studies in which *Trichophyton* species were the predominant pathogens and outcome was assessed at least 12 weeks post-enrollment. The OR was 0.65 (95% CI, 0.042 to 1.01; P=0.054). Analysis III included the four studies that provided outcome data at eight weeks post-enrollment. The OR was 0.84 (95% CI, 0.54 to 1.32; P=0.462). Secondary: Not reported
Caceres-Rios et al.[20] (2000) Griseofulvin (microsize) 125 mg, 250 mg, or 500 mg daily for 8 weeks	DB, PRO, RCT Patients 1 to 14 years of age with a clinical and mycological diagnosis of non-inflammatory tinea capitis	N=50 12 weeks	Primary: Clinical outcomes (complete cure= negative culture and resolution of signs and symptoms; mycological cure= negative mycological	Primary: At the end of eight weeks, no significant difference was observed between groups with respect to proportion of patients with negative cultures. At the end of week 12, the proportion of patients with negative cultures decreased in the griseofulvin group and increased or remained steady in the terbinafine group. A significant difference in favor of the terbinafine group was observed (P<0.05). At the end of week eight, the efficacy (as measured by complete cure) of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs terbinafine 62.5 mg, 125 mg, or 250 mg daily for 4 weeks then 4 weeks of placebo			findings and slight erythema, desquamation or pruritus) Secondary: Not reported	griseofulvin was 76 and 72% for terbinafine. No significant difference between groups was observed. By week 12, the efficacy (as measured by complete cure) of griseofulvin had decreased to 44% and terbinafine had risen to 76% (P<0.05). Secondary: Not reported
Elewski et al.[21] (2008) Griseofulvin suspension 125 mg to 500 mg (10 to 20 mg/kg) once daily for 6 weeks vs terbinafine granules 125 mg to 250 mg (5 to 8 mg/kg) once daily for 6 weeks	2 RCT (pooled), SB, MC Children between 4 and 12 years of age with a clinical diagnosis of tinea capitis confirmed by positive potassium hydroxide microscopy at baseline	N=1,549 10 weeks	Primary: End-of-study complete cure rate defined as mycologic cure (negative culture and microscopy) and clinical cure Secondary: End-of-study mycologic cure rate, end-of-study clinical cure rate, and adverse events	Primary: The complete cure rate at the end-of-study (week 10) was statistically higher in the terbinafine group (45.1%) compared to the griseofulvin group (39.2%; P=0.024) in the pooled analysis. In the individual analyses, terbinafine was more effective than griseofulvin in trial 1 (46.23 vs 34.01%, respectively; P<0.01) but not in trial 2 (43.99 vs 43.46%, respectively; P=0.95). Secondary: The end-of-study mycologic cure rate was higher in the terbinafine group (61.5%) compared to the griseofulvin group (55.5%; P=0.029). In the individual analyses, terbinafine was more effective than griseofulvin in trial 1 (62.29 vs 50.25%; P<.01) but not in trial 2 (60.77 vs 59.92%; P=0.89). The end-of-study clinical cure rate were similar between terbinafine and griseofulvin in the pooled analysis (63.0 vs 58.8%; P=0.10) as well as in the individual trials (trial 1: 62.77 vs 56.35%; P=0.06; trial 2: 63.27 vs 60.76%; P=0.59). Overall, 51.9% of patients in the terbinafine group and 49.1% of patients in the griseofulvin group reported an adverse event during the study. The incidence of adverse events by organ class was similar in the two treatment groups.
Tey et al.[22] (2011) Griseofulvin	MA Children and adults with a diagnosis of tinea capitis	N=2,163 (7 trials) Variable duration	Primary: Complete cure rate (defined as the achievement of both clinical and	Primary: The pooled OR did not significantly favor griseofulvin or terbinafine when all studies were pooled (OR, 1.22; 95% CI, 0.785 to 1.919; P=0.37). For those studies with *Trichophyton* species being the predominant

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs terbinafine			mycological cure) Secondary: Mycological cure rate (defined as the absence of dermatophytes on microscopy and culture), clinical cure rate (defined as the resolution of clinical symptoms and signs), adverse events	pathogen, the pooled OR favored terbinafine, but did not reach statistical significance (OR, 1.49; 95% CI, 0.975 to 2.277; P=0.065). For those studies with *Microsporum* species being the predominant pathogen, the pooled OR significantly favored griseofulvin (OR, 0.408; 95% CI, 0.254 to 0.656; P<0.001). Griseofulvin was associated with a small number of adverse effects including gastrointestinal symptoms, headache, upper respiratory tract symptoms, and rash. Severe adverse effects did not occur. The most frequent adverse events reported with terbinafine were gastrointestinal symptoms and upper respiratory tract symptoms. One patient developed asymptomatic neutropenia that was reversible after treatment was terminated prematurely.
Gupta et al.[23] (2013) Griseofulvin (6.25 to 12.50 mg/kg/day) for 8 weeks vs terbinafine (3.125 to 6.250 mg/kg/day) for 4 weeks	MA Patients with mycologically confirmed tinea capitis	N=272 (3 trials) 8 weeks	Primary: Efficacy (clinical and mycologic cure at week 8) Secondary: Efficacy of each treatment in infections caused by different dermatophyte genera	Primary: No statistically significant difference was detected between the two interventions (P=0.81) when considering all cases regardless of organism. Secondary: For *Trichophyton* species, terbinafine is significantly more efficacious than griseofulvin (OR, 0.50; 95% CI, 0.26 to 0.98; P=0.04). For *Microsporum* species, griseofulvin is significantly more efficacious than terbinafine (OR, 6.39; 95% CI, 1.09 to 37.47; P=0.04).
González et al.[24] (2007) Griseofulvin, terbinafine, itraconazole, fluconazole,	MA Children with normal immunity under the age of 18 who had tinea capitis confirmed by	N=1,812 (21 trials) 6 to 26 weeks	Primary: The proportion of participants with complete cure (clinical and mycological)	Primary: <u>Terbinafine vs griseofulvin</u> A pooled analysis of the five trials found that the difference in the cure rates between four weeks of terbinafine and eight weeks griseofulvin was not statistically significant (RR, 1.11; 95% CI, 0.96 to 1.29). <u>Itraconazole vs griseofulvin</u>

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ketoconazole	microscopy or growth of dermatophytes in culture or both		Secondary: Not reported	In the pooled analysis, there was no significant difference in cure rates between itraconazole and griseofulvin (RR, 0.94; CI, 0.80 to 1.09). <u>Itraconazole vs terbinafine</u> In the pooled analysis, there was no significant difference in cure rates between itraconazole and terbinafine (as treatment of *Trichophyton* species) when used for periods of two to three weeks (RR, 0.93; 95% CI, 0.72 to 1.19). <u>Ketoconazole vs griseofulvin</u> In the pooled analysis, there was no significant difference in cure rates between ketoconazole and griseofulvin (RR, 0.72; 95% CI, 0.50 to 1.02). <u>Fluconazole vs griseofulvin</u> In the pooled analysis, there was no significant difference in cure rates between fluconazole and griseofulvin (RR, 0.92; 95% CI, 0.80 to 1.05). <u>Fluconazole vs terbinafine</u> In one study, the cure rates were found to be similar between fluconazole and terbinafine (RR, 0.87; 95% CI, 0.75 to 1.01). <u>Fluconazole vs itraconazole</u> In one study, the cure rates were found to be similar between fluconazole and itraconazole (RR, 1.00; 95% CI, 0.83 to 1.20). Secondary: Not reported
Gupta et al.[25] (2008) Griseofulvin (microsize and ultramicrosize formulations)	MA Patients with mycologically-confirmed tinea capitis	N=438 (7 trials) 4 to 6 weeks post-treatment	Primary: Effective cure (negative mycology with few remaining visual signs of infection) Secondary: Not reported	Primary: In the pooled analysis, the overall mean efficacy of griseofulvin at four to six weeks post-treatment was 73.4%. When broken down by species, the mean efficacy for *Trichophyton* and *Microsporum* were 67.6% (five studies, N=396) and 88.1% (two studies, N=42 patients), respectively. Higher efficacy rates were reported for with the use of higher dosages of griseofulvin.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Tinea Corporis and/or Tinea Cruris				
Faergemann et al.[26] (1997) Griseofulvin 500 mg daily for 25 to 28 days vs fluconazole 150 mg weekly for 25 to 28 days Treatment continued for a total of 42 days in patients who were not clinically or mycologically cured at 4 weeks.	DB, MC, PG, RCT Patients 16 to 83 years of age with signs and symptoms of tinea corporis and/or tinea cruris confirmed by microscopy	N=239 42 days	Primary: Clinical cure and mycological cure Secondary: Not reported	Primary: At visit three (days 42 to 44), clinical cure was observed in 74% of fluconazole patients and 62% of griseofulvin patients (P=0.06). At visit three (days 42 to 44) mycological cure was observed in 78% of fluconazole patients and 80% of griseofulvin patients. At visit two (days 25 to 28), clinical cure was observed in 39% of fluconazole patients and 39% of griseofulvin patients. At visit two (days 25 to 28) mycological cure was observed in 72% of fluconazole patients and 70% of griseofulvin patients. Secondary: Not reported
Voravutinon[27] (1993) Griseofulvin 500 mg daily for 2 weeks vs terbinafine 250 mg daily for 2 weeks	CS, DB, RCT Patients with mycologically diagnosed tinea corporis and tinea cruris	N=64 4 week posttreatment follow-up	Primary: Clinical response (clearance of lesions), mycological response (negative culture), relapse rates Secondary: Not reported	Primary: After two weeks of therapy, the clinical response was the same in both groups. After two weeks of therapy, the mycological response was similar in the two groups (90.3% for terbinafine and 80.7% in the griseofulvin). No significant difference was observed. At six weeks, the mycological cure in the terbinafine group was significantly higher than in the griseofulvin group (87.1 and 54.8% respectively, P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				At six weeks, the clinical response was significantly higher in the terbinafine group compared to the griseofulvin group. A higher relapse rate was observed in the griseofulvin group compared to the terbinafine group. Secondary: Not reported
Tinea Pedis				
Roberts et al.[28] (1987) Griseofulvin 1 g daily for up to 8 weeks vs ketoconazole 200 mg daily for up to 8 weeks	RCT Patients with mycologically proven tinea pedis	N=29 8 weeks	Primary: Mycological cure (negative culture) Secondary: Not reported	Primary: At four weeks, the mycological cure rate was 33% in the ketoconazole group and 29% in the griseofulvin group. At eight weeks, the mycological cure rate was 53% in the ketoconazole group and 57% in the griseofulvin group. Secondary: Not reported
Tinea Unguium				
Korting et al.[29] (1993) Griseofulvin ultramicrosize (UMSG) 660 mg daily for up to 18 months vs griseofulvin ultramicrosize (UMSG) 990 mg daily for up to 18	OL, RCT Patients with clinically confirmed tinea unguium of the toenails, fingernails, or both	N=109 18 months	Primary: Clinical response (cure=clinical remission with negative culture and microscopy; partial cure=microscopy alone remained positive; marked improvement= minimal clinical involvement of test nail and no dermatophyte	Primary: There was no significant difference in the cure or partial cure rates between the USMG 660 mg, USMG 990 mg, and itraconazole 100 mg groups (6, 14, and 19% respectively, P=0.2097). Three was no significant difference in the rates of marked improvement between the USMG 660 mg, USMG 990 mg, and itraconazole 100 mg groups (36, 44, and 39% respectively). No significant difference in compliance was observed between groups. Itraconazole was significantly better tolerated compared to both USMG groups (P<0.0322). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
months vs itraconazole 100 mg daily for up to 18 months			growth), compliance, adverse effects Secondary: Not reported	Not reported
Haugh et al.[30] (2002) Griseofulvin 500 mg or 1,000 mg daily for 3 months or 11 months vs itraconazole 200 mg daily or 400 mg intermittently (for 1 of every 4 weeks) for 3 or 4 months vs terbinafine 250 mg daily for 3 or 6 months vs placebo	MA Patients diagnosed with onychomycosis	N=2,063 3 to 11 months	Primary: Mycological cure at the end of the studies (negative microscopy or culture) Secondary: Negative microscopy or culture at specified time points	Primary: <u>Terbinafine vs placebo (three trials)</u> After 12 weeks, a significant advantage in mycological cure rates was seen in favor of the terbinafine group compared to the placebo group. <u>Terbinafine vs itraconazole (four trials)</u> At the end of the study periods, a statistically significant advantage in achieving negative culture and microscopy was seen in favor of terbinafine compared to itraconazole. No significant differences in tolerability were reported. <u>Terbinafine vs griseofulvin (two trials)</u> A significantly higher rate of negative microscopy and culture were observed in the terbinafine groups at week 24 compared to the griseofulvin groups.
Haneke et al.[31] (1995) Griseofulvin	DB, MC, RCT Patients 18 years of age and older with	N=180 1 year	Primary: Clinical response (outgrowth from the border of	Primary: Mycological cure rates increased in both groups during active treatment and continued in the terbinafine group during follow-up while remaining steady in the griseofulvin group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
microsize 500 mg daily for 12 weeks vs terbinafine 250 mg daily for 12 weeks After 12 weeks of treatment, all patients received an additional 12 weeks of placebo followed by 6 months follow-up.	clinically confirmed distal subungual onychomycosis of the fingernails		healthy and infected nails), mean global score (based on onycholysis, hyperkeratosis, brittleness, and paronychial inflammation, mycological cure (negative culture), mean time to negative culture Secondary: Not reported	At week 24, 90% of patients in the terbinafine group and 64% in the griseofulvin group were mycologically cured. At the end of the study, 92% of patients in the terbinafine group and 63% in the griseofulvin group were mycologically cured (P<0.001). Mean time to negative culture was 73 days in the terbinafine group and 93 days in the griseofulvin group. The length of unaffected nail increased in the terbinafine group from 3.2 mm to 11.4 mm (week 24) and 12.4 mm (end of study). In the griseofulvin group, it increased from 2.6 mm to 9.5 mm (week 24) and decreased to 8.7 mm at the end of the study (P=0.006 between groups at the end of the study). The mean global scores decreased in the terbinafine group from 5.8 to 0.9 (week 24) and 0.4 (end of study). In the griseofulvin group, the scores decreased from 5.7 to 1.8 (week 24) and increased to 2.2 at the end of the study (P=0.028 at week 24, P<0.001 at end of study). Secondary: Not reported
Faergemann et al.[32] (1995) Griseofulvin 500 mg daily for 52 weeks vs terbinafine 250 mg daily for 16 weeks Patients who did	DB, PG, RCT Adult patients with culture-proven tinea of the toenails	N=89 52 weeks	Primary: Complete cure (no signs and symptoms of infection and negative culture), mycological cure (negative culture) Secondary: Not reported	Primary: Significantly more patients in the terbinafine group were completely cured (42%) compared to the griseofulvin group (2%) at the end of the study (P<0.0005). Significantly more patients in the terbinafine group experienced mycological cure (84%) compared to the griseofulvin group (45%) at the end of the study (P<0.0005). Of the patients who switched to open-label treatment with terbinafine, 44% were cured at the end of the study (week 52 or 20 weeks after cessation of open-label terbinafine) compared to 18% in the griseofulvin group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
not respond after 16 weeks were switched to OL terbinafine for 16 to 20 weeks of follow-up.				Secondary: Not reported
Hoffman et al.[33] (1995) Griseofulvin micronized 1,000 mg daily for 48 weeks vs terbinafine 250 mg daily for 24 weeks followed by 24 weeks of placebo	DB, RCT Patients 21 to 93 years of age with clinically confirmed distal subungual onychomycosis of the toenails	N=195 72 weeks	Primary: Mycological cure (negative culture), clinical response (global score based on growth of unaffected nail and presence of onycholysis, hyperkeratosis, brittleness, and paronychial inflammation), time to mycological cure Secondary: Not reported	Primary: Mycological cure increased during active therapy in both groups, and slightly decreased in the terbinafine group while sharply decreasing in the griseofulvin group during the follow-up period. At week 48, 88% of terbinafine patients and 82% of griseofulvin patients had negative cultures, while these numbers decreased to 81% and 62% respectively at the end of the study (P=0.02). The time to negative culture was 130 days in the terbinafine group and 172 days in the griseofulvin group (P=0.036). The mean global score in the terbinafine group decreased from 6.3 to 1.4 at week 48 and 0.8 at the end of the study, compared to 7.0 in the griseofulvin group decreasing to 1.7 at week 48 and 1.8 at the end of the study (P=0.010). Secondary: Not reported
General Dermatophyte Infections				
Jolly et al.[34] (1983) Griseofulvin ultramicrosize 250 mg daily for 2 to 16 weeks vs ketoconazole 200	DB, RCT Patients with mycologically confirmed dermatophyte infections	N=137 16 weeks	Primary: Clinical response and mycological response Secondary: Not reported	Primary: Clinical response was observed in 20 of 21 patients in the ketoconazole group compared to nine of 11 in the griseofulvin group. Mycological response was better in the ketoconazole group compared to the griseofulvin group. In the ketoconazole group, 61% achieved remission compared to 39% in the griseofulvin group (P=0.02). In the ketoconazole group, 9% of patients relapsed compared to 43% in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg daily for 2 to 16 weeks				the griseofulvin group (P<0.01). Secondary: Not reported
Stratigos et al.[35] (1983) Griseofulvin 500 mg daily until negative culture or 6 weeks vs ketoconazole 200 mg daily until negative culture or 6 weeks	DB, RCT Patients with clinical symptoms and cultures for dermatophytes	N=50 6 weeks	Primary: Cure rate (no symptoms and negative culture results) Secondary: Not reported	Primary: After two weeks of treatment, 50% of patients in the ketoconazole group vs 25% in the griseofulvin group had negative cultures and this difference was not statistically significant between groups. At three weeks, 88.5% of patients in the ketoconazole group vs 66.6% in the griseofulvin group had negative cultures and this difference was not statistically significant between groups. There was no significant difference in cure rates between groups. Secondary: Not reported
Legendre et al.[36] (1980) Griseofulvin ultramicrosize 250 mg daily for 28 to 60 days vs ketoconazole 200 mg daily for 28 to 60 days	DB, RCT Patients with microscopically confirmed dermatophyte infection of the skin	N=58 28 day posttreatment follow-up	Primary: Response to therapy (cure=clearance of lesions and negative culture), relapse rates Secondary: Not reported	Primary: Cure was obtained in 38% of patients in the ketoconazole group and 24% of patients in the griseofulvin group after four weeks of therapy. After 60 days of therapy, cure was obtained in 83% of ketoconazole patients and 32% of griseofulvin patients (P<0.001). Of the patients cured after four weeks of treatment, none of the ketoconazole patients relapsed and all of the griseofulvin patients relapsed (P=0.001). Of all the patients cured regardless of duration of therapy, 7% of ketoconazole patients relapsed within 28 days compared to 80% in the griseofulvin group (P=0.006). Secondary: Not reported
Martinez-Roig et al.[37]	DB, RCT	N=47	Primary: Response to	Primary: After six weeks of therapy, clinical and mycological cure or improvement

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1988) Griseofulvin 350 mg daily divided every 12 hours until lesions had cleared and negative culture was obtained vs ketoconazole 100 mg daily divided every 12 hours until lesions had cleared and negative culture was obtained	Patients 3 months to 14 years of age with dermatophyte infections who had not received previous antifungal therapy	2 week posttreatment follow-up	therapy (clinical cure= clearance of lesions and mycological cure= negative culture), time to clinical cure and negative culture Secondary: Not reported	was seen in 92% of patients treated with ketoconazole and 76% of patients treated with griseofulvin. The time to clinical cure and negative cultures was shorter for patients treated with ketoconazole compared to griseofulvin for tinea capitis, and shorter for griseofulvin compared to ketoconazole for tinea corporis, though no significant difference was observed in overall response to therapy. Secondary: Not reported

Study abbreviations: CI=confidence interval, CS=comparative study, DB=double blind, DD=double dummy, MA=meta-analysis, MC=multi-center, OL=open label, OR=odds ratio, PG=parallel group, PRO=prospective trial, RCT=randomized controlled trial, RR=relative risk, SB=single blind

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 10. Relative Cost of the Antifungals, Miscellaneous

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Griseofulvin microsize	suspension, tablet	Grifulvin V®*	$$$$	$$$
Griseofulvin ultramicrosize	tablet	Gris-Peg®*	$$$$	$$$$

N/A=Not available

X. Conclusions

Griseofulvin is approved for the treatment of tinea barbae, tinea capitis, tinea corporis, tinea cruris, tinea pedis, and tinea unguium (onychomycosis).[1-4] It is available in two formulations (microsize and ultramicrosize), which differ in their pharmacokinetic properties. This allows for the administration of lower doses with the ultramicrosize products; however, there is currently no evidence that this lower dose confers any significant clinical differences with regards to efficacy or safety.[4] All products are available in a generic formulation.

For the treatment of onychomycosis, guidelines recommend the use of systemic antifungals as they are generally more effective than topical treatments.[5-6] Oral monotherapy or combined oral/topical therapy is recommended as initial therapy.[5] Terbinafine should be considered as a first-line treatment option and itraconazole may be considered as a second-line treatment.[6] Clinical trials evaluating the efficacy of griseofulvin in the treatment of onychomycosis have demonstrated greater clinical and/or mycological cure rates with terbinafine compared to griseofulvin.[30-33]

For the treatment of tinea capitis, guidelines recommend the use of systemic antifungals because topical agents do not penetrate the hair follicle.[7-8] Fluconazole, itraconazole, griseofulvin, and terbinafine have similar efficacy and safety profiles for the treatment tinea capitis due to *Trichophyton* species.[7-8] Griseofulvin is recommended as initial therapy for the treatment of tinea capitis due to *Microsporum* species.[7] Several studies have demonstrated similar clinical cure rates with griseofulvin compared to fluconazole, itraconazole, ketoconazole, and terbinafine for the treatment of cutaneous dermatophyte infections.[9,11,13-14,17,20-22,24-28,35,37] There were no studies found in the medical literature that directly compared the different formulations of griseofulvin.

There is insufficient evidence to support that one brand miscellaneous antifungal is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand miscellaneous antifungals within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand miscellaneous antifungal is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Antituberculosis Agents
AHFS Class 081604
November 12, 2014

I. Overview

Tuberculosis is a common and often deadly infectious disease that typically affects the pulmonary system; however, all parts of the body can be affected by the disease. Tuberculosis is contracted through the inhalation of droplet nuclei containing *Mycobacterium tuberculosis* organisms, which are generated when a person with active pulmonary disease coughs, sneezes, talks, or sings.[1] Following the initial infection, viable bacilli can persist for several years resulting in a latent tuberculosis infection, which is asymptomatic and not infectious. Active disease can develop immediately after the initial exposure or after reactivation of latent tuberculosis infection.

The treatment of tuberculosis is a long-term process and focuses on treating active disease, as well as latent infections. Standard treatment regimens for active disease include an initial phase, which kills rapidly multiplying populations of *Mycobacterium tuberculosis*. This is followed by a continuation phase, which kills the intermittently dividing populations.[2-14] The initial phase of treatment includes ≥3 antituberculosis agents to prevent the emergence of drug resistance. Treatment of latent tuberculosis consists of monotherapy for six to nine months. For the treatment of multi-drug resistant tuberculosis, four second-line antituberculosis agents should be used for ≥8 months.[15] Bedaquiline is the newest agent approved for multi-drug resistant tuberculosis and has a novel mechanism of action compared to the other antituberculosis agents.[14]

Mycobacterium avium complex organisms are the most common cause of nontuberculous mycobacterial disease in the United States.[16] Rifabutin is the only antituberculosis agent approved for the prevention of disseminated Mycobacterium avium complex in patients with advanced human immunodeficiency virus infection.

The antituberculosis agents that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Cycloserine, ethambutol, isoniazid, pyrazinamide, rifabutin, rifampin, and rifampin-isoniazid are available in a generic formulation. This class was last reviewed in May 2012.

Table 1. Antituberculosis Agents Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single-entity Agents			
Aminosalicylic acid	packet	Paser®	none
Bedaquiline	tablet	Sirturo®	none
Capreomycin	injection	Capastat Sulfate®	none
Cycloserine	capsule	N/A	cycloserine
Ethambutol	tablet	Myambutol®*	ethambutol
Ethionamide	tablet	Trecator®	none
Isoniazid	injection, syrup, tablet	N/A	isoniazid
Pyrazinamide	tablet	N/A	pyrazinamide
Rifabutin	capsule	Mycobutin®*	rifabutin
Rifampin	capsule, injection	Rifadin®*	rifampin
Rifapentine	tablet	Priftin®	none
Combination Products			
Rifampin and isoniazid	capsule	Rifamate®	none
Rifampin, isoniazid, and pyrazinamide	tablet	Rifater®	none

*Generic is available in at least one dosage form or strength.
N/A=Not available, PDL=Preferred Drug List

The antituberculosis agents have been shown to be active against the strains of microorganisms indicated in Table 2. This activity has been demonstrated in clinical infections and is represented by the Food and Drug Administration (FDA)-approved indications for the antituberculosis agents that are noted in Tables 7 and 8. These agents may also have been found to show activity to other microorganisms in vitro; however, the clinical significance of this is unknown since their safety and efficacy in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials. Although empiric anti-infective therapy may be initiated before culture and susceptibility test results are known, once results become available, appropriate therapy should be selected.

Table 2. Microorganisms Susceptible to the Antituberculosis Agents[2-14]

Organism	Amino-salicylic Acid	Bedaquiline	Capreo-mycin	Cycloserine	Ethambutol	Ethionamide	Isoniazid	Pyrazin-amide	Rifabutin	Rifampin	Rifa-pentine
Gram-Negative Aerobes											
Enterobacter species				✔							
Escherichia coli				✔					✔		
Neisseria meningitidis										✔	
Mycobacteria											
Mycobacterium avium									✔		
Mycobacterium intracellulare									✔		
Mycobacterium tuberculosis	✔	✔	✔	✔	✔	✔	✔	✔		✔	✔

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the antituberculosis agents are summarized in Tables 3 through 6.

Table 3. Treatment Guidelines Using the Antituberculosis Agents

Clinical Guideline	Recommendation(s)
American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: **Controlling Tuberculosis in the United States (2005)**[1]	• Failure to receive and complete a standard course of treatment for tuberculosis has adverse consequences, including treatment failure, relapses, increased tuberculosis transmission, and the emergence of drug-resistant tuberculosis. • These adverse outcomes are preventable by case-management strategies provided by tuberculosis-control programs, including use of directly-observed therapy. • Patient-specific strategies for promoting adherence to treatment should take into account each patient's clinical and social circumstances and needs. • The initial strategy used should emphasize direct observation of medication ingestion by a healthcare worker. • Patient input into this process (e.g., regarding medications to be taken or the location of directly-observed therapy) is often useful as it can minimize the burden of treatment and provide the patient a degree of control over an anticipated lengthy course of therapy.
World Health Organization: **Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis (2011)**[15]	<u>Composition of anti-tuberculosis regimens for multi-drug resistant tuberculosis</u> • In the treatment of patients with multi-drug resistant tuberculosis, four second-line antituberculosis drugs likely to be effective (including a parenteral agent), as well as pyrazinamide, should be included in the intensive phase. • In the treatment of patients with multi-drug resistant tuberculosis, a fluoroquinolone should be used. • A later-generation fluoroquinolone, rather than an earlier-generation fluoroquinolone, should be used. • In the treatment of patients with multi-drug resistant tuberculosis, ethionamide (or prothionamide) should be used. • In the treatment of patients with multi-drug resistant tuberculosis, regimens should include at least pyrazinamide, a fluoroquinolone, a parenteral agent, ethionamide (or prothionamide), and either cycloserine or p-aminosalicylic acid if cycloserine cannot be used. <u>Duration of second-line anti-tuberculosis regimens</u> • In the treatment of patients with multi-drug resistant tuberculosis, an intensive phase of ≥8 months is recommended. • A total of ≥20 months of therapy is recommended for those without any previous multi-drug resistant tuberculosis treatment.
Centers for Disease Control and Prevention: **Recommendations for Use of an Isoniazid-Rifapentine Regimen with Direct Observation to Treat Latent *Mycobacterium tuberculosis* Infection (2011)**[17]	<u>Patients for whom isoniazid-rifapentine is recommended</u> • The combination of isoniazid and rifapentine given as 12 weekly directly observed therapy doses is recommended as an equal alternative to nine months of daily self-supervised isoniazid for treating latent tuberculosis infection in otherwise healthy patients aged ≥12 years who have a predictive factor for greater likelihood of tuberculosis developing. • Human immunodeficiency virus-infected patients who are otherwise healthy and are not taking antiretroviral medications also are included in this category. • Recommendations for using the previous regimens for treating latent tuberculosis infection are unchanged, and the rifampin-pyrazinamide regimen is not recommended. • The choice between isoniazid and isoniazid-rifapentine depends on feasibility of directly observed therapy, resources for drug procurement, program operations including patient monitoring, expectance of treatment completion as foreseen from medical and social circumstances of the patient, and preferences

Clinical Guideline	Recommendation(s)

	of the patient and the prescribing physician.
	• The preferred regimen for children aged two to 11 years is nine months of daily isoniazid.
	
	<u>Patients for whom isoniazid-rifapentine is not recommended</u>
	• Isoniazid-rifapentine is not recommended for the following patients:
	  o Children less than two years of age.
	  o Human immunodeficiency virus-infected patients receiving antiretroviral treatment.
	  o Pregnant women or women expecting to become pregnant during treatment.
	  o Patients who have latent tuberculosis infection with presumed isoniazid or rifampin resistance.

World Health Organization: **Treatment of Tuberculosis (2010)**[18]	<u>General treatment considerations</u> • The essential drugs for the treatment of tuberculosis include isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin. They can be dosed daily or three times weekly. • Fixed-dose combination products are recommended to help prevent drug resistance. Prescription errors are likely to be less frequent because dosage recommendations are more straightforward, and adjustment of dosage according to patient weight is easier. The number of tablets to ingest is smaller and may encourage patient adherence. <u>New patients</u> • The two-month rifampicin regimen (two months isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by six months isoniazid and ethambutol) is associated with more relapses and deaths than the six-month rifampicin regimen (two months isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by four months isoniazid and rifampicin). • New patients with pulmonary tuberculosis should receive a regimen containing six months of rifampicin. The standard regimens for new tuberculosis patients includes two months of isoniazid, rifampicin, pyrazinamide, and ethambutol (intensive phase treatment) and four months of isoniazid and rifampicin (continuation phase). • The two month isoniazid, rifampicin, pyrazinamide, and ethambutol /six month isoniazid and ethambutol treatment regimen should be phased out. • Wherever feasible, the optimal dosing frequency for new patients with pulmonary tuberculosis is daily throughout the course of therapy. • New patients with pulmonary tuberculosis may receive a daily intensive phase followed by three times weekly continuation phase (two months isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by four months isoniazid and rifampicin) provided that each dose is directly observed. • Three times weekly dosing throughout therapy [two months (isoniazid, rifampicin, pyrazinamide, and ethambutol) three/four months (isoniazid and rifampicin)] is another alternative, provided that every dose is directly observed and the patient is not living with human immunodeficiency virus or living in an human immunodeficiency virus-prevalent setting. • New patients with tuberculosis should not receive twice weekly dosing for the full course of treatment unless this is done in the context of formal research. • In populations with known or suspected high levels of isoniazid resistance, new tuberculosis patients may receive isoniazid, rifampicin, and ethambutol as therapy in the continuation phase as an acceptable alternative to isoniazid and rifampicin. <u>Standard regimens for previously treated patients</u>

Clinical Guideline	Recommendation(s)
	• Tuberculosis patients whose treatment has failed or other patient groups with high likelihood of multidrug-resistant tuberculosis should be started on an empirical multidrug-resistant regimen. • Tuberculosis patients returning after defaulting or relapsing from their first treatment course may receive the retreatment regimen containing first-line drugs (two months isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin/one month isoniazid, rifampicin, pyrazinamide, and ethambutol/five months isoniazid, rifampicin, and ethambutol) if country-specific data show low or medium levels of multidrug-resistant in these patients or if such data are not available.
World Health Organization: **Interim Guidance on the Use of Bedaquiline in the Treatment of Multi-drug Resistant Tuberculosis (2013)**[19]	• Bedaquiline may be added to a World Health Organization recommended regimen in adult multi-drug resistance pulmonary tuberculosis patients with the following conditions: o Treatment is administered under closely monitored conditions which adhere to best practices in treatment delivery to enable optimal drug effectiveness and safety. o Proper patient inclusion based on current recommendations for dosage and administration, patient characteristics, and diagnosis. o Informed patient consent is obtained to ensure patient is aware of the risks and benefits of therapy with bedaquiline. o Principles of designing a World Health Organization recommended multi-drug resistant tuberculosis regimen are adhered to. o Vigilance and proper management for early detection of adverse drug reactions and prevention of drug-drug reactions.
Centers for Disease Control and Prevention: **Provisional Centers for Disease Control and Prevention Guidelines for the Use and Safety Monitoring of Bedaquiline Fumarate (Sirturo®) for the Treatment of Multi-drug resistant Tuberculosis (2013)**[20]	• Bedaquiline may be used for 24 weeks of treatment in adults with laboratory-confirmed pulmonary multi-drug resistant tuberculosis when an effective treatment regimen cannot otherwise be provided. • Bedaquiline may be used on a case-by-case basis when an effective treatment regimen cannot otherwise be provided in the following groups: o Children. o Human immunodeficiency virus-infected persons. o Pregnant woman. o Persons with extrapulmonary multi-drug resistant tuberculosis. o Patients with comorbid conditions on concomitant medications. • The use of bedaquiline with rifamycins or other drugs that induce or suppress CYP3A4 should be avoided unless benefits outweigh risks. • Bedaquiline should never be used at monotherapy and should be used in combination with at least three drugs. • Bedaquiline should be administered by directly-observed therapy and with case management.
World Health Organization: **Guidance for Tuberculosis Programmes on the Management of Tuberculosis in Children (2014)**[21]	• For children with suspected or confirmed pulmonary tuberculosis or tuberculosis peripheral lymphadenitis in settings with low human immunodeficiency virus prevalence and/or low prevalence of isoniazid resistance and in human immunodeficiency virus negative children, a three-drug regimen (isoniazid, rifampicin, and pyrazinamide) for two months followed by a two drug regimen (isoniazid and rifampicin) for four months is recommended. • For children with suspected or confirmed pulmonary tuberculosis or tuberculosis peripheral lymphadenitis and or children with extensive pulmonary disease in settings with high human immunodeficiency virus prevalence and/or high prevalence of isoniazid resistance, a four-drug regimen (ethambutol, isoniazid, rifampicin, and pyrazinamide) for two months followed by a two drug regimen (isoniazid and rifampicin) for four months is recommended. • For children zero to three months of age, standard treatment regimens may

Clinical Guideline	Recommendation(s)
	require dosage adjustment to account for the effect of age and possible toxicity in young infants. The decision for dosage adjustment should be made by a clinician experienced in pediatric tuberculosis management. • Thrice-weekly regimens can be considered during the continuation phase for human immunodeficiency virus negative children and in settings with well-established directly-observed therapy. • Streptomycin is not recommended as part of first-line therapy in children with pulmonary tuberculosis or tuberculosis peripheral lymphadenitis. • For children with suspected or confirmed tuberculosis meningitis or suspected or confirmed osteoarticular tuberculosis, a four-drug regimen (ethambutol, isoniazid, rifampicin, and pyrazinamide) for two months followed by a two drug regimen (isoniazid and rifampicin) for ten months is recommended. • Children with human immunodeficiency virus >12 months of age, unlikely to have tuberculosis, and have no contact with a tuberculosis case should be offered isoniazid prevention therapy in settings with high tuberculosis prevalence. In settings with medium to low tuberculosis prevalence, these patients may be offered isoniazid prevention therapy. • Children with suspected or confirmed pulmonary tuberculosis or tuberculosis peripheral lymphadenitis in settings with high human immunodeficiency virus prevalence (or confirmed human immunodeficiency virus infection) should not be treated with intermittent regimens (e.g., twice-weekly, thrice-weekly). • For children with suspected or confirmed pulmonary tuberculosis or tuberculosis meningitis caused by multi-drug resistant bacilli, a fluoroquinolone within and appropriate multi-drug resistant tuberculosis regimen is recommended. The decision to treat should be made by a clinician experienced in pediatric tuberculosis management.

American Thoracic Society:
Hepatotoxicity of Antituberculosis Therapy (2006)[22]
	• Drug-induced liver injury is a concern when treating patients with tuberculosis.
	• Drug-induced liver injury may occur with all currently recommended regimens for the treatment of active tuberculosis and latent tuberculosis infection.
	
	<u>Treatment of latent tuberculosis infection</u>
	• The clinician and patient should determine the appropriate regimen together relative to the risks and the following should be considered:
	  o Isoniazid taken for nine months remains the preferred regimen.
	  o Rifampin is an option for patients who may not tolerate isoniazid, but potential drug interactions should be considered.
	  o Since isoniazid with rifampin is more hepatotoxic than either alone, this combination should be used with caution in patients at risk for hepatotoxicity.
	  o For patients with alanine aminotransferase elevations more than 2.5 to three times the upper limit of normal, chronic alcohol consumption, or severe liver disease (low albumin and coagulopathy or encephalopathy), the risks may outweigh the benefits; if latent tuberculosis infection treatment initiated, monitoring is recommended.
	  o Rifampin and pyrazinamide combination is no longer recommended for the treatment of latent tuberculosis infection.
	• Interventions for hepatotoxicity include the following:
	  o If alanine aminotransferase is at least three times the upper limit of normal when jaundice and/or hepatitis symptoms are reported, or if alanine aminotransferase is at least five times the upper limit of normal in the absence of symptoms, then isoniazid should be withheld. An indication of more frequent monitoring would be a rapid increase in alanine aminotransferase.
	  o In situations where a patient may be initiated on isoniazid for the treatment of latent tuberculosis infection with baseline alanine

Clinical Guideline	Recommendation(s)
	aminotransferase more than three times the upper limit of normal, the treatment should be discontinued if there is more than a two to three-fold increase in alanine aminotransferase above baseline. o For patients with cirrhosis, treatment with rifampin and ethambutol, with levofloxacin, moxifloxacin, gatifloxacin, or cycloserine, for 12 to 18 months may be considered. • Re-challenge strategies include the following: o Once the alanine aminotransferase returns to less than two times the upper limit of normal, rifampin may be started with or without ethambutol. o After three to seven days, isoniazid may be restarted while monitoring alanine aminotransferase. o If symptoms occur or alanine aminotransferase increases, the last agent added should be discontinued. <u>Treatment of tuberculosis</u> • The crucial efficacy of isoniazid and rifampin warrants their use and retention, if at all possible, even in the face of preexisting liver disease. Several regimens are recommended if baseline serum alanine aminotransferase is more than three times the upper limit of normal, and tuberculosis is not believed to be the cause: o Treatment without pyrazinamide might utilize isoniazid and rifampin for nine months with ethambutol until drug susceptibility testing of the *Mycobacterium tuberculosis* isolate is completed. o In patients with cirrhosis, rifampin and ethambutol, with levofloxacin, moxifloxacin, gatifloxacin, or cycloserine, for 12 to 18 months may be considered. o For patients with encephalopathic liver disease, ethambutol combined with a fluoroquinolone, cycloserine, and capreomycin or aminoglycoside for 18 to 24 months may be an option. However, these regimens have not been tested systematically. o Some providers avoid aminoglycosides in severe, unstable liver disease due to concerns about renal insufficiency, or bleeding from injected medication in patients with thrombocytopenia and/or coagulopathy. • Interventions for hepatotoxicity include: o The first-line anti-tuberculosis drugs, especially rifampin, should not be discontinued for mild gastrointestinal complaints, which may be relatively frequent in the initial weeks of anti-tuberculosis treatment. o If serum transaminase concentrations are more than five times the upper limit of normal (with or without symptoms) or more than three times the upper limit of normal with jaundice and/or hepatitis symptoms, then potentially hepatotoxic medications should be stopped immediately and the patient evaluated promptly. o Serologic tests for hepatitis A, B, and C viruses should be obtained, and the patient should be evaluated for biliary disease, use of alcohol, and other hepatotoxic drugs. o Some experts recommend interrupting treatment for lesser increases in patients with cirrhosis or encephalopathy. o If indicated, until the specific cause of abnormalities can be determined, clinicians should treat with at least three anti-tuberculosis agents that are less likely to cause hepatotoxicity. • Re-challenge strategies include the following: o After alanine aminotransferase returns to less than two times the upper limit of normal, rifampin may be restarted with or without ethambutol.

Clinical Guideline	Recommendation(s)
	o After three to seven days, isoniazid may be reintroduced, subsequently rechecking alanine aminotransferase. o If symptoms recur or alanine aminotransferase increases, the last drug added should be stopped. o For those who have experienced prolonged or severe hepatotoxicity, but tolerate reintroduction with rifampin and isoniazid, re-challenge with pyrazinamide may be hazardous. In this circumstance, pyrazinamide may be permanently discontinued, with treatment extended to nine months. Although pyrazinamide can be reintroduced in some milder cases of hepatotoxicity, the benefit of a shorter treatment course likely does not outweigh the risk of severe hepatotoxicity from pyrazinamide re-challenge.
Pediatric Tuberculosis Collaborative Group: **Targeted Tuberculin Skin Testing and Treatment of Latent Tuberculosis Infection in Children and Adolescents (2004)**[23]	• Treatment of latent tuberculosis infection with nine months of daily isoniazid remains the recommended regimen for children and adolescents without a known source case or with a source case whose *Mycobacterium tuberculosis* isolate is susceptible to isoniazid. • Intermittent (two- or three-times-per-week) regimens are acceptable if these regimens are administered by using a directly-observed therapy program. • Daily rifampin for six months is a suitable alternative for patients with latent tuberculosis infection who have been exposed to a source case whose isolate is resistant to isoniazid but susceptible to rifampin or for those who cannot tolerate isoniazid. • Shorter-course regimens with rifampin and pyrazinamide are not recommended because of hepatotoxicity observed in adults and the lack of clinical data in children.
Centers for Disease Control and Prevention: **Adverse Event Data and Revised American Thoracic Society/Centers for Disease Control and Prevention Recommendations Against the use of Rifampin and Pyrazinamide for Treatment of Latent Tuberculosis Infection—United States (2003)**[24]	• The Centers for Disease Control and Prevention reported data of severe liver injury in patients treated for latent tuberculosis infections with a daily and twice-weekly two-month regimen of rifampin and pyrazinamide. • It is recommended that rifampin and pyrazinamide not be offered to persons with latent tuberculosis infection. • Clinicians are advised to use the recommended alternative regimens for the treatment of latent tuberculosis infection (refer to Table 6 for specific treatment regimens). • Rifampin and pyrazinamide should continue to be administered in multidrug regimens for the treatment of persons with active tuberculosis disease.
American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: **Practice Guidelines for the Treatment of Tuberculosis (2003)**[25]	• Of the approved drugs, isoniazid, rifampin, ethambutol, and pyrazinamide are considered first-line antituberculosis agents and form the core of initial treatment regimens. • Rifabutin and rifapentine may also be considered first-line agents under the specific situations described below. • Streptomycin was formerly considered to be a first-line agent and, in some instances, is still used in initial treatment; however, an increasing prevalence of resistance to streptomycin in many parts of the world has decreased its overall usefulness. • Because of the relatively high proportion of adult patients with tuberculosis caused by organisms that are resistant to isoniazid, four drugs are necessary in the initial phase for the six-month regimen to be maximally effective. • In most circumstances, the treatment regimen for all adults with previously untreated tuberculosis should consist of a two-month initial phase of isoniazid,

Clinical Guideline	Recommendation(s)
	rifampin, pyrazinamide, and ethambutol. When drug susceptibility test results are known and the organisms are fully susceptible, ethambutol need not be included. • For children whose visual acuity cannot be monitored, ethambutol is usually not recommended except when there is an increased likelihood of the disease being caused by isoniazid-resistant organisms or when the child has "adult-type" (upper lobe infiltration, cavity formation) tuberculosis. • If pyrazinamide cannot be included in the initial phase of treatment, or if the isolate is resistant to pyrazinamide alone, the initial phase should consist of isoniazid, rifampin, and ethambutol given daily for two months. Examples of circumstances in which pyrazinamide may be withheld include severe liver disease, gout, and, perhaps, pregnancy. • Although clinical trials have shown that the efficacy of streptomycin is approximately equal to that of ethambutol in the initial phase of treatment, the increasing frequency of resistance to streptomycin globally has made the drug less useful. Thus, streptomycin is not recommended as being interchangeable with ethambutol unless the organism is known to be susceptible to the drug or the patient is from a population in which streptomycin resistance is unlikely. • Streptomycin is the only antituberculosis drug documented to have harmful effects on the human fetus (congenital deafness) and should not be used in pregnancy. • Amikacin and kanamycin are two closely related injectable second-line drugs that are used for patients with drug-resistant tuberculosis whose isolate has demonstrated or presumed susceptibility to the agents. There is nearly always complete cross-resistance between the two drugs, but most streptomycin-resistant strains are susceptible to both. Because it is used to treat a number of other types of infections, amikacin may be more easily obtained, and serum drug concentration measurements are readily available.

American Thoracic Society/Centers for Disease Control and Prevention:
Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection (2000)[26]
	• (Recommendations were updated in 2003 – see above guideline)
	• Treatment of latent tuberculosis infection is an essential part of the strategy to eliminate tuberculosis in the United States.
	• Persons with latent tuberculosis infection who are included among those at increased risk for tuberculosis should be offered treatment.
	• Four treatment regimens are recommended:
	  o Isoniazid treatment for six months or nine months – human immunodeficiency virus negative.
	  o Isoniazid should be given for nine months – human immunodeficiency virus positive.
	  o Rifampin and pyrazinamide should be given for two months – both human immunodeficiency virus positive and negative.
	  o Rifampin should be given for four months for both human immunodeficiency virus positive and human immunodeficiency virus negative.
	• The preferred regimen for treatment of latent tuberculosis infection in pregnant women is isoniazid, administered either daily or twice weekly.
	• The only recommended regimen for treatment of latent tuberculosis infection in human immunodeficiency virus-uninfected children is a nine-month course of isoniazid as self-administered daily therapy or by directly observed therapy twice weekly.
	• No studies have been published regarding the efficacy of any form of treatment for latent tuberculosis infection in human immunodeficiency virus -infected children. The American Academy of Pediatrics currently recommends a nine-month course of isoniazid.
	• The optimal length of rifampin therapy in children with latent tuberculosis infection is not known; however, the American Academy of Pediatrics

Clinical Guideline	Recommendation(s)
	recommends six months of treatment.
National Institutes of Health, the Centers for Disease Control and Prevention, and the Human Immunodeficiency Virus Medicine Association of the Infectious Diseases Society of America: **Guidelines for Prevention and Treatment of Opportunistic Infections in Human Immunodeficiency Virus -Infected Adults and Adolescents (2013)**[27]	Aspergillosis • Voriconazole is the drug of choice but should be used cautiously with human immunodeficiency virus protease inhibitors and efavirenz. Amphotericin B deoxycholate at 1 mg/kg daily or lipid-formulation amphotericin B at 5 mg/kg daily are alternatives, as is caspofungin at 50 mg daily and posaconazole. • Other echinocandins, such as micafungin and anidulafungin, are reasonable alternatives. • For treatment failure (if voriconazole was used initially) substitution with amphotericin B, posaconazole, or echinocandins might be considered; the amphotericin B or echinocandins would be rational for those who began therapy with voriconazole or posaconazole. Candidiasis (mucocutaneous) • Oral fluconazole is as effective as topical therapy for oropharyngeal candidiasis and is considered the drug of choice. Initial episodes of oropharyngeal candidiasis can be adequately treated with topical therapy, including clotrimazole troches, nystatin suspension or pastilles, or miconazole mucoadhesive tablets. Itraconazole oral solution for seven to 14 days is as effective as oral fluconazole but less well tolerated. Posaconazole oral solution is also as effective as fluconazole and is generally better tolerated than itraconazole. Intravenous amphotericin B is usually effective and can be used among patients with refractory disease. Both conventional amphotericin B and lipid complex and liposomal amphotericin B have been used. • Systemic antifungals are required for effective treatment of esophageal candidiasis. A 14 to 21-day course of either fluconazole (oral or intravenous) or oral itraconazole solution is highly effective. Oral ketoconazole or itraconazole capsules are less effective than fluconazole because of variable absorption. Although intravenous caspofungin or intravenous voriconazole are effective in treating esophageal candidiasis among human immunodeficiency virus -infected patients, oral or intravenous fluconazole remain the preferred therapies. Azole-refractory esophageal candidiasis can be treated with posaconazole, amphotericin B, anidulafungin, caspofungin, micafungin, or voriconazole. • Vulvovaginal candidiasis in human immunodeficiency virus -infected women is usually uncomplicated (90%) and responds readily to short-course oral or topical treatment with any of several therapies, including oral fluconazole, topical azoles, and itraconazole oral solution. Severe or recurrent episodes of vaginitis require oral fluconazole or topical antifungal therapy for ≥7 days. Coccidioidomycosis • For patients with clinically mild infection, such as focal pneumonia or a positive coccidioidal serologic test alone, initial therapy with a triazole antifungal is appropriate. • For patients with either diffuse pulmonary involvement or severely ill patients with extrathoracic disseminated disease, amphotericin B is the preferred initial therapy. Therapy with amphotericin B should continue until clinical improvement is observed. Some specialists would use a triazole antifungal concurrently with amphotericin B and continue the triazole once amphotericin B is stopped. Cryptococcosis • The recommended initial standard treatment is amphotericin B combined with flucytosine for ≥2 weeks for those with normal renal function. • The combination of amphotericin B with fluconazole is less effective than amphotericin B combined with flucytosine in terms of clearing *Cryptococcus*

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	from the cerebrospinal fluid but is better than amphotericin B alone. • Fluconazole combined with flucytosine is an alternative to amphotericin B plus flucytosine, but is less effective than amphotericin B and is recommended only for persons unable to tolerate or unresponsive to standard treatment. • After at least a two-week period of successful induction therapy, amphotericin B and flucytosine may be discontinued and follow-up therapy initiated with fluconazole. This should continue for eight weeks. Itraconazole is an acceptable though less effective alternative. • The optimal therapy for those with treatment failure is not established. For those initially treated with fluconazole, therapy should be changed to amphotericin B, with or without flucytosine, and continued until a clinical response occurs. Liposomal amphotericin B may have improved efficacy over the deoxycholate formulation and should be considered in treatment failures. Higher doses of fluconazole in combination with flucytosine might also be useful. <u>Cryptosporidiosis</u> • In the setting of severe immunosuppression, antiretroviral therapy with immune restoration to a CD4+ count >100 cells/µL leads to resolution of clinical cryptosporidiosis and is the mainstay of treatment. • All patients with cryptosporidiosis should be offered antiretroviral therapy as part of the initial management of their infection. • Management should include symptomatic treatment of diarrhea. Rehydration and repletion of electrolyte losses by either the oral or intravenous route are important. Severe diarrhea can exceed >10 L/day among patients with acquired immunodeficiency syndrome, often requiring intensive support. Aggressive efforts at oral rehydration should be made with oral rehydration solutions. <u>Prevention of Cytomegalovirus</u> • Cytomegalovirus end-organ disease is best prevented by using antiretroviral therapy to maintain the CD4+ count >100 cells/µL. • Although oral valganciclovir would likely prevent the occurrence of cytomegalovirus retinitis in patients with CD4+ counts <50 cells/µL, such therapy is not generally recommended because of the potential to induce cytomegalovirus resistance, the utility of treating disease when it occurs, and the lack of demonstrated survival advantage. <u>Treatment of Cytomegalovirus disease</u> • Oral valganciclovir, intravenous ganciclovir, intravenous ganciclovir followed by oral valganciclovir, intravenous foscarnet, and intravenous cidofovir are all effective treatments for cytomegalovirus retinitis. • The ganciclovir implant, a surgically-implanted reservoir of ganciclovir, which lasts approximately six months, also is very effective but it no longer is being manufactured. In its absence, some clinicians will use intravitreal injections of ganciclovir or foscarnet in conjunction with oral valganciclovir, at least initially, to provide immediate high intraocular levels of drug and presumably faster control of the retinitis. • Systemic therapy has been shown to reduce morbidity in the contralateral eye. This should be considered when choosing between the oral, intravenous, and local options. • The choice of initial therapy for cytomegalovirus retinitis should be individualized based on the location and severity of the lesion(s), the level of underlying immune suppression, and other factors such as concomitant medications and ability to adhere to treatment. • No one regimen has been proven in a clinical trial to have greater efficacy in

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	terms of protecting vision, and thus clinical judgment must be used when choosing a regimen. • In studies conducted in the pre-antiretroviral therapy era, ganciclovir intraocular implant plus oral ganciclovir was superior to once-daily intravenous ganciclovir for treatment of cytomegalovirus retinitis; however, the implant is no longer manufactured. Assuming that this observation can be extended to other combinations of systemically and locally administered drugs, human immunodeficiency virus-specialists often recommend intravitreal ganciclovir or foscarnet injections plus oral valganciclovir as the preferred initial therapy for patients with immediate sight-threatening lesions. Intravitreal injections deliver high concentrations of the drug to the target organ immediately while steady-state concentrations in the eye are achieved with systemically delivered medications. For patients with small peripheral lesions, oral valganciclovir alone often is adequate. • After induction therapy, secondary prophylaxis (i.e., chronic maintenance therapy) should be continued until immune reconstitution occurs as a result of antiretroviral therapy. Regimens demonstrated to be effective for chronic suppression in randomized, controlled clinical trials include parenteral ganciclovir, oral valganciclovir, parenteral foscarnet, combined parenteral ganciclovir and foscarnet, and parenteral cidofovir. <u>Management of Cytomegalovirus retinitis treatment failures</u> • When patients relapse while receiving maintenance therapy, induction with the same drug followed by reinstitution of maintenance therapy can control the retinitis, although for progressively shorter periods of time with each relapse. • Ganciclovir and foscarnet in combination appear to be superior in efficacy to either agent alone and should be considered for patients whose disease does not respond to single-drug therapy, and for patients with multiple relapses of retinitis. This drug combination, however, is associated with substantial toxicity. <u>Treatment of Hepatitis B Virus coinfection in patients not receiving antiretroviral therapy</u> • For patients with CD4+ counts >350 cells/µL who are not receiving antiretroviral therapy but meet criteria for hepatitis B virus treatment, adefovir or peginterferon alfa-2a monotherapy for 48 weeks might be considered, with close monitoring of hepatitis B virus deoxyribonucleic acid levels and follow-up to evaluate for hepatitis B e antigen seroconversion. However, early initiation of antiretroviral therapy should also be considered for human immunodeficiency virus/hepatitis B virus -coinfected persons with CD4+ counts >350 cells/µL. <u>Treatment of Hepatitis B Virus coinfection in patients who require antiretroviral therapy</u> • For human immunodeficiency virus-infected persons, some experts recommend combination therapy with two agents active against hepatitis B virus to reduce the risk of hepatitis B virus drug resistance; although, there are no results from controlled trials as yet to support this strategy. • Among patients infected with hepatitis B virus, hepatitis C virus, and human immunodeficiency virus, consideration of the need for antiretroviral therapy should be the first priority. If antiretroviral therapy is not required, interferon-based therapy, which suppresses both hepatitis C virus and hepatitis B virus, should be considered. If interferon-based therapy for hepatitis C virus has failed, treatment of chronic hepatitis B with nucleoside or nucleotide analogs is recommended.

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	Treatment of Hepatitis C coinfection
	• Antiviral treatment for hepatitis C virus infection should be considered for all human immunodeficiency virus-infected persons with acute or chronic hepatitis C virus infection.
	• The combination of peginterferon alfa (PegIFN) plus ribavirin is the recommended backbone of therapy for HIV/HCV-co-infected patients regardless of HCV genotype.
	• Antiviral treatment with PegIFN is not recommended in patients with decompensated liver disease.
	• For HCV-genotype-1-infected patients who are not co-infected with HIV, a HCV NS3/4A protease inhibitor (PI), either boceprevir or telaprevir, in combination with PegIFN/ribavirin is recommended on the basis of large clinical trials demonstrating significantly higher SVR rates with an acceptable safety/tolerability profile compared to PegIFN/ribavirin alone.
	• For HIV/HCV co-infected patients, preliminary data from small, ongoing clinical trials of boceprevir or telaprevir plus PegIFN/ribavirin for the treatment of HCV genotype 1 infection in HIV/HCV co-infected patients demonstrate greater efficacy than PegIFN/ribavirin alone, with a safety and tolerability profile similar to that observed in HCV monoinfected patients treated with boceprevir or telaprevir plus PegIFN/ribavirin. Preliminary recommendations are as follows:
	  o PegIFN is recommended for use for all HCV genotypes
	  o Ribavirin is recommended for use with PegIFN for all HCV genotypes.
	  o Boceprevir is approved for use in combination with PegIFN/ribavirin in HCV-genotype-1-monoinfected-patients. For HIV/HCV-co-infected patients, the regimen being evaluated is PegIFN/ribavirin administered for four weeks (lead-in phase) followed by boceprevir 800 mg orally every 7 to 9 hours (with a light snack) added to PegIFN/ribavirin for an additional 44 weeks.
	  o Telaprevir is approved for use in combination with PegIFN/ribavirin in HCV-genotype-1-monoinfected-patients. Dosing regimens lasting 48 weeks are being evaluated.
	• Patients with contraindications to the use of ribavirin can be treated with peginterferon alfa (2a or 2b) monotherapy. However, substantially lower sustained viral response rates are expected in persons not receiving ribavirin. HCV PIs should not be administered without ribavirin because of the high likelihood of virologic failure.
	
	Treatment of herpes simplex virus disease
	• Orolabial lesions can be treated with oral valacyclovir, famciclovir, or acyclovir for five to 10 days.
	• Severe mucocutaneous herpes simplex virus lesions are best treated initially with intravenous acyclovir. Patients may be switched to oral therapy after the lesions have begun to regress. Therapy should be continued until the lesions have completely healed.
	• Genital herpes simplex virus infection should be treated with oral valacyclovir, famciclovir, or acyclovir for five to 14 days. Short-course therapy (one, two, or three days) should not be used in patients with human immunodeficiency virus infection.
	• Most recurrences of genital herpes can be prevented by use of daily anti-herpes simplex virus therapy, and this is recommended for persons who have frequent or severe recurrences.
	• Suppressive therapy with oral acyclovir, valacyclovir, or famciclovir is effective in preventing recurrences. Suppressive therapy with valacyclovir should be 500 mg twice daily in human immunodeficiency virus -infected

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	persons or twice-daily regimens with acyclovir or famciclovir should be used. Management of herpes simplex virus treatment failure • The treatment of choice for acyclovir-resistant herpes simplex virus is intravenous foscarnet. Topical trifluridine, cidofovir, and imiquimod also have been used successfully for lesions on external surfaces, although prolonged application for 21 to 28 days or longer might be required. Histoplasmosis • Patients with moderately severe to severe disseminated histoplasmosis should be treated with an intravenous lipid formulation of amphotericin B for ≥2 weeks or until they clinically improve followed by oral itraconazole (200 mg three times daily for three days and then 200 mg twice daily for a total of ≥12 months). • In patients with less severe disseminated histoplasmosis, oral itraconazole at 200 mg three times daily for three days followed by 200 mg twice daily is appropriate initial therapy. Treatment of Isosporiasis (also known as Cystoisosporiasis) • Sulfamethoxazole-trimethoprim is the antimicrobial agent of choice for treatment of isosporiasis. It is the only agent whose use is supported by substantial published data and clinical experience. Therefore, potential alternative therapies should be reserved for patients with documented sulfa intolerance or in whom treatment fails. The traditional treatment regimen has been a 10-day course of Sulfamethoxazole-trimethoprim (800-160 mg) administered orally four times daily. • Intravenous administration of Sulfamethoxazole-trimethoprim should be considered for patients with potential or documented malabsorption. • Single-agent therapy with pyrimethamine has been used, with anecdotal success for treatment and prevention of isosporiasis. Pyrimethamine (50 to 75 mg/day) plus leucovorin (10 to 25 mg/day) to prevent myelosuppression may be an effective treatment alternative; it is the option for sulfa-intolerant patients. Leishmaniasis • Due to similar efficacy and a better toxicity profile, clinicians consider liposomal amphotericin B as the drug of choice for visceral leishmaniasis in human immunodeficiency virus-coinfected patients. The optimal amphotericin B dosage has not been determined. • Regimens with efficacy include conventional amphotericin B 0.5 to 1.0 mg/kg body weight/day intravenous to achieve a total dose of 1.5 to 2.0 g, or liposomal or lipid complex preparations of two to four mg/kg body weight administered on consecutive days or in an interrupted schedule (e.g., 4 mg/kg on Days 1 to 5, 10, 17, 24, 31, and 38) to achieve a total cumulative dose of 20 to 60 mg/kg body weight. A higher daily dosage is recommended for liposomal or lipid complex preparations than for conventional amphotericin B. Preventing disseminated *Mycobacterium avium* complex disease • Human immunodeficiency virus-infected adults and adolescents should receive chemoprophylaxis against disseminated *Mycobacterium avium* complex disease if they have a CD4+ count <50 cells/µL. • Azithromycin or clarithromycin are the preferred prophylactic agents. • The combination of clarithromycin and rifabutin is no more effective than clarithromycin alone for chemoprophylaxis, is associated with a higher rate of adverse effects than either drug alone, and should not be used.

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	• The combination of azithromycin with rifabutin is more effective than azithromycin alone; however, the additional cost, increased occurrence of adverse effects, potential for drug interactions, and absence of a survival difference compared to azithromycin alone do not warrant a routine recommendation for this regimen. • Azithromycin and clarithromycin also each confer protection against respiratory bacterial infections. • If azithromycin or clarithromycin cannot be tolerated, rifabutin is an alternative prophylactic agent for *Mycobacterium avium* complex disease, although drug interactions may make this agent difficult to use. • Primary *Mycobacterium avium* complex disease prophylaxis should be discontinued among adult and adolescent patients who have responded to antiretroviral therapy with an increase in CD4+ counts to >100 cells/µL for ≥3 months. Primary prophylaxis should be reintroduced if the CD4+ count decreases to <50 cells/µL. Treatment of disseminated *Mycobacterium avium* Complex Disease • Initial treatment of *Mycobacterium avium* complex disease should consist of two or more antimycobacterial drugs to prevent or delay the emergence of resistance. • Clarithromycin is the preferred first agent; however, azithromycin can be substituted for clarithromycin when drug interactions or clarithromycin intolerance preclude the use of clarithromycin. • Testing of *Mycobacterium avium* complex disease isolates for susceptibility to clarithromycin or azithromycin is recommended for all patients. Treatment of Penicilliosis marneffei • Penicilliosis is caused by the dimorphic fungus *Penicillium marneffei*, which is known to be endemic in Southeast Asia (especially Northern Thailand and Vietnam) and southern China. • The recommended treatment is liposomal amphotericin B, three to five mg/kg body weight/day intravenously for two weeks, followed by oral itraconazole, 400 mg/day for a subsequent duration of 10 weeks, followed by secondary prophylaxis. • Patients with mild disease can be initially treated with oral itraconazole 400 mg/day for eight weeks, followed by 200 mg/day for prevention of recurrence. • The alternative drug for primary treatment in the hospital is intravenous voriconazole, 6 mg/kg every 12 hours on day one and then 4 mg/kg every 12 hours for at least three days, followed by oral voriconazole, 200 mg twice daily for a maximum of 12 weeks. • Patients with mild disease can be initially treated with oral voriconazole 400 mg twice a day on day one, and then 200 mg twice daily for 12 weeks. The optimal dose of voriconazole for secondary prophylaxis after 12 weeks has not been studied. Primary prophylaxis of *Pneumocystis (carinii) jiroveci* pneumonia • Sulfamethoxazole-trimethoprim is the recommended prophylactic agent. One double-strength tablet daily is the preferred regimen. However, one single-strength tablet daily is also effective and might be better tolerated than one double-strength tablet daily. One double-strength tablet three times weekly is also effective. Sulfamethoxazole-trimethoprim at a dose of one double-strength tablet daily confers cross-protection against toxoplasmosis and selected common respiratory bacterial infections. Lower doses of sulfamethoxazole-trimethoprim likely also confer such protection. • For patients who have an adverse reaction that is not life threatening,

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	chemoprophylaxis with sulfamethoxazole-trimethoprim should be continued if clinically feasible; for those who have discontinued such therapy because of an adverse reaction, reinstituting sulfamethoxazole-trimethoprim should be strongly considered after the adverse event has resolved. Patients who have experienced adverse events, including fever and rash, might better tolerate reintroduction of the drug with a gradual increase in dose (i.e., desensitization), according to published regimens or reintroduction of sulfamethoxazole-trimethoprim at a reduced dose or frequency; as many as 70% of patients can tolerate such reinstitution of therapy. • If sulfamethoxazole-trimethoprim cannot be tolerated, alternative prophylactic regimens include dapsone, dapsone/pyrimethamine plus leucovorin, aerosolized pentamidine and atovaquone. • Primary *Pneumocystis (carinii) jiroveci* pneumonia prophylaxis should be discontinued for adult and adolescent patients who have responded to antiretroviral therapy with an increase in CD4+ counts to >200 cells/µL for >3 months. Prophylaxis should be reintroduced if the CD4+ count decreases to <200 cells/µL. <u>Treatment of *Pneumocystis (carinii) jiroveci* pneumonia</u> • Sulfamethoxazole-trimethoprim is the treatment of choice. The dose must be adjusted for abnormal renal function. Multiple randomized clinical trials indicate that sulfamethoxazole-trimethoprim is as effective as parenteral pentamidine and more effective than other regimens. Adding leucovorin to prevent myelosuppression during acute treatment is not recommended because of questionable efficacy and some evidence for a higher failure rate. Oral outpatient therapy of sulfamethoxazole-trimethoprim is highly effective among patients with mild-to-moderate disease. • Patients who have *Pneumocystis (carinii) jiroveci* despite sulfamethoxazole-trimethoprim prophylaxis are usually effectively treated with standard doses of sulfamethoxazole-trimethoprim. • Patients with documented or suspected *Pneumocystis (carinii) jiroveci* and moderate-to-severe disease, as defined by room air pO_2 <70 mm Hg or arterial-alveolar O_2 gradient >35 mm Hg, should receive adjunctive corticosteroids as early as possible, and certainly within 72 hours after starting specific *Pneumocystis (carinii) jiroveci* therapy. • The recommended duration of therapy for *Pneumocystis (carinii) jiroveci* is 21 days. • Patients who have a history of *Pneumocystis (carinii) jiroveci* should be administered chemoprophylaxis for life (i.e., secondary prophylaxis or chronic maintenance therapy) with sulfamethoxazole-trimethoprim unless immune reconstitution occurs as a result of antiretroviral therapy. • Secondary prophylaxis should be discontinued for adult and adolescent patients whose CD4+ count has increased from <200 cells/µL to >200 cells/µL for >3 months as a result of antiretroviral therapy. Prophylaxis should be reintroduced if the CD4+ count decreases to <200 cells/µL. If *Pneumocystis (carinii) jiroveci* recurs at a CD4+ count of ≥200 cells/µL, lifelong prophylaxis should be administered. <u>Primary prophylaxis of *Toxoplasma* encephalitis</u> • The double-strength tablet daily dose of sulfamethoxazole-trimethoprim recommended as the preferred regimen for *Pneumocystis (carinii) jiroveci* prophylaxis is effective against *Toxoplasma* encephalitis as well and is therefore recommended. Sulfamethoxazole-trimethoprim, one double-strength tablet three times weekly, is an alternative. • If patients cannot tolerate sulfamethoxazole-trimethoprim, the recommended alternative is dapsone-pyrimethamine plus leucovorin, which is also effective

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	against *Pneumocystis (carinii) jiroveci* pneumonia.
	• Atovaquone with or without pyrimethamine/leucovorin can also be considered.
	• Prophylactic monotherapy with dapsone, pyrimethamine, azithromycin, or clarithromycin cannot be recommended on the basis of available data. Aerosolized pentamidine does not protect against *Toxoplasma* encephalitis and is not recommended.
	• Prophylaxis against *Toxoplasma* encephalitis should be discontinued among adult and adolescent patients who have responded to antiretroviral therapy with an increase in CD4+ counts to >200 cells/µL for >3 months. Prophylaxis for *Toxoplasma* encephalitis should be reintroduced if the CD4+ count decreases to <100–200 cells/µL.
	
	<u>Treatment of *Toxoplasma* encephalitis</u>
	• The initial therapy of choice for *Toxoplasma* encephalitis consists of the combination of pyrimethamine plus sulfadiazine plus leucovorin.
	• The preferred alternative regimen for patients with *Toxoplasma* encephalitis who are unable to tolerate or who fail to respond to first-line therapy is pyrimethamine plus clindamycin plus leucovorin.
	• Sulfamethoxazole-trimethoprim was reported in a small randomized trial to be effective and better tolerated than pyrimethamine-sulfadiazine. On the basis of less in vitro activity and less experience with sulfamethoxazole-trimethoprim, treatment with this drug may be considered an option.
	• Acute therapy for *Toxoplasma* encephalitis should be continued for at least six weeks, if there is clinical and radiologic improvement.
	
	<u>Treatment of latent tuberculosis infection</u>
	• Human immunodeficiency virus-infected persons, regardless of age, should be treated for latent tuberculosis infection if they have no evidence of active tuberculosis and:
	  o A positive diagnostic test for latent tuberculosis infection and no prior history of treatment for active or latent tuberculosis.
	  o A negative diagnostic test for latent tuberculosis infection but are close contacts of persons with infectious pulmonary tuberculosis.
	  o A history of untreated or inadequately treated healed tuberculosis (i.e., old fibrotic lesions on chest radiography) regardless of diagnostic tests for latent tuberculosis infection.
	• Treatment options for latent tuberculosis infection include isoniazid daily or twice weekly for nine months.
	• Due to an increased risk of fatal and severe hepatotoxicity, a two-month regimen of daily rifampin and pyrazinamide is not recommended for latent tuberculosis infection treatment regardless of human immunodeficiency virus status.
	• Human immunodeficiency virus-infected persons receiving isoniazid should receive pyridoxine to minimize the risk of developing peripheral neuropathy. Alternatives for individuals who cannot take isoniazid or who have been exposed to a known isoniazid-resistant index case include either rifampin or rifabutin alone for four months.
	• For persons exposed to isoniazid- and/or rifampin-resistant tuberculosis, decisions to treat with one or two drugs other than isoniazid, rifampin, or rifabutin should be based on the relative risk of exposure to organisms broadly resistant to other antimycobacterial drugs and should be made in consultation with public health authorities.
	• Directly observed therapy should be used with intermittent dosing regimens when otherwise feasible to maximize regimen completion rates.
	• There is no evidence to suggest that latent tuberculosis infection treatment

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	should be continued beyond the recommended duration in persons with human immunodeficiency virus infection. Therefore, latent tuberculosis infection treatment should be discontinued after completing the appropriate number of doses. Treatment of active tuberculosis disease • Recommendations for anti-tuberculosis treatment regimens in human immunodeficiency virus -infected adults follow the same principles as for adults without human immunodeficiency virus -infection. • Treatment of drug susceptible tuberculosis disease should include a six-month regimen with an initial phase of isoniazid, rifampin or rifabutin, pyrazinamide, and ethambutol administered for two months followed by isoniazid and rifampin (or rifabutin) for four additional months. • When drug-susceptibility testing confirms the absence of resistance to isoniazid, rifampin, and pyrazinamide, ethambutol may be discontinued before two months of treatment have been completed. • For patients with cavitary lung disease and cultures positive for *Mycobacterium tuberculosis* after completion of two months of therapy, treatment should be extended with isoniazid and rifampin for an additional three months for a total of nine months. • All human immunodeficiency virus-infected patients treated with isoniazid should receive pyridoxine supplementation. • For patients with extrapulmonary tuberculosis, a six- to nine-month regimen (two months of isoniazid, rifampin, pyrazinamide, and ethambutol followed by four to seven months of isoniazid and rifampin) is recommended. • Exceptions to the recommendation for a six- to nine-month regimen for extrapulmonary tuberculosis include central nervous system disease (tuberculoma or meningitis) and bone and joint tuberculosis, for which many experts recommend nine to 12 months. • Adjuvant corticosteroids should be added when treating central nervous system and pericardial disease. • Treatment with corticosteroids should be started intravenously as early as possible with change to oral therapy individualized according to clinical improvement. • Recommended corticosteroid regimens are dexamethasone 0.3 to 0.4 mg/kg tapered over six to eight weeks or prednisone 1 mg/kg for three weeks, then tapered for three to five weeks. Treatment of varicella zoster virus disease • For uncomplicated varicella, the preferred treatment options are valacyclovir (1 gram orally three times daily), or famciclovir (500 mg orally three times daily) for five to seven days. Oral acyclovir (20 mg/kg body weight up to a maximum dose of 800 mg five times daily) can be an alternative. • Prompt antiviral therapy should be instituted in all human immunodeficiency virus-seropositive patients whose herpes zoster is diagnosed within one week of rash onset (or any time before full crusting of lesions). The recommended treatment options for acute localized dermatomal herpes zoster in human immunodeficiency virus-infected patients are oral valacyclovir, famciclovir, or acyclovir (doses as above) for seven to 10 days, although longer durations of therapy should be considered if lesions resolve slowly. Valacyclovir or famciclovir are preferred because of their improved pharmacokinetic properties and simplified dosing schedule. • If cutaneous lesions are extensive or if visceral involvement is suspected, intravenous acyclovir should be initiated and continued until clinical improvement is evident. A switch from intravenous acyclovir to oral antiviral

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	therapy (to complete a 10 to 14 day treatment course) is reasonable when formation of new cutaneous lesions has ceased and the signs and symptoms of visceral varicella zoster virus infection are clearly improving. • Optimal antiviral therapy for progressive outer retinal necrosis remains undefined. Specific treatment should include systemic therapy with at least one intravenous drug (selected from acyclovir, ganciclovir, foscarnet, and cidofovir) coupled with injections of at least one intravitreal drug (selected from ganciclovir and foscarnet). Treatment regimens for progressive outer retinal necrosis recommended by certain specialists include a combination of intravenous ganciclovir and/or foscarnet plus intravitreal injections of ganciclovir and/or foscarnet. The prognosis for visual preservation in involved eyes is poor, despite aggressive antiviral therapy. • Other infectious disease states mentioned within these guidelines note that the treatment guidelines for that disease state should be utilized. • The guideline specifies that detailed recommendations for the treatment of human herpesvirus-8 and associated malignancies are beyond the scope of these guidelines. • Other excluded infectious disease states offer no specific therapy or utilize medications not licensed in the United States.
American Thoracic Society/Infectious Diseases Society of America **Diagnosis, Treatment, and Prevention of Nontuberculous Mycobacterial Diseases (2007)**[16]	• For patients with nodular/bronchiectatic disease, a three times a week regimen consisting of clarithromycin 1,000 mg or azithromycin 500 mg, rifampin 600 mg, and ethambutol 25 mg/kg is recommended. The treatment regimen should be considered until the culture is negative for one year while on therapy. • For patients with fibrocavitary *Mycobacterium avium* complex lung disease or severe nodular/bronchiectatic disease, a daily regimen consisting of clarithromycin 500 to 1,000 mg or azithromycin 250 mg, rifampin 600 mg or rifabutin 150 to 300 mg, and ethambutol 15 mg/kg (with possible consideration of amikacin or streptomycin administered three times a week) is recommended. The treatment regimen should be considered until the culture is negative for one year while on therapy. • For patients with disseminated *Mycobacterium avium* complex disease, a regimen consisting of clarithromycin 1,000 mg/day or azithromycin 250 mg/day and ethambutol 15 mg/kg/day with or without rifabutin 150 to 350 mg/day is recommended. The treatment regimen can be discontinued with resolution of symptoms and reconstitution of cell-mediated immune function. • For prophylaxis of disseminated *Mycobacterium avium* complex disease, therapy should be initiated in adults with acquired immunodeficiency syndrome with CD4 T-lymphocyte counts less than 50 cells/µL and consists of azithromycin 1,200 mg/week or clarithromycin 1,000 mg/day. Rifabutin at a dose of 300 mg/day is also effective but is not tolerated as well. • For patients with *Mycobacterium kansasii* pulmonary disease, a regimen consisting of isoniazid 300 mg/day, rifampin 600 mg/day, ethambutol 15 mg/kg/day is recommended. The treatment regimen should be considered until the culture is negative for one year while on therapy.

Table 4. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Disease Society of America-Recommended Drug Regimens for Culture-Positive Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms[25]

Initial Phase			Continuation Phase			Range of Total Doses Minimal Duration	Rating*	
Regimen	Drugs	Interval and Doses† (Minimal Duration)	Regimen	Drugs	Interval and Doses‡ (Minimal Duration)		HIV–	HIV+
1	INH RIF PZA EMB	Seven days per week for 56 doses (eight week) or five days/week for 40 doses (eight week)§	1a	INH/RIF	Seven days per week for 126 doses (18 week) or five days/week for 90 doses (18 week)	182 to 130 (26 week)	A(I)	A(II)
			1b	INH/RIF	Twice weekly for 36 doses (18 week)	92 to 76 (26 week)	A(I)	A(II)‖
			1c¶	INH/RPT	Once weekly for 18 doses (18 week)	74 to 58 (26 week)	B(I)	E(I)
2	INH RIF PZA EMB	Seven days per week for 14 doses (two week), then twice weekly for 12 doses (six week) or five days/week for 10 doses (two week)§, then twice weekly for 12 doses (six week)	2a	INH/RIF	Twice weekly for 36 doses (18 week)	62 to 58 (26 week)	A	B(II)‖
			2b¶	INH/RPT	Once weekly for 18 doses (18 week)	44 to 40	B(I)	E(I)
3	INH RIF PZA EMB	Three times weekly for 24 doses (eight week)	3a	INH/RIF	Three times weekly for 54 doses (18 week)	78 (26 week)	B(I)	B(II)
4	INH RIF EMB	Seven days per week for 56 doses (eight week) or 5 days/week for 40 doses (eight week)	4a	INH/RIF	Seven days per week for 217 doses (31 week) or five days/week for 155 doses (31 week)	273 to 195 (39 week)	C(I)	C(II)
			4b	INH/RIF	Twice weekly for 62 doses (31 week)	118 to 102 (39 week)	C(I)	C(II)

Abbreviations: EMB=ethambutol, INH=isoniazid, HIV=human immunodeficiency virus, PZA=pyrazinamide, RIF=rifampin, RPT=rifapentine

*Definitions of ratings: A=preferred; B=acceptable alternative; C=offer when A and B cannot be given; E=should never be given; I=randomized clinical trial, II=data from clinical trials that were not randomized or were conducted in other populations; III=expert opinion

†When direct observed therapy is used, drugs may be given five days/week and the necessary number of doses adjusted accordingly. Although there are no studies that compare five with seven daily doses, extensive experience indicated this would be an effective practice.

‡Patients with cavitation on initial chest radiograph and positive cultures at completion of two months of therapy should receive a seven-month (31-week; either 217 doses [daily] or 62 doses [twice weekly]) continuation phase.

§Five-day-a-week administration is always given by direct observed therapy. Rating for five day/week regimens is A.

‖Not recommended for human immunodeficiency virus-infected patients with CD4 cell counts <100 cells/mL.

¶Options 1c and 2b should be used only in human immunodeficiency virus-negative patients who have negative sputum smears at the time of completion of two months of therapy and who do not have cavitation on the initial chest radiograph. For patients started on this regimen and found to have a positive culture from the two month specimen, treatment should be extended an extra three months.

Table 5. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Disease Society of America -Recommended Potential Regimens for the Management of Patients with Drug-Resistant Pulmonary Tuberculosis[25]

Pattern of Drug Resistance	Suggested Regimen	Duration of Treatment (months)
INH (±SM)	RIF, PZA, EMB (an FQN may strengthen the regimen for patients with extensive disease)	6
INH & RIF (±SM)	FQN, PZA, EMB, IA, ± alternative agent	18 to 24
INH, RIF (±SM), & EMB or PZA	FQN (EMB or PZA if active), IA, & two alternative agents	24
RIF	INH, EMB, FQN, supplemented with PZA for the first two months (an IA may be included for the first two to three months for patients with extensive disease)	12 to 18

EMB=ethambutol; FQN=fluoroquinolone; IA=injectable agent which may include an aminoglycoside (streptomycin, amikacin, or kanamycin) or the polypeptide capreomycin; INH=isoniazid; PZA=pyrazinamide; RIF=rifampin; SM=streptomycin; alternative agents=ethionamide, cycloserine, aminosalicylic acid, clarithromycin, amoxicillin-clavulanate, linezolid

Table 6. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Disease Society of America -Recommended Drug Regimens for the Treatment of Latent Tuberculosis Infection (LTBI)[17]

Drug(s)	Duration (months)	Interval	Minimum # of Doses for Treatment Completion	Rating: Persons HIV-Negative*†	Rating: Persons HIV-Positive*†
Isoniazid	9	Daily	270	A (II)	A (II)
Isoniazid	9	Twice weekly	76	B (II)	B (II)
Isoniazid	6	Daily	180	B (I)	C (I)
Isoniazid	6	Twice weekly	52	B (II)	C (II)
Rifampin	4	Daily	120	B (II)	B (III)
Rifampin and pyrazinamide	2	Due to reports of severe liver injury and deaths, the combination rifampin and pyrazinamide should generally not be offered for latent tuberculosis infection treatment.		D (II)	D (II)

Abbreviations: HIV=human immunodeficiency virus
Using the United States Public Health Service system, Centers for Disease Control and Prevention and American Thoracic Society have ranked these regimens according to the strength of the recommendation and the quality of supporting evidence.
*Strength of recommendation: A=preferred; B=acceptable alternative; C=offer when A and B cannot be given; D=should generally not be offered.
†Quality of supporting evidence: I=randomized clinical trial data; II=data from clinical trials that are not randomized or were conducted in other populations; III=expert opinion.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the antituberculosis agents are noted in Tables 7 and 8. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 7. FDA-Approved Indications for the Antituberculosis Single-entity Agents[2-14]

Indication	Amino-salicylic Acid	Beda-quiline	Capreo-mycin	Cyclo-serine	Etham-butol	Ethion-amide	Iso-niazid	Pyrazin-amide	Rifa-butin	Rifam-pin	Rifa-pentine
Prevention of disseminated *Mycobacterium avium* complex disease in patients with advanced human immunodeficiency virus infection									✔		
Prevention of tuberculosis							✔				
Treatment of active tuberculosis								✔			
Treatment of active tuberculosis in patients intolerant of or refractory to isoniazid or rifampin						✔ *					
Treatment of all forms of tuberculosis							✔			✔	
Treatment of multidrug resistant tuberculosis as part of combination therapy in adults (≥18 years of age)		✔									
Treatment of pulmonary tuberculosis	✔ *		✔ *		✔						✔
Treatment of pulmonary and extrapulmonary tuberculosis				✔ *							
Treatment of asymptomatic carriers of *Neisseria meningitides* to eliminate meningococci from the nasopharynx										✔	

*Second-line therapy when the primary/conventional treatments are ineffective.

Table 8. FDA-Approved Indications for the Antituberculosis Combination Agents[2-14]

Indication	Rifampin and Isoniazid	Rifampin, Isoniazid and Pyrazinamide
Treatment of pulmonary tuberculosis	✔ ^	✔ †

^When the patient has been titrated on the individual components and it has been established that this fixed dosage is therapeutically effective.
†Treatment should be administered on a daily, continuous basis for 2 months only. Following this initial phase, treatment should be changed to rifampin and isoniazid.

IV. Pharmacokinetics

The pharmacokinetic parameters of the single entity antituberculosis agents and components of the combination products are listed in Table 9.

Table 9. Pharmacokinetic Parameters of the Antituberculosis Agents[2-14]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Aminosalicylic acid	60 to 65	50 to 60	Liver	Renal (80)	1.10 to 1.62
Bedaquiline	Not reported	>99.9	Liver, significant	Renal (<0.001%) Feces (extensive)	5.5 months
Capreomycin	Not reported	Not reported	Minimal	Renal (50 to 52)	4 to 6
Cycloserine	Not reported	Not reported	Liver (35)	Renal (50 to 70)	10
Ethambutol	80	10 to 30	Liver (10 to 20)	Renal (50 to 90) Feces (20 to 22)	2.5 to 4.0
Ethionamide	80	Not reported	Liver, extensive	Renal (1)	1.92
Isoniazid	90	4 to 30	Liver, extensive	Renal (5 to 30)	0.7 to 4.0
Pyrazinamide	~100	Not reported	Not reported	Renal (70)	9 to 23
Rifabutin	20	85	Not reported	Renal(53) Feces (30)	45
Rifampin	90 to 95	80	Liver (60 to 80) Intestinal wall (30 to 45)	Renal (15 to 30) Feces (60)	3 to 4
Rifapentine	70	98	Liver	Renal (17) Feces (70)	14 to 17

V. Drug Interactions

Significant drug interactions with the antituberculosis agents are listed in Table 10.

Table 10. Significant Drug Interactions with the Antituberculosis Agents[2]

Generic Name(s)	Significance Level	Interaction	Mechanism
Rifamycins	1	Anticoagulants	The hypoprothrombinemic effect of oral anticoagulants may be decreased by rifamycins.
Rifamycins	1	Direct factor Xa inhibitors	Induction of P-glycoprotein and CYP3A4 by rifamycins may increase the metabolic elimination of direct factor Xa inhibitors.
Rifamycins	1	Hepatitis c virus protease inhibitors	Induction of CYP3A4 by rifamycins may increase the metabolic elimination of Hepatitis c virus protease inhibitors.
Rifamycins	1	Human immunodeficiency virus protease inhibitors	Inhibition of prehepatic or hepatic cytochrome P450 3A isoenzymes by human immunodeficiency virus protease inhibitors may increase the oral bioavailability of rifamycins. Induction of CYP3A4 by rifamycins may decrease the oral bioavailability of human immunodeficiency virus protease inhibitors.
Rifamycins	1	Imidazoles	Rifamycins induce CYP3A4-mediated metabolism of imidazoles. Conversely, imidazoles inhibit CYP3A4-mediated metabolism of rifamycins.

Generic Name(s)	Significance Level	Interaction	Mechanism
Rifamycins	1	Macrolide immuno-suppressants	Pharmacologic effects of macrolide immunosuppressants may be decreased by rifamycins. Immunosuppression may be inadequate.
Rifamycins	1	Oral contraceptives	Rifampin induces hepatic microsomal enzymes that result in more rapid elimination of the estrogenic and progestational components of oral contraceptives.
Rifamycins	1	Progestins	Interaction is probably due to induction of metabolism (CYP3A4) by rifamycins.
Rifamycins	1	Axitinib	Induction of CYP3A4 or CYP3A5 by rifamycins may increase the metabolic elimination of axitinib.
Rifamycins	1	Bortezomib	Induction of CYP3A4 by rifamycins may increase the metabolic elimination of bortezomib.
Rifamycins	1	Brentuximab	Induction of CYP3A4 by rifamycins may decrease the plasma concentrations of monomethyl auristatin E, the microtubule disrupting agent in brentuximab.
Rifamycins	1	Crizotinib	Induction of CYP3A4 by rifamycins may increase the metabolic elimination of crizotinib.
Rifamycins	1	Cyclosporine	Rifamycins induce hepatic and intestinal metabolism (CYP3A4) of cyclosporine.
Rifamycins	1	Dienogest	Rifamycins may induce hepatic microsomal metabolism of the estrogenic and progestational components of dienogest.
Rifamycins	1	Ranolazine	Induction of CYP3A4 by rifamycins may increase the metabolic elimination of the ranolazine.
Rifamycins	1	Rilpivirine	Induction of CYP3A4 by rifabutin Oral may increase the metabolic elimination of rilpivirine.
Rifamycins	1	Voriconazole	Rifamycins increase the metabolism (CYP3A4) of voriconazole and voriconazole inhibits the metabolism (CYP3A4) of rifabutin.
Bedaquiline	1	Strong CYP3A4 Inhibitors	Inhibition of CYP3A4 may decrease the plasma concentrations of bedaquiline.
Bedaquiline	1	Strong CYP3A4 Inhibitors	Induction of CYP3A4 may increase the plasma concentrations of bedaquiline.
Isoniazid	1	Acetaminophen	The toxic effects of acetaminophen may be increased by isoniazid.
Pyrazinamide	1	Rifamycins	The combination of rifamycins and pyrazinamide may lead to additive liver necrosis and failure as a result of hepatitis.
Rifampin	1	Dabigatran	Induction of P-glycoprotein by rifampin may decrease the absorption of dabigatran.
Rifamycins	2	Aromatase inhibitors	Induction of cytochrome P450 3A4 isoenzymes by rifamycins may increase

Generic Name(s)	Significance Level	Interaction	Mechanism
			the metabolic elimination of aromatase inhibitors.
Rifamycins	2	Benzodiazepines	The oxidative metabolism of benzodiazepines may be increased during coadministration.
Rifamycins	2	β-Blockers	The hepatic metabolism of β-blockers is increased due to enzyme induction by rifamycins.
Rifamycins	2	Corticosteroids	Induction of hepatic microsomal enzymes by rifamycins may increase the metabolic elimination of corticosteroids.
Rifamycins	2	Epothilones	Induction of cytochrome CYP 3A4 isoenzymes by rifamycins may increase the metabolic elimination of epothilones.
Rifamycins	2	Hydantoins	Rifampin increases the hepatic microsomal enzyme metabolism of hydantoins.
Rifamycins	2	Integrase inhibitors	Induction of uridine diphosphate glucuronosyltransferase 1A1 by rifamycins may increase the metabolic elimination of integrase inhibitors.
Rifamycins	2	Macrolides and ketolides	Pharmacologic and toxic effects of rifamycins may be increased by macrolides and ketolides. Plasma concentrations and pharmacologic effects of macrolides and ketolides may be decreased by rifamycins.
Rifamycins	2	Meglitinides	Rifamycins may increase metabolism (CYP3A4) of the meglitinides during the first-pass and elimination phases.
Rifamycins	2	Melatonin receptor agonists	Plasma concentrations and pharmacologic effects of melatonin receptor agonists may be decreased be rifamycins. Reductions in efficacy of melatonin receptor agonists may be expected.
Rifamycins	2	Narcotic analgesics	Rifamycins may decrease pharmacologic effects and plasma concentrations of narcotic analgesics. Pain control may be decreased.
Rifamycins	2	Nifedipine and derivatives	Rifamycins may induce hepatic enzymes and increase the first-pass metabolism of nifedipine and derivatives.
Rifamycins	2	Non-nucleoside reverse transcriptase inhibitors	Plasma concentrations and pharmacologic effects of non-nucleoside reverse transcriptase inhibitors may be decreased by rifamycins.
Rifamycins	2	Quinine derivatives	Rifamycins increase the hepatic metabolism of quinine derivatives during coadministration.
Rifamycins	2	Statins	Pharmacologic effects and plasma concentrations of statins may be decreased by rifamycins. Impaired cholesterol-lowering efficacy of statins may result.
Rifamycins	2	Sulfones	Plasma concentrations and

Generic Name(s)	Significance Level	Interaction	Mechanism
			pharmacologic effects of sulfones may be decreased by rifamycins. The antimicrobial effectiveness of sulfones may be reduced.
Rifamycins	2	Sulfonylureas	The pharmacologic effects of sulfonylureas may be decreased by rifamycins.
Rifamycins	2	Thiazolidinediones	Hepatic metabolism of thiazolidinediones (CYP2C8) may be increased by rifamycins.
Rifamycins	2	Tyrosine kinase receptor inhibitors	Plasma concentrations and pharmacologic effects of tyrosine kinase receptor inhibitors may be decreased by rifamycins. A reduction in therapeutic effectiveness of tyrosine kinase receptor inhibitors may occur.
Rifamycins	2	Verapamil and derivatives	Plasma concentrations and pharmacologic effects of verapamil and derivatives may be decreased by rifamycins.
Rifamycins	2	Atovaquone	Plasma concentrations of atovaquone may be decreased by rifamycins.
Rifamycins	2	Bupropion	Induction of cytochrome CYP450 2B6 by rifamycins may increase the metabolic elimination of bupropion.
Rifamycins	2	Cabazitaxel	Inhibition of CYP3A4 by rifamycins may increase the metabolic elimination of cabazitaxel.
Rifamycins	2	Clopidogrel	Induction of cytochrome P450 3A4 and/or 2C19 by rifamycins may increase the metabolic transformation of clopidogrel from a prodrug to its pharmacologically active metabolite
Rifamycins	2	Delavirdine	Rifamycins may increase the metabolism of delavirdine by enzyme induction (CYP3A4).
Rifamycins	2	Digitoxin	Rifamycins may increase the hepatic metabolism of digitoxin. Pharmacologic effects of digitoxin may be decreased.
Rifamycins	2	Dronedarone	Induction of CYP 3A isoenzymes by rifamycins may increase the metabolic elimination of dronedarone.
Rifamycins	2	Efavirenz	Induction of CYP P450 2B6 isoenzymes by rifamycins may reduce the blood levels of efavirenz. Induction of hepatic CYP P450 3A4, 3A5, and 3A7 isoenzymes by efavirenz may affect the blood levels of rifamycins.
Rifamycins	2	Erlotinib	Rifamycins may induce the metabolism (CYP3A4) of erlotinib. Erlotinib plasma concentrations may be reduced, decreasing the therapeutic effects.
Rifamycins	2	Estradiol valerate	Induction of CYP3A4 isoenzymes by rifamycins may increase the metabolic elimination of estradiol valerate.
Rifamycins	2	Eszopiclone	Induction of CYP 3A4 isoenzymes by

Generic Name(s)	Significance Level	Interaction	Mechanism
			rifamycins may increase the metabolic elimination of eszopiclone.
Rifamycins	2	Fluconazole	Rifamycins may increase the metabolism of fluconazole by inducing hepatic microsomal enzymes. Fluconazole may also inhibit cytochrome P450 3A4.
Rifamycins	2	Gefitinib	Rifamycins may increase the metabolism (CYP3A4) of gefitinib during coadministration.
Rifamycins	2	Haloperidol	Induction of haloperidol metabolism by rifamycins is suspected.
Rifamycins	2	Imatinib	Interaction is due to increased metabolism (CYP3A4) of imatinib by rifamycins.
Rifamycins	2	Indinavir	Indinavir may decrease rifamycin metabolism (CYP3A4), while rifamycin may increase the metabolism of indinavir.
Rifamycins	2	Ivacaftor	Induction of CYP3A by rifamycins may increase the metabolic elimination of ivacaftor.
Rifamycins	2	Lamotrigine	Interaction is due to induction of hepatic enzymes responsible for the glucuronidation of lamotrigine.
Rifamycins	2	Lurasidone	Induction of CYP3A4 by rifabutin may increase the metabolic elimination of lurasidone.
Rifamycins	2	Maraviroc	The pharmacologic effects of maraviroc may be decreased by rifamycins.
Rifamycins	2	Methadone	Pharmacologic effects of methadone may be decreased by rifamycins. Methadone withdrawal may be precipitated.
Rifamycins	2	Mexiletine	The antiarrhythmic action of mexiletine may be decreased by rifamycins.
Rifamycins	2	Mycophenolate	Plasma concentrations and pharmacologic effects of mycophenolate may be decreased by concomitant administration of rifamycins.
Rifamycins	2	Nevirapine	Reduced nevirapine concentrations are listed in the manufacturer's package labeling as a possibility when rifamycins and nevirapine are coadministered.
Rifamycins	2	Praziquantel	Induction of cytochrome P450 3A4 isoenzymes by rifamycins may increase the metabolic elimination of praziquantel.
Rifamycins	2	Propafenone	Rifamycins may induce the hepatic microsomal enzymes responsible for metabolizing propafenone.
Rifamycins	2	Quetiapine	Plasma concentrations and pharmacologic effects of quetiapine may be decreased when co-administered with rifamycins. Reductions in therapeutic effect may occur.
Rifamycins	2	Quinidine	Increased metabolism of quinidine due to induction of hepatic microsomal enzymes by rifamycins.

Generic Name(s)	Significance Level	Interaction	Mechanism
Rifamycins	2	Ranolazine	Pharmacologic effects and plasma concentrations of ranolazine may be decreased by rifamycins.
Rifamycins	2	Roflumilast	Induction of CYP3A4 by rifamycins may increase the metabolic elimination of roflumilast and roflumilast N-oxide, the active metabolite of roflumilast.
Rifamycins	2	Ticagrelor	Induction of CYP3A4 by rifamycins may increase the metabolic elimination of ticagrelor and its active metabolite.
Rifamycins	2	Tocainide	The antiarrhythmic effectiveness of tocainide may be decreased by rifamycins.
Rifamycins	2	Tolvaptan	Plasma concentrations and pharmacologic effects of tolvaptan may be decreased by rifamycins compromising therapeutic effectiveness.
Rifamycins	2	Ulipristal	Induction of CYP3A4 enzymes by rifamycins may increase the metabolic elimination of ulipristal.
Rifamycins	2	Vandetanib	Induction of CYP3A4 by rifamycins may increase the metabolic elimination of vandetanib.
Aminosalicylic acid	2	Rifamycins	The antitubercular action of rifamycins may be decreased by aminosalicylic acid.
Capreomycin	2	Nondepolarizing neuromuscular blockers	Capreomycin enhances or prolongs neuromuscular blockade via decreased presynaptic release of acetylcholine and/or postjunctional blocking activity.
Isoniazid	2	Hydantoins	Isoniazid inhibits the hepatic microsomal enzyme metabolism of hydantoins.
Isoniazid	2	Rifamycins	Rifamycins and isoniazid may cause additive adverse effects when co-administered. Hepatotoxicity may occur.
Isoniazid	2	Carbamazepine	Isoniazid is suspected to inhibit carbamazepine metabolism, and carbamazepine may increase isoniazid degradation to hepatotoxic metabolites.
Rifampin	2	Aprepitant	Induction of cytochrome P450 3A4 isoenzymes by rifampin may increase the metabolic elimination of aprepitant.
Rifampin	2	Deferasirox	Induction of UDP-glucuronosyltransferase by rifampin may increase the metabolic elimination of deferasirox.

Significance level 1=major severity; significance level 2=moderate severity

VI. Adverse Drug Events

The most common adverse drug events reported with the single entity antituberculosis agents and components of the combination products are listed in Table 11. The boxed warnings for the antituberculosis agents are listed in Tables 12 to 14.

Table 11. Adverse Drug Events (%) Reported with the Antituberculosis Agents[2-14]

Adverse Events	Aminosalicylic Acid	Bedaquiline	Capreo-mycin	Cyclo-serine	Etham-butol	Ethion-amide	Isoniazid	Pyrazin-amide	Rifabutin	Rifampin	Rifa-pentine
Cardiovascular											
Chest pain	-	9	-	-	-	-	-	-	1	-	6
Congestive heart failure	-	-	-	✔	✔	-	-	-	-	-	-
Hypertension	-	-	-	-	-	-	-	-	-	-	2
Myocarditis	-	-	-	-	✔	-	-	-	-	-	-
Pericarditis	✔	-	-	-	-	-	-	-	-	-	-
Postural hypotension	-	-	-	-	-	✔	-	-	-	-	-
Central Nervous System											
Aggression	-	-	-	✔	-	-	-	-	-	-	✔
Ataxia	-	-	-	-	-	-	-	-	-	✔	-
Coma	-	-	-	✔	-	-	-	-	-	-	-
Confusion	-	-	-	✔	✔	-	✔	-	-	✔	-
Drowsiness	-	-	-	✔	-	✔	-	-	-	✔	-
Encephalopathy	✔	-	-	-	-	-	✔	-	-	-	-
Fatigue	-	-	-	-	-	-	✔	-	-	✔	1
Fever	✔	-	✔	-	✔	-	✔	✔	2	✔	1
Hallucinations	-	-	-	-	✔	-	-	-	-	-	-
Headache	-	27.8	-	✔	✔	✔	-	-	3	✔	4
Hyperirritability	-	-	-	✔	-	-	-	-	-	-	-
Hyperreflexia	-	-	-	✔	-	-	-	-	-	-	-
Insomnia	-	-	-	-	-	-	-	-	1	-	1
Malaise	-	-	-	-	✔	-	✔	-	-	-	-
Numbness	-	-	-	-	-	-	-	-	-	✔	-
Paresthesia	-	-	-	✔	✔	-	✔	-	-	-	-
Peripheral neuropathy	-	-	-	-	-	-	✔	-	-	-	-
Psychosis	-	-	-	✔	-	✔	✔	-	-	✔	-
Restlessness	-	-	-	-	-	✔	-	-	-	-	-
Seizures	-	-	-	✔	-	-	✔	-	-	-	-
Tremor	-	-	-	✔	-	-	-	-	-	-	1
Vertigo	-	-	✔	✔	✔	✔	-	-	-	-	<1
Dermatologic											
Acne	-	-	-	-	-	✔	-	✔	-	-	3
Maculopapular rash	-	-	✔	-	-	-	✔	-	-	-	2
Photosensitivity	-	-	-	-	-	✔	-	✔	-	-	-
Pruritus	-	-	-	-	✔	-	-	✔	-	✔	4
Rash	✔	6	✔	✔	✔	✔	✔	✔	11	✔	6
Skin discoloration	-	-	-	-	-	-	-	-	<1	-	✔
Urticaria	-	-	✔	-	-	-	-	✔	-	✔	-

Adverse Events	Aminosalicylic Acid	Bedaquiline	Capreo-mycin	Cyclo-serine	Etham-butol	Ethion-amide	Isoniazid	Pyrazin-amide	Rifabutin	Rifampin	Rifa-pentine
Endocrine and Metabolic											
Goiter	✔	-	-	-	-	-	-	-	-	-	-
Gout	-	-	-	-	-	-	-	-	-	-	1
Gynecomastia	-	-	-	-	-	-	✔	-	-	-	-
Pellagra	-	-	-	-	-	✔	✔	-	-	-	-
Gastrointestinal											
Abdominal pain	✔	-	-	-	✔	✔	-	-	4	-	2
Anorexia	-	7	-	-	✔	✔	✔	✔	2	✔	6
Constipation	-	-	-	-	-	-	-	-	-	-	<1
Diarrhea	✔	-	-	-	-	✔	✔	-	3	✔	<1
Dyspepsia	-	-	-	-	-	-	-	-	3	-	3
Epigastric distress	-	-	-	-	-	-	✔	-	-	✔	-
Eructation	-	-	-	-	-	-	-	-	3	-	-
Esophagitis	-	-	-	-	-	-	-	-	-	-	✔
Excessive salivation	-	-	-	-	-	✔	-	-	-	-	-
Flatulence	-	-	-	-	-	-	-	-	2	✔	-
Gastritis	-	-	-	-	-	-	-	-	-	-	✔
Gastrointestinal upset	-	-	-	-	✔	-	-	-	-	-	-
Heartburn	-	-	-	-	-	-	-	-	-	✔	-
Nausea	✔	38	-	-	✔	✔	✔	✔	6	✔	3
Pancreatitis	-	-	-	-	-	-	-	-	-	-	✔
Pseudomembranous colitis	-	-	-	-	-	-	-	-	-	1 to 2	-
Stomatitis	-	-	-	-	-	✔	-	-	-	-	-
Taste perversions	-	-	-	-	-	✔	-	-	3	-	-
Vomiting	✔	-	-	-	✔	✔	✔	✔	1	✔	3
Weight loss	-	-	-	-	-	✔	-	-	-	-	-
Genitourinary											
Discolored urine	-	-	-	-	-	-	-	-	30	-	-
Dysuria	-	-	-	-	-	-	-	✔	-	-	-
Urinary casts	-	-	-	-	-	-	-	-	-	-	8
Hematologic											
Agranulocytosis	✔	-	-	-	-	-	✔	-	-	✔	-
Anemia	✔	-	-	-	-	-	✔	-	6	✔	12
Eosinophilia	-	-	>5	-	✔	-	✔	-	1	✔	-
Hematoma	-	-	-	-	-	-	-	-	-	-	✔
Hemolysis	-	-	-	-	-	-	-	-	<1	✔	-
Leukocytosis	-	-	✔	-	-	-	-	-	-	-	3
Leukopenia	✔	-	✔	-	✔	-	-	-	17	✔	7
Lymphopenia	-	-	-	-	-	-	-	-	-	-	13
Neutropenia	-	-	-	-	✔	-	-	-	25	-	13
Neutrophilia	-	-	-	-	-	-	-	-	-	-	3
Thrombocytopenia	✔	-	✔	-	✔	✔	✔	✔	5	✔	3
Thrombocytosis	-	-	-	-	-	-	-	-	-	-	6
Hepatic											
Abnormal liver function test	-	-	✔	✔	✔	✔	✔	-	✔	✔	✔
Bilirubinemia	-	-	-	-	-	-	✔	-	-	-	✔

Adverse Events	Aminosalicylic Acid	Bedaquiline	Capreo-mycin	Cyclo-serine	Etham-butol	Ethion-amide	Isoniazid	Pyrazin-amide	Rifabutin	Rifampin	Rifa-pentine
Hepatitis	✔	-	-	-	-	✔	✔	✔	<1	✔	✔
Jaundice	✔	-	-	-	-	✔	✔	-	-	✔	-
Transaminases increased	-	7	-	-	-	-	-	-	-	-	-
Laboratory Test Abnormalities											
Blood amylase increased	-	2	-	-	-	-	-	-	-	-	-
Blood urea nitrogen increased	-	-	36	-	-	-	-	-	-	✔	-
Hyperglycemia	-	-	-	-	-	-	✔	-	-	-	4
Hyperkalemia	-	-	-	-	-	-	-	-	-	-	✔
Hyperuricemia	-	-	-	-	-	-	-	-	-	-	32
Hypocalcemia	-	-	✔	-	-	-	-	-	-	-	-
Hypoglycemia	✔	-	-	-	-	-	-	-	-	-	10
Hypokalemia	-	-	✔	-	-	-	-	-	-	-	9
Hypomagnesemia	-	-	✔	-	-	-	-	-	-	-	-
Serum creatinine increased	-	-	✔	-	-	-	-	-	-	-	-
Uric acid increased	-	-	-	-	✔	-	-	-	-	✔	-
Musculoskeletal											
Arthralgia	-	26	-	-	-	-	-	-	<1	-	4
Dysarthria	-	-	-	✔	-	-	-	✔	-	-	-
Myalgia	-	-	-	-	-	-	-	✔	2	✔	-
Myositis	-		-	-	-	-	-	-	<1	-	-
Renal											
Acute renal failure	-	-	-	-	-	-	-	-	-	✔	-
Acute tubular necrosis	-	-	✔	-	-	-	-	-	-	✔	-
Hematuria	-	-	-	-	-	-	-	-	-	✔	18
Hemoglobinuria	-	-	-	-	-	-	-	-	-	✔	-
Interstitial nephritis	-	-	-	-	-	-	-	✔	-	✔	-
Nephrotoxicity	-	-	✔	-	-	-	-	-	-	-	-
Proteinuria	-	-	-	-	-	-	-	-	-	-	13
Pyuria	-	-	-	-	-	-	-	-	-	-	22
Special Senses											
Clinical hearing loss	-	-	3	-	-	-	-	-	-	-	-
Color blindness	-	-	-	-	✔	-	-	-	-	-	-
Conjunctivitis	-	-	-	-	-	-	-	-	-	✔	3
Optic neuritis	✔	-	-	-	✔	✔	✔	-	-	-	-
Subclinical hearing loss	-	-	11	-	-	-	-	-	-	-	-
Tinnitus	-	-	✔	-	-	-	-	-	-	-	-
Visual acuity decreases	-	-	-	-	✔	-	-	-	-	-	-
Visual changes	-	-	-	-	-	-	-	-	-	✔	-
Visual defect	-	-	-	-	✔	-	-	-	-	-	-
Other											
Anaphylactic reactions	-	-	-	-	✔	-	-	-	-	✔	-
Bleeding at injection site	-	-	✔	-	-	-	-	-	-	-	-
Edema	-	-	-	-	-	-	-	-	-	✔	1
Flushing	-	-	-	-	-	-	-	-	-	✔	-
Hemoptysis	-	14	-	-	-	-	-	-	-	-	-

Adverse Events	Aminosalicylic Acid	Bedaquiline	Capreo-mycin	Cyclo-serine	Etham-butol	Ethion-amide	Isoniazid	Pyrazin-amide	Rifabutin	Rifampin	Rifa-pentine
Hypersensitivity	-	-	-	-	✔	-	✔	✔	-	-	-
Joint pain	-	-	-	-	✔	-	-	-	-	-	-
Pain	-	-	-	-	-	-	-	-	1	-	6
Pain at injection site	-	-	✔	-	-	-	-	-	-	-	-
Pulmonary infiltrates	✔	-	-	-	✔	-	-	-	-	-	-
Rheumatic syndrome	-	-	-	-	-	-	✔	-	-	-	-
Sterile abscesses	-	-	✔	-	-	-	-	-	-	-	-
Vasculitis	✔	-	-	-	-	-	-	-	-	-	-
Weakness	-	-	-	-	-	-	✔	-	-	✔	-

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 12. Boxed Warning for Bedaquiline[14]

WARNING
An increased risk of death was seen in the bedaquiline treatment group (9/79, 11.4%) compared to the placebo treatment group (2/81, 2.5%) in one placebo-controlled trial. Only use bedaquiline when an effective treatment regimen cannot otherwise be provided. QT prolongation can occur with bedaquiline. Use with drugs that prolong the QT interval may cause additive QT prolongation.

Table 13. Boxed Warning for Capreomycin[5]

WARNING
The use of capreomycin for injection in patients with renal insufficiency or preexisting auditory impairment must be undertaken with great caution, and the risk of additional cranial nerve VIII impairment or renal injury should be weighed against the benefits derived from therapy. Since other parenteral antituberculosis agents (streptomycin, viomycin) also have similar and sometimes irreversible toxic effect, particularly on cranial nerve VIII and renal function, simultaneous administration of these agents with capreomycin is not recommended. Use with non-antituberculosis drugs (polymyxin A sulfate, colistin sulfate, amikacin, gentamicin, tobramycin, vancomycin, kanamycin, and neomycin) having ototoxic or nephrotoxic potential should be undertaken only with great caution. Pregnancy: The safety of the use capreomycin in pregnancy has not been determined. Children: Safety and effectiveness in pediatric patients have not been established.

Table 14. Boxed Warning for Isoniazid[2]

WARNING
Hepatitis: Severe and sometimes fatal hepatitis associated with isoniazid therapy has been reported and may occur or may develop even after many months of treatment. The risk of developing hepatitis is age related. Approximate case rates by age are as follows: less than 1/1,000 for persons younger than 20 years of age, 3/1,000 for persons in the 20 to 34-years of age group, 12/1,000 for persons in the 35 to 49-years of age group, 23/1,000 for persons in the 50 to 64-years of age group, and 8/1,000 for persons older than 65 years of age. The risk of hepatitis is increased with daily consumption of alcohol. Precise data to provide a fatality rate for isoniazid-related hepatitis is not available; however, in a United States public health service surveillance study of 13,838 persons taking isoniazid, there were eight deaths among 174 cases of hepatitis. Therefore, carefully monitor patients given isoniazid and interview patients at monthly intervals. For persons older than 35 years of age, in addition to monthly symptom reviews, measure hepatic enzymes (specifically, aspartate aminotransferase and alanine aminotransferase) prior to starting isoniazid therapy and periodically throughout treatment. Isoniazid-associated hepatitis usually occurs during the first three months of treatment. Usually, enzyme levels return to normal despite continuance of drug, but, in some cases, progressive liver dysfunction occurs. Other factors associated with an increased risk of hepatitis include daily use of alcohol, chronic liver disease, and injection drug use. A recent report suggests an increased risk of fatal hepatitis associated with isoniazid among women, particularly black and Hispanic women. The risk may also be increased during the postpartum period. Consider more careful monitoring in these groups, possibly including more frequent laboratory monitoring. If abnormalities of liver function exceed three to five times the upper limit of normal, strongly consider discontinuation of isoniazid. Liver function tests are not a substitute for a clinical evaluation at monthly intervals or for the prompt assessment of signs or symptoms of adverse reactions occurring between regularly scheduled evaluations. Instruct patients to immediately report signs or symptoms consistent with liver damage or other adverse reactions. These include any of the following: unexplained anorexia, nausea, vomiting, dark urine, icterus, rash, persistent paresthesias of the hands and feet, persistent fatigue, weakness or fever of greater than three-day duration or abdominal tenderness, especially right-upper-

WARNING

quadrant discomfort. If these symptoms appear or if signs suggestive of hepatic damage are detected, promptly discontinue isoniazid, because continued use of the drug in these cases has been reported to cause a more severe form of liver damage.

Give patients with tuberculosis who have hepatitis attributed to isoniazid appropriate treatment with alternative drugs. If isoniazid must be reinstituted, do so only after symptoms and laboratory abnormalities have cleared. Restart the drug in very small and gradually increasing doses and withdraw immediately if there is any indication of recurrent liver involvement. Treatment should be deferred in persons with acute hepatic diseases.

VII. Dosing and Administration

The usual dosing regimens for the antituberculosis agents are listed in Table 15.

Table 15. Usual Dosing Regimens for the Antituberculosis Agents[2-14]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single-entity Agents			
Aminosalicylic acid	Treatment of pulmonary tuberculosis: Packet: 4 g three times per day	Treatment of pulmonary tuberculosis: Packet: 150 mg/kg/day (divided three times daily) up to a maximum of 12 g/day	Packet: 4 g
Bedaquiline	Treatment of multidrug resistant tuberculosis as part of combination therapy in adults (≥18 years of age): Tablet: initial, 400 mg once daily for two weeks; maintenance, 200 mg three times weekly for 22 weeks	Safety and efficacy in children have not been established.	Tablet: 100 mg
Capreomycin	Treatment of pulmonary tuberculosis: Injection: initial, 1 g daily for 60 to 120 days; maintenance, 1 g two or three times weekly for 12-24 months; maximum 20 mg/kg/day	Safety and efficacy in children have not been established.	Injection: 1 g
Cycloserine	Treatment of pulmonary and extrapulmonary tuberculosis: Capsule: initial, 250 mg twice daily every 12 hours for the first two weeks; maintenance, as tolerated to 250 mg every six to eight hours up to maximum 1 g daily	Safety and efficacy in children have not been established.	Capsule: 250 mg
Ethambutol	Treatment of pulmonary tuberculosis: Tablet: initial, 15 mg/kg once daily; retreatment: 25 mg/kg once daily for 60 days; maintenance, 15 mg/kg once daily	Treatment of pulmonary tuberculosis in patients ≥13 years of age: Tablet: initial, 15 mg/kg once daily; retreatment: 25 mg/kg once daily for 60 days; maintenance, 15 mg/kg once daily	Tablet: 100 mg 400 mg
Ethionamide	Treatment of active tuberculosis in patients intolerant of or refractory to isoniazid or rifampin:	Treatment of active tuberculosis in patients intolerant of or refractory to	Tablet: 250 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Tablet: initial, 250 mg/day for one to two days, then increase to 250 mg twice daily for once to two days, with gradual increases to highest tolerated dose; maximum dose 1 g/day	isoniazid or rifampin: Tablet: 10 to 20 mg/kg daily in two or three divided doses or 15 mg/kg as a single daily dose	
Isoniazid	Prevention of tuberculosis: Injection, syrup, tablet: 300 mg daily for nine months Treatment of all forms of tuberculosis: Injection, syrup, tablet: 5 mg/kg once daily (maximum 300 mg/dose) or 15 mg/kg one to three times per week (maximum 900 mg/dose)	Prevention of tuberculosis: Syrup, tablet: 10 mg/kg daily for six to 12 months (maximum 300 mg/dose) Treatment of all forms of tuberculosis: Syrup, tablet: 10 to 15 mg/kg daily (maximum 300 mg/dose) or 20 to 40 mg/kg twice per week (maximum 900 mg/dose)	Injection: 100 mg/mL Syrup: 50 mg/5 mL Tablet: 100 mg 300 mg
Pyrazinamide	Treatment of active tuberculosis: Tablet: 15 to 30 mg/kg once daily (maximum 3 g/day) or 50 to 75 mg/kg twice weekly based on lean body weight	Treatment of active tuberculosis: Tablet: 15 to 30 mg/kg once daily (maximum 3 g/day) or 50 to 75 mg/kg twice weekly based on lean body weight	Tablet: 500 mg
Rifabutin	Prevention of disseminated *Mycobacterium avium* complex disease in patients with advanced human immunodeficiency virus infection: Capsule: 300 mg once daily or 150 mg two times daily	Safety and efficacy in children have not been established.	Capsule: 150 mg
Rifampin	Treatment of asymptomatic carriers of *Neisseria meningitides* to eliminate *meningococci* from the nasopharynx: Capsule: 600 mg twice daily for two days Treatment of all forms of tuberculosis: Capsule, injection: 10 mg/kg once daily; maximum 600 mg/day	Treatment of asymptomatic carriers of *Neisseria meningitides* to eliminate *meningococci* from the nasopharynx in patients <1 month of age: Capsule: 5 mg/kg every 12 hours for two days Treatment of asymptomatic carriers of *Neisseria meningitides* to eliminate *meningococci* from the nasopharynx in patients ≥1 month of age: Capsule:10 mg/kg every 12 hours for two days; maximum 600 mg per dose Treatment of all forms of tuberculosis: Capsule, injection: 10 to 20 mg/kg once daily; maximum 600 mg/day	Capsule: 150 mg 300 mg Injection: 600 mg
Rifapentine	Treatment of all forms of tuberculosis:	Treatment of all forms of tuberculosis in patients ≥12	Tablet: 150 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Tablet: initial, 600 mg twice a week for two months; continuation, 600 mg once weekly for four months	years of age: Tablet: initial, 600 mg twice a week for two months; continuation, 600 mg once weekly for four months	
Combination agents			
Rifampin and isoniazid	Treatment of pulmonary tuberculosis: Capsule: two capsules (600 mg rifampin, 300 mg isoniazid) once daily	Safety and efficacy in children have not been established.	Capsule: 300-150 mg
Rifampin, isoniazid, and pyrazinamide	Treatment of pulmonary tuberculosis: Tablet: <44 kg, four tablets daily; 45 to 54 kg, five tablets daily; ≥55kg, six tablets daily	Safety and efficacy in children <15 years of age have not been established.	Tablet: 120-50-300 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the antituberculosis agents are summarized in Table 16.

Table 16. Comparative Clinical Trials with the Antituberculosis Agents

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Treatment of Tuberculosis Infection in Human Immunodeficiency Virus-Negative Patients				
Diacon et al.[28] (2009) Bedaquiline 400 mg once daily for two weeks followed by 200 mg three times weekly for six weeks in combination with other medications for multi-drug resistant tuberculosis vs placebo in combination with other medications for multi-drug resistant tuberculosis Other multi-drug resistant tuberculosis medications consisted of a combination of ethionamide, kanamycin, pyrazinamide, ofloxacin and cycloserine/terizidon	DB, PC, RCT Patients 18 to 65 years of age with newly diagnoses multi-drug resistant tuberculosis	N=47 8 weeks	Primary: Time to sputum culture conversion, rates of culture conversion Secondary: Safety	Primary: Patients in the bedaquiline group had a reduced time to conversion to a negative sputum culture as compared to placebo (HR, 11.8; 95% CI, 2.3 to 61.3; P=0.003). The rates of conversion to a negative culture were 48% in the bedaquiline group compared to 9% in the placebo group. Secondary: There were no premature discontinuations due to adverse events in either treatment group. Overall adverse events were similar in both groups with nausea, unrelated deafness, arthralgia, hemoptysis, hyperuricemia, pain in the extremities, rash, and chest pain being the most common adverse events associated with treatment. Of these, only nausea occurred significantly more frequently in patients treated with bedaquiline compared to placebo (26 vs 4%; P=0.04). Increases in the mean corrected QT interval were observed in both groups but were more pronounced in the bedaquiline group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
e or available alternative				
Conde et al.[29] (2009) Ethambutol 15 to 20 mg/kg, plus isoniazid 300 mg, rifampicin 450 mg (<50 kg) or 600 mg (>50 kg), and pyrazinamide 20 to 25 mg/kg by directly-observed therapy for eight weeks vs moxifloxacin 400 mg plus isoniazid 300 mg, rifampicin 450 mg (<50 kg) or 600 mg (>50 kg), and pyrazinamide 20 to 25 mg/kg by directly-observed therapy for eight weeks At the end of 8 weeks, all patients were placed on OL treatment with isoniazid and rifampicin two times	DB, RCT Patients ≥18 years of age with clinical signs and symptoms of pulmonary tuberculosis, including an abnormal chest radiograph and at least one sputum smear with acid-fast bacilli	N=146 Up to 18 months	Primary: Proportion of patients with negative sputum cultures after eight weeks of treatment Secondary: Adverse events, mortality, treatment discontinuation, tuberculosis reoccurrence	Primary: Patients assigned to moxifloxacin became culture negative more rapidly than those assigned to ethambutol. After week one, 13% of patients in the moxifloxacin group had negative sputum cultures compared to 3% of patients in the ethambutol group (P=0.03). At every week after enrollment, patients assigned to moxifloxacin had a higher rate of culture conversion than those assigned to ethambutol (difference was significant at all time points apart from weeks six and seven). The median time to consistently negative cultures was 35 days for patients in the moxifloxacin group compared to 48.5 days for patients receiving ethambutol (P=0.005). Treatment with ethambutol was associated with a smaller proportion of patients with negative sputum cultures after eight weeks of treatment (73.8%) compared to moxifloxacin (92.2%) in the univariate and multivariate analyses (OR, 1.86; P=0.0001 and OR, 1.75; P=0.0009, respectively). Secondary: Adverse events did not differ by treatment group. There were 16 serious adverse events (eight in each group) in 12 patients; one grade 3 cutaneous reaction in the ethambutol group was judged to be related to study drugs by the treating physicians who were not aware of treatment assignment. All other serious adverse events were judged not related to study drugs. Eight patients died during the study, including one in each group still receiving study phase treatment. No death was attributed to study treatment. Only five patients discontinued treatment because of toxic effects; two patients in the moxifloxacin group stopped because of grade 2 nausea and vomiting and one because of grade 2 paraesthesia and ataxia. Two patients in the ethambutol group stopped because of grade 2 rash and pruritus and one because of grade 3 peripheral neuropathy. No clinically

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
per week to complete another 4 months of treatment				or statistically significant changes in the QTc interval were recorded in patients in either group of the trial. Seven patients (5%) had recurrence of tuberculosis confirmed by positive culture and compatible clinical symptoms: three patients in the moxifloxacin group (at 11, 16, and 27 months after completing treatment) and four in the ethambutol group (at six, seven, 22, and 32 months after completion). Six of seven isolates were tested for drug resistance, and all remained susceptible to isoniazid and rifampicin.
Hong Kong Chest Service et al.[30] (1987) Isoniazid, rifampin, pyrazinamide, streptomycin and ethambutol given three times a week vs isoniazid, rifampin, pyrazinamide, streptomycin but no ethambutol given three times a week vs isoniazid, rifampin, pyrazinamide, ethambutol but no streptomycin given three times a week vs	RCT Patients with sputum-smear-positive pulmonary tuberculosis	N=833 5 year	Primary: Rate of bacteriologic response and bacteriologic relapse in patients with drug-susceptible strains at two years Secondary: Rate of relapse at five years	Primary: For patients with drug-susceptible strains; bacteriologic relapse during the two years occurred in 1.4% of patients treated with pyrazinamide regimens compared to 7.8% of patients treated with a non-pyrazinamide regimen (P<0.001). Secondary: The total relapse rates for patients with drug-susceptible strains were 3.4% for the pyrazinamide regimens compared to 10.3% for the non-pyrazinamide regimens (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
isoniazid, rifampin, pyrazinamide, ethambutol given every day vs isoniazid, rifampin, streptomycin, and ethambutol given three times a week				
Su et al.[31] (2002) Isoniazid, rifampin, ethambutol and pyrazinamide in a fixed-dose combination formulation^ for two months, followed by isoniazid and rifampin fixed-dose combination for four months vs isoniazid, rifampin, ethambutol and pyrazinamide taken as separate tablets for two months, then isoniazid and rifampin taken as separate tablets for four months	RCT Patients with newly diagnosed smear-positive pulmonary tuberculosis	N=105 2 years	Primary: Development of resistance, sputum conversion, compliance and radiological improvement Secondary: Safety	Primary: A total of 51 patients were available for evaluation after two years. Four patients in the fixed-dose combination group (7.0%) had bacilli resistant to pyrazinamide. Two patients (4.2%) had bacilli resistant to ethambutol and six patients (12.5%) had bacilli resistant to pyrazinamide in the group that received separate formulations. The two regimens were of similar effectiveness with regard to sputum conversion, compliance and radiological improvement. Secondary: No patient with fixed-dose combination treatment developed gastrointestinal symptoms, visual disturbance or peripheral neuropathy ($P<0.05$). Fixed-dose combination treatment resulted in drug-induced fever in one patient. One patient in the fixed-dose combination group relapsed five months after completing treatment.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Teo et al.[32] (1999) Isoniazid, rifampin, and pyrazinamide fixed-dose combination formulation once daily for six months, followed by intermittent treatment with isoniazid and rifampin given three times per week vs isoniazid, rifampin, and pyrazinamide administered as separate formulations, followed by intermittent treatment with isoniazid and rifampin given three times per week	OL, RCT Patients with pulmonary tuberculosis	N=310 5 years	Primary: Relapse rates Secondary: Adverse events	Primary: At the end of five years, there were 15 relapses: three (2.2%) in the separate drugs group and 12 (9.3%) in the fixed-dose combination group. Exclusion of two cases in the fixed-dose combination group, one with silicotuberculosis and another with no bacteriological confirmation of diagnosis, gave a relapse rate of 7.9% (P=0.03 for the comparison of relapse rates in the two groups). Secondary: The frequency of adverse events was similar in both groups.
Macnab et al.[33] (1994) Isoniazid, rifampin, and pyrazinamide fixed-dose combination formulation vs	RCT Adults with a first episode of pulmonary tuberculosis	N=106 Duration not specified	Primary: Rate of conversion to a negative sputum culture Secondary: Rate of inadequate compliance and side effects	Primary: All patients who took the treatment as prescribed (67 patients receiving the fixed-dose combination formulation and 30 patients receiving the four-drug regimen as separate formulations) converted to a negative sputum culture by the time 90 doses had been taken. Secondary: The rates of inadequate compliance and of side effects were similar in the two groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
isoniazid, rifampicin, pyrazinamide and ethambutol administered as separate formulations				
Lienhardt et al.[34] (2011) Rifampicin 150 mg, isoniazid 75 mg, pyrazinamide 400 mg, ethambutol 275 mg in a fixed-dose combination once daily for eight weeks vs rifampicin 150 mg, isoniazid 75 mg, pyrazinamide 400 mg, ethambutol 275 mg in separate formulations once daily for eight weeks Both groups: continuation therapy with rifampicin 150 mg and isoniazid 150 mg three times weekly for 18 weeks (control)	MC, OL, RCT Adults with newly diagnosed pulmonary tuberculosis who have received less than four weeks of antibiotic therapy	N=1,585 30 months	Primary: Negative culture at 18 months post randomization Secondary: Safety	Primary: The per-protocol analysis shows that 18 months after the start of treatment, 93.9% of patients in the fixed-dose combination group had favorable outcome vs 94.6% in the control group (90% CI, −3.0 to 1.5). This was within the predefined margin of non-inferiority. In the modified intent-to-treat analysis, 83.3% of patients in the fixed-dose combination group had a favorable outcome compared to 84.8% of patients in the control group (90% CI, −4.7 to 1.8). Secondary: A total of 67 patients (31 in the fixed-dose combination group and 36 in the control group) reported at least one adverse event. They were primarily dermatologic, rheumatologic, hepatic, or gastrointestinal disorders and were mostly of mild or moderate severity. They were similarly distributed among the treatment groups (P=0.10).
Hong Kong Chest Service[35] (1991)	RCT Patients with	N=1,386 3 years	Primary: Bacteriologic failure and relapse	Primary: Bacteriologic failure occurred in four patients, all in the Z6noS group (2%; P<0.005 for the comparison with the streptomycin-containing

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Isoniazid and rifampin for six months, streptomycin for the first four months and pyrazinamide for the first two months (Group Z2) vs isoniazid and rifampin for six months, streptomycin for the first four months and pyrazinamide for the first four months (Group Z4) vs isoniazid and rifampin for six months, streptomycin for the first four months and pyrazinamide for the first six months (Group Z6) vs isoniazid and rifampin for six months, and	sputum smear-positive pulmonary tuberculosis	(6 months of active treatment and 30 months of follow-up)	rates Secondary: Not reported	regimens). During 30 months of follow-up after the end of chemotherapy, bacteriologic relapse occurred in 3% of patients in the Z2 group receiving the fixed-dose combination product and in 3% of patients in the Z2 group who received treatment with separate formulations. Relapse occurred in 3% of patients in the Z4 group who received the fixed-dose combination product and in 6% of patients in the Z4 group who received treatment with separate formulations. Relapse occurred in 6% of patients in the Z6 group receiving the fixed-dose combination product and in 1% of patients in the Z6 group who received treatment with separate formulations. Relapse occurred in 9% of patients in the Z6noS group receiving the fixed-dose combination product and in 4% of patients in the Z6noS group who received treatment with separate formulations. There were no significant differences in relapse rates with the fixed-dose combination regimens and the separate-drug regimens. There were no significant differences in relapse rates among the regimens with different durations of pyrazinamide, or among the regimens with and without streptomycin. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
pyrazinamide for six months (Group Z6noS) During the latter part of the study, patients were allocated at random to receive isoniazid, rifampin, and pyrazinamide either as a fixed-dose combination or as three separate formulations.				
Cowie et al.[36] (1990) Isoniazid, rifampin and pyrazinamide administered as a fixed-dose combination five tablets per day on weekdays for 100 treatment days (RHZ) vs streptomycin, isoniazid, rifampin and pyrazinamide administered as separate formulations (RHZS)	RCT Male gold miners with a first case of tuberculosis	N=150 100 treatment days	Primary: Treatment success Secondary: Rates of non-compliance	Primary: Treatment was unsuccessful in 10 patients in the RHZ group, four men were lost to follow-up, three cases of failure of conversion of sputum on the regimen, and three relapses. The results for the separate-drug group were similar, with four lost to follow-up, two treatment failures and four relapses. Secondary: Noncompliance was detected in 42% of the RHZ group and in 16% of the RHZS group.
Gonzalez-Montaner et al.[38]	MC, RCT	N=520	Primary: Bacteriologic	Primary: Considering all patients with positive baseline culture, the success rates

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1994) Rifampin (rifampicin*) 150 mg daily for six months vs rifabutin 150 mg daily for six months vs rifabutin 300 mg daily for six months All three regimens also included isoniazid daily for six months plus ethambutol and pyrazinamide daily for the first two months.	HIV-negative patients with newly-diagnosed drug-sensitive, radio-graphically active and bacteriologically confirmed pulmonary tuberculosis	2 years	conversion rates, median time to culture conversion Secondary: Signs and symptoms of tuberculosis	for each patient were 89, 94 and 92% in the rifampin 150 mg, rifabutin 150 mg, and rifabutin 300 mg groups, respectively (P=0.357). The median time to culture conversion was comparable in the three groups and was 34 days for rifampin and 37 days for each of the rifabutin groups. Secondary: There was no significant difference between the treatment groups in the signs and symptoms of tuberculosis.
Bock et al.[38] (2002) <u>Stage 1:</u> Rifapentine 900 mg plus isoniazid 15 mg/kg once weekly vs rifapentine 600 mg plus isoniazid 15 mg/kg once-weekly	DB, RCT Patients aged 18 years of age with culture-confirmed, drug-susceptible pulmonary or extrapulmonary tuberculosis and documentation of adequate induction phase therapy	N=150 6 months	Primary: Proportion of subjects that failed to complete study for any reason, including adverse events, intolerance to the medications, clinical or bacteriologic failure, refusal to undergo further study therapy, or	Primary: Treatment was discontinued in three of 52 (6%), two of 51 (4%), and three of 47 (6%) in the rifapentine 600, 900, and 1,200 mg treatment arms, respectively. Secondary: Only one discontinuation, in the rifapentine 1,200 mg arm, was due to an adverse event possibly associated with study therapy. There was a trend toward more adverse events, possibly associated with study therapy, in the highest-dose arms (P=0.051).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Stage 2: Rifapentine 1,200 mg plus isoniazid 15 mg/kg once-weekly vs rifapentine 600 mg plus isoniazid 15 mg/kg once-weekly			withdrawal of consent Secondary: Safety	
Benator et al.[39] (2002) Rifapentine 600 mg plus isoniazid 900 mg once weekly vs rifampin 600 mg plus isoniazid 900 mg twice weekly	MC, OL, RCT Patients 18 years of age or older, who were HIV-negative with pulmonary tuberculosis	N=1,004 2 years	Primary: Rates of treatment failure/relapse (defined by positive sputum culture or clinical signs of tuberculosis) Secondary: Rate of relapse in patients without cavitation	Primary: Rates of failure/relapse were 46/502 (9.2%) in those on rifapentine once weekly, and 28/502 (5.6%) in those given rifampin twice weekly (P=0.04). Secondary: In patients without cavitation, rates of failure/relapse were 6/210 (2.9%) in the once weekly group and 6/241 (2.5%) in the twice weekly group (P=0.81).
Am Rev Respir Dis.[40] (1977) Streptomycin plus isoniazid plus pyrazinamide given daily vs streptomycin plus isoniazid plus	RCT Patients with newly diagnosed active pulmonary tuberculosis	N=404 30 months	Primary: Rate of treatment failure Secondary: Rate of relapse at 30 months	Primary: The rates of treatment failure at six months were 4, 1, and 0% with twice weekly, three times weekly, or daily therapy for patients with drug susceptible isolates. Secondary: The relapse rate at 30 months for patients treated for six months was 21% compared to 6% for those treated for nine months.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
pyrazinamide given three times per week vs streptomycin plus isoniazid plus pyrazinamide given twice per week				
Gelband et al.[41] (2000) Streptomycin, isoniazid, rifampin, pyrazinamide administered for <6 months vs streptomycin, isoniazid, rifampin, pyrazinamide administered for >6 months	MA Randomized trials comparing two or more tuberculosis drug regimens, in which at least one regimen was <6 months and it was compared to at least one regimen that lasted longer, in patients with active tuberculosis	N=4,100 (7 trials) Variable duration	Primary: Relapse rates Secondary: Rate of adverse drug reactions	Primary: Relapse rates were consistently higher after shorter duration treatment regimens. Results were significantly better in the longer duration groups. Secondary: There was little or no difference in the rates of adverse reactions or toxicity requiring a change of regimen or discontinuation of treatment.
Singapore Tuberculosis Service[42] (1991) Streptomycin (SM), isoniazid (INH), rifampin (RIF) and pyrazinamide (PZA) for two months vs	RCT Patients with sputum smear-positive pulmonary tuberculosis	N=310 18 months	Primary: Bacteriologic failures during chemotherapy and relapse at 18 months Secondary: Adverse effects	Primary: Among 271 patients with drug-susceptible strains of tubercle bacilli pretreatment, there were no bacteriologic failures during chemotherapy. Relapse occurred in 7% of patients in the group that received SM and INH/RIF/PZA as a fixed-dose combination for two months and 0% of patients in the group that received the same agents as separate formulations. Relapse occurred in 5% of patients in the group that received SM and INH/RIF/PZA as a fixed-dose combination for one month and 2% of patients in the group that received the same agents as separate

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
streptomycin, isoniazid, rifampin and pyrazinamide for one month vs isoniazid, rifampin and pyrazinamide for 2 months During the initial period of daily chemotherapy, the patients were also allocated at random to be given their isoniazid, rifampin and pyrazinamide either as a fixed-dose combination or as three separate formulations.				formulations. Relapse occurred in 8% of patients in the group that received INH/RIF/PZA as a fixed-dose combination for two months and 2% of patients in the group that received the same agents as separate formulations. The overall relapse rates were higher with the fixed-dose combination regimens (P=0.04). Secondary: The most common spontaneous complaints were nausea and vomiting reported by 8% of patients receiving the fixed-dose combination and 7% of patients receiving the drugs in separate formulations.
Treatment of Tuberculosis Infection in Human Immunodeficiency Virus-Positive Patients				
Swaminathan et al.[43] (2010) Ethambutol 1,200 mg, isoniazid 600 mg, rifampicin 450 to 600 mg and pyrazinamide, 1,500 mg three times/weekly for two months, followed by four months of	MC, OL, RCT HIV-infected patients with newly diagnosed pulmonary or extra-pulmonary tuberculosis	N=327 36 months	Primary: Favorable outcome, recurrence, all-cause mortality Secondary: Not reported	Primary: In the intent-to-treat analysis, 83% of patients in the six-month group and 76% of patients in the nine-month group had a favorable outcome (RR, 1.08; 95% CI, 0.97 to 1.21; P=0.15). In the per protocol analysis, there was no difference in favorable outcome at the end of treatment between the two regimens (85% with the six-month regimen and 78% with the nine-month regimen; P=not significant). There was no significant difference between the treatment groups in overall recurrence rates (19% with the six-month regimen and 13% with the nine-month regimen; P=0.2).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
isoniazid and rifampicin at the same doses vs ethambutol 1,200 mg, isoniazid 600 mg, rifampicin 450 to 600 mg and pyrazinamide, 1,500 mg three times/weekly for two months, followed by seven months of isoniazid and rifampicin at the same doses				Overall, 116 deaths (35%) occurred among 327 patients. In the six-month regimen, 15 deaths occurred during treatment (5 tuberculosis, 10 non- tuberculosis) and 45 during follow-up (12 tuberculosis, 33 non-tuberculosis). In the nine-month regimen, there were 19 deaths during treatment (9 tuberculosis, 10 non-tuberculosis) and 37 (10 tuberculosis, 27 non-tuberculosis) during the follow-up phase. There was no significant difference in overall mortality between the study regimens: 36 and 35% of patients. Secondary: Not reported
Vernon et al.[44] (1999) Isoniazid 900 mg and rifapentine 600 mg once weekly vs isoniazid 900 mg and rifampin 600 mg twice weekly	MC, OL, RCT HIV-seropositive patients 18 years of age or older with culture-positive pulmonary tuberculosis susceptible to isoniazid and rifampin	N=61 16 weeks	Primary: Rate of relapse Secondary: Resistant to a rifamycin (rifabutin, rifampin, or rifapentine)	Primary: Five of 30 patients in the once-weekly isoniazid/rifapentine group relapsed, compared to three of 31 patients in the twice-weekly isoniazid/rifampin group (P=0.41). Secondary: Four of five relapses in the once-weekly isoniazid/rifapentine group had mono-resistance to rifamycin, compared to 0 out of three in the rifampin group (P=0.05).
Murray et al.[45] (1999) Isoniazid, rifampin, pyrazinamide, and ethambutol for two months, followed	PRO Patients with sputum culture-positive new or recurrent pulmonary tuberculosis	N=376 6 months	Primary: Impact of HIV status on drug resistance Secondary: Mortality	Primary: There was no association between HIV status and history of previous tuberculosis or drug resistance. Treatment interruption rates (2.0%) and the rate at which patients transferred out of the treatment program (1.6%) were not associated with HIV status.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
by four months of isoniazid and rifampin	diagnosed in 1995 were prospectively enrolled in the cohort			Secondary: Mortality was 0.5% in HIV-negative patients vs 13.7% in HIV-positive patients, and in the latter group was associated with CD4 lymphocyte depletion.
Nettles et al.[46] (2004) Four-drug tuberculosis therapy, followed by twice-weekly isoniazid and rifampin vs isoniazid and rifabutin	OB Patients were included if they had culture-confirmed rifamycin-susceptible tuberculosis	N=108 1 year	Primary: Rates of acquired rifamycin resistance Secondary: Rates of recurrent tuberculosis	Primary: Among the 108 HIV-seropositive patients, three (3.7%) of 81 who were treated with rifampin and 0 of 27 who were treated with rifabutin had acquired rifamycin-resistant tuberculosis (P=0.57). None of the HIV-seronegative patients or the patients with unknown HIV status developed acquired rifamycin-resistant tuberculosis. Secondary: Among HIV-seropositive patients, the only risk factor for recurrent tuberculosis was a low median initial CD4 T lymphocyte count (51 vs 138 cells/mm^3; P=0.02).
Perriens et al.[47] (1995) Isoniazid, rifampin, pyrazinamide, and ethambutol daily for two months, followed by isoniazid and rifampin, twice weekly for four months, followed by isoniazid and rifampin twice weekly for a further six months vs isoniazid, rifampin,	OL, PRO HIV-seropositive patients with first episode of pulmonary tuberculosis	N=335 24 months	Primary: Rates of relapse at 24 months Secondary: Not reported	Primary: At 24 months, the HIV-seropositive patients who received extended treatment (isoniazid and rifampin for six months longer) had a relapse rate of 1.9%, as compared to 9.0% for the HIV-seropositive patients who received placebo for the corresponding six months (P<0.01). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
pyrazinamide, and ethambutol daily for two months, followed by isoniazid and rifampin twice weekly for four months, followed by placebo twice weekly for a further six months				
Treatment of Latent Tuberculosis Infection in Human Immunodeficiency Virus-Negative Patients				
Fraser et al.[48] (2006) Study 1 Isoniazid 15 to 20 mg/kg/day, pyrazinamide 25 to 35 mg/kg/day, ethionamide 10 to 15 mg/kg/day and/or ethambutol 15 to 20 mg/kg/day and/or ofloxacin 15 mg/kg/day Study 2 Isoniazid 400 mg/day	MA Individuals with a sputum culture positive for *Mycobacterium tuberculosis*, which was multi-drug resistant	N=169 (2 trials) 6 months	Primary: Effectiveness of treatment of latent tuberculosis infection in patients at risk for developing multi-drug resistant tuberculosis Secondary: Not reported	Primary: A PRO cohort study found individualized treatment to be effective for preventing active tuberculosis in children (OR, 0.20; 95% CI, 0.04 to 0.94), while a retrospective cohort study found isoniazid not to be effective (OR, 0.46; 95% CI, 0.07 to 2.32). Secondary: Not reported
Hanta et al.[49] (2007) Isoniazid 300 mg daily for 9 months (latent tuberculosis infection) vs	OL Patients who administered anti-tumor necrosis factorα treatment for a rheumatologic disease and were also receiving	N=86 9 months	Primary: Development of hepatotoxicity Secondary: Not reported	Primary: The rate of development of hepatotoxicity among those taking isoniazid was found to be five cases (8.3%), whereas among those who were not given isoniazid, no hepatotoxicity was detected (P=0.317). Active tuberculosis infection was not encountered in any patient throughout the study period in all groups. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
no tuberculosis treatment (no latent tuberculosis infection present) All patients received active treatment with anti- tumor necrosis factorα α therapy.	treatment with isoniazid for latent tuberculosis infection			Not reported
Spyridis et al.[50] (2007) <u>Period 1 (1995-1998)</u> Isoniazid 10 mg/kg once daily for nine months (group A) vs isoniazid 10 mg/kg and rifampin 10 mg/kg once daily for four months (group B) <u>Period 2 (1999-2002)</u> Isoniazid 10 mg/kg and rifampin 10 mg/kg once daily for four months (group C) vs	RCT Children ≤15 years of age with latent tuberculosis infection	N=926 11 years	Primary: Compliance and radiographic findings Secondary: Not reported	Primary: A total of 850 (91.8%) of 926 patients had either excellent or moderate compliance. The rest of the patients had poor compliance either with treatment or with follow-up examinations. Poor compliance was more common for patients initially assigned to group A than for patients in group B (P=0.029). The rate of poor compliance was not significantly different between groups C and D (P=0.533). Of the 32 patients with poor compliance in group A, 17 (53%) either did not return for follow-up examinations after the fourth month or received <80% of total treatment. Among the patients with excellent or moderate compliance, new radiographic findings, such as hilar adenopathy and/or parenchymal lesions suggestive of possible active disease, were seen during follow-up examination four months after the initiation of treatment in 48 (24%) of 200 patients in group A, compared to 26 (11.8%) of 220 patients in group B (P=0.001). New radiographic findings were found in 30 (13.6%) of 221 compliant patients in group C and in 23 (11%) of 209 compliant patients in group D (P=0.418). All of these patients were subsequently treated for active disease and received a total of nine months of treatment with isoniazid and rifampin. All children who participated in the study responded well to treatment, and no cases of clinical tuberculosis were documented at the end of therapy and during follow-up. Serious drug-related adverse events were not detected in any of the patients participating in the study. Nausea and epigastric pain were

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
isoniazid 10 mg/kg and rifampin 10 mg/kg once daily for three months (group D)				reported by 13 (6.5%) of 200 compliant patients in group A, and a transient increase in liver enzyme levels (≤3 times the upper limit of normal) was reported in 12 patients (6%). Of the 650 patients enrolled in the short-term treatment groups, eight children (1.2%) had a transient increase in liver enzyme levels, five (0.7%) reported nausea or epigastric pain, nine (1.3%) had a transient maculopapular rash, and five (0.7%) had a photosensitivity reaction. Discontinuation or modification of treatment was not required in any patient. Secondary: Not reported
Ziakas et al.[51] (2009) Rifampin 10 mg/kg/day for four months vs isoniazid 5 mg/kg/day for nine months	MA Patients with latent tuberculosis infection	N=3,586 (4 trials) 9 months	Primary: Non-completion rates, hepatotoxicity and failures Secondary: Not reported	Primary: Non-completion rates in the rifampin arm ranged from 8.6 to 28.4% compared to 24.1 to 47.4% in the isoniazid arm. Among 2,118 patients in the four month-rifampin arm and 1,468 patients in the nine month-isoniazid arm, the pooled effect of rifampin was protective under the random-effects model (RR, 0.53; 95% CI, 0.44 to 0.63). Patients in the four month-rifampin arm had half of the risk of not completing the treatment course than patients in the nine month-isoniazid arm. Hepatotoxicity rates ranged from 0 to 0.7% in the four month-rifampin arm and from 1.4 to 5.2% in the nine month-isoniazid arm. Regarding hepatotoxicity, the pooled effect of four month-rifampin was also protective under the fixed-effects model (RR, 0.12; 95% CI, 0.05 to 0.30). There was limited information regarding tuberculosis reactivation in the included studies. The internal validity of the studies included in this MA is limited by a lack of blinding in two randomized trials and a retrospective design in the other two trials. Secondary: Not reported
Bright-Thomas et al.[52] (2010)	OB Children with latent tuberculosis	N=334 Mean 12.35 years	Primary: Proportion and rate of tuberculosis	Primary: Of the 252 patients who were still registered with the local database, three (1.19%) patients developed tuberculosis. This was six months, six years 11 months and seven years 10 months after the commencement of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Rifampicin and isoniazid prophylaxis for three months (3RH)	infection who were treated with rifampicin and isoniazid		Secondary: Not reported	prophylaxis. The three cases of clinical tuberculosis occurred during a total of 3,113 years of follow-up. The rate of clinical tuberculosis was 0.964/1,000 person-years (95% CI, 0.0199 to 2.816). No patient developed significant hepatitis on 3RH requiring cessation of treatment during the active treatment period. Secondary: Not reported
Gao et al.[53] (2006) Rifampin 450 mg and pyrazinamide 1,500 mg (<40 kg) or rifampin 450 mg and pyrazinamide 2,000 mg (40 to 50 kg) or rifampin 600 mg and pyrazinamide 2,500 mg twice weekly (>50 kg) for two months vs isoniazid 600 mg and vitamin B6 25 mg (<50 kg) or isoniazid 800 mg and vitamin B6 25 mg (>50 kg) twice weekly for six months vs rifampin 600 mg/day	MA Studies were included if the study population included in the trials were at high risk of developing active tuberculosis	6 trials 12 months	Primary: Development of active tuberculosis Secondary: Serious adverse effects and death	Primary: Rates of tuberculosis in the rifampin and pyrazinamide group were similar to those in the isoniazid group, whether the subjects were HIV-infected or not (HIV-infected patients; P=0.89, non-HIV-infected persons; P=0.55). Secondary: There was no difference in mortality between the two treatment groups (HIV-infected patient; P=0.53, non-HIV-infected persons; P=1.00). Subgroup analyses showed that a higher incidence of all severe adverse events was associated with rifampin plus pyrazinamide than isoniazid among non-HIV-infected persons (P=0.0005).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
and pyrazinamide 3,500 mg twice weekly for six months vs isoniazid 900 mg twice weekly for six months vs rifampin 600 mg/day and pyrazinamide 200 mg/kg/day for two months vs isoniazid 300 mg/day and vitamin B6 50 mg/day for 12 months vs rifampin 600 mg/day and pyrazinamide 20 mg/kg/day for two months vs isoniazid 300 mg daily for six months				

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs rifampin 450 mg/day and pyrazinamide 1,000 mg/day or 20 mg/kg/day (weight <50 kg) or rifampin 600 mg/day and pyrazinamide 1,500 mg/day or 20 mg/kg/day (weight >50 kg) for two months vs isoniazid 300 mg/day for six months vs rifampin 10 mg/kg/day (maximum 600 mg/day) and pyrazinamide 25 mg/kg/day or 20 mg/kg/day (maximum 2,000 mg) for two months vs isoniazid 5 mg/kg/day (maximum 300 mg/day) for six				

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
months Rifampin and pyrazinamide were used for two to three months and compared to standard isoniazid therapy for 6 to 12 months.				
Menzies et al.[54] (2008) Rifampin 10 mg/kg/day for four months vs isoniazid 5 mg/kg/day for nine months	MC, OL, RCT Patients with a positive tuberculin skin test requiring treatment for latent tuberculosis infection	N=847 9 months	Primary: Frequency of grade 3 or 4 adverse events that resulted in study drug discontinuation Secondary: On-time treatment completion (defined as taking more than 80% of doses within a maximum of 150 days for four months of rifampin or 301 days (43 weeks) for nine months of isoniazid)	Primary: Of the 418 who started rifampin, seven developed grade 3 or 4 adverse events attributed to study therapy by the independent panel compared to 17 of the 422 patients who started isoniazid (95% CI, -5 to -0.1; P=0.040). The difference in adverse events was entirely attributable to drug-induced hepatitis, which developed in three patients (0.7%) taking rifampin compared to 16 patients (3.8%) taking isoniazid (95% CI, -5 to -1; P=0.003). Of these, 11 had grade 3 hepatitis and eight had grade 4 hepatitis. In an analysis restricted to patients who took at least one month of therapy, three of 389 taking rifampin and 16 of 392 taking isoniazid developed grade 3 or 4 hepatotoxicity (95% CI, -5.5 to -1.1). Grade 1 or 2 adverse events that resulted in permanent discontinuation of therapy and were judged by the study's independent panel to be related to the study drug were less common and similar in frequency in the two regimens. The more common of these problems was rash, which occurred in more patients taking rifampin. Secondary: Of the patients assigned to four months of rifampin, 78% completed therapy compared to 60% of patients assigned to nine months of isoniazid (95% CI, 12 to 24; P<0.001).
Martinson et al.[55] (2011) Rifapentine	OL, RCT Adults with HIV infection and a	N=1,148 Median 4 years	Primary: Tuberculosis-free survival	Primary: Tuberculosis was diagnosed in 78 patients, of whom 62 (79%) had confirmed tuberculosis, 11 (14%) had probable tuberculosis, and five (6%) had possible tuberculosis. The overall incidence of all tuberculosis

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
900 mg plus isoniazid 900 mg weekly for 12 weeks vs rifampin 600 mg plus isoniazid 900 mg twice weekly for 12 weeks vs isoniazid 300 mg daily for up to six years vs isoniazid 300 mg daily for six months (control group)	positive tuberculin skin test who were not taking anti-retroviral therapy		Secondary: Adherence to the study regimen, adverse events, discontinuation of study medication for any reason, and mycobacterial drug resistance in patients with tuberculosis	was 1.9 cases per 100 person-years. There were 66 deaths during the follow-up period, for an overall incidence of 1.6 deaths per 100 person-years. Incidence rates of active tuberculosis or death were 3.1 per 100 person-years in the rifapentine–isoniazid group, 2.9 per 100 person-years in the rifampin–isoniazid group, and 2.7 per 100 person-years in the continuous-isoniazid group, as compared to 3.6 per 100 person-years in the control group (P>0.05 for all comparisons). Secondary: The proportions of patients who reported taking or were observed taking more than 90% of their assigned doses of study medication in the time allotted were 95.7% in the rifapentine–isoniazid group, 94.8% in the rifampin–isoniazid group, and 83.8% in the six-month–isoniazid group. Patients in the continuous-isoniazid group took isoniazid for 89.1% of the total follow-up time. The median duration of receipt of continuous isoniazid was 3.3 years. There were no deaths attributed to a study drug. A grade 3 or 4 elevation in the aspartate or alanine aminotransferase level occurred during the treatment phase in 1.5, 2.4, 28.0, and 5.5% of patients in the rifapentine–isoniazid, rifampin–isoniazid, continuous-isoniazid, and six-month–isoniazid groups, respectively (P<0.001 for the comparison of continuous isoniazid with six-month isoniazid). Drug-susceptibility testing was performed in 58 of 62 *Mycobacterium tuberculosis* isolates (94%). Two cases of isoniazid-resistant tuberculosis and three cases of rifampin-resistant tuberculosis were detected. Multidrug-resistant tuberculosis (resistance to both isoniazid and rifampin) was detected in two of the isolates (3%), one from a patient in the rifapentine–isoniazid group and the other from a patient in the continuous-isoniazid group.
Treatment of Latent Tuberculosis Infection in HIV-Positive Patients				
Halsey et al.[56]	PRO, RCT	N=784	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1998) Isoniazid 600 mg twice weekly for 24 weeks (<50 kg) or isoniazid 800 mg twice weekly for 24 weeks (≥50 kg) vs rifampin 450 mg with pyrazinamide 1,500 mg twice weekly for eight weeks (<40 kg) or rifampin 450 mg with pyrazinamide 2,000 mg twice weekly for eight weeks (40 to 50 kg) or rifampin 600 mg with pyrazinamide 2,500 twice weekly for eight weeks (>50 kg)	Patients 16 to 77 years of age, HIV-1 seropositive, with a positive purified-protein derivative skin test, and who had a normal chest radiograph	4 years	Risk of tuberculosis during first 10 months Secondary: Risk of tuberculosis during first 36 months	Risk of tuberculosis during the first 10 months after entry was 3.7% among patients who received rifampin and pyrazinamide compared to 1.0% (P=0.03) among patients who received isoniazid. Secondary: Risk of tuberculosis at 36 months after entry was 5.4% among patients who received rifampin and pyrazinamide vs 5.1% among patients who received isoniazid (P=0.9).
Woldehanna et al.[57] (2004) Previous therapy (any antituberculosis agent) vs placebo	MA HIV-positive patients without active tuberculosis	N=8,130 Variable duration	Primary: Effectiveness of tuberculosis preventive therapy in reducing the risk of active tuberculosis and death Secondary: Not reported	Primary: Preventative therapy was associated with a lower incidence of active tuberculosis (RR, 0.64; 95% CI, 0.51 to 0.81). In individuals with a positive tuberculin skin test this result was even more pronounced (RR, 0.38; 95% CI, 0.25 to 0.57) compared to patients with a negative skin test (RR, 0.83; 95% CI, 0.58 to 1.18). Overall there was no evidence that preventative therapy when compared to placebo reduced all-cause mortality (RR, 0.95; 95% CI, 0.85 to 1.06). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Ena et al.[58] (2005) Isoniazid for 6 to 12 months vs rifampin plus isoniazid daily for three months	MA Patients with latent tuberculosis (both HIV positive and negative patients)	N=1,926 (5 trials) 12 months	Primary: Incidence of tuberculosis, side effects requiring drug withdrawal, mortality Secondary: Not reported	Primary: A total of 4.1% of patients in the monotherapy group compared to 4.2% of patients in the combination group developed tuberculosis, a difference that was not significant (P=0.083). A total of 4.8% of patients in the monotherapy group compared to 4.9% of patients in the combination group required drug withdrawal due to severe adverse events, a difference that was not significant. A total of 10.4% of patients in the monotherapy group compared to 9.5% of patients in the combination group died during the trail, a difference that was not significant (P=0.36). Secondary: Not reported
Prophylaxis of Tuberculosis Infection in Human Immunodeficiency Virus-Positive Patients				
Zar et al.[59] (2007) Isoniazid 10 mg/kg/day daily or three times weekly as prophylaxis vs placebo Sulfamethoxazole-trimethoprim 5 mg/kg/dose (trimethoprim component) was also given to all patients daily or three times weekly as	DB, PC, RCT Children ≥8 weeks with HIV	N=263 Median 5.7 months	Primary: Mortality Secondary: Incidence of tuberculosis, toxicity	Primary: Mortality was lower in the isoniazid group (8%) than in the placebo group (16%; HR, 0.46; 95% CI, 0.22 to 0.95). The benefit applied to children across all categories of severity of clinical disease and in all ages. The reduction in mortality was similar in children assigned to isoniazid three times/week compared to every day (P=0.943). There were no deaths among children with positive results on tuberculin skin testing. Secondary: The incidence of confirmed or probable tuberculosis was lower in the isoniazid group (4%) than in the placebo group (10%; HR, 0.28; 95% CI, 0.10 to 0.78). The protective effect of isoniazid on incidence of tuberculosis occurred in all categories of severity of clinical disease in children aged >1 year and in both dose regimens. All *Mycobacterium tuberculosis* isolates were sensitive to anti-tuberculosis drugs including isoniazid. The incidence of grade 3 or 4 toxicity was l4% in the isoniazid group and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
prophylaxis for opportunistic infections.				6.1% in the placebo group. No child required permanent discontinuation of trial drug. No cutaneous or neurological toxicity was observed.
Madhi et al.[60] (2011) Isoniazid 10 to 20 mg/kg daily vs placebo All infants received sulfamethoxazole-trimethoprim prophylaxis and the Bacille Calmette-Guérin vaccine against tuberculosis within 30 days after birth.	DB, MC, RCT HIV-infected infants and uninfected infants exposed to HIV during the perinatal period	N=1,352 96 to 108 weeks	Primary: Rate of tuberculosis disease and death in HIV-infected children (tuberculosis-disease-free survival); rate of latent tuberculosis infection, tuberculosis disease, and death in HIV-uninfected children (tuberculosis-infection-free survival) Secondary: Not reported	Primary: HIV-infected cohort: A total of 274 HIV-infected infants were enrolled in each study group. Either protocol-defined tuberculosis or death occurred in 52 children (19.0%) in the isoniazid group as compared to 53 children (19.3%) in the placebo group (HR, 0.98; 95% CI, 0.67 to 1.44). Tuberculosis accounted for 31 (59.6%) of the primary end points in the isoniazid group and for 38 (71.7%) in the placebo group (P=0.40). Death accounted for 21 (40.4%) and 15 (28.3%) of the primary end points in the two groups, respectively (P=0.12). HIV-uninfected cohort: Eighty-four children (10.4%) reached a primary end point, a composite of tuberculosis disease, latent tuberculosis infection, or death. The estimated HR for the isoniazid group as compared to the placebo group was 0.85 (95% CI, 0.55 to 1.30). There was no significant difference between study groups (P=0.44). Secondary: Not reported
Samandari et al.[61] (2011) Isoniazid 300 or 400 mg/day for six months (control) vs isoniazid 300 or 400 mg/day for 36 months	DB, MC, RCT Adults with HIV infection in Botswana	N=1,995 36 months	Primary: Incident tuberculosis Secondary: Death, safety	Primary: Overall, there were 54 incident cases of tuberculosis. Thirty-four (3.4%) patients in the control group and 20 (2.0%) of patients in the long-term isoniazid group had incident tuberculosis. Incidence was 1.26% per year in the control group compared to 0.72% per year in the long-term isoniazid group (HR, 0.57; 95% CI, 0.33 to 0.99; P=0.047). Tuberculosis incidence in the two groups diverged about 200 days after completion of the initial six months' isoniazid prophylaxis, suggesting that the benefit of the initial treatment was lost by this time. Secondary: Mortality was 1.3% per year and did not differ between study groups for all enrolled participants. However, for patients with a positive tuberculin

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				skin test, mortality was three times lower in the long-term isoniazid group than in the control group (P=0.03). A total of 1% of patients in the control group had severe adverse events associated with study drugs, compared to 1.3% of patients who received long-term isoniazid (P=0.36). There were 6 cases of hepatitis and one case of rash in the control group. There were nine cases of hepatitis, one case of rash, and one case of peripheral neuropathy in the long-term isoniazid group.
le Roux et al.[62] (2009) Isoniazid 10 mg/kg once daily vs isoniazid 10 mg/kg three times/week Sulfamethoxazole-trimethoprim prophylaxis was administered on the same dosing schedule as isoniazid.	RCT Children >8 weeks with HIV infection	N=324 2 to 4 years	Primary: Adherence Secondary: Not reported	Primary: Similar mean adherence was achieved by the group taking daily medication (93.8%; 95% CI, 92.1 to 95.6) and by the three times/week group (95.5%; 95% CI, 93.8 to 97.2). Two-hundred and seventeen (78.6%) children achieved a mean adherence of ≥90%. Adherence was similar for the daily and three times/week dosing schedules (univariate model: OR, 0.88; 95% CI, 0.66 to 1.17; P=0.38; multivariate model: OR, 0.85; 95% CI, 0.64 to 1.11; P=0.23). Age at study visit was predictive of adherence, with better adherence achieved in children >4 years of age (OR, 1.96; 95% CI, 1.16 to 3.32; P=0.01). Secondary: Not reported
Miscellaneous				
Nelson et al.[63] (2011) Metronidazole, vancomycin, fusidic acid, nitazoxanide, teicoplanin, rifampin, rifaximin,	MA Patients with *Clostridium difficile*-associated diarrhea	N=1,152 (15 trials) Variable duration	Primary: Initial resolution of diarrhea; initial conversion of stool to *Clostridium difficile* cytotoxin or negative stool culture; recurrence of diarrhea; recurrence of	Primary: Only three of the 15 studies could be analyzed for direct comparison of metronidazole and vancomycin. There was no difference in symptomatic cure minus recurrences between the two medications (RR, 0.91; 95% CI, 0.81 to 1.03). Vancomycin was favored over bacitracin for symptomatic cure (RR, 0.58; 95% CI, 0.34 to 0.99) and bacteriologic initial response (RR, 0.52; 95% CI, 0.31 to 0.86). There was no difference in symptomatic recurrence.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
bacitracin, fidaxomicin			*Clostridium difficile* cytotoxin or positive stool culture; patient response to cessation of prior antibiotic therapy; emergent surgery; death Secondary: Not reported	Teicoplanin was found to be more effective than vancomycin for: symptomatic cure of *Clostridium difficile* (RR, 1.21; 95% CI, 1.00 to 1.46); bacteriologic initial response (RR, 1.43; 95% CI, 1.14 to 1.81); bacteriologic cure (RR, 1.82; 95% CI, 1.19 to 2.78). There was no difference in symptomatic initial response, symptomatic recurrence, or bacteriologic recurrence. There was no difference between fusidic acid and vancomycin in symptomatic initial response, symptomatic cure, bacteriologic initial response, bacteriologic cure, symptomatic recurrence or bacteriologic recurrence. There was no difference between nitazoxanide and vancomycin in symptomatic initial response, recurrence of diarrhea within 31 days or symptomatic cure. There was no difference between rifaximin and vancomycin in symptomatic initial response or bacteriologic initial response. There was no difference between metronidazole and nitazoxanide in initial resolution of diarrhea or recurrence of diarrhea at 31 days. There was no difference between metronidazole and metronidazole plus rifampin in initial resolution of diarrhea or recurrence of diarrhea within 40 days. Teicoplanin was more effective than metronidazole for bacteriologic initial cure (RR, 0.76; 95% CI, 0.6 to 0.98); bacteriologic cure (RR, 0.76; 95% CI, 0.58 to 1.00). There was no difference between teicoplanin and metronidazole in outcome of symptomatic cure, initial symptomatic response, or symptomatic recurrence. There was no difference between metronidazole and fusidic acid in symptomatic initial response, symptomatic cure, bacteriologic initial

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				cure, bacteriologic cure or symptomatic response. Teicoplanin was more effective than fusidic acid for symptomatic cure (RR, 1.36; 95% CI, 1.02 to 1.83); bacteriologic initial cure (RR, 1.68; 95% CI, 1.19 to 2.37); bacteriologic cure (RR, 1.73; 95% CI, 1.19 to 2.51). There was no difference between teicoplanin and fusidic acid in symptomatic initial response or symptomatic recurrence. There was no difference between high-dose and low-dose vancomycin or teicoplanin therapy for symptomatic initial response. There was no difference between high-dose and low-dose vancomycin, fidaxomicin, or teicoplanin therapy for symptomatic recurrence. There was no difference between high-dose and low-dose vancomycin or teicoplanin therapy for symptomatic cure. There was no difference between high-dose and low-dose vancomycin or teicoplanin therapy for bacteriologic cure. Secondary: Not reported

*Rifampicin is the international name for rifampin.
^Not commercially available in the United States.
Study abbreviations: CI=confidence interval, DB=double-blind, HR=hazard ratio, MA=meta-analysis, MC=multicenter, OB=observational, OL=open-label, OR=odds ratio, PC=placebo controlled, PRO=prospective, RCT=randomized controlled trial, RR=relative risk
Abbreviations: HIV=human immunodeficiency virus

Additional Evidence

Dose Simplification
Several studies have compared the efficacy and safety of the fixed-dose combination products to the individual components administered as separate formulations. Four studies reported no difference in efficacy between the treatment arms, while two studies found that the fixed-dose combination products were associated with an increase in relapse rates.[31-33,36,42] There was no difference in the incidence of adverse events in three studies, while a fourth study found that there were fewer reports of gastrointestinal adverse events, visual disturbances and peripheral neuropathy with the use of the fixed-dose combination product.[31-33,42] Patient compliance was also assessed; two studies found no difference in compliance with the fixed-dose combination product, while a third study reported a higher rate of noncompliance with the fixed-dose combination product compared to the administration of the individual components as separate formulations.[31,33,36]

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 17. Relative Cost of the Antituberculosis Agents

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single-entity Agents				
Aminosalicylic acid	packet	Paser®	$$$$$	N/A
Bedaquiline	tablet	Sirturo®	N/A	N/A
Capreomycin	injection	Capastat Sulfate®	$$$$$	N/A
Cycloserine	capsule	N/A	$$$$$	N/A
Ethambutol	tablet	Myambutol®*	$$$-$$$$	$$$
Ethionamide	tablet	Trecator®	$$$$$	N/A
Isoniazid	injection, syrup, tablet	N/A	N/A	$
Pyrazinamide	tablet	N/A	N/A	$$$$$
Rifabutin	capsule	Mycobutin®*	$$$$$	$$$$$
Rifampin	capsule, injection	Rifadin®*	$$-$$$$$	$$$
Rifapentine	tablet	Priftin®	$$$$	N/A

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Combination Products				
Rifampin and isoniazid	capsule	Rifamate®	$$$$$	$$$$
Rifampin, isoniazid, and pyrazinamide	tablet	Rifater®	$$$$	N/A

*Generic is available in at least one dosage form or strength.
N/A=Not available.

X. Conclusions

The treatment of tuberculosis is a long-term process and focuses on treating active disease, as well as latent infections. The initial phase of treatment kills rapidly multiplying populations of *Mycobacterium tuberculosis*. The recommended treatment regimen during this phase includes isoniazid, rifampin, pyrazinamide and ethambutol to prevent the emergence of drug resistance.[18,25,27] This is followed by a continuation phase, which kills the intermittently dividing populations; rifampin and isoniazid are the preferred treatment options during this phase.[25,27]

Treatment of latent tuberculosis consists of monotherapy for six to nine months and isoniazid is the preferred agent.[22-24,27] The combination of isoniazid and rifapentine (given as directly observed therapy) is as an equal alternative to isoniazid (self-supervised therapy) in patients ≥12 years of age who have a predictive factor for a greater likelihood of tuberculosis developing.[14] The preferred regimen for children two to 11 years of age is daily isoniazid. Rifampin is an alternative treatment option for patients who may not tolerate isoniazid; however, potential drug interactions should be considered.[22-24,27] Due to reports of severe liver injury and deaths, shorter-course regimens with rifampin and pyrazinamide are not recommended for the treatment of latent tuberculosis infections.[24]

Cycloserine, ethambutol, isoniazid, pyrazinamide, rifabutin, rifampin, and rifampin-isoniazid are available in a generic formulation. There are two fixed-dose combination products that are currently available for the treatment of tuberculosis. The three-drug combination containing rifampin, isoniazid, and pyrazinamide is approved for the treatment of pulmonary tuberculosis during the two-month initial phase. The two-drug combination containing rifampin and isoniazid is approved for the treatment of pulmonary tuberculosis during the continuation phase. Several studies have found no difference in relapse rates, or demonstrated higher relapse rates, with the fixed-dose combination products compared to the individual components administered as separate formulations.[31-33,35,36,42] Available studies do not demonstrate an improvement in patient compliance with the use of fixed-dose combination products.[31,33,36]

Azithromycin and clarithromycin are recommended for the prophylaxis of *Mycobacterium avium* complex disease in adults with acquired immunodeficiency syndrome.[16] Rifabutin is also effective, but it is not as well tolerated.[16] Both azithromycin and clarithromycin are available generically.

There is insufficient evidence to support that one brand antituberculosis agent is more efficacious than another within its given indication. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand antituberculosis agents within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand antituberculosis agent is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Antimycobacterials, Miscellaneous
AHFS Class 081692
November 12, 2014

I. Overview

Dapsone is approved for the treatment of leprosy and dermatitis herpetiformis.[1-3] Leprosy is an infectious disease caused by *Mycobacterium leprae* and involving the skin and peripheral nerves.[4] Dapsone was introduced as a treatment for leprosy in the late 1940's and was used extensively as monotherapy. However, bacterial resistance to dapsone became an increasing concern. The World Health Organization has issued official recommendations for multi-drug therapy and currently recommends treating patients with leprosy with a combination of anti-infective drugs.[5]

Dermatitis herpetiformis is a cutaneous manifestation of celiac disease, which is characterized by pruritic papulovesicular skin eruptions.[6] While dapsone may be used to treat dermatitis herpetiformis; it is generally used in combination with a lifelong gluten-free diet. Eventually, patients adhering to a gluten-free diet may exhibit a reduced requirement for dapsone, or may be able to discontinue its use completely.

Dapsone is a sulfone antimicrobial. The mechanism of action of the sulfones is similar to sulfonamides, which involves inhibition of folic acid synthesis in susceptible organisms.[1-3] Dapsone is bacteriostatic against *Mycobacterium leprae*; however, the mechanism of action in dermatitis herpetiformis is not fully understood.

The miscellaneous antimycobacterials that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Dapsone is available in a generic formulation. This class was last reviewed in May 2012.

Table 1. Antimycobacterials, Miscellaneous Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Dapsone	tablet	N/A	dapsone

N/A=Not available, PDL=Preferred Drug List

The miscellaneous antimycobacterials have been shown to be active against the strains of microorganisms indicated in Table 2. This activity has been demonstrated in clinical infections and is represented by the Food and Drug Administration (FDA)-approved indications for the miscellaneous antimycobacterials that are noted in Table 4. These agents may also have been found to show activity to other microorganisms in vitro; however, the clinical significance of this is unknown since their safety and efficacy in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials. Although empiric antibacterial therapy may be initiated before culture and susceptibility test results are known, once results become available, appropriate therapy should be selected.

Table 2. Microorganisms Susceptible to the Antimycobacterials, Miscellaneous[1]

Organism	Dapsone
Mycobacterium leprae	✔

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the miscellaneous antimycobacterials are summarized in Table 3.

Table 3. Treatment Guidelines Using the Antimycobacterials, Miscellaneous

Clinical Guideline	Recommendation(s)
World Health	Standard multidrug therapy regimens

Clinical Guideline	Recommendation(s)
Organization: **World Health Organization Eighth Expert Committee Report on Leprosy (2012)**[5]	• Three standard first-line drugs, rifampicin, clofazimine, and dapsone, are available for use in multidrug regimens of fixed duration, none of which should be used as monotherapy. • Note that children less than ten years of age should receive appropriately reduced weight-based doses of drugs. *Multibacillary leprosy* standard treatment regimen in adults • Rifampicin 600 mg once a month, clofazimine 300 mg once a month and 50 mg daily, and dapsone 100 mg daily for a duration of 12 months. *Multibacillary leprosy* standard treatment regimen in children • Rifampicin 450 mg once a month, clofazimine 150 mg once a month and 50 mg every other day, and dapsone 50 mg daily for a duration of 12 months. *Paucibacillary leprosy* standard treatment regimen in adults • Rifampicin 600 mg once a month and dapsone 100 mg daily for a duration of 12 months. *Paucibacillary leprosy* standard treatment regimen in children • Rifampicin 450 mg once a month and dapsone 50 mg daily for a duration of six months. Special treatment regimen for individual patients who cannot take rifampicin because of side-effects or intercurrent diseases, such as chronic hepatitis, or who have been infected with rifampicin-resistant *Multibacillary leprae*. The following 24-month regimen is recommended: • Daily administration of 50 mg clofazimine, together with two of the following drugs – 400 mg ofloxacin, 100 mg minocycline or 500 mg clarithromycin – for six months, followed by daily administration of 50 mg clofazimine, together with 100 mg minocycline or 400 mg ofloxacin for an additional 18 months. If available, ofloxacin may be replaced by moxifloxacin 400 mg, which has stronger bactericidal activity against *Multibacillary leprae.* Special treatment regimen for individual patients who cannot take dapsone • If dapsone produces severe toxic effects in any *Paucibacillary leprosy* or *Multibacillary leprosy* patient, it must be stopped immediately. • No further modification of the regimen is required for patients with *Multibacillary leprosy*. For *Paucibacillary leprosy*, however, clofazimine – in the dosage used in the standard multidrug therapy for *Multibacillary leprosy*– should be substituted for dapsone in the 6-month treatment regimen. Guidelines for the management of Severe Type 1 or reversal reaction • Severe reversal (Type 1) reactions should be treated with a course of steroids usually lasting three to six months. Patients still on antileprosy treatment should continue the standard course of multidrug therapy. Guidelines for the management of Severe Type 2 or erythema nodosum leprosum reaction • Severe erythema nodosum leprosum reaction should be treated with a standard course of prednisolone (daily dosage not exceeding 1 mg/kg body weight) for 12 weeks. Patients who experience reactions while still on multidrug therapy should continue the standard treatment with multidrug therapy. If multidrug therapy has been completed, the management of erythema nodosum leprosum should not include restarting of multidrug therapy. Adequate doses of analgesics to control fever and pain should be prescribed.

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	• A combination of clofazimine and corticosteroids is indicated for management of patients with severe erythema nodosum leprosum who are not responding satisfactorily to treatment with corticosteroids alone or for whom the risk of corticosteroid toxicity is high. Prednisolone should be given in daily dosage not exceeding 1 mg/kg body weight. Treatment with clofazimine should start with 100 mg three times a day for a maximum of 12 weeks, with the dose then tapering to 100 mg twice a day for 12 weeks and to 100 mg once a day for 12 to 24 weeks. • Management of erythema nodosum leprosum reaction with clofazimine alone is indicated in cases of severe erythema nodosum leprosum when the use of corticosteroids is contraindicated. Treatment with clofazimine should follow the same guidelines as when it is used in combination with prednisolone. However, the total duration of treatment with high-dose clofazimine should not exceed 12 months. • It should be noted that it takes about four to six weeks for clofazimine to take full effect in controlling erythema nodosum leprosum. Management of severe erythema nodosum leprosum reaction is complex and should be undertaken only by physicians at referral facilities, who will adjust the dose and duration of antireaction drugs according to patients' individual needs.
United States Department of Health and Human Services Health Resources and Services Administration: **National Hansen's Disease (Leprosy) Program**[7]	General considerations • National Hansen's disease Program recommendations are for daily rifampin, and for longer duration of treatment than the World Health Organization recommendations, largely due to World Health Organization's cost considerations for developing countries. Treatment that is more intensive and of longer duration is medically preferable. Treatment guidelines for immunologically competent adults • Tuberculoid (*Paucibacillary leprosy*): Dapsone 100 mg daily and rifampicin 600 mg daily for a duration of 12 months. • Lepromatous (*Multibacillary leprosy*): Dapsone 100 mg daily, rifampicin 600 mg daily, and clofazimine 50 mg daily for a duration of 24 months. Treatment guidelines for children • Tuberculoid (*Paucibacillary leprosy*): Dapsone 1 mg/kg daily and rifampicin 10 to 20 mg/kg daily (not >600 mg) for a duration of 12 months. • Lepromatous (*Multibacillary leprosy*): Dapsone 1 mg/kg daily, rifampicin 10 to 20 mg/kg daily (not >600 mg), and clofazimine 1 mg/kg (as there is no formulation less than 50 mg, and the capsule should never be cut open, alternate day dosing may be used at 2 mg/kg) daily for a duration of 24 months. Alternative anti-microbial agents • Minocycline, 100 mg daily, can be used as a substitute for dapsone in individuals who do not tolerate this drug. It can also be used instead of clofazimine, although evidence of the efficacy of its anti-inflammatory activity against Type 2 reactions is not as substantial as the evidence for clofazimine. • Clarithromycin, 500 mg daily is also effective against *Multibacillary leprosy*, and can be used as a substitute for any of the other drugs in a multiple drug regimen. • Ofloxacin, 400 mg daily, may also be used in place of clofazimine, for adults. This is not recommended for children.
National Institutes of Health, the Centers for Disease Control and Prevention, and the	Aspergillosis • Voriconazole is the drug of choice but should be used cautiously with human immunodeficiency virus protease inhibitors and efavirenz. Amphotericin B deoxycholate at 1 mg/kg daily or lipid-formulation amphotericin B at 5 mg/kg

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Human Immunodeficiency Virus Medicine Association of the Infectious Diseases Society of America: **Guidelines for Prevention and Treatment of Opportunistic Infections in Human Immunodeficiency Virus -Infected Adults and Adolescents (2013)**[8]	daily are alternatives, as is caspofungin at 50 mg daily and posaconazole. • Other echinocandins, such as micafungin and anidulafungin, are reasonable alternatives. • For treatment failure (if voriconazole was used initially) substitution with amphotericin B, posaconazole, or echinocandins might be considered; the amphotericin B or echinocandins would be rational for those who began therapy with voriconazole or posaconazole. <u>Candidiasis (mucocutaneous)</u> • Oral fluconazole is as effective as topical therapy for oropharyngeal candidiasis and is considered the drug of choice. Initial episodes of oropharyngeal candidiasis can be adequately treated with topical therapy, including clotrimazole troches, nystatin suspension or pastilles, or miconazole mucoadhesive tablets. Itraconazole oral solution for seven to 14 days is as effective as oral fluconazole but less well tolerated. Posaconazole oral solution is also as effective as fluconazole and is generally better tolerated than itraconazole. Intravenous amphotericin B is usually effective and can be used among patients with refractory disease. Both conventional amphotericin B and lipid complex and liposomal amphotericin B have been used. • Systemic antifungals are required for effective treatment of esophageal candidiasis. A 14 to 21-day course of either fluconazole (oral or intravenous) or oral itraconazole solution is highly effective. Oral ketoconazole or itraconazole capsules are less effective than fluconazole because of variable absorption. Although intravenous caspofungin or intravenous voriconazole are effective in treating esophageal candidiasis among human immunodeficiency virus -infected patients, oral or intravenous fluconazole remain the preferred therapies. Azole-refractory esophageal candidiasis can be treated with posaconazole, amphotericin B, anidulafungin, caspofungin, micafungin, or voriconazole. • Vulvovaginal candidiasis in human immunodeficiency virus -infected women is usually uncomplicated (90%) and responds readily to short-course oral or topical treatment with any of several therapies, including oral fluconazole, topical azoles, and itraconazole oral solution. Severe or recurrent episodes of vaginitis require oral fluconazole or topical antifungal therapy for ≥7 days. <u>Coccidioidomycosis</u> • For patients with clinically mild infection, such as focal pneumonia or a positive coccidioidal serologic test alone, initial therapy with a triazole antifungal is appropriate. • For patients with either diffuse pulmonary involvement or severely ill patients with extrathoracic disseminated disease, amphotericin B is the preferred initial therapy. Therapy with amphotericin B should continue until clinical improvement is observed. Some specialists would use a triazole antifungal concurrently with amphotericin B and continue the triazole once amphotericin B is stopped. <u>Cryptococcosis</u> • The recommended initial standard treatment is amphotericin B combined with flucytosine for ≥2 weeks for those with normal renal function. • The combination of amphotericin B with fluconazole is less effective than amphotericin B combined with flucytosine in terms of clearing *Cryptococcus* from the cerebrospinal fluid but is better than amphotericin B alone. • Fluconazole combined with flucytosine is an alternative to amphotericin B plus flucytosine, but is less effective than amphotericin B and is recommended only for persons unable to tolerate or unresponsive to standard treatment. • After at least a two-week period of successful induction therapy, amphotericin

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	B and flucytosine may be discontinued and follow-up therapy initiated with fluconazole. This should continue for eight weeks. Itraconazole is an acceptable though less effective alternative. • The optimal therapy for those with treatment failure is not established. For those initially treated with fluconazole, therapy should be changed to amphotericin B, with or without flucytosine, and continued until a clinical response occurs. Liposomal amphotericin B may have improved efficacy over the deoxycholate formulation and should be considered in treatment failures. Higher doses of fluconazole in combination with flucytosine might also be useful. <u>Cryptosporidiosis</u> • In the setting of severe immunosuppression, antiretroviral therapy with immune restoration to a CD4+ count >100 cells/µL leads to resolution of clinical cryptosporidiosis and is the mainstay of treatment. • All patients with cryptosporidiosis should be offered antiretroviral therapy as part of the initial management of their infection. • Management should include symptomatic treatment of diarrhea. Rehydration and repletion of electrolyte losses by either the oral or intravenous route are important. Severe diarrhea can exceed >10 L/day among patients with acquired immunodeficiency syndrome, often requiring intensive support. Aggressive efforts at oral rehydration should be made with oral rehydration solutions. <u>Prevention of Cytomegalovirus</u> • Cytomegalovirus end-organ disease is best prevented by using antiretroviral therapy to maintain the CD4+ count >100 cells/µL. • Although oral valganciclovir would likely prevent the occurrence of cytomegalovirus retinitis in patients with CD4+ counts <50 cells/µL, such therapy is not generally recommended because of the potential to induce cytomegalovirus resistance, the utility of treating disease when it occurs, and the lack of demonstrated survival advantage. <u>Treatment of Cytomegalovirus disease</u> • Oral valganciclovir, intravenous ganciclovir, intravenous ganciclovir followed by oral valganciclovir, intravenous foscarnet, and intravenous cidofovir are all effective treatments for cytomegalovirus retinitis. • The ganciclovir implant, a surgically-implanted reservoir of ganciclovir, which lasts approximately six months, also is very effective but it no longer is being manufactured. In its absence, some clinicians will use intravitreal injections of ganciclovir or foscarnet in conjunction with oral valganciclovir, at least initially, to provide immediate high intraocular levels of drug and presumably faster control of the retinitis. • Systemic therapy has been shown to reduce morbidity in the contralateral eye. This should be considered when choosing between the oral, intravenous, and local options. • The choice of initial therapy for cytomegalovirus retinitis should be individualized based on the location and severity of the lesion(s), the level of underlying immune suppression, and other factors such as concomitant medications and ability to adhere to treatment. • No one regimen has been proven in a clinical trial to have greater efficacy in terms of protecting vision, and thus clinical judgment must be used when choosing a regimen. • In studies conducted in the pre-antiretroviral therapy era, ganciclovir intraocular implant plus oral ganciclovir was superior to once-daily intravenous ganciclovir for treatment of cytomegalovirus retinitis; however,

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	the implant is no longer manufactured. Assuming that this observation can be extended to other combinations of systemically and locally administered drugs, human immunodeficiency virus-specialists often recommend intravitreal ganciclovir or foscarnet injections plus oral valganciclovir as the preferred initial therapy for patients with immediate sight-threatening lesions. Intravitreal injections deliver high concentrations of the drug to the target organ immediately while steady-state concentrations in the eye are achieved with systemically delivered medications. For patients with small peripheral lesions, oral valganciclovir alone often is adequate. • After induction therapy, secondary prophylaxis (i.e., chronic maintenance therapy) should be continued until immune reconstitution occurs as a result of antiretroviral therapy. Regimens demonstrated to be effective for chronic suppression in randomized, controlled clinical trials include parenteral ganciclovir, oral valganciclovir, parenteral foscarnet, combined parenteral ganciclovir and foscarnet, and parenteral cidofovir. <u>Management of Cytomegalovirus retinitis treatment failures</u> • When patients relapse while receiving maintenance therapy, induction with the same drug followed by reinstitution of maintenance therapy can control the retinitis, although for progressively shorter periods of time with each relapse. • Ganciclovir and foscarnet in combination appear to be superior in efficacy to either agent alone and should be considered for patients whose disease does not respond to single-drug therapy, and for patients with multiple relapses of retinitis. This drug combination, however, is associated with substantial toxicity. <u>Treatment of Hepatitis B Virus coinfection in patients not receiving antiretroviral therapy</u> • For patients with CD4+ counts >350 cells/µL who are not receiving antiretroviral therapy but meet criteria for hepatitis B virus treatment, adefovir or peginterferon alfa-2a monotherapy for 48 weeks might be considered, with close monitoring of hepatitis B virus deoxyribonucleic acid levels and follow-up to evaluate for hepatitis B e antigen seroconversion. However, early initiation of antiretroviral therapy should also be considered for human immunodeficiency virus/hepatitis B virus -coinfected persons with CD4+ counts >350 cells/µL. <u>Treatment of Hepatitis B Virus coinfection in patients who require antiretroviral therapy</u> • For human immunodeficiency virus-infected persons, some experts recommend combination therapy with two agents active against hepatitis B virus to reduce the risk of hepatitis B virus drug resistance; although, there are no results from controlled trials as yet to support this strategy. • Among patients infected with hepatitis B virus, hepatitis C virus, and human immunodeficiency virus, consideration of the need for antiretroviral therapy should be the first priority. If antiretroviral therapy is not required, interferon-based therapy, which suppresses both hepatitis C virus and hepatitis B virus, should be considered. If interferon-based therapy for hepatitis C virus has failed, treatment of chronic hepatitis B with nucleoside or nucleotide analogs is recommended. <u>Treatment of Hepatitis C coinfection</u> • Antiviral treatment for hepatitis C virus infection should be considered for all human immunodeficiency virus-infected persons with acute or chronic hepatitis C virus infection. • The combination of peginterferon alfa (PegIFN) plus ribavirin is the

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	recommended backbone of therapy for HIV/HCV-co-infected patients regardless of HCV genotype.
	• Antiviral treatment with PegIFN is not recommended in patients with decompensated liver disease.
	• For HCV-genotype-1-infected patients who are not co-infected with HIV, a HCV NS3/4A protease inhibitor (PI), either boceprevir or telaprevir, in combination with PegIFN/ribavirin is recommended on the basis of large clinical trials demonstrating significantly higher SVR rates with an acceptable safety/tolerability profile compared to PegIFN/ribavirin alone.
	• For HIV/HCV co-infected patients, preliminary data from small, ongoing clinical trials of boceprevir or telaprevir plus PegIFN/ribavirin for the treatment of HCV genotype 1 infection in HIV/HCV co-infected patients demonstrate greater efficacy than PegIFN/ribavirin alone, with a safety and tolerability profile similar to that observed in HCV monoinfected patients treated with boceprevir or telaprevir plus PegIFN/ribavirin. Preliminary recommendations are as follows:
	  o PegIFN is recommended for use for all HCV genotypes
	  o Ribavirin is recommended for use with PegIFN for all HCV genotypes.
	  o Boceprevir is approved for use in combination with PegIFN/ribavirin in HCV-genotype-1-monoinfected-patients. For HIV/HCV-co-infected patients, the regimen being evaluated is PegIFN/ribavirin administered for four weeks (lead-in phase) followed by boceprevir 800 mg orally every 7 to 9 hours (with a light snack) added to PegIFN/ribavirin for an additional 44 weeks.
	  o Telaprevir is approved for use in combination with PegIFN/ribavirin in HCV-genotype-1-monoinfected-patients. Dosing regimens lasting 48 weeks are being evaluated.
	• Patients with contraindications to the use of ribavirin can be treated with peginterferon alfa (2a or 2b) monotherapy. However, substantially lower sustained viral response rates are expected in persons not receiving ribavirin. HCV PIs should not be administered without ribavirin because of the high likelihood of virologic failure.
	
	<u>Treatment of herpes simplex virus disease</u>
	• Orolabial lesions can be treated with oral valacyclovir, famciclovir, or acyclovir for five to 10 days.
	• Severe mucocutaneous herpes simplex virus lesions are best treated initially with intravenous acyclovir. Patients may be switched to oral therapy after the lesions have begun to regress. Therapy should be continued until the lesions have completely healed.
	• Genital herpes simplex virus infection should be treated with oral valacyclovir, famciclovir, or acyclovir for five to 14 days. Short-course therapy (one, two, or three days) should not be used in patients with human immunodeficiency virus infection.
	• Most recurrences of genital herpes can be prevented by use of daily anti-herpes simplex virus therapy, and this is recommended for persons who have frequent or severe recurrences.
	• Suppressive therapy with oral acyclovir, valacyclovir, or famciclovir is effective in preventing recurrences. Suppressive therapy with valacyclovir should be 500 mg twice daily in human immunodeficiency virus -infected persons or twice-daily regimens with acyclovir or famciclovir should be used.
	
	<u>Management of herpes simplex virus treatment failure</u>
	• The treatment of choice for acyclovir-resistant herpes simplex virus is intravenous foscarnet. Topical trifluridine, cidofovir, and imiquimod also have

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	been used successfully for lesions on external surfaces, although prolonged application for 21 to 28 days or longer might be required. Histoplasmosis • Patients with moderately severe to severe disseminated histoplasmosis should be treated with an intravenous lipid formulation of amphotericin B for ≥2 weeks or until they clinically improve followed by oral itraconazole (200 mg three times daily for three days and then 200 mg twice daily for a total of ≥12 months). • In patients with less severe disseminated histoplasmosis, oral itraconazole at 200 mg three times daily for three days followed by 200 mg twice daily is appropriate initial therapy. Treatment of Isosporiasis (also known as Cystoisosporiasis) • Sulfamethoxazole-trimethoprim is the antimicrobial agent of choice for treatment of isosporiasis. It is the only agent whose use is supported by substantial published data and clinical experience. Therefore, potential alternative therapies should be reserved for patients with documented sulfa intolerance or in whom treatment fails. The traditional treatment regimen has been a 10-day course of Sulfamethoxazole-trimethoprim (800-160 mg) administered orally four times daily. • Intravenous administration of Sulfamethoxazole-trimethoprim should be considered for patients with potential or documented malabsorption. • Single-agent therapy with pyrimethamine has been used, with anecdotal success for treatment and prevention of isosporiasis. Pyrimethamine (50 to 75 mg/day) plus leucovorin (10 to 25 mg/day) to prevent myelosuppression may be an effective treatment alternative; it is the option for sulfa-intolerant patients. Leishmaniasis • Due to similar efficacy and a better toxicity profile, clinicians consider liposomal amphotericin B as the drug of choice for visceral leishmaniasis in human immunodeficiency virus-coinfected patients. The optimal amphotericin B dosage has not been determined. • Regimens with efficacy include conventional amphotericin B 0.5 to 1.0 mg/kg body weight/day intravenous to achieve a total dose of 1.5 to 2.0 g, or liposomal or lipid complex preparations of two to four mg/kg body weight administered on consecutive days or in an interrupted schedule (e.g., 4 mg/kg on Days 1 to 5, 10, 17, 24, 31, and 38) to achieve a total cumulative dose of 20 to 60 mg/kg body weight. A higher daily dosage is recommended for liposomal or lipid complex preparations than for conventional amphotericin B. Preventing disseminated *Mycobacterium avium* complex disease • Human immunodeficiency virus-infected adults and adolescents should receive chemoprophylaxis against disseminated *Mycobacterium avium* complex disease if they have a CD4+ count <50 cells/µL. • Azithromycin or clarithromycin are the preferred prophylactic agents. • The combination of clarithromycin and rifabutin is no more effective than clarithromycin alone for chemoprophylaxis, is associated with a higher rate of adverse effects than either drug alone, and should not be used. • The combination of azithromycin with rifabutin is more effective than azithromycin alone; however, the additional cost, increased occurrence of adverse effects, potential for drug interactions, and absence of a survival difference compared to azithromycin alone do not warrant a routine recommendation for this regimen.

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	• Azithromycin and clarithromycin also each confer protection against respiratory bacterial infections.
	• If azithromycin or clarithromycin cannot be tolerated, rifabutin is an alternative prophylactic agent for *Mycobacterium avium* complex disease, although drug interactions may make this agent difficult to use.
	• Primary *Mycobacterium avium* complex disease prophylaxis should be discontinued among adult and adolescent patients who have responded to antiretroviral therapy with an increase in CD4+ counts to >100 cells/µL for ≥3 months. Primary prophylaxis should be reintroduced if the CD4+ count decreases to <50 cells/µL.
	
	Treatment of disseminated *Mycobacterium avium* Complex Disease
	• Initial treatment of *Mycobacterium avium* complex disease should consist of two or more antimycobacterial drugs to prevent or delay the emergence of resistance.
	• Clarithromycin is the preferred first agent; however, azithromycin can be substituted for clarithromycin when drug interactions or clarithromycin intolerance preclude the use of clarithromycin.
	• Testing of *Mycobacterium avium* complex disease isolates for susceptibility to clarithromycin or azithromycin is recommended for all patients.
	
	Treatment of Penicilliosis marneffei
	  • Penicilliosis is caused by the dimorphic fungus *Penicillium marneffei*, which is known to be endemic in Southeast Asia (especially Northern Thailand and Vietnam) and southern China.
	  • The recommended treatment is liposomal amphotericin B, three to five mg/kg body weight/day intravenously for two weeks, followed by oral itraconazole, 400 mg/day for a subsequent duration of 10 weeks, followed by secondary prophylaxis.
	  • Patients with mild disease can be initially treated with oral itraconazole 400 mg/day for eight weeks, followed by 200 mg/day for prevention of recurrence.
	  • The alternative drug for primary treatment in the hospital is intravenous voriconazole, 6 mg/kg every 12 hours on day one and then 4 mg/kg every 12 hours for at least three days, followed by oral voriconazole, 200 mg twice daily for a maximum of 12 weeks.
	  • Patients with mild disease can be initially treated with oral voriconazole 400 mg twice a day on day one, and then 200 mg twice daily for 12 weeks. The optimal dose of voriconazole for secondary prophylaxis after 12 weeks has not been studied.
	
	Primary prophylaxis of *Pneumocystis (carinii) jiroveci* pneumonia
	• Sulfamethoxazole-trimethoprim is the recommended prophylactic agent. One double-strength tablet daily is the preferred regimen. However, one single-strength tablet daily is also effective and might be better tolerated than one double-strength tablet daily. One double-strength tablet three times weekly is also effective. Sulfamethoxazole-trimethoprim at a dose of one double-strength tablet daily confers cross-protection against toxoplasmosis and selected common respiratory bacterial infections. Lower doses of sulfamethoxazole-trimethoprim likely also confer such protection.
	• For patients who have an adverse reaction that is not life threatening, chemoprophylaxis with sulfamethoxazole-trimethoprim should be continued if clinically feasible; for those who have discontinued such therapy because of an adverse reaction, reinstituting sulfamethoxazole-trimethoprim should be strongly considered after the adverse event has resolved. Patients who have

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	experienced adverse events, including fever and rash, might better tolerate reintroduction of the drug with a gradual increase in dose (i.e., desensitization), according to published regimens or reintroduction of sulfamethoxazole-trimethoprim at a reduced dose or frequency; as many as 70% of patients can tolerate such reinstitution of therapy. • If sulfamethoxazole-trimethoprim cannot be tolerated, alternative prophylactic regimens include dapsone, dapsone/pyrimethamine plus leucovorin, aerosolized pentamidine and atovaquone. • Primary *Pneumocystis (carinii) jiroveci* pneumonia prophylaxis should be discontinued for adult and adolescent patients who have responded to antiretroviral therapy with an increase in CD4+ counts to >200 cells/µL for >3 months. Prophylaxis should be reintroduced if the CD4+ count decreases to <200 cells/µL. <u>Treatment of *Pneumocystis (carinii) jiroveci* pneumonia</u> • Sulfamethoxazole-trimethoprim is the treatment of choice. The dose must be adjusted for abnormal renal function. Multiple randomized clinical trials indicate that sulfamethoxazole-trimethoprim is as effective as parenteral pentamidine and more effective than other regimens. Adding leucovorin to prevent myelosuppression during acute treatment is not recommended because of questionable efficacy and some evidence for a higher failure rate. Oral outpatient therapy of sulfamethoxazole-trimethoprim is highly effective among patients with mild-to-moderate disease. • Patients who have *Pneumocystis (carinii) jiroveci* despite sulfamethoxazole-trimethoprim prophylaxis are usually effectively treated with standard doses of sulfamethoxazole-trimethoprim. • Patients with documented or suspected *Pneumocystis (carinii) jiroveci* and moderate-to-severe disease, as defined by room air pO_2 <70 mm Hg or arterial-alveolar O_2 gradient >35 mm Hg, should receive adjunctive corticosteroids as early as possible, and certainly within 72 hours after starting specific *Pneumocystis (carinii) jiroveci* therapy. • The recommended duration of therapy for *Pneumocystis (carinii) jiroveci* is 21 days. • Patients who have a history of *Pneumocystis (carinii) jiroveci* should be administered chemoprophylaxis for life (i.e., secondary prophylaxis or chronic maintenance therapy) with sulfamethoxazole-trimethoprim unless immune reconstitution occurs as a result of antiretroviral therapy. • Secondary prophylaxis should be discontinued for adult and adolescent patients whose CD4+ count has increased from <200 cells/µL to >200 cells/µL for >3 months as a result of antiretroviral therapy. Prophylaxis should be reintroduced if the CD4+ count decreases to <200 cells/µL. If *Pneumocystis (carinii) jiroveci* recurs at a CD4+ count of ≥200 cells/µL, lifelong prophylaxis should be administered. <u>Primary prophylaxis of *Toxoplasma* encephalitis</u> • The double-strength tablet daily dose of sulfamethoxazole-trimethoprim recommended as the preferred regimen for *Pneumocystis (carinii) jiroveci* prophylaxis is effective against *Toxoplasma* encephalitis as well and is therefore recommended. Sulfamethoxazole-trimethoprim, one double-strength tablet three times weekly, is an alternative. • If patients cannot tolerate sulfamethoxazole-trimethoprim, the recommended alternative is dapsone-pyrimethamine plus leucovorin, which is also effective against *Pneumocystis (carinii) jiroveci* pneumonia. • Atovaquone with or without pyrimethamine/leucovorin can also be considered. • Prophylactic monotherapy with dapsone, pyrimethamine, azithromycin, or

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	clarithromycin cannot be recommended on the basis of available data. Aerosolized pentamidine does not protect against *Toxoplasma* encephalitis and is not recommended.
	• Prophylaxis against *Toxoplasma* encephalitis should be discontinued among adult and adolescent patients who have responded to antiretroviral therapy with an increase in CD4+ counts to >200 cells/µL for >3 months. Prophylaxis for *Toxoplasma* encephalitis should be reintroduced if the CD4+ count decreases to <100 to 200 cells/µL.
	
	<u>Treatment of *Toxoplasma* encephalitis</u>
	• The initial therapy of choice for *Toxoplasma* encephalitis consists of the combination of pyrimethamine plus sulfadiazine plus leucovorin.
	• The preferred alternative regimen for patients with *Toxoplasma* encephalitis who are unable to tolerate or who fail to respond to first-line therapy is pyrimethamine plus clindamycin plus leucovorin.
	• Sulfamethoxazole-trimethoprim was reported in a small randomized trial to be effective and better tolerated than pyrimethamine-sulfadiazine. On the basis of less in vitro activity and less experience with sulfamethoxazole-trimethoprim, treatment with this drug may be considered an option.
	• Acute therapy for *Toxoplasma* encephalitis should be continued for at least six weeks, if there is clinical and radiologic improvement.
	
	<u>Treatment of latent tuberculosis infection</u>
	• Human immunodeficiency virus-infected persons, regardless of age, should be treated for latent tuberculosis infection if they have no evidence of active tuberculosis and:
	  o A positive diagnostic test for latent tuberculosis infection and no prior history of treatment for active or latent tuberculosis.
	  o A negative diagnostic test for latent tuberculosis infection but are close contacts of persons with infectious pulmonary tuberculosis.
	  o A history of untreated or inadequately treated healed tuberculosis (i.e., old fibrotic lesions on chest radiography) regardless of diagnostic tests for latent tuberculosis infection.
	• Treatment options for latent tuberculosis infection include isoniazid daily or twice weekly for nine months.
	• Due to an increased risk of fatal and severe hepatotoxicity, a two-month regimen of daily rifampin and pyrazinamide is not recommended for latent tuberculosis infection treatment regardless of human immunodeficiency virus status.
	• Human immunodeficiency virus-infected persons receiving isoniazid should receive pyridoxine to minimize the risk of developing peripheral neuropathy. Alternatives for individuals who cannot take isoniazid or who have been exposed to a known isoniazid-resistant index case include either rifampin or rifabutin alone for four months.
	• For persons exposed to isoniazid- and/or rifampin-resistant tuberculosis, decisions to treat with one or two drugs other than isoniazid, rifampin, or rifabutin should be based on the relative risk of exposure to organisms broadly resistant to other antimycobacterial drugs and should be made in consultation with public health authorities.
	• Directly observed therapy should be used with intermittent dosing regimens when otherwise feasible to maximize regimen completion rates.
	• There is no evidence to suggest that latent tuberculosis infection treatment should be continued beyond the recommended duration in persons with human immunodeficiency virus infection. Therefore, latent tuberculosis infection treatment should be discontinued after completing the appropriate number of

Clinical Guideline	Recommendation(s)
	doses. Treatment of active tuberculosis disease • Recommendations for anti-tuberculosis treatment regimens in human immunodeficiency virus -infected adults follow the same principles as for adults without human immunodeficiency virus -infection. • Treatment of drug susceptible tuberculosis disease should include a six-month regimen with an initial phase of isoniazid, rifampin or rifabutin, pyrazinamide, and ethambutol administered for two months followed by isoniazid and rifampin (or rifabutin) for four additional months. • When drug-susceptibility testing confirms the absence of resistance to isoniazid, rifampin, and pyrazinamide, ethambutol may be discontinued before two months of treatment have been completed. • For patients with cavitary lung disease and cultures positive for *Mycobacterium tuberculosis* after completion of two months of therapy, treatment should be extended with isoniazid and rifampin for an additional three months for a total of nine months. • All human immunodeficiency virus-infected patients treated with isoniazid should receive pyridoxine supplementation. • For patients with extrapulmonary tuberculosis, a six- to nine-month regimen (two months of isoniazid, rifampin, pyrazinamide, and ethambutol followed by four to seven months of isoniazid and rifampin) is recommended. • Exceptions to the recommendation for a six- to nine-month regimen for extrapulmonary tuberculosis include central nervous system disease (tuberculoma or meningitis) and bone and joint tuberculosis, for which many experts recommend nine to 12 months. • Adjuvant corticosteroids should be added when treating central nervous system and pericardial disease. • Treatment with corticosteroids should be started intravenously as early as possible with change to oral therapy individualized according to clinical improvement. • Recommended corticosteroid regimens are dexamethasone 0.3 to 0.4 mg/kg tapered over six to eight weeks or prednisone 1 mg/kg for three weeks, then tapered for three to five weeks. Treatment of varicella zoster virus disease • For uncomplicated varicella, the preferred treatment options are valacyclovir (1 gram orally three times daily), or famciclovir (500 mg orally three times daily) for five to seven days. Oral acyclovir (20 mg/kg body weight up to a maximum dose of 800 mg five times daily) can be an alternative. • Prompt antiviral therapy should be instituted in all human immunodeficiency virus-seropositive patients whose herpes zoster is diagnosed within one week of rash onset (or any time before full crusting of lesions). The recommended treatment options for acute localized dermatomal herpes zoster in human immunodeficiency virus-infected patients are oral valacyclovir, famciclovir, or acyclovir (doses as above) for seven to 10 days, although longer durations of therapy should be considered if lesions resolve slowly. Valacyclovir or famciclovir are preferred because of their improved pharmacokinetic properties and simplified dosing schedule. • If cutaneous lesions are extensive or if visceral involvement is suspected, intravenous acyclovir should be initiated and continued until clinical improvement is evident. A switch from intravenous acyclovir to oral antiviral therapy (to complete a 10 to 14 day treatment course) is reasonable when formation of new cutaneous lesions has ceased and the signs and symptoms of visceral varicella zoster virus infection are clearly improving.

Clinical Guideline	Recommendation(s)
	• Optimal antiviral therapy for progressive outer retinal necrosis remains undefined. Specific treatment should include systemic therapy with at least one intravenous drug (selected from acyclovir, ganciclovir, foscarnet, and cidofovir) coupled with injections of at least one intravitreal drug (selected from ganciclovir and foscarnet). Treatment regimens for progressive outer retinal necrosis recommended by certain specialists include a combination of intravenous ganciclovir and/or foscarnet plus intravitreal injections of ganciclovir and/or foscarnet. The prognosis for visual preservation in involved eyes is poor, despite aggressive antiviral therapy. • Other infectious disease states mentioned within these guidelines note that the treatment guidelines for that disease state should be utilized. • The guideline specifies that detailed recommendations for the treatment of human herpesvirus-8 and associated malignancies are beyond the scope of these guidelines. • Other excluded infectious disease states offer no specific therapy or utilize medications not licensed in the United States.
World Gastroenterology Organization: **Practice Guideline: Celiac Disease (2012)**[9]	• The only treatment for celiac disease is a strictly gluten-free diet for life. No foods or medications containing gluten from wheat, rye, and barley or their derivatives can be taken, as even small quantities of gluten may be harmful. • Complete removal of gluten from the diet of celiac disease patients will result in symptomatic, serologic, and histological remission in most patients. Growth and development in children returns to normal with adherence to the gluten-free diet, and many disease complications in adults are avoided.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the miscellaneous antimycobacterials are noted in Table 4. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 4. FDA-Approved Indications for the Antimycobacterials, Miscellaneous[1-3]

Indication	Dapsone
Dermatitis herpetiformis	✔
Leprosy	✔

IV. Pharmacokinetics

The pharmacokinetic parameters of the miscellaneous antimycobacterials are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Antimycobacterials, Miscellaneous[1-3]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Dapsone	86 to 104	70 to 90	Liver	Renal (85)	10 to 50

V. Drug Interactions

Significant drug interactions with the miscellaneous antimycobacterials are listed in Table 6.

Table 6. Significant Drug Interactions with the Antimycobacterials, Miscellaneous[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Dapsone	2	Rifamycins	Plasma concentrations and pharmacologic effects of dapsone may be decreased by rifamycins. The antimicrobial effectiveness of dapsone may be reduced.
Dapsone	2	Trimethoprim	Increased serum concentrations of trimethoprim and dapsone may lead to a greater risk of toxicity with each drug.

Significance level 1=major severity; significance level 2=moderate severity

VI. Adverse Drug Events

The most common adverse drug events reported with the miscellaneous antimycobacterials are listed in Table 7. Fatal cases of agranulocytosis, aplastic anemia and other blood dyscrasias have been reported with dapsone.[1-3] Serious dermatologic reactions (including toxic epidermal necrolysis) are rare, but potential complications of sulfone therapy.

Table 7. Adverse Drug Events (%) Reported with the Antimycobacterials, Miscellaneous[1-3]

Adverse Reactions	Dapsone
Central Nervous System	
Fever	✔
Headache	✔
Insomnia	✔
Peripheral neuropathy	✔
Psychosis	✔
Vertigo	✔
Dermatological	
Bullous dermatitis	✔
Erythema nodosum	✔
Exfoliative dermatitis	✔
Morbilliform and scarlatiniform reactions	✔
Phototoxicity	✔
Stevens-Johnson syndrome	✔
Toxic epidural necrolysis	✔
Urticaria	✔
Gastrointestinal	
Abdominal pain	✔
Nausea	✔
Pancreatitis	✔
Vomiting	✔
Genitourinary	
Albuminuria	✔
Male infertility	✔
Nephrotic syndrome	✔
Renal papillary necrosis	✔
Hematological	
Agranulocytosis	✔
Anemia	✔
Hemolysis	>10
Hemoglobin decreased	>10
Leukopenia	✔
Methemoglobinemia	>10
Pure red cell aplasia	✔
Red cell life span shortened	>10

Adverse Reactions	Dapsone
Reticulocyte count increased	2 to 12
Hepatic	
Cholestatic jaundice	✔
Hepatitis	✔
Respiratory	
Interstitial pneumonitis	✔
Pulmonary eosinophilia	✔
Other	
Blurred vision	✔
Drug-induced lupus erythematosus	✔
Hypoalbuminemia	✔
Mononucleosis-like syndrome	✔
Motor loss/muscle weakness	✔
Tachycardia	✔
Tinnitus	✔

✔ Percent not specified.
- Event not reported or incidence <1%.

VII. Dosing and Administration

The usual dosing regimens for the miscellaneous antimycobacterials are listed in Table 8.

Table 8. Usual Dosing Regimens for the Antimycobacterials, Miscellaneous[1-3]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Dapsone	Dermatitis herpetiformis: Tablet: Initial, 50 mg once daily; maintenance, 50 to 300 mg once daily Leprosy: Tablet: 100 mg daily with one or more other anti-leprosy drugs	Dermatitis herpetiformis: Tablet: Initial and maintenance dose schedule is the same as in adults, but administered at "correspondingly smaller doses" Leprosy: Tablet: "correspondingly smaller doses" than adults with one or more other anti-leprosy drugs	Tablet: 25 mg 100 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the miscellaneous antimycobacterials are summarized in Table 9.

Table 9. Comparative Clinical Trials with the Antimycobacterials, Miscellaneous

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Dermatitis Herpetiformis				
Fry et al.[10] (1982) Dapsone 100 mg QD plus a gluten-free diet vs dapsone 100 mg QD plus a normal diet	RCT Patients 15 to 64 years of age presenting with dermatitis herpetiformis and Immunoglobulin A deposits in the dermal papillae of uninvolved skin	N=78 3 to 14 years of follow-up	Primary: Medication discontinuation, dose reduction, macroscopic intestinal abnormality, intra-epithelial lymphocyte count, adverse effects Secondary: Not reported	Primary: While 71% of patients adhering to the gluten-free diet were able to discontinue their medication, only 14% of patients maintained on the normal diet were able to stop therapy. Furthermore, 96% of patients on a strict gluten-free diet were able to stop dapsone or equivalent. On average, it took eight months to reduce the drug dose and 29 months to discontinue therapy in patients adhering to the gluten-free diet. The incidence of an abnormal intestinal biopsy decreased from 69% to 15% in patients on the gluten-free diet. The mean intra-epithelial lymphocyte count decreased significantly from 393+SE, 28 to 218+SE, 18 in patients maintained on the gluten-free diet; while, the change in the regular diet group was not statistically significant. Side effects occurred in 26% of patients on dapsone therapy. Secondary: Not reported
Leprosy				
THELEP Controlled Clinical Drug Trials[11] (1987) Dapsone 100 mg QD, rifampin 600 mg QD, and prothionamide* 500 mg QD for 2 years (A_2)	MC, RCT Patients with leprosy previously untreated, without detectable dapsone or its metabolites in the urine	N=215 39 months	Primary: *Mycobacterium leprae* persistence, bacterial index Secondary: Not reported	Primary: *Mycobacterium leprae* persistence did not differ between the centers or treatment groups; *Mycobacterium leprae* was detected in 9% of all skin biopsy samples. This finding was consistent at all evaluated time intervals (three, 12, and 24 months). After three-month treatment with the combined regimens, the mean bacterial index from the examined samples was 4.42.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs dapsone 100 mg QD for 2 years and rifampin as a single 1,500 mg dose (C) vs dapsone 100 mg QD for 2 years, rifampin 900 mg once weekly, and prothionamide* 500 mg QD for 3 months (E_2) vs dapsone 100 mg QD, rifampin 600 mg QD, and clofazimine*100 mg QD for 2 years (A_1) vs dapsone 100 mg QD for 2 years, rifampin as a single 1,500 mg dose, and clofazimine*100 mg QD for 3 months (D_1)				Secondary: Not reported
Smith et al.[12] (2000) Dapsone 20 to 300 mg	MA Randomized or non-randomized trials	N=20,076 (14 trials) Duration not	Primary: Disease prevention	Primary: There was a significant reduction in the risk of acquiring leprosy in patients receiving a prophylactic regimen compared to placebo (RR, 0.40; 95% CI, 0.29 to 0.55).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
weekly to twice weekly or acedapsone* 125 to 225 mg via an intramuscular injection every 75 days	evaluating chemoprophylaxis with dapsone or acedapsone	specified	Secondary: Not reported	Secondary: Not reported
Kroger et al.[13] (2008) Adults Dapsone 100 mg daily and clofazimine 50 mg daily (unsupervised); rifampicin 600 mg and clofazimine 300 mg once every 4 weeks (supervised) for 6 months Children (10 to 14 years) Dapsone 50 mg daily and clofazimine 50 mg every other day (unsupervised); rifampicin 450 mg and clofazimine 150 mg once every 4 weeks (supervised) for 6 months Children (<10 years) Dapsone 1-2 mg/kg daily and clofazimine 1-2 mg/kg daily	OL Newly detected and treatment-naive leprosy patients	N=2,912 5 years	Primary: Relapse rate and adverse events Secondary: Not reported	Primary: Twenty-seven patients developed new lesions. Of these, 11 developed new lesions during treatment and the remaining 16 during follow-up. Of these 27 patients, 21 developed new lesions on account of reactions. Six patients were clinically compatible with relapse. Three of these relapses occurred in the first year, two were reported during the second year and one patient developed relapse in the third year of follow-up. All these patients were assessed as 'lesion inactive' at the completion of treatment. There were 55 reaction episodes (38 type 1 and 17 type 2 reactions). Of these, 23 occurred during the treatment phase, the remaining 29 occurred afterwards. Thirty-nine neuritis events were reported, of which 16 occurred along with reactions. Eleven patients reported neuritis during the treatment phase, 13 patients reported adverse drug reactions. Of these 13 events, 11 were due to dapsone (seven had exfoliative dermatitis and four had non-specific dermatitis). One patient reported hepatitis whose cause was not known. One patient developed mononucleosis. Approximately 99% (n=2,480) of patients completed treatment within the stipulated period. Of these, 19% were assessed as 'lesion inactive', 78% as 'improved', 3% as static and 0.2% as deteriorated at completion of treatment. A total of 2,284 patients were due for first year followup; 16 were lost and 2,013 (88%) patients completed first year follow-up. Of these, 1,004 (49%) were classified as 'lesion inactive', 996 (49%) as 'improved' and 0.6% as 'static'. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(unsupervised); rifampicin 10-20 mg/kg (supervised) for 6 months				
Prophylaxis of *Pneumocystis jiroveci* Pneumonia and Toxoplasmosis				
El-Sadr et al.[14] (1998) Atovaquone 1,500 mg daily vs dapsone 100 mg daily	MC, OL, RCT Patients ≥13 years old with a history of PCP, or with a CD4 cell count no higher than 200 per mm^3 or no more than 15% of the total lymphocyte count, and a history of treatment-limiting reaction to sulfonamides or trimethoprim	N=1,057 Mean 27 months	Primary: Onset of probable or micro-biologically confirmed PCP Secondary: Confirmed or probable toxoplasmosis, death, combined end point of death or PCP, discontinuation of the drug due to intolerable adverse events	Primary: There was no statistically significant difference in PCP development between the dapsone- and atovaquone-treated groups (RR, 0.85; 95% CI, 0.67 to 1.09; P=0.20). Secondary: There was no statistically significant difference in toxoplasmosis development between the dapsone- and atovaquone-treated groups (RR, 1.18; 95% CI, 0.26 to 5.30; P=0.83). There was no statistically significant difference in mortality between the dapsone- and atovaquone-treated groups (RR, 1.07; 95% CI, 0.89 to 1.30; P=0.45). There was no statistically significant difference in the cumulative endpoint between the two groups (RR, 0.98; 95% CI, 0.89 to 1.16; P=0.80). There was no statistically significant difference in the number of patients discontinuing treatment because of intolerable toxicity between the two groups (RR, 0.94; 95% CI, 0.74 to 1.19; P=0.59). Among patients receiving a dapsone-based prophylactic regimen at baseline, the risk of discontinuation due to adverse effects was higher in the atovaquone group (RR, 3.78; 95% CI, 2.37 to 6.01; P<0.001). Among patients not receiving a dapsone-based prophylactic regimen at baseline, the risk of discontinuation due to adverse effects was lower in the atovaquone group (RR, 0.42; 95% CI, 0.30 to 0.58; P<0.001). Among patients who cannot tolerate SMX-TMP, atovaquone and dapsone are similarly effective for the prevention of PCP. Our results

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				support the continuation of dapsone prophylaxis among patients who are already receiving it. However, among those not receiving dapsone, atovaquone is better tolerated and may be the preferred choice for prophylaxis against PCP.
Payen et al.[15] (1997) Dapsone 50 mg QD vs pyrimethamine-sulfadoxine once weekly	OL, PRO, RCT HIV-positive patients with a CD4 cell count no higher than 200 per mm^3 or 20% of the total lymphocyte count	N=209 Mean 533 days	Primary: Onset of PCP (confirmed by pneumopathy and *Pneumocystis jiroveci* cysts isolated at induced sputum, bronchoalveolar lavage, or transbronchial biopsy), intolerable adverse events, and death Secondary: Not reported	Primary: There were no statistically significant differences between the two prophylactic regimens in any of the evaluated primary endpoints (P>0.1). Secondary: There were no statistically significant differences between the two prophylactic regimens in any of the evaluated secondary endpoints (P>0.1). Secondary: Not reported
Ioannidis et al.[16] (1996) Pentamidine, aerosolized vs dapsone-based regimens vs SMX-TMP	MA Trials comparing dapsone, aerosolized pentamidine, or SMX-TMP in preventing PCP	N=6,583 (35 trials) Variable duration	Primary: Number of *Pneumocystis jiroveci* episodes, *Pneumocystis jiroveci*-related deaths, toxoplasmosis episodes, all-cause mortality Secondary: Not reported	Primary: There was a significant decrease in the incidence of *Pneumocystis jiroveci* events in patients on any primary or secondary prophylactic regimen compared to placebo (RR, 0.39; 95% CI, 0.27 to 0.55 and RR, 0.16; 95% CI, 0.08 to 0.35, respectively). There was no significant difference in mortality between the different prophylactic regimens in all 35 trials. Oral prophylactic regimens were significantly more effective in reducing *Pneumocystis jiroveci* events compared to aerosolized pentamidine (RR, 0.39; 95% CI, 0.27 to 0.55). Oral prophylactic regimens were significantly more effective in reducing toxoplasmosis events compared to aerosolized pentamidine (RR, 0.67;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				95% CI, 0.50 to 0.88). There was no statistically significant difference in the occurrence of *P jiroveci* and toxoplasmosis events between patients receiving SMX-TMP or dapsone-based regimens (RR, 0.61; 95% CI, 0.34 to 1.10 and RR, 1.26; 95% CI, 0.68 to 2.34, respectively). While SMX-TMP exhibited greater efficacy in reducing *Pneumocystis jiroveci* events (RR, 0.58; 95% CI, 0.45 to 0.75), dapsone-based regimens were comparable to the aerosolized pentamidine regimen (RR, 0.93; 95% CI, 0.72 to 1.19). Compared to aerosolized pentamidine, oral regimens were overall 5 times more likely to be discontinued due to adverse events (RR, 5.38; 95% CI, 3.69 to 7.83). There was no significant difference between the SMX-TMP and dapsone-based regimens in the patient attrition rate as a result of treatment-related adverse effects (RR, 1.30; 95% CI, 1.04 to 1.62). SMX-TMP-treated groups exhibited the smallest prophylaxis failure rates, 0.5% for both primary and secondary prophylaxis. Secondary: Not reported
Bucher et al.[17] (1997) Pentamidine, aerosolized vs dapsone vs	MA Trials comparing dapsone, dapsone-pyrimethamine, aerosolized pentamidine or SMX-TMP in preventing PCP events	N=4,870 (22 trials) Variable duration	Primary: Opportunistic infections with PCP, *Toxoplasma* encephalitis, or both, mortality, drug-limiting toxicity requiring a change in therapy Secondary:	Primary: Compared to aerosolized pentamidine, dapsone-based regimens were more effective in preventing PCP events (RR, 0.90; 95% CI, 0.71 to 1.15) but not significantly different in terms of *Toxoplasma* encephalitis prevention (RR, 0.78; 95% CI, 0.55 to 1.11). Compared to dapsone-based regimens, SMX-TMP was more effective in preventing PCP events (RR, 0.49; 95% CI, 0.26 to 0.92) but not significantly different in terms of *Toxoplasma* encephalitis prevention (RR, 1.17; 95% CI, 0.68 to 2.04). SMX-TMP was significantly more effective compared to aerosolized

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
dapsone-pyrimethamine vs SMX-TMP			Not reported	pentamidine in preventing PCP events (RR, 0.59; 95% CI, 0.45 to 0.76). Drug-limiting toxicity was experienced by 29.7% of patients treated with a dapsone-based regimen, 6.8% of patients treated with aerosolized pentamidine, and 31.5% of patients on SMX-TMP therapy. There was no significant difference in mortality between the dapsone-based regimen and SMX-TMP (RR, 0.98; 95% CI, 0.80 to 1.08; P>0.20) or the aerosolized pentamidine regimen (RR, 1.07; 95% CI, 0.90 to 1.27; P>0.18). The mortality risk ratio in patients with CD4 cell count <100 cells/mm^3 treated with SMX-TMP compared to dapsone-based regimen was 0.43 (95% CI, 0.21 to 0.88). Mortality was lower in the SMX-TMP-treated group compared to patients on the aerosolized pentamidine therapy (RR, 0.88; 95% CI, 0.74 to 1.06; P=0.04). Secondary: Not reported
Green et al.[18] (2007) Atovaquone vs pentamidine vs SMX-TMP vs dapsone	MA Immuno-compromised patients with cancer, bone marrow transplant patients, solid organ transplant patients, patients receiving corticosteroids, patients receiving other immune suppressive medications, severe malnutrition, primary immune-	N=1,155 (11 trials) Variable duration	Primary: Documented Pneumocystis infections Secondary: All-cause mortality at end of study follow-up, PCP-related mortality at end of study follow-up, infections other than Pneumocystis	Primary: There was a significant reduction in the occurrence of PCP infections in the SMX-TMP prophylaxis group compared to others (RR, 0.09; 95% CI, 0.02 to 0.32). The corresponding number of patients needed to treat to prevent one episode of PCP was 15 patients (95% CI, 13 to 20). Five trials compared daily-administrated SMX-TMP prophylaxis vs no intervention or placebo. Prophylaxis resulted in a significant decrease in the occurrence of PCP infections (RR, 0.08; 95% CI, 0.02 to 0.38). Three trials compared SMX-TMP prophylaxis vs a non anti-PCP antibiotic (quinolones). Prophylaxis with SMX-TMP was better than quinolones in the prevention of PCP (RR, 0.09; 95% CI, 0.01 to 1.57). Secondary: All-cause mortality was reported in five trials. Three trials compared SMX-TMP to placebo (RR, 0.79; 95% CI, 0.18 to 3.46), and two trials

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs pyrimethamine vs clindamycin vs mycophenolate mofetil	deficiency diseases			compared SMX-TMP vs quinolones (RR, 0.49; 95% CI, 0.02 to 10.73). SMX-tmp prophylaxis reduced PCP-related mortality (RR, 0.17; 95% CI, 0.03 to 0.94).Four trials compared SMX-TMP vs no intervention or placebo. PCP related mortality was reduced in the prophylaxis group (RR, 0.18; 95% CI, 0.02 to 1.56). Three studies compared SMX-TMP vs quinolones. PCP related mortality was reduced in the SMX-TMP group (RR, 0.14; 95% CI, 0.01 to 2.65). In the analysis of any infection other than PCP, one study comparing SMX-TMP prophylaxis vs no intervention or placebo found no statistically significant difference between the groups (RR, 0.86; 95% CI, 0.68 to 1.08). Three studies that compared SMX-TMP prophylaxis vs quinolones found significantly more infections other than PCP in the SMX-TMP arm compared to quinolones (RR, 1.59; 95% CI, 1.17 to 2.14).
Treatment of *Pneumocystis jiroveci* Pneumonia				
Medina et al.[19] (1990) Dapsone 100 mg QD plus trimethoprim 20 mg/kg QD vs sulfamethoxazole 100 mg/kg QD plus trimethoprim 20 mg/kg QD	MA Patients with acquired immunodeficiency syndrome and mild-to-moderately-severe new onset *Pneumocystis jiroveci* pneumonia, and whose room air PAO_2-PaO_2 was 60 mm Hg or greater	33 trials Mean 21 days	Primary: Therapeutic failure, discontinuation of therapy due to treatment-related adverse effects Secondary: Not reported	Primary: Treatment failure was observed in three patients treated with SMX-TMP and two patients on dapsone-based regimen (P>0.3). More patients in the SMX-TMP group (57%) required a change of therapy due to intolerable adverse effects compared to the dapsone-based regimen group (30%; P<0.025). Secondary: Not reported

*Not commercially available in the United States.
Drug regimen abbreviations: QD=once daily
Study abbreviations: CI=confidence interval, MA=meta-analysis, MC=multicenter, PRO=prospective, OL=open-label, RCT=randomized controlled trial, RR=risk ratio/relative risk
Miscellaneous abbreviations: HIV= human immunodeficiency virus, PCP=*Pneumocystis carinii* pneumonia, SE=standard error, SMX-TMP= sulfamethoxazole-trimethoprim

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription.

Table 10. Relative Cost of the Antimycobacterials, Miscellaneous

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Dapsone	tablet	N/A	N/A	$$

N/A=Not available.

X. Conclusions

Dapsone is approved for the treatment of leprosy and dermatitis herpetiformis. It is available in a generic formulation. Dapsone has been shown to be effective for the treatment of leprosy as monotherapy and in combination with other agents.[11,13] However, due to the spread of bacterial resistance, the World Health Organization and the National Hansen's Disease Program no longer recommend dapsone monotherapy.[5,7] Both organizations recommend the use of dapsone in combination with one or more other anti-infective agents.[5,7]

Dermatitis herpetiformis is a cutaneous manifestation of celiac disease and it is treated with a gluten-free diet.[8-9] Dapsone has also been used to control the rash associated with dermatitis herpetiformis. There were no comparative clinical trials found in the medical literature evaluating the use of dapsone for the treatment of dermatitis herpetiformis. However, one study reported that patients on a gluten-free diet were able to reduce the dose of dapsone following eight months of therapy and discontinue treatment after 29 months.[10]

Guidelines for the prevention and treatment of opportunistic infections in patients with human immunodeficiency virus recommend sulfamethoxazole-trimethoprim as the treatment of choice for *Pneumocystis jiroveci* pneumonia and *Toxoplasma* encephalitis.[8] Dapsone has a similar spectrum of activity as the sulfonamides and it is

recommended as an alternative treatment option for patients who cannot tolerate sulfamethoxazole-trimethoprim.[8] Clinical trials have demonstrated similar efficacy with dapsone and sulfamethoxazole-trimethoprim.[16-17,19]

Therefore, all brand miscellaneous antimycobacterials within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand miscellaneous antimycobacterial is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Adamantanes
AHFS Class 081804
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I. Overview

Influenza A viruses (primarily H1N1 and H3N2) and influenza B viruses circulate worldwide. Influenza epidemics occur nearly every year making this disease a major cause of respiratory illness in the United States.[1-3] The majority of complications, hospitalizations and deaths from seasonal influenza occur in persons over 65 years of age, children younger than two years of age, and persons of any age with certain underlying health conditions. The most effective way to minimize the negative impact of influenza is through annual vaccination.[1-3]

Antiviral medications are an important adjunct to vaccination for the control and prevention of influenza disease. The adamantanes inhibit two stages of viral replication by interfering with the influenza A M2 protein.[4-6] The M2 protein plays an important role in the uncoating of the infecting virus particle, as well as regulation of the ion channels. Although clinical trials have shown that the adamantanes are effective for the treatment and chemoprophylaxis of influenza, these agents have become less useful in recent years due to the development of resistant strains of influenza A virus.[1-6] Another limitation to the use of adamantanes is that they only have activity against influenza A viruses.[1-6]

Amantadine is also approved for the treatment of Parkinson's disease and drug-induced extrapyramidal reactions.[3-5] The mechanism of action of amantadine in the treatment of Parkinson's disease and drug-induced extrapyramidal reactions is not known. Data from earlier studies suggest that it may have direct and indirect effects on dopamine neurons. More recent studies have demonstrated that amantadine is a non-competitive N-methyl-D-aspartate (NMDA) receptor antagonist.

The adamantanes that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Amantadine and rimantadine are available in a generic formulation. This class was last reviewed in May 2012.

Table 1. Adamantanes Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Amantadine	capsule, solution, tablet	N/A	amantadine
Rimantadine	tablet	Flumadine®*	rimantadine

*Generic is available in at least one dosage form or strength.
N/A=Not available; PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the adamantanes are summarized in Table 2.

Table 2. Treatment Guidelines Using the Adamantanes

Clinical Guideline	Recommendation(s)
Centers for Disease Control and Prevention Morbidity and Mortality Weekly Report: **Antiviral Agents for the Treatment and Chemoprophylaxis of Influenza: Recommendations of the Advisory Committee on**	• Annual influenza vaccination is the most effective method for preventing seasonal influenza virus infection and its complications. • Antiviral treatment is recommended as soon as possible for: o Patients with confirmed or suspected influenza who have severe, complicated, or progressive illness or who require hospitalization. o Outpatients with confirmed or suspected influenza who are at higher risk for influenza complications on the basis of their age or underlying medical conditions. • Persons at higher risk for influenza complications recommended for antiviral treatment include:

Clinical Guideline	Recommendation(s)
Immunization Practices (2011)[1]	o Children less than two years of age. o Adults aged ≥65 years. o Persons with chronic pulmonary (including asthma), cardiovascular (except hypertension alone), renal, hepatic, hematological (including sickle cell disease), metabolic disorders (including diabetes mellitus), or neurologic and neurodevelopment conditions (including disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy [seizure disorders], stroke, intellectual disability [mental retardation], moderate to severe developmental delay, muscular dystrophy, or spinal cord injury). o Persons with immunosuppression, including that caused by medications or by human immunodeficiency virus infection. o Women who are pregnant or postpartum (within two weeks after delivery). o Persons aged <19 years who are receiving long-term aspirin therapy. o American Indians/Alaska Natives. o Persons who are morbidly obese (i.e., body-mass index ≥40). o Residents of nursing homes and other chronic-care facilities. • Four licensed prescription influenza antiviral agents are available in the United States: amantadine, rimantadine, zanamivir, and oseltamivir. Oseltamivir and zanamivir, neuraminidase inhibitors, are active against both influenza A and B. Rimantadine and amantadine are only active against influenza A. • Recommended antiviral medications include oseltamivir and zanamivir. Greater than 99% of currently circulating influenza virus strains are sensitive to these medications. Amantadine and rimantadine should not be used because of the high levels of resistance to these drugs. Local antiviral resistance surveillance data should be monitored. Currently circulating influenza A (H3N2) and 2009 H1N1 viruses are resistant to adamantanes. These medications are not recommended for use against influenza A virus infections. • Oseltamivir may be used for treatment or chemoprophylaxis of influenza among infants less than one year of age when indicated. • Antiviral treatment is recommended as soon as possible for all persons with suspected or confirmed influenza requiring hospitalization or who have progressive, severe or complicated illness regardless of previous health or vaccination status. The greatest benefit is when initiated within 48 hours of influenza onset. However, it may be beneficial in those with severe, complicated, or progressive illness and in hospitalized patients if administered >48 hours from onset. Health-care providers and patients should make this decision on an individual basis. • Randomized, controlled trials conducted primarily among persons with mild illness in outpatient settings have demonstrated that zanamivir or oseltamivir can reduce the duration of uncomplicated influenza A and B illness by approximately one day when administered within 48 hours of illness onset compared to placebo. • Data are limited about the effectiveness of zanamivir and oseltamivir treatment in preventing serious influenza-related complications. • Chemoprophylaxis with antiviral medications is not a substitute for influenza vaccination when influenza vaccine is available. • Post-exposure chemoprophylaxis lowers but does not eliminate the risk for influenza. Susceptibility to influenza returns once the antiviral medication is stopped, and influenza vaccination is recommended. Duration should be for a total of no more than 10 days after the most recent known exposure to

Clinical Guideline	Recommendation(s)

	a close contact known to have influenza.
	• Pre-exposure chemoprophylaxis must be administered for the duration of time when exposure might occur and should only be used for persons who are at very high risk for influenza-related complications who cannot otherwise be protected during times when a high risk for exposure exists. The duration of pre-exposure chemoprophylaxis based on potential exposure in the community depends on the duration of community influenza activity.
	• Zanamivir is approved for treatment of adults with uncomplicated acute illness caused by influenza A or B virus, and for chemoprophylaxis of influenza among adults. It is also approved for treatment of influenza among children seven years of age and older and for chemoprophylaxis of influenza among children five years of age and older.
	• Oseltamivir is approved for treatment of adults with uncomplicated acute illness caused by influenza A or B virus and for chemoprophylaxis of influenza among adults. It is also approved for the treatment and chemoprophylaxis of influenza among children one year of age and older.
	• Rimantadine is Food and Drug Administration approved for children one year of age and older and for treatment and chemoprophylaxis of only influenza A virus infections among adults. Use of rimantadine among children less than one year of age has not been evaluated adequately.
	• Oseltamivir, zanamivir, and rimantadine are "Pregnancy Category C" medications. Oseltamivir is preferred for treatment of pregnant women.
	
	<u>2009 Influenza A (H1N1)</u>
	• In the post-pandemic period, 2009 H1N1 virus strains now are considered to be the predominant seasonal influenza A (H1N1) virus strains.
	• Reverse transcription polymerase chain reaction is the most accurate and sensitive test for detecting influenza viruses, including the 2009 H1N1 virus.
	• Epidemiologic studies of seasonal influenza or 2009 H1N1 suggest that persons at higher risk for influenza complications include:
	  o Children less than five years of age (especially those less than two years of age).
	  o Adults aged ≥65 years.
	  o Persons with chronic pulmonary (including asthma), cardiovascular (except hypertension alone), renal, hepatic, hematologic (including sickle cell disease), metabolic disorders (including diabetes mellitus) or neurologic and neurodevelopment conditions (including disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy (seizure disorders), stroke, intellectual disability (mental retardation), moderate to severe developmental delay, muscular dystrophy, or spinal cord injury).
	  o Persons with immunosuppression, including that caused by medications or by human immunodeficiency virus infection.
	  o Women who are pregnant or postpartum (within two weeks after delivery).
	  o Persons aged ≤18 years who are receiving long-term aspirin therapy.
	  o American Indians/Alaska Natives.
	  o Persons who are morbidly obese (i.e., body mass index ≥40).
	  o Residents of nursing homes and other chronic-care facilities.
	• Studies conducted during the 2009 influenza A (H1N1) pandemic indicate that viral shedding, clinical illness, and transmissibility in a household setting are similar compared to seasonal influenza.
	• During the 2009 H1N1 pandemic, the clinical syndrome most likely to be

Clinical Guideline	Recommendation(s)
	the cause of hospitalization was diffuse viral pneumonitis, which in some instances led to shock and respiratory failure. • Influenza complications among children during the 2009 influenza A (H1N1) pandemic were generally similar to those observed among children with seasonal influenza. However, much higher rates of illness among children observed during the 2009 H1N1 pandemic compared to most influenza seasons resulted in much higher rates of children hospitalized with complications. • Circulating 2009 H1N1 virus strains are resistant to adamantanes. These are not recommended for treatment or prophylaxis. • The World Health Organization has recommended empiric neuraminidase inhibitor treatment for all persons with suspected or confirmed 2009 H1N1 virus infection that are at increased risk for influenza complications. • Similar recommendations were made by Centers for Disease Control and Prevention during the 2009 H1N1 pandemic and the subsequent 2009-2010 influenza season. • Oseltamivir or zanamivir is recommended for antiviral chemoprophylaxis of 2009 H1N1. • Those with a potential exposure to a person with laboratory-confirmed 2009 H1N1 should receive chemoprophylaxis. • Sporadic oseltamivir-resistant 2009 H1N1 virus infections have been identified. • Transmission of oseltamivir-resistant influenza B virus strains or 2009 H1N1 virus strains acquired from persons treated with oseltamivir is rare but has been documented. • Nearly all sporadic cases of oseltamivir-resistant 2009 H1N1 virus infections identified to date also have been associated with the H275Y mutation in neuraminidase; these oseltamivir-resistant H275Y virus infections are susceptible to zanamivir. • Intravenous zanamivir is the recommended antiviral treatment for severely ill patients with highly suspected or confirmed oseltamivir-resistant 2009 H1N1 virus infection. • As of December 2010, no evidence existed of ongoing transmission of oseltamivir-resistant 2009 H1N1 virus strains worldwide. • During the 2009 H1N1 pandemic, recommendations for oseltamivir dosing of children less than one year of age were developed, on the basis of very limited pharmacokinetic data. • The Emergency Use Authorization issued during the 2009 H1N1 pandemic for this indication expired on June 23, 2010, but recommendations on dosing for children less than one year of age are available. • Centers for Disease Control and Prevention recommends that clinicians who treat children aged three to 11 months administer 3 mg/kg/dose twice per day for treatment, and 3 mg/kg/dose once per day for chemoprophylaxis. • Infants less than three months of age are recommended to receive 3 mg/kg/dose twice per day for treatment. However, chemoprophylaxis for infants less than three months of age is not recommended unless the exposure situation was judged to be critical, because of a lack of data on use of oseltamivir on this age group. • World Health Organization subsequently recommended that children aged <14 days who are being treated for suspected or confirmed influenza receive 3 mg/kg/dose once daily. Lower doses should be considered for infants who are not receiving regular oral feedings or those who have substantially reduced renal function.
American Academy of	• Seasonal influenza immunization is recommended for all children six

Clinical Guideline	Recommendation(s)
Pediatrics: **Recommendations for Prevention and Control of Influenza in Children, 2013-2014 (2013)**[2]	months and older. • Healthy children two years and older can receive either inactivated influenza vaccines or live-attenuated influenza vaccine. • Particular focus should be on the administration of inactivated influenza vaccines for all children and adolescents with underlying medical conditions associated with an increased risk of complications from influenza, including the following: o Asthma or other chronic pulmonary diseases, including cystic fibrosis. o Hemodynamically significant cardiac disease. o Immunosuppressive disorders or therapy. o Human immunodeficiency virus infection. o Sickle cell anemia and other hemoglobinopathies. o Diseases that require long-term aspirin therapy, including juvenile idiopathic arthritis or Kawasaki disease. o Chronic renal dysfunction. o Chronic metabolic disease, including diabetes mellitus. o Any condition that can compromise respiratory function or handling of secretions or can increase the risk of aspiration, such as neurodevelopmental disorders, spinal cord injuries, seizure disorders, or neuromuscular abnormalities. • Although universal immunization for all people six months and older is recommended for the 2013–2014 influenza season, particular immunization efforts with either inactivated influenza vaccine or live-attenuated influenza vaccine should be made for the following groups to prevent transmission of influenza to those at risk, unless contraindicated: o Household contacts and out-of home care providers of children younger than five years of age and at-risk children of all ages (healthy contacts two through 49 years of age can receive either inactivated influenza vaccines or live-attenuated influenza vaccine). o Any woman who is pregnant, is considering pregnancy, has recently delivered, or is breastfeeding during the influenza season (inactivated influenza vaccines only). Studies have shown that infants born to immunized women have better influenza-related health outcomes. However, according to Internet panel surveys conducted by the Centers for Disease Control and Prevention, only 47% of pregnant women reported receiving an influenza vaccine during the 2011–2012 season, even though both pregnant women and their infants are at higher risk of complications. In addition, data from some studies suggest that influenza vaccination in pregnancy may decrease the risk of preterm birth as well as giving birth to infants who are small for gestational age. Pregnant women can safely receive the influenza vaccine during any trimester. o Children and adolescents of American Indian/Alaskan Native heritage. o Health care professionals or health care volunteers. Despite the recent American Academy of Pediatrics recommendation for mandatory influenza immunization for all health care professionals, many health care professionals remain unvaccinated. As of November 2012, the Centers for Disease Control and Prevention estimated that only 62.9% of health care professionals received the seasonal influenza vaccine. The American Academy of Pediatrics recommends mandatory vaccination of health care professionals, because they frequently come into contact with patients at high risk of influenza illness in

Clinical Guideline	Recommendation(s)
	their clinical settings. o Close contacts of immunosuppressed people. <u>Use of antiviral medications</u> • Oseltamivir remains the antiviral drug of choice for the management of influenza infections. Zanamivir is an acceptable alternative but is more difficult to administer. • Treatment should be offered for the following: o Any child hospitalized with presumed influenza or with severe, complicated, or progressive illness attributable to influenza, regardless of influenza immunization status. o Influenza infection of any severity in children at high risk of complications of influenza infection. • Treatment should be considered for the following: o Any otherwise healthy child with influenza infection for whom a decrease in duration of clinical symptoms is felt to be warranted by his or her pediatrician; the greatest impact on outcome will occur if treatment can be initiated within 48 hours of illness onset. • Although immunization is the preferred approach to prevention of infection, chemoprophylaxis during an influenza outbreak, as defined by the Center for Disease Control and Prevention, is recommended: o For children at high risk of complications from influenza for whom influenza vaccine is contraindicated. o For children at high risk during the two weeks after influenza immunization. o For family members or health care professionals who are unimmunized and are likely to have ongoing, close exposure to unimmunized children at high risk; or unimmunized infants and toddlers who are younger than 24 months. o For control of influenza outbreaks for unimmunized staff and children in a closed institutional setting with children at high risk (e.g., extended-care facilities). o As a supplement to immunization among children at high risk, including children who are immunocompromised and may not respond to vaccine. o As postexposure prophylaxis for family members and close contacts of an infected person if those people are at high risk of complications from influenza. o For children at high risk and their family members and close contacts, as well as health care professional, when circulating strains of influenza virus in the community are not matched with seasonal influenza vaccine strains, on the basis of current data from the Centers for Disease Control and Prevention and local health departments. • Amantadine and rimantadine should not be used because circulating influenza A viruses have sustained high levels of resistance to these drugs, and they are not effective against influenza B viruses.
Infectious Diseases Society of America: **Seasonal Influenza in Adults and Children-Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management: Clinical Practices Guidelines of the**	<u>Antivirals for treatment</u> • Treatment is recommended for adults and children with influenza virus infection who meet the following criteria: o Patients with laboratory-confirmed or highly susceptible influenza virus infection at high risk for developing complications within 48 hours after symptom onset. Treatment is recommended regardless of influenza vaccination status and severity of illness. o Patients requiring hospitalization for laboratory-confirmed or highly suspected influenza illness, regardless of underlying illness

Clinical Guideline	Recommendation(s)
Infectious Diseases Society of America (2009)[3]	or influenza vaccination status, if treatment can be initiated within 48 hours after onset of symptoms. • Treatment should be considered for adults and children with influenza virus infection who meet the following criteria: o Outpatients at high risk of complications, with illness that is not improving and with a positive influenza test result from a specimen obtained >48 hours after symptom onset. o Outpatients with laboratory-confirmed or highly suspected influenza virus infection who are not at increased risk for complications, whose symptom onset is <48 hours before presentation and who wish to shorten the duration of illness and to further reduce their relatively low risk of complications or who are in close contact with persons at high risk of complications secondary to influenza infection. • Patients at high risk for complications from influenza include: o Unvaccinated infants 12 to 24 months old. o Patients with asthma or other chronic pulmonary diseases. o Patients with hemodynamically significant cardiac disease. o Patients who have immunosuppressive disorders or who are receiving immunosuppressive therapy. o Human immunodeficiency virus infected patients. o Patients with sickle cell anemia and other hemoglobinopathies. o Patients with diseases requiring long term aspirin therapy. o Patients with chronic renal dysfunction. o Patients with cancer. o Patients with chronic metabolic disease. o Patients with neuromuscular disorders, seizure disorders or cognitive dysfunction that may compromise the handling of respiratory secretions. o Patients ≥65 years old. o Residents of any age in nursing homes or other long term care institutions. • On the basis of antiviral susceptibility patterns current as of March 2009: o Influenza A (H1N1) virus infections should be treated with either zanamivir or an adamantine (preferably rimantadine due to a more tolerable adverse event profile). Oseltamivir should not be used. o Influenza A (H3N2) virus infections should be treated with oseltamivir or zanamivir. The adamantanes should not be used. o If subtype information is unavailable, influenza A should be treated with either zanamivir or combination oseltamivir and rimantadine therapy. o Influenza B virus infection should be treated with oseltamivir or zanamivir. <u>Antivirals for chemoprophylaxis</u> • Antiviral chemoprophylaxis is not a substitute for influenza vaccination, which is the primary tool to prevent influenza. • When influenza viruses are circulating in the community, chemoprophylaxis can be considered for high risk patients during the two weeks after vaccination before an adequate immune response to inactivated vaccine develops. • Antiviral chemoprophylaxis should be considered for adults and children at least one year old who are at high risk of developing complications from influenza for whom influenza vaccination is contraindicated, unavailable or expected to have low effectiveness. • Antiviral chemoprophylaxis, in conjunction with prompt administration of

Clinical Guideline	Recommendation(s)

	the inactivated vaccine, should be considered for adults and children at least one year old who are at high risk of developing complications from influenza virus infection and have not yet received influenza vaccine when influenza activity has already been detected in the community.
	• Antiviral chemoprophylaxis may be considered for unvaccinated adults, including health care workers, and for children at least one year old who are in close contact with patients at high risk of developing influenza complications during periods of influenza activity.
	• Antiviral chemoprophylaxis is recommended for all residents, vaccinated and unvaccinated, in institutions (i.e., nursing homes, long term care facilities) that are experiencing influenza outbreaks.
	• The strongest consideration for use of antiviral chemoprophylaxis should be given to patients at the highest risk of influenza-associated complications.
	• Antiviral chemoprophylaxis should be considered for patients at high risk of developing complications from influenza if influenza vaccine is not available due to a shortage.
	• Antiviral chemoprophylaxis can be considered for high risk patients in situations where there is documented low influenza vaccine clinical effectiveness because of the circulation of influenza virus strains that are antigenically distant from the vaccine strains.
	• Antiviral chemoprophylaxis should be initiated at the onset of sustained community influenza activity in patients at high risk of complications who are not adequately protected as a result of poor immune response, lack of influenza vaccination or ineffective vaccine.
	• Antiviral chemoprophylaxis use for appropriate persons within households should be initiated when one family member develops suspected or confirmed influenza and any other family member is at high risk of complications secondary to infection, including infants less than six months old.
	  o In this setting, all non-infected family members should receive antiviral chemoprophylaxis.
	  o All eligible family members in this setting should be vaccinated, making chemoprophylaxis unnecessary.
	• Antiviral chemoprophylaxis and other control measures should be initiated in institutions when an influenza outbreak is detected or when influenza is strongly suspected but the etiology of the outbreak is unknown.
	• If inactivated influenza vaccine is administered, antiviral chemoprophylaxis can generally be stopped after two weeks for patients in non-institutional settings. At least six weeks of chemoprophylaxis will be required for children less than nine years of age.
	• When antiviral chemoprophylaxis is used in a household after the diagnosis of influenza in one family member, chemoprophylaxis should be continued for 10 days.
	• In patients at high risk for complications from influenza for whom influenza vaccination is contraindicated, unavailable or expected to have low effectiveness, chemoprophylaxis should continue for the duration that influenza viruses are circulating in the community during influenza season.
	• On the basis of antiviral susceptibility patterns current as of March 2009:
	  o For influenza A (H1N1), zanamivir or an adamantine (preferably rimantadine due to a more tolerable adverse event profile) should be used for chemoprophylaxis. Oseltamivir should not be used.
	  o For influenza A (H3N2), oseltamivir or zanamivir should be used for chemoprophylaxis. The adamantanes should not be used.
	  o If subtype information is unavailable, either zanamivir or

Clinical Guideline	Recommendation(s)
	combination oseltamivir and rimantadine therapy should be used for influenza A chemoprophylaxis. o Oseltamivir or zanamivir should be used for influenza B chemoprophylaxis. <u>Outbreak management in institutional settings</u> • All residents with laboratory-confirmed influenza virus infection should be treated with an appropriate influenza antiviral medication. • After one case of laboratory-confirmed influenza, all patients in the facility subsequently developing influenza-like illness should be considered for treatment. • During documented outbreaks of influenza in long term care facilities, all resident should receive influenza antiviral chemoprophylaxis, regardless of influenza vaccination status. • For all institutional employees who are unable to receive influenza vaccine or for whom vaccine is contraindicated or expected to be ineffective, antiviral chemoprophylaxis should be administered. • Antiviral chemoprophylaxis should be continued for 14 days or for seven days after the onset of symptoms in the last person infected, whichever is longer.
American Academy of Neurology Practice Parameter: **Initiation of Treatment for Parkinson's Disease: An Evidence Based Review (2002)**[7] **(Reaffirmed October 2005)**	• Patients with Parkinson's disease, who require symptomatic treatment, may be started with selegiline prior to the administration of dopaminergic therapy. • Selegiline has mild symptomatic benefits in Parkinson's disease, and no convincing evidence of neuroprotective benefits. • Levodopa, cabergoline, ropinirole and pramipexole are effective in ameliorating motor complications and impairment in the activities of daily living in patients with Parkinson's disease who require dopaminergic therapy. Of these agents, levodopa is more effective in treating motor complications and activities of daily living disability and is associated with a higher incidence of dyskinesias than dopamine agonists. • Levodopa or a dopamine agonist may be initiated in patients with Parkinson's disease who require dopaminergic therapy. • Cabergoline, ropinirole and pramipexole resulted in fewer motor complications (i.e., wearing off, dyskinesias, on-off fluctuations) compared to levodopa. • Treatment with a dopamine agonist was associated with more frequent adverse drug reactions (hallucinations, somnolence and edema in the lower extremities) than levodopa. • When initiating treatment with levodopa in patients with Parkinson's disease, either an immediate-release or sustained-release formulation may be used. In clinical trials, there was no difference in the rate of motor complications between the two formulations.
American Academy of Neurology Practice Parameter: **Neuroprotective Strategies and Alternative Therapies for Parkinson Disease (2006)**[8] **(Reaffirmed October 2009 and July 2013)**	<u>Therapies that can slow the progression of Parkinson's disease</u> • Neuroprotection has the potential to delay the decline of motor symptoms and preserve quality of life. • Currently, the measurement of neurons can only be done postmortem; therefore, surrogate clinical markers (e.g., ratings of motor impairment, general disability, quality of life measures, time to a specific event such as delay for the initiation of symptomatic therapy; motor fluctuation or death) that are thought to reflect nigrostriatal neuron counts need to be employed. Because none of the surrogate markers have been validated, cautious interpretation of clinical trials is required. • Treatment with 2,000 units of vitamin E should not be considered for neuroprotection.

Clinical Guideline	Recommendation(s)
	• There is insufficient evidence to support or refute the use of the following agents for neuroprotection: riluzole, coenzyme Q10, pramipexole, ropinirole, rasagiline, amantadine, or thalamotomy. • Levodopa may be considered for initial treatment (nine months) as it does not accelerate disease progression and is safe; however, there is no long term evidence to recommend its use for neuroprotection. • There is insufficient evidence to recommend the use of selegiline for neuroprotection. <u>Nonstandard pharmacologic or nonpharmacologic therapies that have been shown to improve motor function in Parkinson's disease</u> • Use of complementary medication and treatment is common in patients with Parkinson's disease. • There is insufficient evidence to support or refute the use of *Mucuna pruriens* for the treatment of motor symptoms. • Vitamin E (2,000 units) should not be considered for symptomatic treatment. • There is insufficient evidence to support or refute the use of acupuncture in Parkinson's disease. • There is insufficient evidence to support or refute the use of the following therapies for the treatment of Parkinson's disease: manual therapy, biofeedback and Alexander technique. • Exercise therapy may be considered to improve function. • Speech therapy may be considered to improve speech volume in patients with Parkinson's disease complicated by dysarthria.
American Academy of Neurology Practice Parameter: **Treatment of Parkinson's Disease with Motor Fluctuations and Dyskinesia (2006)**[9]	• Rasagiline and entacapone demonstrated statistically significant reduction in off time as compared to placebo in clinical trials. It is recommended that these two agents should be offered to reduce off-time. • Pergolide demonstrated some improvement in the reduction in off-time as compared to placebo in clinical trials. However, a large number of patients on pergolide experienced more dyskinesias. Pramipexole demonstrated some reduction in off-time in placebo controlled trials. Ropinirole and tolcapone showed reduction in off-time compared to placebo. It is recommended that pergolide, pramipexole, ropinirole and tolcapone can be considered to reduce off-time. Due to adverse events and the strength of the studies, entacapone and rasagiline are preferred over pergolide, pramipexole, ropinirole and tolcapone. • Apomorphine, cabergoline and selegiline were studied in clinical trials that lacked proper enrollment and methods to provide conclusive evidence of reducing off-time. It is recommended that these agents may be considered to reduce off-time. • Bromocriptine and extended-release carbidopa/levodopa do not help to reduce off-time. • Amantadine is possibly effective in reducing dyskinesia and has demonstrated reduction in dyskinesia compared to placebo in clinical trials. It is recommended that amantadine may be considered for patients with Parkinson's disease for reducing dyskinesias. • Deep brain stimulation of the subthalamic nucleus may be considered as a treatment option in Parkinson's disease patients to help improve motor function and to reduce motor fluctuations, dyskinesias and medication usage.
European Journal of Neurology: **Parkinson's Disease: Summary of the**	<u>Early untreated Parkinson's disease</u> • The choice of drug depends on the impact of improving motor disability (better with levodopa) compared with the risk of motor complications (more common in younger patients, delayed by agonists) and

Clinical Guideline	Recommendation(s)
Recommendations of the European Federation of Neurological Societies/ Movement Disorder Society Review on Therapeutic Management of Parkinson's Disease (2013)[10]	neuropsychiatric complications (more common in older and cognitively impaired patients; greater with agonists). • Options include the following: o Monoamine oxidase-B inhibitor (selegiline, rasagiline). o Oral or transdermal dopamine agonist. Pramipexole, piribedil, ropinirole and rotigotine are effective. Initial treatment with an agonist can be recommended in younger patients. o Ergot derivatives are not recommended as first-line medication because of the risk of fibrotic reactions. o Levodopa is the most effective symptomatic drug. Controlled-release formulations or adding entacapone is not effective in the delay of motor complications. o Amantadine or an anticholinergic. o Rehabilitation: because of the lack of evidence in early-stage disease, a recommendation cannot be made. <u>Adjustment of initial therapy in patients without motor complications</u> • If a patient has started on a monoamine oxidase-B inhibitor, anticholinergic, amantadine or a combination of these, a stage will come when there is a requirement for adding levodopa or a dopamine agonist. • If on dopamine agonist therapy: o Increase the dose. o Switch between agonists. o Add levodopa. • If on levodopa: o Increase the dose. o Add an agonist. o Add a catechol-O-methyltransferase inhibitor. • If significant tremor persists: o Anticholinergics. o Clozapine. o Beta-blockers. o Deep brain stimulation. <u>Treatment of motor fluctuations</u> • Wearing-off (end-of-dose akinesia, predictable "on"-"off") • Adjust levodopa dosing: adjustments in the frequency of dosing may attenuate wearing-off. • Add catechol-O-methyltransferase or monoamine oxidase-B inhibitors: no recommendations can be made on which should be chosen first – all reduce "off" time by about 1 to 1.5 hours/day. The only direct comparison showed no difference between entacapone and rasagiline. Tolcapone, although more effective than entacapone, is potentially hepatotoxic and only recommended in patients failing on other medications • Add dopamine agonists: non-ergot dopamine agonists are first-line compounds. Dopamine agonists reduce "off" time. None has proven superior, but switching from one agonist to another can be helpful. • Controlled release levodopa: may improve wearing-off and night-time akinesia. • Add amantadine or an anticholinergic: the addition of an anticholinergic (in younger patients) or amantadine may improve symptoms. <u>Treatment of severe motor fluctuations</u> • Deep brain stimulation is effective against motor fluctuations and dyskinesia, but because of risk for adverse events, the procedure is only

Clinical Guideline	Recommendation(s)
	recommended for patients below the age of 70 without major psychiatric or cognitive problems. • Subcutaneous apomorphine as penject or pump. • Intrajejunal levodopa-carbidopa enteric gel administered through percutaneous gastrostomy. Treatment of unpredictable "on"-"off" • Deep brain stimulation is effective. • In studies of treatment for wearing-off, patients with unpredictable "on"-"off" were either not included or uncommon. Therefore, insufficient evidence exists to conclude whether the results are valid for unpredictable "on"-"off". • The strategies described for dyskinesia and wearing-off should be considered. • For delayed "on", dispersible levodopa and subcutaneous injections of apomorphine have some value. • Reduction or redistribution of dietary proteins may be helpful, more practical approach is to take levodopa on an empty stomach about one hour before, or at least one hour after, each meal. Freezing • Options for "off" freezing are the same as for wearing-off. • Freezing during "on" often does not respond to dopaminergic strategies. • Visual or auditory cues are empirically useful for facilitating the start of motor acts. Dyskinesias • Reduce levodopa dose, at the risk of increasing "off". The latter can be compensated for by increasing the number of doses or a dopamine agonist. • Discontinue/reduce catechol-O-methyltransferase or monoamine oxidase-B inhibitors, at the risk of worsening wearing-off. • Amantadine (200 to 400 mg/day). • Deep brain stimulation allows reduction in dopaminergic treatment. Add atypical antipsychotics, clozapine or quetiapine. Clozapine is associated with potential serious adverse events (agranulocytosis, myocarditis). • Apomorphine continuous subcutaneous infusion allows reduction of levodopa. • Intrajejunal levodopa infusion. Biphasic dyskinesia • Biphasic dyskinesias can be very difficult to treat and have not been studied. • Deep brain stimulation is effective. • The strategies described for peak-dose dyskinesias can be considered. • Another option is increasing the size and frequency of levodopa doses, at the risk of increasing peak-dose dyskinesia. • Larger, less frequent doses may give more predictable responses. • Apomorphine and intrajejunal levodopa infusion can be tried. Off-period and early-morning dystonias • Strategies for wearing-off can be applied. • Additional doses of levodopa or dopamine agonist at night may be effective. • Deep brain stimulation.

Clinical Guideline	Recommendation(s)
	• Botulinum toxin can be employed in "off"-period and early-morning dystonia.

European Journal of Neurology: **Joint Task Force Report: European Federation of Neurological Societies/Movement Disorder Society; Early (Uncomplicated) Parkinson's Disease (2011)**[11]	• No adequate clinical trial has provided definitive evidence for pharmacological neuroprotection or disease modifying effect.
	• Initiation of treatment is recommended when signs and symptoms begin to have an impact on patient quality of life.
	• When determining therapy, factors relating to the drug, patient and environment should be taken into account.
	• Symptom control and the prevention of motor complications are the main issues to consider when determining therapy.
	• In the management of early untreated Parkinson's disease, monoamine oxidases-B inhibitors (i.e., rasagiline and selegiline) have a modest benefit in treating the symptomatic complications of Parkinson's disease compared to levodopa and (probably) dopamine agonists. These agents are more convenient due to the ease of administration (i.e., one dose, once daily, no titration) and are well tolerated (especially rasagiline).
	• Amantadine and anticholinergics offer minimal symptom control compared to levodopa.
	• Anticholinergics are poorly tolerated in the elderly and use should be restricted to younger patients.
	• Levodopa is the most effective anti-Parkinson's drug for symptomatic relief.
	• Early use of levodopa in the elderly is recommended as they are less prone to developing motor complications but more sensitive to neuropsychiatric adverse events.
	• In the prevention of motor complications the early use of controlled-release levodopa is not effective.
	• Pramipexole and ropinirole (immediate or controlled release) are effective dopamine agonists as monotherapy in the treatment of early Parkinson's disease.
	• Convincing evidence that older agents in the class are less effective than the newer non-ergot agents in managing patients with early Parkinson's disease is lacking.
	• Dopamine agonists have a lower risk of developing motor complications. These agents do have a smaller effect on symptoms and a greater incidence of adverse events which include hallucinations, somnolence and edema in the lower extremities.
	• Younger patients should be started on a dopamine agonist as initial treatment to prolong the use of levodopa and the development of motor complications.
	• Due to the risk of fibrotic reactions ergot derivatives (i.e., bromocriptine, cabergoline and pergolide) are not recommended as first line medications.
	• The benefits of the early combination of low doses of a dopamine agonist with low doses of levodopa have not been appropriately documented.
	• A recommendation cannot be made concerning the efficacy of physical therapy and speech therapy in early Parkinson's disease due to a lack of evidence.
	• Therapy adjustments for patients on dopamine agonist therapy include:
	  o Increase dopamine agonist dose.
	  o Switch to another dopamine agonist.
	  o Add levodopa.
	• Therapy adjustments for patients on dopamine agonist therapy include:
	  o Increase levodopa dose.
	  o Add a dopamine agonist (efficacy has not been sufficiently evaluated).

Clinical Guideline	Recommendation(s)
	o Add a catechol-O-methyltransferase inhibitor if motor symptoms evolve (older and multi-morbid patients of any age preferred). • For the treatment of tremor at rest the following are treatment options: o Anticholinergics (possibly useful). o Clozapine (routine use not recommended due to safety concerns). o Beta-blockers (may be effective). • Deep brain stimulation.
European Journal of Neurology: **Joint Task Force Report: European Federation of Neurological Societies/Movement Disorder Society; Late (Complicated) Parkinson's Disease (2011)**[12]	<u>Symptomatic control of wearing-off</u> • Adjusting the levodopa dose by increasing the dosing frequency (to four to six daily doses) may attenuate wearing off. • Adding a catechol-O-methyltransferase-inhibitor or a monoamine oxidases-B inhibitor as they are effective in reducing off-time by one to 1.5 hours/day. A recommendation cannot be mad as to which agent should be utilized first. However tolcapone is only recommended for patients who fail all other available agents due to safety concerns with the agent. • Adding a dopamine agonist. All dopamine agonists are equally effective and efficacious in reducing off-time. While non-ergot dopamine agonists are first-line compounds, pergolide and other ergot derivatives are reserved for second-line use, due to the adverse events of valvulopathy. • Switching from the standard formulation of levodopa to the controlled-release formulation improves wearing-off symptoms and this formulation is useful in the treatment of night time akinesia. • Addition of amantadine or anticholinergics may improve symptoms in some cases and should be considered in patients with severe off symptoms who fail the recommended strategies listed above. <u>Symptomatic control of dyskinesias</u> • Reducing the dose size of levodopa has been beneficial in reducing dyskinesias. The risk of off-time increases but can be compensated by increasing the frequency of levodopa dosing. • Discontinuing or reducing the dose of monoamine oxidases-B inhibitors or catechol-O-methyltransferase inhibitors can help control dyskinesias, however the risk of worsening off-time increases. • Patients may benefit for up to eight months by adding amantadine 200 to 400 mg/day for the treatment of dyskinesias. • Deep brain stimulation of the subthalamic nucleus allows the reduction of dopaminergic treatment. • The addition of clozapine or quetiapine has shown to be beneficial in reducing peak dose dyskinesia. Clozapine's adverse events of agranulocytosis limit its use. • Apomorphine given as a continuous subcutaneous infusion under direct medical supervision allows for the reduction of levodopa therapy and helps control dyskinesias. • Intrajejunal levodopa infusion may be beneficial in patients with marked peak dose dyskinesia and motor fluctuations. <u>Symptomatic control of off-period and early morning dystonias</u> • In cases of off-period dystonia usual strategies for wearing off can be applied. • For the control of dystonia appearing during the night or early in the morning, additional doses of levodopa or dopamine agonist therapy may be effective. • Deep brain stimulation of the subthalamic nucleus may be used for off-

Clinical Guideline	Recommendation(s)
	period and early morning dystonias. • In both off-period and early morning dystonia botulinum toxin can be employed. <u>Treatment of dementia in Parkinson's disease</u> • Most recommendations are off-label. • Discontinue potential aggravators (i.e., anticholinergics, amantadine, tricyclic antidepressants, tolterodine and oxybutynin and benzodiazepines). • Add cholinesterase inhibitors (i.e., rivastigmine, donepezil, galantamine). Tacrine is not recommended due to associated hepatotoxicity. An alternative agent should be tried prior to abandoning. • If cholinesterase inhibitors not tolerated or lacking efficacy, add or substitute with memantine. <u>Treatment of psychosis in Parkinson's disease</u> • Control triggering factors (i.e., infections, metabolic disorders, electrolyte imbalances, sleep disorders). • Reduce polypharmacy. • Reduce anti-Parkinson's disease agents. • The addition of an atypical antipsychotic has shown to be beneficial. Clozapine's adverse event of agranulocytosis limits its use. Quetiapine is thought to be relatively safe and possibly useful; however, sufficient data does not exist. Olanzapine and risperidone are not recommended. • Typical antipsychotics should not be used as they worsen Parkinsonism. • Add cholinesterase inhibitors (i.e., rivastigmine, donepezil). <u>Treatment of depression in Parkinson's disease</u> • Optimize antiparkinson therapy. • Initiate tricyclic antidepressants. • Compared to tricyclic antidepressants selective serotonin reuptake inhibitors are less likely to produce adverse events. • No recommendations can be made concerning "new" antidepressants (i.e., mirtazapine, reboxetine, venlafaxine). <u>Treatment of orthostatic hypotension in Parkinson's disease</u> • Aggravating factors should be avoided (i.e., large meals, alcohol, caffeine at night, warm environment exposure, volume depletion, drugs known to cause orthostatic hypotension). Drugs that are known to cause orthostatic hypotension include: diuretics, antihypertensive agents, tricyclic antidepressants, nitrates, alpha blockers, levodopa, dopamine agonists, and monoamine oxidases-B inhibitors. • In symptomatic orthostatic hypotension increase salt intake (1 gram per meal). • Head up, tilt the bed at night (30 to 40º), may be helpful. • Wear wait high elastic stockings and/or abdominal binders. • Exercise as tolerated. • Maneuvers to prolong patient upright should be introduced (i.e., leg crossing, toe raising, thigh contraction, bending at waist). • For drug therapy, midodrine is the preferred option. The addition of fludrocortisone is a secondary option as it is possibly effective. <u>Treatment of urinary disturbances in Parkinson's disease</u> • An urologist should be referenced to for Parkinson's disease patients with bladder problems, at least if response to anticholinergic therapy is insufficient or if intolerance is present.

Clinical Guideline	Recommendation(s)
	• Intake after 6 PM should be reduced for the management of nocturia. • Night time dopaminergic therapy should be optimized. • Anticholinergic agents should be utilized with priority given to agents that do not pass the blood-brain barrier. • The efficacy of botulinum was demonstrated in a pilot study with a small sample size. <u>Symptomatic control of dysphagia in Parkinson's disease</u> • A priority should be given to optimization of motor symptoms. In some patients levodopa and apomorphine can improve dysphagia. • Early referral to speech therapist for assessment, swallowing advice and further instrumental investigations if needed. • In selected cases, video fluoroscopy to exclude silent aspiration. • Enteral feeding options may need to be considered. • There is still very limited experience with the following therapies and cannot generally be recommended: surgical therapies, rehabilitative treatments and botulinum toxin. <u>Symptomatic control of gastric dysfunction</u> • In Parkinson's disease gastric emptying is often delayed. • Domperidone can be considered to accelerate gastric emptying. • Transdermal patches may be considered for patients with severe fluctuations in gastric emptying. <u>Symptomatic control of nausea and vomiting</u> • Droperidol is effective and ondansetron may be used as a second line agent. No other antiemetic is recommended. <u>Symptomatic control of constipation</u> • In Parkinson's disease patients constipation is the most commonly reported gastrointestinal symptom. • Anticholinergics should be discontinued as they may worsen constipation. • Increased fluid and fiber intake are recommended. • Increased physical activity may be beneficial. • Polyethylene glycol solution is the preferred therapeutic option with alternative agents being fiber supplements such as psyllium or methylcellulose and osmotic laxatives. • Irritant laxatives should be reserved for selected patients and short duration of treatment. <u>Treatment of erectile dysfunction</u> • Erectile dysfunction is more common in Parkinson's disease patients compared to matched controls. • Agents that are associated with erectile dysfunction should be discontinued. • A positive and negative effect on symptoms may be seen with dopaminergic therapy. • Sildenafil as well as tadalafil and vardenafil may be tried. • Apomorphine injections and intracavernous injections papaverine or alprostadil may be considered in select patients. <u>Treatment of daytime somnolence and sudden onset of sleep</u> • Nocturnal sleep disturbances should be assessed. • Disturbances should be reduced to optimize nocturnal sleep. • Driving should be stopped.

Clinical Guideline	Recommendation(s)
	• Medications prescribed for other medical conditions should be decreased or discontinued. • The dose of dopaminergic agents should be decreased as they may induce daytime somnolence. • Switch the dopamine agonist to another dopamine agonist. • Add modafinil. • Add other wake-promoting agents (i.e., methylphenidate). <u>Treatment of rapid eye movement sleep behavior disorder</u> • Protective measures such as safeguarding the bedroom should be employed to prevent sleep related injuries. • Antidepressants, specifically selective serotonin reuptake inhibitors should be reduced or withdrawn. • Clozapine may be added at bedtime. <u>Treatment of sleep problems</u> • A standard or slow-release dose of levodopa should be added at bed time. • The following agents improve sleep quality in patients with advanced Parkinson's disease with motor fluctuations: transdermal rotigotine, pramipexole and prolonged release ropinirole. • With the exception of nocturnal motor phenomena of sleep disorders deep brain stimulation improves sleep quality in patients with advanced Parkinson's disease.
National Institute for Health and Clinical Excellence: **Parkinson's Disease: Diagnosis and Management in Primary and Secondary Care (2011)**[13]	• There is no universal first-choice therapy for patients with Parkinson's disease. Clinical and lifestyle characteristics of the patient should be taken into account. • Levodopa may be used in patients with early Parkinson's disease for symptomatic treatment with doses kept as low as possible to reduce the development of motor complications. • Dopamine agonists may be used in patients with early Parkinson's disease for symptomatic treatment. Dopamine agonists should be titrated to a clinically efficacious dose and another agent in the class may be used if the patient fails therapy or adverse events prevent titration. • Monoamine oxidase-B inhibitors may be used in patients with early Parkinson's disease for symptomatic treatment. • Beta-blockers may be used for symptomatic treatment of selected people with postural tremor, but are not considered first-line agents. • Amantadine may be used in patients with early Parkinson's disease, but is not considered a first-line agent. • Anticholinergics may be used in young patients with early Parkinson's disease for symptomatic treatment associated with severe tremor. These agents are not considered first-line due to limited efficacy and the propensity to cause neuropsychiatric adverse events. • Extended-release levodopa should not be used to delay the onset of motor complications in patients with early Parkinson's disease. • Most patients with Parkinson's disease will develop motor complications over time and will require levodopa therapy. Adjuvant medications have been developed to take concomitantly with levodopa to help reduce the motor complications and improve quality of life associated with late stage Parkinson's disease. • There is no single agent of choice for late stage Parkinson's disease. • Extended-release levodopa may help reduce motor complications in patients with late stage Parkinson's disease, but is not considered a first-line agent. • Dopamine agonists may be used to reduce motor fluctuations in patients

Clinical Guideline	Recommendation(s)
	with late stage Parkinson's disease. Dopamine agonists should be titrated to a clinically efficacious dose and another agent in the class may be used if adverse events prevent titration. • Monoamine oxidase-B inhibitors may be used to reduce motor fluctuations in patients with late stage Parkinson's disease. • Catechol-o-methyl transferase inhibitors may be used to reduce motor fluctuations in patients with late stage Parkinson's disease. This class of medication is taken concomitantly with levodopa. • Amantadine may be used to reduce dyskinesias in patients with late stage Parkinson's disease. • "Drug holidays" should be avoided because of the risk of developing neuroleptic malignant syndrome.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the adamantanes are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Adamantanes[4-6]

Indication	Amantadine	Rimantadine
Influenza A prophylaxis	✔	
Influenza A treatment	✔	
Parkinson disease	✔	
Drug-induced extrapyramidal reactions	✔	
Prophylaxis of illness caused by various strains of influenza A virus in patients one year of age and older		✔
Treatment of illness caused by various strains of influenza A virus in adults (17 years and older)		✔

IV. Pharmacokinetics

The pharmacokinetic parameters of the adamantanes are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Adamantanes[4-6]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Amantadine	Well absorbed	67	Not reported	Renal	17
Rimantadine	Not reported	40	Liver	Renal (74)	25.4 to 32.0

V. Drug Interactions

No significant drug interactions with the adamantanes have been reported.[4]

VI. Adverse Drug Events

The most common adverse drug events reported with the adamantanes are listed in Table 5.

Table 5. Adverse Drug Events (%) Reported with the Adamantanes[4-6]

Adverse Events	Amantadine	Rimantadine
Cardiovascular		
Arrhythmia	<1	-
Cardiac arrest	<1	-
Cardiac failure	-	<1
Heart block	-	<1
Heart failure	<1	-
Hypertension	-	<1
Orthostatic hypotension	1 to 10	-
Palpitation	-	<1
Peripheral edema	1 to 10	<1
Syncope	-	<1
Tachycardia	-	<1
Central Nervous System		
Aggressive behavior	<1	-
Agitation	1 to 10	<1
Amnesia	<1	-
Anxiety	1 to 10	-
Ataxia	1 to 10	<1
Concentration impaired	-	≤2
Confusion	1 to 10	<1
Delirium	1 to 10	-
Delusions	<1	-
Depression	1 to 10	<1
Dizziness	1 to 10	1 to 2
Dream abnormality	1 to 10	-
Euphoria	<1	<1
Fatigue	1 to 10	1
Gait abnormality	-	<1
Hallucinations	1 to 10	<1
Headache	1 to 10	1
Insomnia	1 to 10	2 to 3
Irritability	1 to 10	-
Lightheadedness	1 to 10	-
Mania	<1	-
Nervousness	1 to 10	1 to 2
Paresthesia	<1	-
Psychosis	<1	-
Seizure	<1	<1
Somnolence	1 to 10	-
Suicidal ideation	<1	-
Suicide	<1	-
Tremor	-	<1
Dermatologic		
Eczematoid dermatitis	<1	-
Livedo reticularis	1 to 10	-
Photosensitivity	<1	-
Rash	<1	<1
Gastrointestinal		

Adverse Events	Amantadine	Rimantadine
Abdominal pain	-	1
Anorexia	1 to 10	2
Constipation	1 to 10	-
Diarrhea	1 to 10	<1
Dysphagia	<1	-
Nausea	1 to 10	3
Taste alteration	-	<1
Vomiting	-	2
Xerostomia	1 to 10	2
Hematologic		
Agranulocytosis	<1	-
Leukopenia	<1	-
Neutropenia	<1	-
Laboratory Test Abnormalities		
Alkaline phosphatase increased	<1	-
Alanine transaminase increased	<1	-
Aspartate aminotransferase increased	<1	-
Bilirubin increased	<1	-
Blood urea nitrogen increased	<1	-
Creatine phosphokinase increased	<1	-
Gamma-glutamyl transferase increased	<1	-
Lactate dehydrogenase increased	<1	-
Serum creatinine increased	<1	-
Respiratory		
Bronchospasm	-	<1
Dry nose	1 to 10	-
Dyspnea	<1	<1
Pulmonary edema	<1	-
Respiratory failure	<1	-
Other		
Allergic reaction	<1	-
Anaphylaxis	<1	-
Diaphoresis	<1	-
Hyperkinesia	<1	<1
Lactation	-	<1
Neuroleptic malignant syndrome	<1	-
Oculogyric episodes	<1	-
Urinary retention	<1	-
Withdrawal reactions	<1	-
Visual disturbances	<1	-
Weakness	-	1

✓ Percent not specified.
- Event not reported or incidence <1%.

VII. Dosing and Administration

The usual dosing regimens for the adamantanes are listed in Table 6.

Table 6. Usual Dosing Regimens for the Adamantanes[4-6]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Amantadine	Drug-induced extrapyramidal reactions: Capsule, solution, tablet: 100 mg twice daily; maximum, 300 mg	Influenza A prophylaxis in patients one to nine years of age: Capsule, solution, tablet: 4.4	Capsule: 100 mg Solution:

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	daily in divided doses Parkinson disease (monotherapy): Capsule, solution, tablet: 100 mg twice daily Parkinson disease (concomitant therapy): Capsule, solution, tablet: 100 mg once or twice daily Influenza A prophylaxis: Capsule, solution, tablet: 200 mg as a single daily dose or 100 mg twice daily for two to four weeks Influenza A treatment: Capsule, solution, tablet: 200 mg as a single daily dose or 100 mg twice daily for 24 to 48 hours after the disappearance of signs and symptoms	to 8.8 mg/kg/day divided twice daily; maximum, 150 mg/day for two to four weeks Influenza A prophylaxis in patients nine to 12 years of age: Capsule, solution, tablet: 100 mg twice daily for two to four weeks Influenza A treatment in patients one to nine years of age: Capsule, solution, tablet: 4.4 to 8.8 mg/kg/day divided twice daily; maximum, 150 mg/day for 24 to 48 hours after the disappearance of signs and symptoms Influenza A treatment in patients nine to 12 years of age: Capsule, solution, tablet: 100 mg twice daily for 24 to 48 hours after the disappearance of signs and symptoms	50 mg/5 mL Tablet: 100 mg
Rimantadine	Prophylaxis of illness caused by various strains of influenza A virus: Tablet: 100 mg twice daily for 11 days to six weeks Treatment of illness caused by various strains of influenza A virus in adults (17 years and older): Tablet: 100 mg twice daily for seven days	Prophylaxis of illness caused by various strains of influenza A virus in patients one to nine years of age: Tablet: 5 mg/kg once daily for five to six weeks; maximum, 150 mg/day Prophylaxis of illness caused by various strains of influenza A virus in patients >9 years of age: Tablet: 100 mg twice daily for five to six weeks	Tablet: 100 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the adamantanes are summarized in Table 7.

Table 7. Comparative Clinical Trials with the Adamantanes

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Influenza Prophylaxis				
Bryson et al.[14] (1980) Amantadine for 4 weeks vs placebo	DB, PRO, RCT, XO Young adults attending college	N=88 4 weeks	Primary: Gross and subtle side effects Secondary: Not reported	Primary: Adverse events occurred in 33% of those receiving amantadine and in 10% of those receiving placebo (P<0.005). Cessation of adverse events occurred in more than half of those continuing amantadine. Sixteen students receiving amantadine had decreased performance on sustained attention tasks as compared to ones receiving placebo (P<0.05). Secondary: Not reported
Reuman et al.[15] (1989) <u>Study 1 (naturally occurring influenza):</u> Amantadine 100 mg QD vs amantadine 200 mg QD vs placebo <u>Study 2 (experimental</u>	DB, PC, RCT Healthy hospital personnel 18 to 55 years of age	<u>Study 1:</u> N=476 6 weeks <u>Study 2:</u> N=78 13 days	Primary: Efficacy, as measured by number of influenza-like illnesses, number of laboratory-confirmed influenza cases using blood tests and viral assays from nasal washouts Secondary: Not reported	Primary: In the first study, adverse reactions were not significantly different between the group receiving 100 mg/day of amantadine and the placebo group, but significantly greater in the group given 200 mg/day (P<0.009). The study authors concluded that the influenza attack rate in this study was too low to assess efficacy. In the experimental challenge study of influenza A/Beth/1/85, the prophylactic administration of amantadine 50, 100 or 200 mg/day doses was more effective than placebo in preventing influenza illness (P<0.02, 66, 74 and 82% protection, respectively), and in suppressing viral replication (P=0.02). There was no significant difference between amantadine groups in influenza illness or viral shedding. Compared to the placebo group the 100 and 200 mg amantadine groups showed a significant decrease in infection rate (100 mg, 40% protection; P=0.012 and 200 mg, 32% protection; P=0.045) whereas the 50 mg group did not (20% protection; P=0.187).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
challenge): Amantadine 50 mg QD vs amantadine 100 mg QD vs amantadine 200 mg QD				Secondary: Not reported
Brady et al.[16] (1990) Rimantadine 100 mg QD vs placebo	DB, MC, PC Healthy adult volunteers 18 to 55 years of age	N=228 3 months	Primary: Prophylactic efficacy, as judged from laboratory-confirmed influenza virus infections and number of illnesses from influenza A Secondary: Adverse effects	Primary: Compared to placebo, low-dose rimantadine was associated with significantly fewer cases of influenza A virus infection (20 of 110 in the placebo group vs seven of 112 in the rimantadine group; P<0.01) and influenza illness (seven of 110 in the placebo group vs one of 112 in the rimantadine group; P=0.04). Secondary: Only 10 (8.7%) of 114 rimantadine recipients and five (4.4%) of 114 placebo control recipients reported one or more mild-to-moderate adverse symptoms, most of which were related to the gastrointestinal or central nervous system.
Crawford et al.[17] (1988) Rimantadine vs placebo	DB, PC, RCT Children 1 to 18 years of age and adult members from 29 families	N=110 A naturally occurring outbreak of influenza A (H3N2)	Primary: Efficacy against influenza A infection and associated illness, prevention of transmission of infection to adult members of the child's family, and adverse effects	Primary: Influenza infections, defined as a positive viral throat culture or a four-fold increase in antibody titer, occurred in 31% of children in the placebo group and 7.4% in the rimantadine group (P=0.026). Clinical illness with laboratory evidence of influenza infection occurred in 24.1% of children in the placebo group and none in the rimantadine group (P=0.007). Rimantadine was well-tolerated by the children, with no significant differences in adverse events between the treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: Not reported	Secondary: Not reported
Hayden et al.[18] (1989) Rimantadine 200 mg QD for 10 days vs placebo	DB, PC, RCT Household members of patients with influenza A	N=237 (families) Two influenza seasons	Primary: Development of illness and resistance Secondary: Not reported	Primary: Among households with documented influenza A infections, symptomatic illness occurred in one or more contacts in 10 of 28 families treated with rimantadine and in 10 of 209 families treated with placebo. Asymptomatic secondary influenza A infections were found in five families assigned to receive rimantadine and in four families assigned to receive placebo. Rimantadine-resistant strains of influenza A virus (H3N2 subtype) with mutations consisting of single amino acid changes in the M2 protein (residue 27, 30, or 31) were recovered from eight index patients and five contacts treated with rimantadine. There was apparent transmission of drug-resistant strains of virus in six contacts with secondary illnesses in five families. Secondary: Not reported
Monto et al.[19] (1995) Rimantadine 100 mg QD up to 8 weeks vs rimantadine 200 mg QD up to 8 weeks vs placebo	DB, PC, RCT Elderly residents in 10 nursing homes	N=328 8 weeks	Primary: Incidence of adverse effects Secondary: Influenza like illness; laboratory-confirmed clinical influenza; influenza virus infection with or without clinical illness	Primary: The most commonly reported symptom in all groups was confusion (10 to 14%). Nausea (8 to 11%) and loss of appetite (6 to 10%) were also frequently reported. Four (3%) patients in the 200 mg/day group and one (2%) participant in the placebo group experienced a seizure or clonic twitching while receiving study drug or placebo. Patients in all three groups were equally likely to experience each of the specified symptoms. Patients in the 200 mg/day-prophylaxis group were 2.3 times more likely to experience a significant health event than those in the placebo group (P=0.031). Patients in the 200 mg/day group were 1.9 times more likely to withdraw from the study than patients in the placebo group. A total of 31/132 patients withdrew from the 200 mg group (P=0.041). Increased risk of withdrawal from the study was also observed when comparing the 100 mg/day group with the placebo group. A total of 23/130 patients withdrew from the 100 mg group (P=0.213).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Rimantadine at both dosages was associated with reductions in the likelihood of clinical influenza-like illness and laboratory-confirmed influenza virus infection; however, in no case were the estimates statistically significant. Efficacy analyses were limited to vaccinated individuals. Efficacy analyses to be carried out in two of the 10 nursing homes where study patients had documented influenza virus infection. Rimantadine was most efficacious at reducing the likelihood of clinical illness; the RR was 0.40 (95% CI, 0.13 to 1.25; P=0.115) and 0.43 (95% CI, 0.14 to 1.35; P=0.147) for 100 and 200 mg doses respectively. However, rimantadine was less effective in reducing the likelihood of laboratory-confirmed infection; the RR were 0.50 (95% CI, 0.12 to 2.18; P=0.355) and 0.54 (95% CI, 0.12 to 2.34; P=0.409) for 100 and 200 mg doses, respectively. The efficacy of rimantadine in reducing the likelihood of clinical influenza-like illness was estimated to be 58% (RR, 0.42; CI, 0.16 to 1.11; P=0.079) for the groups receiving prophylaxis vs placebo.
Jefferson et al.[20] (2006) Amantadine, rimantadine, or neuraminidase inhibitors as prophylaxis and/or treatment for influenza vs placebo, no intervention, or	MA Healthy individuals 16 to 65 years of age	52 trials Variable duration	Primary: Prophylactic efficacy, duration of nasal shedding, time to alleviate symptoms, adverse events, lower respiratory tract complications Secondary: Not reported	Primary: For the prophylaxis of influenza A and influenza-like illness, amantadine prevented 61% (95% CI, 35 to 76) and 25% (95% CI, 13 to 36) of cases respectively. The use of amantadine was associated with nausea (OR, 2.56; 95% CI, 1.37 to 4.79), insomnia and hallucinations (2.54; 95% CI, 1.50 to 4.31). The duration of fever in days was significantly shortened with amantadine compared to placebo (0.99; 95% CI, –1.26 to -0.71); in comparison with nasal shedding of influenza A, there were no significant difference was seen (0.93; 95% CI, 0.71 to 1.21). Compared to placebo when used for prophylaxis, neuraminidase inhibitors have no significant effect on influenza-like illness (1.28; 95% CI, 0.45 to 3.66 for oseltamivir 75 mg a day and 1.51; 95% CI, 0.77 to 2.95 for

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
symptomatic medication				zanamivir 10 mg a day). Against symptomatic influenza, oseltamivir was 61 or 73% (75 and 150 mg doses) effective, while zanamivir was 62% efficacious. Nausea was associated with the use of oseltamivir (OR, 1.79; 95% CI, 1.10 to 2.93). The protective efficacy of oseltamivir was 58.8% from household contacts and from 68 to 89% in contacts of index cases. Compared to placebo the HRs for the time-to-alleviate symptoms were 1.33 (95% CI, 1.29 to 1.37) for zanamivir and 1.30 (95% CI, 1.13 to 1.50) for oseltamivir, when the medications were started within 48 hours of onset of symptoms. In preventing lower respiratory tract complications in influenza cases, oseltamivir 150 mg a day was judged to be effective (OR, 0.32; 95% CI, 0.18 to 0.57). Secondary: Not reported
Dolin et al.[21] (1982) Amantadine 100 mg BID for 6 weeks vs rimantadine 100 mg BID for 6 weeks vs	DB, PC, RCT Healthy non-vaccinated adults 18 to 45 years of age who volunteered for the study	N=450 6 weeks	Primary: Efficacy, defined as number of influenza-like illnesses, and number of laboratory-confirmed influenza cases Secondary: Adverse events	Primary: Influenza-like illness occurred in 41% of the patients receiving placebo, 14% of those receiving rimantadine, and 9% of those receiving amantadine (P<0.001 for either drug vs placebo). Laboratory-documented influenza occurred in 21% of placebo recipients, 3% of rimantadine recipients, and 2% of amantadine recipients (P<0.001 for either drug vs placebo). These findings represent efficacy rates of 85% for rimantadine and 91% for amantadine, as compared to placebo. Secondary: More recipients of amantadine (13%) than recipients of rimantadine (6%; P<0.05) or placebo (4%; P<0.01) withdrew from the study because of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				central nervous system side effects.
Kimberlin et al.[22] (2010) Amantadine vs rimantadine vs oseltamivir	RETRO Children <12 months of age with influenza	N=180 Variable duration	Primary: Frequency of neurologic adverse events and all adverse events Secondary: Not reported	Primary: Abnormalities that potentially reflected neurologic involvement were consistent with influenza disease, related to preexisting underlying neurologic conditions, or explainable by a concomitant medication. Two patients had possible seizures or seizure-like movements during therapy with no preexisting history of such events, but in both cases the seizures were not thought to be related to antiviral therapy. Only 33% of the patients had Glasgow Coma Score information available in their medical records. The end-of-treatment ranked verbal score was slightly lower for oseltamivir treated patients (P=0.04). Total scores were identical between the two therapies (P=0.40). One death occurred within 30 days following initiation of the influenza antiviral medications. Secondary: Not reported
Jackson et al.[23] (2011) Amantadine vs oseltamivir vs zanamivir vs placebo or no treatment	MA Patients who received antiviral agents for the prevention of influenza	20 trials Variable duration	Primary: Prevention of symptomatic laboratory-confirmed influenza Secondary: Complications prevented, hospitalizations prevented, length of influenza illness and time to return to normal activities	Primary: Oseltamivir was efficacious in seasonal prophylaxis against (RR, 0.24; 95% CI, 0.09 to 0.54). A protective effect of oseltamivir in seasonal prophylaxis was found in one study which included the frail elderly living in residential care (RR, 0.08; 95% CI, 0.01 to 0.63). Oseltamivir was effective in preventing the transmission of symptomatic laboratory-confirmed influenza in households of mixed composition (RR, 0.19; 95% CI, 0.08 to 0.45). Oseltamivir have a preventative effect against symptomatic laboratory-confirmed influenza when employed as post-exposure prophylaxis in pediatric contacts (≥1 year of age; RR, 0.36; 95% CI, 0.15 to 0.84). Zanamivir demonstrated a protective efficacy of 68% for seasonal prophylaxis in adults (RR, 0.32; 95% CI, 0.17 to 0.63) and at-risk adolescents/adults (RR, 0.17; 95% CI, 0.07 to 0.44). There was no significant different in older people with zanamivir.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Zanamivir was effective in preventing the transmission of symptomatic laboratory-confirmed influenza in households of mixed composition (RR, 0.21; 95% CI, 0.13 to 0.33). There was no significant difference in the elderly in long-term care (RR, 0.68; 95% CI, 0.33 to 1.27). Evidence for the use of amantadine against symptomatic laboratory-confirmed influenza in seasonal prophylaxis was limited. One trial demonstrated a non-significant preventative effect among healthy adults in seasonal prophylaxis (RR, 0.40; 95% CI, 0.08 to 2.03). Amantadine was effective in preventing symptomatic laboratory-confirmed influenza in healthy adolescents (RR, 0.10; 95% CI, 0.03 to 0.34). Secondary: Oseltamivir seasonal prophylaxis was associated with a non-significant 78% reduction in secondary complications among at-risk elderly patients with laboratory-confirmed influenza (P=1.14). In a study of post-exposure prophylaxis, the proportion of contacts with laboratory-confirmed influenza with at least one secondary complication was equivalent among patients who received oseltamivir and those in the control arm who received expectant treatment upon the onset of influenza-like illness (7 vs 5%). However, the more severe respiratory complications occurred among the expectant treatment group. The median duration of illness in contacts was shorter in the oseltamivir post-exposure prophylaxis group vs those receiving treatment on influenza onset (5.5 vs 39.8 hours; P=0.103). Fewer contacts with laboratory-confirmed influenza in the oseltamivir post-exposure prophylaxis group were bedbound compared to patients in those receiving treatment on influenza onset (7 vs 28%). Significantly less work absence was reported among patients who received zanamivir as seasonal prophylaxis vs control group patients (mean hours lost 0.6 vs 1.4; P=0.001). Total productive time lost was also less in the zanamivir group (1.8 vs 3.0 hours; P=0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Significantly fewer households who received zanamivir post-exposure prophylaxis reported a contact developing a complication of laboratory-confirmed influenza (2 vs 6%; P=0.01). Complications of symptomatic laboratory-confirmed influenza during the first 28 days following postexposure prophylaxis initiation were lower among the zanamivir-treated patients vs placebo (5 vs 6%; P=0.653). The proportion of cases with complications requiring antibiotics was marginally lower among patients receiving zanamivir post-exposure prophylaxis compared to placebo (5 vs 8%). Among household contacts with laboratory-confirmed influenza, the median time to alleviation of symptoms without use of medication was 5.5 days in the prophylaxis and 8.0 days in the placebo groups. Mean duration of significant influenza-like symptoms was shorter in the zanamivir post-exposure prophylaxis vs placebo group (0.2 vs 0.6 days; P=0.016). No secondary outcomes were described relating to the use of amantadine in seasonal prophylaxis. Limited evidence was identified for milder influenza illness of shorter duration as a result of the use of amantadine in post-exposure prophylaxis. The severity of symptoms was reported as 56.0% mild and 9.0% severe in the amantadine group, and 38.0% mild and 19.0% severe in the placebo group (P<0.01 for severe symptoms, P<0.001 for mild symptoms). Mean duration of illness was found to be shorter in the amantadine group vs the placebo group (P<0.05).
Influenza Treatment				
Hayden et al.[24] (1986) Rimantadine 200 mg QD for 5 days vs placebo	DB, PC, RCT Patients with uncomplicated influenza A (H3N2) virus infection	N=14 2 months	Primary: Therapeutic activity Secondary: Not reported	Primary: Rimantadine treatment was associated with significant reductions in nasal secretion viral titers (days two through four; P<0.01), maximal temperature (days two and three; P<0.01), and systemic symptoms compared to placebo treatment (P<0.01). Secondary: Not reported
Hsu et al[25]	MA	N=Not	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2012) Antiviral drugs (amantadine, oseltamivir, rimantadine, zanamivir) vs placebo	Patients receiving any of the antiviral drugs for the treatment of laboratory-confirmed influenza or influenza-like illness (not confirmed)	reported Duration not reported	Mortality, hospitalization, intensive care until admission, mechanical ventilation and respiratory failure, duration of hospitalization, duration of signs and symptoms, time to return to normal activity, complications, critical adverse events (major psychotic disorders, encephalitis, stroke, or seizure), important adverse events (pain in extremities, clonic twitching, body weakness, or dermatologic changes), influenza viral shedding and emergence of antiviral resistance Secondary: Not reported	There was a reduction in mortality with oseltamivir treatment compared to no antiviral therapy (OR, 0.23; 95% CI, 0.13 to 0.43). The overall grade for the quality of evidence was low. A pooled estimate of unadjusted effects from nine studies resulted in a more modest reduction in mortality (OR, 0.51; 95% CI, 0.23 to 1.14). Treatment with oseltamivir reduced hospitalizations in outpatients compared to patients treated with placebo (OR, 0.75; 95% CI, 0.66 to 0.89). Oseltamivir reduces the duration of fever by approximately 33 hours (95% CI, 21 to 45 hours) from onset of symptoms compared to no antiviral therapy (standardized mean difference, -0.91; 95% CI, -1.25 to -0.57). Oseltamivir may be associated with fewer adverse events compared to no antiviral therapy (RR, 0.76; 95% CI, 0.70 to 0.81). At six months, one study found a reduction in risk for stroke and transient ischemic attacks in patients <65 years who received oseltamivir (HR, 0.66; 95% CI, 0.56 to 0.77). Oseltamivir was not associated with fewer complications, such as pneumonia (OR, 0.83; 95% CI, 0.59 to 1.16) or any recurrent cardiovascular outcome (OR, 0.58; 95% CI, 0.31 to 1.10); however, there was a reduction in otitis media (OR, 0.75; 95% CI, 0.64 to 0.87). The incidence of resistance to oseltamivir treatment across five studies was 30 per 1000 patients (95% CI, 10 to 60) and influenza virus was detectable in 330 per 1000 patients (95% CI, 280 to 370) approximately five days after treatment with oseltamivir. No study compared the persistence of influenza virus between patients who received oseltamivir and those who did not. There was no significant reduction in hospitalization following inhaled zanamivir treatment compared to those who receive no antiviral therapy (OR, 0.66; 95% CI, 0.37 to 1.18). Zanamivir reduced the duration of symptoms by approximately 23 hours (95% CI, 17 to 28) on the basis of a large standardized mean difference (-0.94; 9% CI, -1.21 to -0.66).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was no increased risk of including otitis media (OR, 1.19; 95% CI, 0.67 to 2.14), respiratory disease (OR, 1.17; 95% CI, 0.98 to 1.39). The combined results of five Japanese studies in patients with confirmed influenza suggest that inhaled zanamivir may be associated with slightly shorter symptom duration than oseltamivir (difference, 7 hours; 95% CI, 2 to 12). There was no statistically significant difference between oseltamivir and inhaled zanamivir with regard to hospitalizations (OR, 1.40; 95% CI, 0.45 to 4.35) or intensive care until admissions (OR, 0.58; 95% CI, 0.16 to 2.18) in pregnant women. The results of another study demonstrated no statistically significant difference in influenza viral detection after five days between the treatments (OR, 3.05; 95% CI, 0.78 to 11.96). The results of one study reported that amantadine may reduce mortality (OR, 0.04; 95% CI, 0.00 to 0.73) and pneumonia (OR, 0.76; CI, 0.38 to 1.53) compared to no antiviral therapy; however, time to alleviation of symptoms did not significantly between treatments. No studies that compared rimantadine with no antiviral therapy. Secondary: Not reported
Younkin et al.[26] (1983) Amantadine 100 mg orally QD for 5 days vs amantadine 200 mg orally QD for 5 days	DB, PRO College students, 17 to 20 years of age with symptoms of less than 48 hours duration	N=48 7 days	Primary: Symptomatic improvement; symptoms measured included upper respiratory symptoms (earache or obstruction, nasal discharge or obstruction, sore throat, hoarseness), lower respiratory	Primary: The aspirin treatment group defervesced more rapidly, in 10.3 vs 21.5 hours for the amantadine 100 mg group and 23.6 hours for the amantadine 200 mg group (P<0.01). When mean daily symptom scores were tabulated, the volunteers receiving 100 mg of amantadine daily had significantly lower values at 48 and 72 hours than did the volunteers receiving aspirin (P<0.01). Although the group who received 200 mg of amantadine had substantially lower overall symptom scores than the aspirin treatment group, this difference did not achieve statistical significance (0.05<P<0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs aspirin 3.25 g orally QD for 5 days			symptoms (chest pain, cough), and systemic symptoms (feverishness, chills, myalgias, malaise, headache, and anorexia). Secondary: Side effects	Secondary: Bothersome side effects resulted in discontinuation of therapy by 35% of patients in the aspirin group but only 3% of patients in the amantadine treatment group (P<0.05).
Hall et al.[27] (1987) Rimantadine 6.6 mg/kg/day up to 150 mg/day for children ≤9 years; 200 mg/day for children >9 years for 5 days vs acetaminophen 10 mg/kg/dose up to 500 mg/dose for 5 days	DB, RCT Children 1 to 15 years of age with influenza-like illness	N=69 7 days	Primary: Reduction in fever, improvement in daily scores for symptoms, severity of illness, and viral shedding Secondary: Not reported	Primary: Children receiving rimantadine showed significantly greater reduction in fever and improvement in daily scores for symptoms and severity of illness during the first three days (P<0.04). Viral shedding also diminished significantly during the first two days but subsequently increased such that by days six and seven the proportion of children shedding virus, as well as the quantity of virus shed, was significantly greater in the rimantadine group (P<0.04). During the seven-day study, of the 22 children in the rimantadine group with serial isolates tested, ten (45.5%) had resistant isolates compared to two (12.5%) of those with serial isolates in the acetaminophen group (P<0.03). Thus, of the total 37 children in the rimantadine group, 27% were found to have resistant isolates compared to 6% in the total group receiving acetaminophen (P<0.04). Furthermore, the mean inhibitory concentration of rimantadine increased with time in the rimantadine group (P=0.002) but not in the acetaminophen group. Secondary: Not reported
Kawai et al.[28] (2005) Amantadine 50 mg for adults and 1.5 to 2.5 mg/kg for	OL Patients diagnosed with influenza who received oseltamivir or amantadine	N=2,163 5 days	Primary: Time from onset of symptoms to start of treatment, duration of fever, impact of age on	Primary: For all three groups the duration of fever was significantly shorter in patients who received the medication within 12 hours after the onset of symptoms compared to greater than 12 hours after the honest of symptoms (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
children was administered BID for 5 days to patients with influenza A (Group 3) vs oseltamivir 75 mg for adults and 2 mg/kg for children (<37.5 kg) given BID for 5 days to patients with either influenza A (Group 1) or influenza B (Group 2)	therapy within 48 hours after symptom onset		outcome Secondary: Not reported	For patients in group 2 the duration of fever was significantly longer when compared to groups 1 and 3, however there was no significant differences between groups 1 and 3 (P<0.01 to <0.05). The duration of fever was significantly longer for patients in groups 2 and 3 aged 0 to six years when compared to those aged seven to 15 and 16 to 64; P<0.001 to 0.01). The duration of fever of patients 0 to six in group 1 was significantly shorter than for those same aged patients in group 2 (P<0.01). For patients aged 16 to 64 and >65 there was no significant difference found between groups in duration of fever (P=NS).
Influenza Prophylaxis or Treatment				
Jefferson et al.[29] (2006) Oral or inhaled amantadine or oral rimantadine as prophylaxis and/or treatment for influenza vs placebo, standard medications (aspirin and other antipyretic or antiinflammatory	MA Healthy individuals aged 14 to 60	36 trials Variable duration	Primary: Numbers of influenza cases, severity of cases, rate of death, length of nasal shedding, persistence of virus in the upper airways, adverse effects Secondary: Not reported	Primary: For the comparison of prophylaxis of influenza and influenza-like illness, amantadine prevented 61% (95% CI, 35 to 76) and 25% (95% CI, 13 to 36) of the cases respectively. The duration of fever was significantly shortened by amantadine compared to placebo (0.99 days; 95% CI, 0.71 to 1.26). However, there was no effect on nasal shedding of influenza A viruses in the upper airways after up to five days of treatment (RR, 0.96; 95% CI, 0.72 to 1.27). Amantadine use was associated with gastrointestinal symptoms (OR, 2.56; 95% CI, 1.37 to 4.79), insomnia and hallucinations (OR, 2.54; 95% CI, 1.50 to 4.31), and withdrawals from the trials because of adverse events (OR, 2.54; 95% CI, 1.60 to 4.06) in the prophylaxis trials. There was no evidence that amantadine use was associated with increased adverse effect rates compared to placebo use in treatment trials.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
medications), other antiviral medications, or no intervention				For the prophylaxis of influenza and influenza-like illness, rimantadine was not effective against either influenza (RR, 0.28; 95% CI, 0.08 to 1.08) or influenza-like-illness (RR, 0.65; 95% CI, 0.35 to 1.20). The duration of fever was significantly shortened by rimantadine compared to placebo (1.24 days; 95% CI, -0.76 to -1.71). However, there was no effect on nasal shedding of influenza A viruses in the upper airways after up to five days of treatment (RR, 0.67; 95% CI, 0.22 to 2.07). Rimantadine use was associated with experiencing all adverse effects more than placebo recipients (OR, 1.96; 95% CI, 1.19 to 3.22). In the comparison of amantadine vs rimantadine for prophylaxis of influenza or influenza-like illness, there was no difference in efficacy (RR, 0.88; 95% CI, 0.57 to 1.35). There was no difference in efficacy comparing amantadine compared to rimantadine for treatment. The comparison of amantadine with rimantadine confirmed that central nervous system adverse effects (OR, 3.11; 95% CI, 1.67 to 5.78) and withdrawal from trials (OR, 2.49; 95% CI, 1.26 to 4.93) were significantly more frequent among amantadine recipients. The effects of oral or inhaled amantadine on the shedding of influenza A viruses were NS (RR, 0.93; 95% CI, 0.71 to 1.21). There was no difference in the duration of fever in the comparison of amantadine against standard medications (weighted mean difference, 0.25; 95% CI, - 0.37 to 0.87). In the comparison of inhaled amantadine vs placebo, amantadine was no more effective than placebo in bringing down the respiratory or constitutional symptom score (weighted mean difference, 1.0; 95% CI, 3.64 to 1.64 and -2.0; 95% CI, 16.9 to 12.9 respectively). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Alves Galvão et al.[30] (2012) Amantadine (AMT) and rimantadine (RMT) vs placebo, control drugs, or no intervention	MA Studies evaluating the prevention and treatment of influenza with amantadine and/or rimantadine in children (<19 years of age) and the elderly (≥65 years of age)	12 trials Variable duration	Primary: Response to treatment, cases of influenza, adverse events Secondary: Not reported	Primary: AMT and RMT compared to control (placebo and acetaminophen) in the treatment of influenza A in children There was a protective effect of AMT and RMT in the occurrence of fever on day three of antiviral treatment, when trials using both antivirals were combined (RR, 0.39; 95% CI, 0.20 to 0.79). The number of children needed to treat to benefit to prevent one case of fever on day three of treatment was 5.88 (95% CI, 4.55 to 16.67). A protective effect of RMT for this outcome was also demonstrated (RR, 0.36; 95% CI, 0.14 to 0.91). The number needed to treat to benefit to prevent one case of fever on day three of treatment was 4.12 (95% CI, 3.03 to 33.33). No protective effect of AMT was observed in the occurrence of fever on day three of treatment (RR, 0.37; 95% CI, 0.08 to 1.75). No protective effect of RMT was seen regarding the occurrence of any of the following outcomes assessed: cases of pain on movement and visual distortion on day five (RR, 0.58; 95% CI, 0.10 to 3.24), conjunctivitis on day five (RR, 0.17; 95% CI, 0.01 to 3.49), malaise on day six (RR, 1.04; 95% CI, 0.63 to 1.70), and cough on day seven (RR, 0.83; 95% CI, 0.63 to 1.10). AMT and RMT compared to control (placebo and to specific treatment) in the prophylaxis of influenza A in children A protective effect of AMT was observed (RR, 0.11; 95% CI, 0.04 to 0.30). The number needed to treat to benefit was 11.1 (95% CI, 10 to 14.29) for a period ranging from 14 to 18 weeks. No protective effect of RMT was seen in the prophylaxis of cases of influenza (RR, 0.49; 95% CI, 0.21 to 1.15). Adverse effects of AMT and RMT compared to control (placebo and acetaminophen) in children AMT was not related to a higher risk of the following adverse effects: diarrhea (RR, 0.79; 95% CI, 0.42 to 1.47), exanthema (RR, 0.69; 95% CI, 0.21 to 2.34), muscular limb pain (RR, 0.85; 95% CI, 0.46 to 1.59), headache (RR, 0.73; 95% CI, 0.52 to 1.03), and stimulation and insomnia (RR, 0.46; 95% CI, 0.12 to 1.74).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				RMT was not related to a higher risk of any of the following adverse effects assessed: central nervous system symptoms (RR, 0.23; 95% CI, 0.01 to 4.70); change in behavior (RR, 0.23; 95% CI, 0.01 to 4.70); diarrhea (RR, 0.36; 95% CI, 0.02 to 8.41); dizziness (RR, 3.21; 95% CI, 0.14 to 75.68); gastrointestinal manifestations (RR, 1.17; 95% CI, 0.08 to 18.05); hyperactivity (RR, 0.36; 95% CI, 0.02 to 8.41); tinnitus (RR, 3.21; 95% CI, 0.14 to 75.68); and cerebellar ataxia (RR, 2.61; 95% CI, 0.11 to 61.80) RMT compared to control (placebo and zanamivir) in the prophylaxis of influenza A in the elderly No protective effect of RMT was seen regarding the prophylaxis of influenza in the elderly (RR, 0.74; 95% CI, 0.13 to 4.07). Adverse effects of RMT compared to control (placebo) in the elderly No effect of RMT was seen regarding any of the adverse outcomes assessed in the combined studies: stimulation and insomnia (RR, 1.61; 95% CI, 0.43 to 6.02), confusion (RR, 0.79; 95% CI, 0.40 to 1.56), fatigue (RR, 0.81; 95% CI, 0.41 to 1.60) and vomiting (RR, 0.99, 95% CI, 0.38 to 2.60). Use of different doses of AMT and RMT for prophylaxis and treatment of influenza A in the elderly A reduced RMT dose of 100 mg/day was comparable to the full dose of 200 mg daily for prophylaxis of influenza in the elderly (RR 0.93; 95% CI 0.21 to 4.20). Adverse effects related to different doses of RMT in the elderly There was no protective effect of a reduced dose of RMT in the occurrence of the following adverse reactions in the elderly: confusion (RR, 0.83; 95% CI, 0.41 to 1.65), depression (RR, 0.44; 95% CI, 0.12 to 1.65), impaired concentration (RR, 0.68; 95% CI, 0.11 to 3.98), insomnia or sleeplessness (RR, 1.02; 95% CI, 0.26 to 3.97), loss of appetite (RR, 0.62; 95% CI, 0.27 to 1.46), rash or allergic reaction (RR, 0.34; 95% CI, 0.04 to 3.21), seizures or clonic twitching (RR, 0.11; 95% CI, 0.01 to 2.07), dry mouth (RR, 1.16; 95% CI, 0.43 to 3.11), fatigue or drowsiness

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(RR, 1.14; 95% CI, 0.45 to 2.87), headache (RR, 1.02; 95% CI, 0.30 to 3.42), and body weakness or debility (RR, 0.91; 95% CI, 0.38 to 2.18).
Parkinson's Disease				
Sawada et al.[31] (2010) Observation period (2 to 3 weeks), amantadine treatment period (27 days), washout period (15 days), and placebo treatment period (27 days; Arm 1) vs observation period, placebo period, a washout period, and an amantadine treatment period (Arm 2) Amantadine was increased in a stepwise manner.	DB, MC, PC, RCT, XO Patients 20 to 75 years of age with Parkinson's disease	N=35 Duration varied	Primary: Changes in the Rush Dyskinesia Rating Scale Secondary: Changes in the Unified Parkinson's Disease Rating Scale-III for motor functions, Unified Parkinson's Disease Rating Scale-IVa for dyskinesia and Unified Parkinson's Disease Rating Scale-IVb for motor fluctuations	Primary: Following amantadine treatment, Rush Dyskinesia Rating Scale scores improved in 64% of patients, and placebo treatment resulted in improvement in 16% of patients (P=0.016), although the period effect was not statistically significant (P=0.31). Secondary: Unified Parkinson's Disease Rating Scale-IVa scores improved by 1.83 following amantadine treatment and 0.03 following placebo (P<0.001). Unified Parkinson's Disease Rating Scale-IVb and III scores remained unchanged following amantadine or placebo treatment (Unified Parkinson's Disease Rating Scale-IVb: P=0.87, and Unified Parkinson's Disease Rating Scale-III; P=0.26). The most common adverse effect was visual hallucinations, which was observed in three patients during the amantadine treatment period. The prevalence of adverse effects was significantly greater in patients receiving amantadine treatment compared to placebo treatment (P=0.048).
Crosby et al.[32] (2003) Amantadine monotherapy or adjuvant therapy for idiopathic Parkinson's disease	MA Patients of all ages with a clinical diagnosis of idiopathic Parkinson's disease	N=215 (6 trials) Variable duration	Primary: Parkinson's disease motor impairment rating scales, tests of motor impairments Secondary: Not reported	Primary: Four of the six studies were not eligible for efficacy analysis. Three trials were XO trails that did not present data from the first arm. One of those three trials also only presented data from the amantadine arm. The 4th trail compromised randomization and did not analyze the results on an intention to treat basis. Of the remaining two studies, one study found that amantadine treated patients were 15.0 points better in Parkinsonian symptoms severity scale

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				after nine weeks of treatment (average baseline score of 21.4). The study also found that patients treated with amantadine scored 28.1 points better (average baseline score of 38.3) on the activity impairment scale compared to placebo. The remaining study did not provide standard deviations or baseline scores so the study was unable to be analyzed. Secondary: Not reported
Drug-Induced Extrapyramidal Reactions				
Del Dotto et al.[33] (2001) Amantadine 200 mg IV over 2 hours vs placebo 2 infusion sessions were completed at either a 48- or 72-hour time interval. Patients received either drug or placebo after their first morning dose of levodopa.	DB, PC, RCT, XO Patients with Parkinson's disease with levodopa-induced dyskinesias, and not previously exposed to amantadine; order in which the drugs were administered (XO study) was determined by random assignment	N=9 77 hours	Primary: Average dyskinesia score as determined by a version of the Abnormal Involuntary Movement Scale modified to quantify dyskinesias in the face, neck, trunk, and limbs Secondary: Parkinsonian symptoms	Primary: The average dyskinesia score was lower on the days amantadine was taken compared to placebo days (4.1±1.7 and 8.3±1.8, respectively; P<0.01). Dyskinesia ratings from videotapes was lower on the days amantadine was taken compared to placebo days (3.5±1.1 and 7.3±1.6, respectively, P<0.01). The order of drug administration (amantadine-placebo vs placebo-amantadine) was apparent to seven of the nine patients. Secondary: There were no differences in parkinsonian symptoms as quantified by the average tapping and Unified Parkinson's Disease Rating Scale-III scores on days when patients received amantadine vs days on placebo.
Metman et al.[34] (1998) Amantadine 100 mg for 3 weeks vs	DB, PC, XO Patients with advanced Parkinson's disease complicated by motor fluctuations	N=18 3 weeks	Primary: Parkinsonian symptoms and choreiform dyskinesias as observed during the last two hours	Primary: In the 14 patients completing this trial, amantadine reduced dyskinesia severity by 60% compared to placebo (P=0.001), without altering the antiparkinsonian effect of levodopa. Motor fluctuations occurring with patients' regular oral levodopa regimen also improved according to Unified Parkinson's Disease Rating Scale and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	and peak-levodopa-dose (also known as "on") dyskinesia. Mean age was 60 years and mean symptom duration was 13 years		of a seven-hour levodopa infusion, symptoms were scored using an abbreviated Unified Parkinson's Disease Rating Scale and a modified Abnormal Involuntary Movement Scale Secondary: Dyskinesias scored by a neurologist who observed the patients via study videotapes	patient-kept diaries. Parkinsonian symptoms measured during the levodopa infusion were similar with the addition of amantadine to the symptoms observed with placebo. Although 4 patients had to discontinue because of adverse effects from active treatment, including confusion, hallucinations, palpitations, and nausea, all 14 patients completing the study requested that amantadine be added to their usual antiparkinsonian regimen. Secondary: Dyskinesia ratings from videotapes scored by a second masked rater decreased by 49% with amantadine (3.6±0.6) compared to placebo (7.0±0.9; P<0.01).
Metman et al.[35] (1999) Amantadine 100 mg 3 or 4 times a day vs placebo All other antiparkinsonian medications were continued until the night before levodopa infusion	DB, PC Patients from the above study on the effects of amantadine on levodopa-induced motor complications, evaluated 1 year later	N=17 1 year + 7 to 10 days of supervised administration	Primary: Parkinsonian symptoms and dyskinesia severity evaluated after a seven-hour levodopa infusion, symptoms were scored using standard rating scales and compared to results from one year earlier. Secondary: Dyskinesias scored	Primary: One year after initiation of amantadine cotherapy, its antidyskinetic effect was similar in magnitude (56% reduction in dyskinesia; P<0.01, as compared to the placebo arm of the preceding trial. The reduction with amantadine one year earlier had been 60%). Motor complications occurring with the patients' regular oral levodopa regimen also remained improved according to the Unified Parkinson's Disease Rating Scale-IV. The beneficial effects of amantadine on motor response complications were maintained for at least one year after treatment initiation. Secondary: Dyskinesia ratings from videotapes scored by a second masked rater decreased by 43% with amantadine (3.6±0.6) compared to placebo (6.3±0.8; P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
was administered.			by a neurologist via watching a videotape	
Thomas et al.[36] (2004) Amantadine 300 mg per day vs placebo	DB, RCT Patients with severe Parkinson's disease and peak dose or dysphasic dyskinesia with or without pain levodopa-induced dyskinesia. All patients had also been receiving dopamine agonists as part of their treatment	N=40 9 months	Primary: Dyskinesia measured by the Unified Parkinson's Disease Rating Scale, the Dyskinesias Rating Scale, and an Investigator Global Assessment of dyskinesia; change in dyskinesia from study initiation to study end. Secondary: Scale score changes and the durations of the "on" and "off" states (periods when levodopa is exerting its effect vs periods when levodopa effect has worn off)	Primary: After 15 days of amantadine treatment, there was a reduction by 45% in the Dyskinesias Rating Scale total dyskinesia scores (P<0.001). Unified Parkinson's Disease Rating Scale scores also decreased significantly with amantadine as compared to placebo (P<0.01). Within the next eight months, all patients in the amantadine group withdrew from the study as dyskinesia increased according to all scales. By the time of withdrawal there were no significant changes in dyskinesia from study baseline. Three patients in the amantadine group withdrew because of side effects (tachycardia, psychosis, or livedo reticularis. Eighteen patients in the placebo group withdrew from the study within three months because dyskinesia had not improved or had gotten worse. The other two patients in the placebo group withdrew because of side effects. Secondary: Unified Parkinson's Disease Rating Scale I-III scores and "off" time were reduced and "on" time was increased in the amantadine group, but this improvement did not persist over the course of the study. Only the initial Unified Parkinson's Disease Rating Scale score reductions were statistically significant vs baseline and placebo (P<0.01).
Pappa et al.[37] (2010) Amantadine 100 mg up to 4 times per day for 2 weeks	DB, PC, XO Patients with tardive dyskinesia and stable psychiatric condition	N=22 4 weeks	Primary: Changes in Abnormal Involuntary Movements Scale Secondary:	Primary: After amantadine treatment, patients exhibited a reduced average score of total Abnormal Involuntary Movements Scale (from 13.5 to 10.5; P=0.000), of facial and oral Abnormal Involuntary Movements Scale (from 5.5 to 4.2; P=0.002), of extremity Abnormal Involuntary Movements Scale (from 4.18 to 2.8; P=0.000), and of severity Abnormal Involuntary Movements Scale (from 2.04 to 1.54; P=0.002).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo for 2 weeks			Not reported	With amantadine, the average total Abnormal Involuntary Movements Scale reduction was 21.81%. With placebo treatment, no reduction was noted. There were no serious adverse events during amantadine treatment. In the amantadine group, the following adverse events have occurred: insomnia in three patients, constipation in two patients, and dizziness in two patients. Secondary: Not reported
Crosby et al.[38] (2003) Amantadine as treatment for dyskinesia of idiopathic Parkinson's disease vs placebo	MA Patients of all ages with a diagnosis of idiopathic Parkinson's disease who had developed dyskinesia, patients were allowed to be on levodopa	N=53 (3 trials) >4 weeks	Primary: Changes in dyskinesia rating scales, number of withdrawals due to lack of efficacy and/or side effects Secondary: Not reported	Primary: Two of the three studies could not be analyzed for efficacy because of a lack of a washout period prior to the XO. In regards to the first study, two (8%) of the patients withdrew prior to the XO. In regards to the second study, four (22%) of the patients withdrew prior to the XO. Two of the patients complained of confusion or hallucinations, one complained of nausea, and one complained of a recurrence of pre-existing palpitations. The third study included a one week XO period so it was eligible to be analyzed for efficacy. No difference was found between amantadine in the first or second treatment period. Amantadine was associated with a decrease in dyskinesia severity score by 6.4 points (41%) following the levodopa challenge compared to the placebo arm. One patient experienced reversible edema of both feet during active amantadine treatment. Secondary: Not reported
Paci et al.[39] (2001) Amantadine as adjunctive therapy to current levodopa, carbidopa and	OL Patients with advanced Parkinson's disease complicated by motor fluctuations and levodopa-	N=20 8 months	Primary: Unified Parkinson's Disease Rating Scale, Dyskinesias Rating Scale, and investigator global assessment scale	Primary: Amantadine treatment was associated with a 38% reduction in motor fluctuations (P<0.001) and in the total dyskinesia score compared to baseline. Unified Parkinson's Disease Rating Scale subscale IV mean scores decreased from 10 to 6 (P<0.001), and Dyskinesias Rating Scale mean scores decreased from 18.5 to 7.5 (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
dopamine agonist therapy for severe Parkinson's disease	induced dyskinesia		Secondary: Not reported	The investigator global assessment scale for dyskinesia in patients using amantadine was rated 2.1. After 2-8 months of treatment, dyskinesia scores increased to – 2.2 leading to drug discontinuation in all patients. Secondary: Not reported
Wolf et al[40] (2010) Amantadine, individual daily dose vs placebo	DB, PC, PG, RCT Adult patients with a diagnosis of Parkinson's disease who had developed levodopa-induced dyskinesia and who had been receiving amantadine for ≥1 year	N=32 3 weeks	Primary: Change from baseline of dyskinesia duration and severity assessed by Unified Parkinson's Disease Rating Scale IV items 32 and 33 Secondary: Daily "on" time with troublesome dyskinesias, with non-troublesome dyskinesias and without dyskinesias and total daily "off" time as assessed in 24 hour self-scoring diaries; motor function during "on" periods; safety	Primary: Among the intent to treat population, placebo was associated with a significant increase in dyskinesia disability and duration after three weeks compared to baseline (3.1±1.9 vs 4.3±2.3; P=0.02), while there was no change with amantadine (3.2±2.0 vs 3.6±2.2; P=0.58). Similar results were obtained in the per protocol population (3.1±1.9 vs 4.4±2.3; P=0.02 and 3.2±2.0 vs 3.6±2.2; P=0.58). Among the intent to treat population, there was no difference between the two treatment groups (P=0.14). Secondary: There was no significant difference of "on" time with troublesome dyskinesia from baseline to week three with placebo (1.7±1.8 vs 3.5±3.1 hours; P=0.01). Dyskinesia duration increased significantly with placebo (1.8±1.2 vs 2.5±1.2 hours; P=0.026). There were no changes between baseline and end of treatment in any other secondary outcome with either treatment. There were a total of six adverse events reported by patients during the three weeks. One patient receiving amantadine reported falls and one patient receiving placebo reported a worsening of painful "off" period dystonia during the night. Three patients discontinued treatment earlier due to a worsening of dyskinesias; two receiving placebo and one receiving amantadine.

Drug regimen abbreviations: BID=twice daily, IV=intravenously, QD=once daily
Study abbreviations: DB=double blind, CI=confidence interval, HR=hazard ration, MA=meta-analysis, MC=multicenter, NS=not significant, PC=placebo-controlled, PG=parallel-group, OL=open label, OR=odds ratio, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, SC=single-center, XO=crossover

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 8. Relative Cost of the Adamantanes

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Amantadine	capsule, solution, tablet	N/A	N/A	$-$$
Rimantadine	tablet	Flumadine®*	N/A	$

*Generic is available in at least one dosage form or strength.
N/A=Not available.

X. Conclusions

The adamantanes are approved for the treatment and prophylaxis of influenza A virus infections. Amantadine and rimantadine are available in a generic formulation. Guidelines recommend the use of oseltamivir or zanamivir for the treatment and chemoprophylaxis of all influenza subtypes.[1-3] Due to the emergence of resistance, the adamantanes are not effective. Both amantadine and rimantadine have been shown to be effective for the treatment and chemoprophylaxis of influenza A in older clinical trials.[15-17,20,24,26-27,29,30] However, there are limited clinical trials that directly compare the efficacy and safety of these agents.[21] Due to the emergence of resistance since these studies were published, providers should refer to current treatment guidelines when making therapeutic decisions about the adamantanes.

Amantadine is also approved for the treatment of Parkinson's disease and drug-induced extrapyramidal reactions. Guidelines state that amantadine may be used; however, it is not considered a first-line treatment option.[7-13] According to the prescribing information, amantadine is less effective than levodopa for the treatment of

Parkinson's disease.[4-6] For the treatment of drug-induced extrapyramidal reactions, there is a lower incidence of anticholinergic adverse events with amantadine than anticholinergic antiparkinson drugs.[4-6]

Therefore, all brand adamantanes within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand adamantane is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Interferons
AHFS Class 081820
November 12, 2014

I. Overview

Interferons are naturally occurring proteins with antiviral, antiproliferative, and immunoregulatory properties.[1-7] They are produced and secreted in response to viral infections, as well as to a variety of other synthetic and biological inducers. They do not act directly on the virus, but bind to specific receptors on the cell surface, which activate multiple intracellular signaling pathways.

There are five interferon products included in this review. Interferon alfa-2b and interferon alfacon-1 are recombinant products, whereas interferon alpha-n3 is a purified, natural, human product. Peginterferon alfa-2a and peginterferon alfa-2b are covalently linked interferon alfa-2a and interferon alfa-2b molecules with polyethylene glycol. The attachment of polyethylene glycol (pegylation) reduces the rate of absorption and clearance, which extends the half-life of these products.[8] This allows for once weekly dosing as compared to three times per week dosing with the standard interferon alfa products. Pegylation also decreases the immunogenicity of the interferons.[8]

The interferons are primarily used for the treatment of chronic hepatitis B and hepatitis C. The hepatitis B virus (HBV) is a deoxyribonucleic acid (DNA) virus that is transmitted through exposure with infected blood and body fluids and is a leading cause of death from liver disease.[9-10] Acute infection occurs following HBV exposure and the infection generally clears after one to three months in immunocompetent individuals. However, chronic infections (≥6 months) are increased in immunocompromised patients and patients who are exposed early in life.[10] Treatment of acute infections is generally supportive and antiviral treatment is not indicated.[9] Treatment of chronic hepatitis B is determined by evidence of viral replication and liver injury.[9]

The hepatitis C virus (HCV) is an enveloped ribonucleic acid (RNA) virus that is transmitted through exposure with infected blood. HCV infection is one of the main causes of chronic liver disease worldwide, and the long-term impact of infection is highly variable, from minimal changes to extensive fibrosis and cirrhosis with or without hepatocellular carcinoma.[1] There are seven genotypes of HCV (genotypes 1 to 7), with genotype 1 being the most common in the United States, followed by genotypes 2 and 3.[11-12] There are differences in response to interferon-based therapy among the genotypes.[13] Genotype 1 is associated with a lower response to therapy and a longer duration of therapy is required.

The interferons that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. None of the interferons are available in a generic formulation. This class was last reviewed in May 2012.

Table 1. Interferons Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Interferon alfa-2b	injection	Intron® A	none
Interferon alfacon-1	injection	Infergen®	Infergen®
Interferon alfa-n3	injection	Alferon N®	none
Peginterferon alfa-2a	injection	Pegasys®	none
Peginterferon alfa-2b	injection	PegIntron®	PegIntron®

PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the interferons are summarized in Table 2.

Table 2. Treatment Guidelines Using the Interferons

Clinical Guideline	Recommendation(s)

American Association for the Study of Liver Diseases: **Chronic Hepatitis B Update (2009)**[14]	General information
	• The aims of treatment of chronic hepatitis B virus (HBV) are to achieve sustained suppression of HBV replication and remission of liver disease. The ultimate goal is to prevent cirrhosis, hepatic failure and hepatocellular carcinoma.
	• Parameters used to assess treatment response include normalization of serum alanine aminotransferase (ALT), decrease in serum HBV DNA level, loss of hepatitis B e antigen (HBeAg) with or without detection of anti-HBe, and improvement in liver histology.
	• Responses to antiviral therapy of chronic hepatitis B are categorized as biochemical (BR), virologic (VR), or histologic (HR), and as on-therapy or sustained off therapy.
	• Seven therapeutic agents have been approved for the treatment of adults with chronic hepatitis B in the United States. While interferons are administered for predefined durations, the nucleoside/nucleotide analogues (NAs) are usually administered until specific endpoints are achieved. The difference in approach is related to the additional immune modulatory effects of the interferons.
	
	General treatment recommendations
	• Patients with HBeAg-positive chronic hepatitis B with ALT >2 times normal or moderate/severe hepatitis on biopsy and HBV DNA >20,000 IU/mL should be considered for treatment.
	  o Treatment should be delayed for three to six months in persons with compensated liver disease to determine if spontaneous HBeAg seroconversion occurs.
	  o Patients with icteric ALT flares should be promptly treated.
	  o Treatment may be initiated with any of the seven approved antiviral medications, but peginterferon alfa, tenofovir, or entecavir are preferred.
	  o Clinical trials suggest that the efficacy of peginterferon alfa is similar to or slightly better than standard interferon alfa.
	• Patients with HBeAg-positive chronic hepatitis B and ALT persistently normal or minimally elevated (<2 times normal) generally should not be initiated on treatment.
	• Children with elevated ALT >2 times normal should be considered for treatment if ALT levels remain elevated at this level for longer than six months.
	  o Treatment may be initiated with interferon alfa or lamivudine.
	• Patients with HBeAg-negative chronic hepatitis B (serum HBV DNA >20,000 IU/mL and elevated ALT>2 times normal) should be considered for treatment.
	  o Liver biopsy may be considered for HBeAg-negative patients with lower HBV DNA levels (2,000 to 20,000 IU/mL) and borderline normal or minimally elevated ALT levels.
	  o Treatment may be initiated if there is moderate/severe inflammation or significant fibrosis on biopsy.
	  o Treatment may be initiated with any of the seven approved antiviral medications, but peginterferon alfa, tenofovir, or

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	entecavir are preferred in view of the need for long-term treatment. • Patients who failed to respond to prior interferon alfa (standard or pegylated) therapy may be retreated with nucleoside/nucleotide analogues (NA). • Patients who failed to achieve primary response as evidenced by <2 log decrease in serum HBV DNA level after at least six months of NA therapy should be switched to an alternative treatment or receive additional treatment. • In patients with inactive HBsAg carrier state, antiviral treatment is not indicated, but these patients should be monitored. <u>Patients who develop breakthrough infection while receiving NA therapy</u> • All patients with virologic breakthrough should be considered for rescue therapy. • For patients in whom there was no clear indication for hepatitis B treatment and who continue to have compensated liver disease, withdrawal of therapy may be considered but these patients need to be closely monitored and treatment reinitiated if they experience severe hepatitis flares. <u>Treatment of patients with lamivudine (or telbivudine)-resistant HBV</u> • If adefovir is used, lamivudine (or telbivudine) should be continued indefinitely to decrease the risk of hepatitis flares during the transition period and to reduce the risk of subsequent adefovir resistance. • If tenofovir is used, continuation of lamivudine (or telbivudine) is recommended to decrease the risk of subsequent antiviral resistance. • If entecavir is used, lamivudine or telbivudine should be stopped as continued presence of lamivudine- (or telbivudine-) resistant mutations will increase the risk of entecavir resistance. Entecavir is not an optimal therapy because of increasing risk of resistance to entecavir over time. <u>Treatment of patients with adefovir-resistant HBV</u> • In patients with no prior exposure to other NA, lamivudine, telbivudine, or entecavir may be added. Alternatively, adefovir may be stopped and tenofovir plus lamivudine or emtricitabine may be used. • In patients with prior lamivudine resistance in whom lamivudine had been stopped when treatment was switched to adefovir, adefovir may be stopped and tenofovir plus lamivudine, emtricitabine, or entecavir may be used but the durability of response to this combination is unknown. <u>Treatment of patients with entecavir-resistant HBV</u> • Adefovir or tenofovir can be used as it has been shown to have activity against entecavir-resistant HBV in *in vitro* studies, but clinical data are lacking. <u>Treatment of patients with compensated cirrhosis</u> • Treatment should be considered for patients with ALT >2 times normal, and for patients with normal or minimally elevated ALT if serum HBV DNA levels are high (>2,000 IU/mL). • Patients with compensated cirrhosis are best treated with NAs because of the risk of hepatic decompensation associated with interferon alfa–

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	related flares of hepatitis. In view of the need for long-term therapy, tenofovir or entecavir is preferred. <u>Treatment of patients with decompensated cirrhosis</u> • Treatment should be promptly initiated with a NA that can produce rapid viral suppression with low risk of drug resistance. • Lamivudine or telbivudine may be used as initial treatment in combination with adefovir or tenofovir to reduce the risk of drug resistance. • Entecavir or tenofovir alone would be an appropriate treatment in this setting but clinical data documenting their safety and efficacy in patients with decompensated cirrhosis are lacking. • Treatment should be coordinated with a transplant center. • Interferon alfa or peginterferon alfa should not be used in patients with decompensated cirrhosis. <u>Treatment duration</u> • The recommended treatment duration for HBeAg-positive chronic hepatitis B is 16 weeks for standard interferon alfa and 48 weeks for peginterferon alfa. • The recommended treatment duration for HBeAg-negative chronic hepatitis B is 48 weeks for both standard and peginterferon alfa. • Treatment with NAs should be continued until the patient has achieved HBeAg seroconversion and undetectable serum HBV (for patients with HBeAg-positive chronic hepatitis B). For patients with HBeAg-negative chronic hepatitis B, treatment should be continued until the patient has achieved HBsAg clearance. For patients with compensated cirrhosis, treatment should be received long-term. However, treatment may be stopped in HBeAg-positive patients if they have confirmed HBeAg seroconversion and have completed at least six months of consolidation therapy and in HBeAg-negative patients if they have confirmed HBsAg clearance. For patients with decompensated cirrhosis and recurrent hepatitis B post–liver transplantation, life-long treatment is recommended. <u>Recommendations for treatment of patients with HBV/HIV coinfection</u> • Patients who meet criteria for chronic hepatitis B should be treated. • Patients who are not on highly active antiretroviral therapy (HAART) and are not anticipated to require HAART in the near future should be treated with an antiviral therapy that does not target HIV, such as peginterferon alfa or adefovir. Although telbivudine does not target HIV, it should not be used in this circumstance. • Patients in whom treatment for both HBV and HIV is planned should receive therapies that are effective against both viruses: lamivudine plus tenofovir or emtricitabine plus tenofovir are preferred. • Patients who are already on effective HAART that does not include a drug active against HBV may be treated with peginterferon alfa or adefovir. • In patients with lamivudine resistance, tenofovir should be added. <u>Recommendations for treatment of hepatitis B carriers who require immunosuppressive or cytotoxic therapy</u> • Prophylactic antiviral therapy is recommended for HBV carriers at the onset of cancer chemotherapy or of a finite course of

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	immunosuppressive therapy. • Patients with baseline HBV DNA<2,000 IU/mL level should continue treatment for six months after completion of chemotherapy or immunosuppressive therapy. • Patients with high baseline HBV DNA (>2,000 IU/mL) level should continue treatment until they reach treatment endpoints as in immunocompetent patients. • Lamivudine or telbivudine can be used if the anticipated duration of treatment is short (<12 months) and baseline serum HBV DNA is not detectable. • Tenofovir or entecavir is preferred if longer duration of treatment is anticipated. • Interferon alfa should be avoided in view of the bone marrow suppressive effect. <u>Recommendations for treatment of patients with acute symptomatic hepatitis B</u> • Treatment is only indicated for patients with fulminant hepatitis B and those with protracted, severe acute hepatitis B. • Lamivudine or telbivudine may be used when the anticipated duration of treatment is short; otherwise, entecavir is preferred. • Treatment should be continued until HBsAg clearance is confirmed or indefinitely in those who undergo liver transplantation. • Interferon alfa therapy is contraindicated.

American Association for the Study of Liver Diseases, Infectious Diseases Society of America, and International Antiviral Society-USA: **Recommendations for testing, managing, and treating hepatitis C (2014)**[15]	• It may be advisable to delay treatment for some patients with documented early fibrosis stage (F0 to 2), because waiting for future highly effective, pangenotypic, direct-acting antiviral combinations in interferon-free regimens may be prudent. Potential advantages of waiting to begin treatment will be provided in a future consensus guideline update.
	• A regimen is classified as either "recommended" when it is favored for most patients or "alternative" when optimal in a particular subset of patients in that category. When a treatment is clearly inferior or is deemed harmful, it is classified as "not recommended."
	• Recommendations for peginterferon alfa and ribavirin relapsers are the same as for treatment-naïve persons as described below.
	• Interferon ineligible criteria:
	  o Intolerance to interferon alfa.
	  o Autoimmune hepatitis and other autoimmune disorders.
	  o Hypersensitivity to peginterferon alfa or any of its components.
	  o Decompensated hepatic disease.
	  o Major uncontrolled depressive illness.
	  o A baseline neutrophil count below 1,500/µL, a baseline platelet count below 90,000/µL, or baseline hemoglobin below 10 g/dL.
	  o A history of preexisting cardiac disease.
	
	<u>When and in whom to initiate HCV therapy</u>
	• Treatment is recommended for patients with chronic HCV infection.
	• Liver-related complications in which HCV treatment is most likely to provide the most immediate and impactful benefits are assigned “highest” and “high” priorities.
	• Highest priority due to highest risk for severe complications:

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	o Advanced fibrosis (F3) or compensated cirrhosis (F4) o Organ transplant recipients o Severe extrahepatic hepatitis C (type 2 or 3 essential mixed cryoglobulinemia with end-organ manifestations e.g., vasculitis) o Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis • High priority due to high risk for complications: o Fibrosis (F2) o Human immunodeficiency virus (HIV) or hepatitis B virus (HBV)-coinfection o Other coexistent liver disease (e.g., non-alcoholic steatohepatitis) o Debilitating fatigue o Type 2 Diabetes mellitus (insulin resistant) o Porphyria cutanea tarda • Persons whose risk of HCV transmission is high and in whom HCV treatment may yield transmission reduction benefits: o Men who have sex with men with high-risk sexual practices o Active injection drug users o Incarcerated persons o Persons on long-term hemodialysis • Factors associated with accelerated fibrosis progression: o Fibrosis stage o Inflammation grade o Older age at time of infection o Male sex o Organ transplant o Alcohol consumption o Nonalcoholic fatty liver disease o Obesity o Insulin resistance o Genotype 3 o HIV or HBV-coinfection <u>Treatment of HCV genotype 1 in treatment-naïve patients and relapsers with prior peginterferon alfa and ribavirin</u> • Recommended treatments: o Interferon eligible: sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. o Interferon ineligible: sofosbuvir plus simeprevir with or without ribavirin for 12 weeks. • Alternative treatments: o Interferon eligible: simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks (for genotype 1a, baseline resistance testing for Q80K should be performed and alternative treatments considered if this mutation is present). o Interferon ineligible: sofosbuvir plus ribavirin for 24 weeks. • Treatments that are not recommended: o Boceprevir or telaprevir plus peginterferon alfa and ribavirin for 24 or 48 weeks. o Peginterferon alfa and ribavirin for 48 weeks. o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral.

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	Treatment of HCV genotype 2 in treatment-naïve patients and relapsers with prior peginterferon alfa and ribavirin • Recommended treatments: o Sofosbuvir plus ribavirin for 12 weeks. • Alternative treatments: o None. • Treatments that are not recommended: o Peginterferon alfa and ribavirin for 24 weeks. o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. o Any regimen with boceprevir, telaprevir, or simeprevir. Treatment of HCV genotype 3 in treatment-naïve patients and relapsers with prior peginterferon alfa and ribavirin • Recommended treatments: o Sofosbuvir plus ribavirin for 24 weeks. • Alternative treatments: o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Treatments that are not recommended: o Peginterferon alfa and ribavirin for 24 to 48 weeks. o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. o Any regimen with boceprevir, telaprevir, or simeprevir. Treatment of HCV genotype 4 in treatment-naïve patients and relapsers with prior peginterferon alfa and ribavirin • Recommended treatments: o Interferon eligible: sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. o Interferon ineligible: sofosbuvir plus ribavirin for 24 weeks. • Alternative treatments: o Simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 to 48 weeks. • Treatments that are not recommended: o Peginterferon alfa and ribavirin for 48 weeks. o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. o Any regimen with boceprevir or telaprevir. Treatment of HCV genotype 5 or 6 in treatment-naïve patients and relapsers with prior peginterferon alfa and ribavirin • Recommended treatments: o Interferon eligible: sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Alternative treatments: o Peginterferon alfa and ribavirin for 48 weeks. • Treatments that are not recommended: o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. o Any regimen with boceprevir or telaprevir. Recommendations for patients with HCV genotype 1 with prior null or partial response to peginterferon alfa and ribavirin

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	• Recommended treatments:
	  o Sofosbuvir plus simeprevir with or without ribavirin for 12 weeks.
	• Alternative treatments:
	  o Sofosbuvir for 12 weeks plus peginterferon alfa and ribavirin for 12 to 24 weeks.
	  o Sofosbuvir plus ribavirin for 24 weeks.
	  o Simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks (for genotype 1a, baseline resistance testing for Q80K should be performed and alternative treatments considered if this mutation is present).
	• Treatments that are not recommended:
	  o Boceprevir or telaprevir plus peginterferon alfa and ribavirin.
	  o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral.
	
	<u>Recommendations for patients with HCV genotype 1 with prior null or partial response to peginterferon alfa and ribavirin plus either boceprevir or telaprevir</u>
	• Recommended treatments:
	  o Sofosbuvir for 12 weeks plus peginterferon alfa and ribavirin for 12 to 24 weeks.
	• Alternative treatments:
	  o Interferon eligible: Sofosbuvir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks.
	  o Interferon ineligible: Sofosbuvir plus ribavirin for 24 weeks.
	• Treatments that are not recommended:
	  o Boceprevir, simeprevir, or telaprevir plus peginterferon alfa and ribavirin.
	  o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral.
	  o A recommendation for simeprevir use for patients with previous telaprevir or boceprevir exposure has not been provided due to potential risk of preexistent resistance to protease inhibitor treatment.
	
	<u>Recommendations for patients with HCV genotype 2 with prior null or partial response to peginterferon alfa and ribavirin</u>
	• Recommended treatments:
	  o Sofosbuvir plus ribavirin for 12 weeks;
	  ▪ In treatment-experienced cirrhotics only, the decision to extend therapy to 16 weeks should be made on a case-by-case basis.
	• Alternative treatments:
	  o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks (cirrhotics only)
	• Treatments that are not recommended:
	  o Boceprevir or telaprevir plus peginterferon alfa and ribavirin.
	  o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral.
	
	<u>Recommendations for patients with HCV genotype 3 with prior null or partial response to peginterferon alfa and ribavirin</u>
	• Recommended treatments:

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	o Sofosbuvir plus ribavirin for 24 weeks. • Alternative treatments: o Sofosbuvir plus ribavirin for 16 weeks (cirrhotics only). o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Treatments that are not recommended: o Peginterferon alfa and ribavirin with or without protease inhibitor. o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. <u>Recommendations for patients with HCV genotype 4 with prior null or partial response to peginterferon alfa and ribavirin</u> • Recommended treatments: o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Alternative treatments: o Sofosbuvir plus ribavirin for 24 weeks. • Treatments that are not recommended: o Peginterferon alfa and ribavirin with or without protease inhibitor o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. <u>Recommendations for patients with HCV genotype 5 or 6 with prior null or partial response to peginterferon alfa and ribavirin</u> • Recommended treatments: o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Alternative treatments: o None. • Treatments that are not recommended: o Peginterferon alfa and ribavirin with or without protease inhibitor. o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. <u>Initial treatment of human immunodeficiency virus (HIV)/HCV co-infected patients with HCV genotype 1 who are treatment-naïve or prior peginterferon alfa and ribavirin relapsers</u> • Recommended treatments: o Interferon eligible: sofosbuvir plus peginterferon and ribavirin for 12 weeks. o Interferon ineligible: ▪ Sofosbuvir plus ribavirin for 24 weeks. ▪ Sofosbuvir plus simeprevir with or without ribavirin for 12 weeks. • Alternative treatments: o Interferon eligible: simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks (for genotype 1a, baseline resistance testing for Q80K should be performed and alternative treatments considered if this mutation is present). o Interferon ineligible: none. • Treatments that are not recommended: o Boceprevir or telaprevir plus peginterferon alfa and ribavirin for 24 or 48 weeks. o Peginterferon alfa and ribavirin for 48 weeks.

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	o Simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 48 weeks. • Allowable antiretroviral therapy: o For sofosbuvir use: all except didanosine, zidovudine, or tipranavir. o For simeprevir use: limited to raltegravir, rilpivirine, maraviroc, enfuvirtide, tenofovir, emtricitabine, lamivudine, abacavir. <u>Recommendations for HIV/HCV co-infected patients with HCV genotype 1 with prior null or partial response to peginterferon alfa and ribavirin</u> • Recommended treatments: o Sofosbuvir plus simeprevir with or without ribavirin for 12 weeks. • Alternative treatments: o Interferon eligible: sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. o Interferon ineligible: sofosbuvir plus ribavirin for 24 weeks. • Treatments that are not recommended: same as for treatment-naïve or prior peginterferon alfa and ribavirin relapsers above. • Allowable antiretroviral therapy: same as for treatment-naïve or prior peginterferon alfa and ribavirin relapsers above. <u>Treatment of HIV/HCV co-infected patients with HCV genotype 2</u> • Recommended treatments (regardless of treatment history): o Sofosbuvir plus ribavirin for 12 weeks. • Alternative treatments: o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks (only in prior nonresponders to peginterferon alfa and ribavirin eligible for peginterferon alfa). • Treatments that are not recommended: o Peginterferon alfa and ribavirin for 24 to 48 weeks. o Any regimen with boceprevir, telaprevir, or simeprevir. o Allowable antiretroviral therapy: same as above. <u>Treatment of HIV/HCV co-infected patients with HCV genotype 3</u> • Recommended treatments (regardless of treatment history): o Sofosbuvir plus ribavirin for 24 weeks. • Alternative treatments: o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks (only in prior nonresponders to peginterferon alfa and ribavirin eligible for peginterferon alfa). • Treatments that are not recommended: o Peginterferon alfa and ribavirin for 24 to 48 weeks. o Any regimen with boceprevir, telaprevir, or simeprevir. o Allowable antiretroviral therapy: same as above. <u>Treatment of HIV/HCV co-infected patients with HCV genotype 4</u> • Recommended treatments (regardless of treatment history): o Interferon eligible: sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. o Interferon ineligible: sofosbuvir plus ribavirin for 24 weeks. • Alternative treatments: o None.

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	• Treatments that are not recommended:
	  o Peginterferon alfa and ribavirin for 48 weeks.
	  o Any regimen with boceprevir, telaprevir, or simeprevir.
	  o Allowable antiretroviral therapy: same as above.
	
	Treatment of HIV/HCV co-infected patients with HCV genotype 5 or 6
	• Recommended treatments (regardless of treatment history):
	  o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks.
	• Alternative treatments:
	  o None.
	• Treatments that are not recommended:
	  o Peginterferon alfa and ribavirin for 48 weeks.
	  o Any regimen with boceprevir, telaprevir, or simeprevir.
	  o Allowable antiretroviral therapy: same as above.
	
	Treatment of patients with cirrhosis
	• Treatment-naive patients with compensated cirrhosis, including those with hepatocellular carcinoma, should receive the same treatment as recommended for patients without cirrhosis.
	• Patients with decompensated cirrhosis (moderate or severe hepatic impairment; Child Turcotte Pugh class B or C) should be referred to a medical practitioner with expertise in that condition (ideally in a liver transplant center).
	• Recommended regimen for patients with any HCV genotype who have decompensated cirrhosis (moderate or severe hepatic impairment; Child Turcotte Pugh class B or C) who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma.
	  o Sofosbuvir plus weight-based ribavirin (with consideration of the patient's creatinine clearance and hemoglobin level) for up to 48 weeks.
	  o This regimen should be used only by highly experienced HCV provider.
	• The following regimens are not recommended for patients with decompensated cirrhosis (moderate or severe hepatic impairment; Child Turcotte Pugh class B or C):
	  o Any interferon-based therapy.
	  o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral.
	  o Telaprevir, boceprevir, or simeprevir-based regimens.
	
	Treatment of patients who develop recurrent HCV infection post-liver transplant
	• Recommended regimen for treatment-naive patients with HCV genotype 1 in the allograft liver, including those with compensated cirrhosis.
	  o Sofosbuvir plus simeprevir with or without dose-adjusted ribavirin for 12 to 24 weeks.
	• Alternate regimen for treatment-naive patients with genotype 1 HCV in the allograft liver, including those with compensated cirrhosis.
	  o Sofosbuvir and dose-adjusted ribavirin (with consideration of the patient's creatinine clearance and hemoglobin level), with or without peginterferon alfa, for 24 weeks.
	• Recommended regimen for treatment-naive patients with HCV genotype 2 or 3 in the allograft liver, including those with compensated

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	cirrhosis. o Sofosbuvir plus dose-adjusted ribavirin (with consideration for creatinine clearance and hemoglobin level) for 24 weeks. • Treatment-naive patients with decompensated allograft HCV infection should receive the same treatment as recommended for patients with decompensated cirrhosis (moderate or severe hepatic impairment; Child Turcotte Pugh class B or C).
Department of Veterans Affairs National Hepatitis C Resource Center Program and the Office of Public Health: **HCV Infection: Treatment Considerations (2014)**[16]	Treatment considerations • The urgency of treating HCV should be based on the risk of developing decompensated cirrhosis or dying from liver or liver-related disease, and prolonging graft survival in liver transplant recipients. • Urgent treatment should be considered in patients with advanced cirrhosis, selected patients with hepatocellular carcinoma awaiting liver transplant, post-transplant recipients with cirrhosis, and patients with serious extra-hepatic manifestations of HCV. • Patients with mild liver disease (F0 to F2) may consider waiting until newer therapies are available that may improve the chance of treatment success and reduce treatment-related adverse effects; approval is anticipated over the next 12 to 24 months. • Factors that may complicate adherence, such as active substance abuse, neurocognitive disorders, and lack of social support, should be addressed before initiating medications. • Sofosbuvir or simeprevir should not be used as monotherapy or in reduced dosages; neither drug should be restarted if discontinued. • Interferon ineligible or intolerant criteria: o Platelet count <75,000/mm^3. o Decompensated liver cirrhosis (Child Turcotte Pugh class B or C). o Severe mental health conditions that may be exacerbated by interferon or may respond poorly to medical therapy. o Autoimmune diseases that may be exacerbated by interferon-mediated immune modulation. o Inability to complete a prior treatment course due to documented interferon-related adverse effects. • Treatment of patients with HCV/HIV co-infection is similar to that of HCV mono-infected patients. Drug-drug interactions must be carefully considered. Treatment of HCV genotype 1 in treatment-naïve, non-cirrhotic or cirrhotic interferon eligible patients • Preferred regimen: o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Alternative regimen: o Simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks (do not use in genotype 1a with Q80K polymorphism). Treatment of HCV genotype 1 in treatment-naïve, non-cirrhotic interferon ineligible patients • Preferred regimens: o Sofosbuvir plus ribavirin for 24 weeks. o Sofosbuvir plus simeprevir with or without ribavirin for 12 weeks.

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	• Alternative regimen:
	  o None.
	
	Treatment of HCV genotype 1 in treatment-naïve, cirrhotic interferon ineligible patients
	• Preferred regimen:
	  o Sofosbuvir plus simeprevir with or without ribavirin for 12 weeks.
	• Alternative regimen:
	  o None.
	
	Treatment of HCV genotype 1 in treatment-experienced, non-cirrhotic interferon eligible patients
	• Preferred regimen:
	  o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks.
	• Alternative regimen:
	  o Simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks (relapsers) or 48 weeks (prior partial or null responders); do not use in genotype 1a with Q80K polymorphism or previous failure of boceprevir- or telaprevir-based therapy.
	
	Treatment of HCV genotype 1 in treatment-experienced, cirrhotic interferon eligible patients
	• Preferred regimen:
	  o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks.
	• Alternative regimen (peginterferon alfa and ribavirin null responders only):
	  o Sofosbuvir plus simeprevir with or without ribavirin for 12 weeks.
	
	Treatment of HCV genotype 1 in treatment-experienced, non-cirrhotic or cirrhotic interferon ineligible patients
	• Preferred regimen:
	  o Sofosbuvir plus simeprevir with or without ribavirin for 12 weeks.
	• Alternative regimen:
	  o None.
	
	Treatment of HCV genotype 2 in treatment-naïve patients
	• Preferred regimen:
	  o Sofosbuvir plus ribavirin for 12 weeks.
	• Alternative regimen:
	  o None.
	
	Treatment of HCV genotype 2 in treatment-experienced patients
	• Preferred regimens:
	  o Sofosbuvir plus ribavirin for 12 to 16 weeks.
	  o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks (interferon eligible only).
	• Alternative regimen:
	  o None.
	
	Treatment of HCV genotype 3 in treatment-naïve patients

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	• Preferred regimens:
	  o Sofosbuvir plus ribavirin for 24 weeks.
	• Alternative regimen:
	  o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks (interferon eligible only).
	
	Treatment of HCV genotype 3 in treatment-experienced cirrhotic patients
	• Preferred regimens:
	  o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks (interferon eligible only).
	• Alternative regimen:
	  o Sofosbuvir plus ribavirin for 24 weeks (interferon ineligible only).
	
	Treatment of HCV genotype 1, 2, 3, or 4 in patients with hepatocellular carcinoma
	• Preferred regimens:
	  o Sofosbuvir plus ribavirin for 24 to 48 weeks or until liver transplant, whichever occurs first.
	• Alternative regimen:
	  o None.
	
	Treatment of patients with HCV genotype 1, 2, 3, or 4 infection post-liver transplant
	• Sofosbuvir plus ribavirin with or without peginterferon for 24 weeks
	
	Treatment of patients with HCV genotype 1, 2, 3, or 4 infection post-other solid organ transplant (kidney, heart, or lung)
	• Discuss with transplant center. Do not use peginterferon-containing regimens. Sofosbuvir has not been studied in non-liver transplant recipients.
	
	Discontinuing HCV treatment based on lack of virologic response
	• Patients receiving sofosbuvir-based regimen should have HCV ribonucleic acid (RNA) assessed at week 4 of treatment; if the HCV RNA is detectable at week 4 or at any time point thereafter, reassess HCV RNA in 2 weeks. If the repeated HCV RNA increased (i.e., >1 $\log_{10}$ IU/mL from nadir) or if the HCV RNA is ≥25 IU/mL at week 8 of therapy, discontinuation of all treatment should be strongly considered.
	• Patients receiving simeprevir plus peginterferon and ribavirin regimen should have HCV RNA levels assessed at week 4, 12, and 24; if the HCV RNA is ≥25 IU/mL at any of these time points, all treatment should be discontinued.
	
	Use in renal insufficiency
	• Sofosbuvir use is not recommended if creatinine clearance <30 mL/min or end-stage renal disease due to insufficient safety and efficacy data.
	• No simeprevir dose adjustment is needed if creatinine clearance <30 mL/min.
	• Peginterferon alfa-2a dosage should be reduced to 135 µg/week once weekly for creatinine clearance <30 mL/min, including hemodialysis.
	• Peginterferon alfa-2b dosage should be reduced by 25% for creatinine

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	clearance 30 to 50 mL/min and by 50% for creatinine clearance <30 mL/min, including hemodialysis. • Ribavirin should be dosed at 200 mg daily alternating with 400 mg daily for creatinine clearance 30 to 50 mL/min and 200 mg daily for creatinine clearance <30 mL/min, including hemodialysis. Use in hepatic impairment • No simeprevir dosage recommendation can be provided in moderate to severe hepatic impairment (Turcotte Pugh Class B or C) due to higher simeprevir exposures. • No sofosbuvir dosage adjustment in required for patients with any degree of renal impairment. • Peginterferon alfa use is not recommended in patients with moderate or severe hepatic impairment (Turcotte Pugh Class B or C). Mental health and substance-use disorders • Patients with severe mental health conditions (e.g., psychotic disorders, bipolar disorder, major depression, posttraumatic stress disorder) who are engaged in mental health treatment should be considered for therapy on a case-by-case basis; interferon use may worsen these conditions. Substance or alcohol use • The presence of current heavy alcohol use (>14 drinks per week for men or >7 drinks per week for women), binge alcohol use (>4 drinks per occasion at least once per month), or active injection drug use warrants referral to an addiction specialist before treatment initiation. • There are no published data supporting minimal length of abstinence as an inclusion criterion for HCV antiviral treatment. • Patients with active substance- or alcohol-use disorders should be considered for therapy on a case-by-case basis and care should be coordinated with substance-use treatment specialist.
Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program Office: **Update on the management and treatment of hepatitis C virus infection (2012)**[17]	Recommendations in patients being considered for HCV therapy • All patients with chronic HCV infection should be evaluated for HCV antiviral treatment. • Patients should be counseled on their likelihood of achieving SVR, based upon individual factors such as body mass index, genotype, race, stage of fibrosis, and viral load before initiating therapy. • IL28B genotype testing can be performed before peginterferon-ribavirin therapy with or without a protease inhibitor, if the results would alter treatment decisions. Recommendations for treatment-naïve patients with genotype 1 infection • Peginterferon alfa and ribavirin, in combination with boceprevir (800 mg three times daily with food) or telaprevir (750 mg three times daily with 20 grams of fat), is the standard of care for most treatment-naïve genotype 1-infected patients. • If a telaprevir-containing regimen is used in treatment-naïve noncirrhotic patients who achieve an extended rapid virologic response (eRVR), telaprevir should be discontinued at week 12 and peginterferon-ribavirin should be continued for an additional 12 weeks. If HCV RNA is detectable at week four, but <1,000 IU/mL and remains <1,000 IU/mL or becomes undetectable at week 12, telaprevir should be discontinued at week 12, and peginterferon-ribavirin can be

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	continued for another 36 weeks. • If a telaprevir-containing regimen is used in treatment-naïve cirrhotics who achieve an HCV RNA that is undetectable or <1,000 IU/mL at treatment weeks four and 12, telaprevir should be discontinued at week 12, and peginterferon-ribavirin can be continued for 36 more weeks. • If a boceprevir-containing regimen is used in treatment-naïve noncirrhotics, if HCV RNA declines by ≥1 $\log_{10}$ during the four-week lead-in, and HCV RNA is undetectable at weeks eight to 24, treatment with boceprevir-peginterferon-ribavirin for 24 weeks is sufficient. If HCV RNA is detectable at week eight, but <100 IU/mL at week 12, and negative at week 24, boceprevir-peginterferon-ribavirin should be continued until week 36, followed by peginterferon-ribavirin alone for 12 more weeks. If HCV RNA declines by <1 $\log_{10}$ during the lead-in, boceprevir-peginterferon-ribavirin can be continued for 44 weeks. • If a boceprevir-containing regimen is used in treatment-naïve cirrhotics, 44 weeks of boceprevir-peginterferon-ribavirin is required after the four-week lead-in. <u>Recommendations for treatment of nonresponders and relapsers with genotype 1 infection</u> • For patients who previously failed peginterferon-ribavirin, retreatment with boceprevir or ribavirin and peginterferon-ribavirin may be considered, particularly in patients who were relapsers. • If a boceprevir-containing regimen is used for retreatment of noncirrhotic prior partial responders or relapsers, the treatment duration is 36 weeks if HCV RNA is undetectable from weeks eight to 24. If HCV RNA is detectable at week 12, but <100 IU / mL and is undetectable from weeks 24 to 36, boceprevir can be discontinued at week 36 and peginterferon-ribavirin can be continued for an additional 12 weeks. • If a boceprevir-containing regimen is used for re-treatment in cirrhotics, the treatment duration is 48 weeks if HCV RNA is detectable at week 12, but <100 IU/mL, and becomes undetectable from weeks 24 to 36. • If a boceprevir-containing regimen is used for retreatment of prior null responders, the treatment duration is 48 weeks if HCV RNA is detectable at week 12, but <100 IU/mL, and becomes undetectable from weeks 24 to 36. • If a telaprevir-containing regimen is used for retreatment of prior relapsers, and HCV RNA is undetectable from weeks four and 12, telaprevir should be discontinued at week 12 and peginterferon-ribavirin should be continued for an additional 12 weeks. If HCV RNA is detectable, but <1,000 IU/mL at week four and/or 12, telaprevir can be discontinued at week 12, and peginterferon-ribavirin can be continued for an additional 36 weeks. • If a telaprevir-containing regimen is used for re-treatment of prior partial responders or null responders, and HCV RNA is <1,000 IU/mL at weeks four and 12, telaprevir should be discontinued at week 12 and peginterferon-ribavirin should be continued for an additional 36 weeks. <u>Recommendations for dose modification</u> • Peginterferon alfa and ribavirin doses should be reduced in response to decreases in white blood cells, neutrophils, hemoglobin or platelets. • If ribavirin is stopped for seven or more days in patients concomitantly

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	receiving boceprevir or telaprevir, then the protease inhibitor should also be permanently discontinued. The protease inhibitors should be either continued at full dose or discontinued.
	• A ribavirin dose reduction should be used as initial management of HCV treatment-related anemia in a symptomatic patient with a hemoglobin <10 g/dL. Erythropoietin may be administered in patients with symptomatic anemia related to peginterferon-ribavirin therapy with or without protease inhibitors to limit anemia-related ribavirin dose reductions or dose discontinuations.
	• A peginterferon dose reduction should be used as initial management of HCV treatment-related neutropenia (an absolute neutrophil count of <750, or as clinically indicated). Granulocyte colony-stimulating factor should not be given as primary therapy to prevent peginterferon alfa dose reductions.
	
	<u>Recommendations for treatment monitoring</u>
	• Patients should be monitored for treatment-related adverse effects at least every two weeks early in the course of therapy, and every one to two months during treatment as clinically indicated.
	• Assessment of treatment adherence and screening for depression, suicidal ideation, alcohol, and illicit drug use should be performed at every visit.
	• Patients should be counseled about avoiding pregnancy through the use of two forms of contraception during treatment and for six months posttreatment. If a patient is receiving a boceprevir- or telaprevir-containing regimen, two alternative effective methods of contraception, such as intrauterine devices and barrier methods, should be used in at-risk patients and partners during and for at least six months after treatment.
	• In patients receiving telaprevir-peginterferon-ribavirin, all treatment should be stopped if any of the following occur:
	  o HCV RNA level >1,000 IU/mL at week four or 12.
	  o Detectable HCV RNA levels at week 24 or at any time point thereafter.
	  o HCV RNA rebounds at any time point (≥1 $\log_{10}$ increase from the nadir HCV RNA).
	• In patients receiving boceprevir-peginterferon-ribavirin, all treatment should be stopped if any of the following occur:
	  o HCV RNA level ≥100 IU/mL at week 12 with a boceprevir-containing regimen.
	  o Detectable HCV RNA levels at week 24 or at any time point thereafter.
	  o HCV RNA rebounds at any time point (≥1 $\log_{10}$ increase from the nadir HCV RNA).
	• Do not switch to the other protease inhibitor if virologic failure occurs with one protease inhibitor.
	
	<u>Recommendations for groups with special considerations for therapy</u>
	• Peginterferon alfa monotherapy may be used to treat patients with contraindications to ribavirin.
	• For patients who achieve RVR and have a low baseline viral load (HCV RNA <400,000 IU/mL), 24-weeks of treatment with peginterferon-ribavirin may be sufficient.
	• Treatment can be deferred in patients with minimal inflammation

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	and/or minimal portal fibrosis on liver biopsy. • HCV genotype 1-infected patients with compensated cirrhosis (Child-Pugh Class <7), adequate neutrophils (>1.5 k/mm^3), and adequate platelet counts (>75 k/mm^3) should be considered for treatment with boceprevir (for 44 weeks) or telaprevir (for 12 weeks) combined with peginterferon-ribavirin at standard doses for 48 weeks. • Patients with cirrhosis continue to be at risk for hepatocellular carcinoma and should undergo routine screening regardless of viral clearance status. <u>Recommendations for treatment-naïve and -experienced patients with genotype 2 or 3 infection</u> • Treatment-naïve patients should be treated with peginterferon-ribavirin for 24 weeks. • For patients with low viral load (HCV RNA <600,000 IU/mL) and mild fibrosis who achieve a RVR, 12 to 18 weeks of treatment may be sufficient. • For patients with genotype 3 infection and a high HCV RNA (>600,000 IU/mL), steatosis or advanced fibrosis, treatment beyond 24 weeks may improve response. • Retreatment duration is 48 weeks. <u>Recommendations in patients with genotype 4 infection</u> • Appropriate candidates with HCV genotype 4 infections should be treated with peginterferon alfa-2a 180 µg per week or peginterferon alfa-2b 1.5 µg / kg per week, plus ribavirin up to 1,400 mg per day for 48 weeks. <u>Recommendations in patients with decompensated cirrhosis</u> • Liver transplantation is the treatment of choice in patients with decompensated cirrhosis. • Antiviral therapy is contraindicated in most patients with decompensated cirrhosis. • Interferon-based therapy in combination with ribavirin can be considered for patients awaiting liver transplantation if they have a Child-Pugh score <7 and a Model for End-Stage Liver Disease score ≤18. • If beginning antiviral therapy, the interferon dose should be reduced and growth factors may be used to for treatment-associated cytopenias. <u>Recommendations in patients following solid organ transplantation</u> • Interferon-based antiviral therapy is contraindicated in patients who have received a heart, lung or kidney transplant. • In patients with biopsy-proven chronic HCV disease following liver transplantation, peginterferon-ribavirin for 48 weeks may be considered. • Monitor antiviral therapy in post-liver transplant patients on antiviral therapy and discontinue if rejection is documented. Pre-emptive antiviral therapy early post-transplantation in patients without histological recurrence should be avoided. <u>Recommendations in patients with renal disease</u> • Considered modified doses of antiviral therapy with interferon (standard or pegylated).

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	• Antiviral therapy for HCV treatment is not recommended in patients following renal transplant; however, it may be considered if patients develop fibrosing cholestatic hepatitis. Recommendations in patients with comorbid conditions • Antiviral therapy is not recommended in patients with a limited life expectancy. In addition, peginterferon-ribavirin, treatment should be avoided in comorbid conditions that may be exacerbated by treatment. Recommendations for patients on methadone • Antiviral therapy should be offered to patients enrolled in a methadone maintenance program who meet criteria for therapy. Coordinated HCV treatment between providers and substance abuse specialists should occur. Recommendations in patients with ongoing alcohol use • Encourage patients to decrease alcohol consumption or to abstain, and refer for behavioral intervention to reduce alcohol use. Antiviral therapy may be used in patients who are otherwise appropriate candidates, regardless of prior alcohol use. Alcohol reduces adherence and treatment response. Recommendations in obese patients and those with hepatic steatosis • Patients with a body mass index >30 should be considered for antiviral treatment. Control comorbid conditions prior to initiation of antiviral therapy. Recommendations in patients with human immunodeficiency virus (HIV)/HCV coinfection • Patients with controlled HIV infection and evidence of liver disease on biopsy should be considered for HCV antiviral therapy. Treatment should consist of peginterferon-ribavirin at doses similar to those with HCV for a duration of 48 weeks. Recommendations in patients with acute HCV infection • Observe patients for eight to 20 weeks from time of initial exposure to monitor for spontaneous resolution of infection. • In patients who fail to resolve infection spontaneously, treatment with peginterferon alfa, with or without ribavirin for 24 to 48 weeks should be used, based on genotype and HCV RNA response during therapy.
European Association for the Study of the Liver: **Treatment of Hepatitis (2014)**[18]	Goals and endpoints of HCV therapy • The goal of therapy is to eradicate HCV infection, to prevent hepatic cirrhosis, decompensation of cirrhosis, hepatocellular carcinoma, and death. • The endpoint of therapy is SVR, defined by undetectable HCV RNA 12 and 24 weeks after the end of treatment; SVR usually equates to cure of infection in more than 99% of patients. • Both SVR 12 and SVR 24 have been accepted in the US and Europe, given that their concordance is 99%. Indications for treatment • All treatment-naïve and -experienced patients with compensated disease due to HCV should be considered for therapy. • Treatment should be prioritized for patients with significant fibrosis

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	(F3 to F4).
	• Treatment is justified in patients with moderate fibrosis (F2).
	• In patients with no or mild disease (F0 to F1), the indication for and timing of therapy can be individualized.
	• Patients with decompensated cirrhosis who are on the transplant list should be considered for interferon-free, ideally ribavirin-free therapy.
	
	Treatment considerations for HIV/HCV-coinfection
	• Indications for HCV treatment and treatment regimens in HCV/HIV co-infected persons are identical to those in patients with HCV mono-infection.
	• The use of cobicistat-based regimens, efavirenz, delavirdine, etravirine, nevirapine, ritonavir, and any HIV protease inhibitor, boosted or not by ritonavir, is not recommended in HIV-infected patients receiving simeprevir.
	• Daclatasvir dose should be adjusted to 30 mg daily in HIV-infected patients receiving atazanavir/ritonavir and to 90 mg daily in those receiving efavirenz.
	• No drug-drug interaction has been reported between sofosbuvir and antiretroviral drugs.
	
	Treatment options for HCV genotype 1 infection
	• Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks.
	  o The most efficacious and the easiest to use interferon alfa-containing option, without the risk of selecting resistant viruses in case of treatment failure.
	• Simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks (in treatment-naïve and prior relapsers, including cirrhotics) or 48 weeks (in prior partial and null responders, including cirrhotics).
	  o Not recommended for HCV genotype 1a with Q80K polymorphism.
	  o HCV RNA levels should be monitored on treatment. Treatment should be stopped if HCV RNA level is ≥25 IU/mL at week four, 12, or 24.
	• Daclatasvir plus peginterferon alfa and ribavirin for 24 weeks (HCV genotype 1b only).
	  o Not recommended for HCV genotype 1a given the preliminary data available, pending results of on-going large-scale studies.
	  o Daclatasvir should be given for 12 weeks in combination with peginterferon alfa and ribavirin. Daclatasvir, in combination with peginterferon alfa and ribavirin, should be continued for an additional 12 weeks (24 weeks total) in patients who do not achieve an HCV RNA level <25 IU/mL at week 4 and undetectable at week 10. Peginterferon alfa and ribavirin should be continued alone between week 12 and 24 (24 weeks total) in patients who achieve an HCV RNA level <25 IU/mL at week 4 and undetectable at week 10.
	• Sofosbuvir plus ribavirin for 24 weeks.
	  o Due to suboptimal SVR rates, reserve for interferon alfa ineligible patients when no other interferon-free option is available.
	• Sofosbuvir plus simeprevir for 12 weeks.
	  o The addition of ribavirin should be considered in patients with

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	predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis.
	• Sofosbuvir plus daclatasvir for 12 weeks (treatment-naïve) or 24 weeks (treatment-experienced, including prior telaprevir or boceprevir failures).
	  o The addition of ribavirin should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis.
	
	<u>Treatment options for HCV genotype 2 infection</u>
	• Sofosbuvir plus ribavirin for 12 weeks (or 16 to 20 weeks in cirrhotics, especially treatment-experienced).
	• Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks is an option for cirrhotic and/or treatment-experienced patients.
	
	<u>Treatment options for HCV genotype 3 infection</u>
	• Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks
	• Sofosbuvir plus ribavirin for 24 weeks
	  o Suboptimal in treatment-experienced cirrhotics, who should be proposed an alternative treatment option.
	• Sofosbuvir plus daclatasvir for 12 weeks (treatment-naïve) or 24 weeks (treatment-experienced, pending data with 12 weeks of therapy).
	  o The addition of ribavirin should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis.
	
	<u>Treatment options for HCV genotype 4 infection</u>
	• Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks.
	• Simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks (in treatment-naïve and prior relapsers, including cirrhotics) or 48 weeks (in prior partial and null responders, including cirrhotics).
	  o HCV RNA levels should be monitored on treatment. Treatment should be stopped if HCV RNA level is ≥25 IU/mL at week four, 12, or 24.
	• Daclatasvir plus peginterferon alfa and ribavirin for 24 weeks.
	  o Daclatasvir should be given for 12 weeks in combination with peginterferon alfa and ribavirin. Daclatasvir, in combination with peginterferon alfa and ribavirin, should be continued for an additional 12 weeks (24 weeks total) in patients who do not achieve an HCV RNA level <25 IU/mL at week four and undetectable at week 10. Peginterferon alfa and ribavirin should be continued alone between week 12 and 24 (24 weeks total) in patients who achieve an HCV RNA level <25 IU/mL at week four and undetectable at week 10.
	• Sofosbuvir plus ribavirin for 24 weeks.
	  o Should be reserved for interferon alfa intolerant or -ineligible patients.
	• Sofosbuvir plus simeprevir for 12 weeks.
	  o The addition of ribavirin should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis.
	• Sofosbuvir plus daclatasvir for 12 weeks (treatment-naïve) or 24 weeks (treatment-experienced).
	  o The addition of ribavirin should be considered in patients with

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	predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis. Treatment options for HCV genotype 5 or 6 infection • Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Sofosbuvir plus ribavirin for 24 weeks. o Should be reserved for interferon alfa intolerant or -ineligible patients. Treatment monitoring • A real-time polymerase chain reaction-based assay with a lower limit of detection of <15 IU/mL should be used to monitor HCV RNA levels during and after therapy. • In patients treated with sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks, HCV RNA should be measured at baseline and at weeks 4, 12, and 12 or 24 weeks after the end of therapy. • In patients treated with simeprevir for 12 weeks plus peginterferon alfa and ribavirin for an additional 24 or 48 weeks, HCV RNA should be measured at baseline, week four, 12, 24 (end of treatment in treatment-naïve and prior relapsers), week 48 (end of treatment in prior partial and null responders), and 12 or 24 weeks after the end of therapy. • In patients treated with daclatasvir for 12 to 24 weeks plus peginterferon alfa and ribavirin for 24 weeks, HCV RNA should be measured at baseline, week four, 10, and 24 (end of treatment), and 12 or 24 weeks after the end of therapy. • In patients treated with sofosbuvir plus simeprevir with or without ribavirin for 12 weeks; sofosbuvir plus daclatasvir with or without ribavirin for 12 or 24 weeks; and sofosbuvir plus ribavirin 12 or 24 weeks, HCV RNA should be measured at baseline, week 2 (assessment of adherence), week four, week 12 or 24 (end of treatment), and 12 or 24 weeks after the end of therapy. Stopping (futility) rules • Treatment with simeprevir plus peginterferon alfa and ribavirin should be stopped if HCV RNA level is ≥25 IU/mL at treatment week four, 12 or 24. • No futility rules have been defined for other treatment regimens. Virological response-guided triple therapy • With the triple combination of daclatasvir plus peginterferon alfa and ribavirin, patients who do not achieve an HCV RNA level <25 IU/mL at week 4 and undetectable at week 10 should receive the three drugs for 24 weeks. • Patients who achieve an HCV RNA level <25 IU/mL at week four and undetectable at week 10 should stop daclatasvir at week 12 and continue with peginterferon alfa and ribavirin dual therapy until week 24. • No response-guided therapy is used in other treatment regimens. Measures to improve treatment adherence • HCV treatment should be delivered within a multidisciplinary team setting, with experience in HCV assessment and therapy. • Counseling on the importance of adherence is recommended. • In persons who actively inject drugs, access to harm reduction

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	programs is mandatory. • Patients should be counseled to abstain from alcohol during antiviral therapy; patients with on-going alcohol consumption during treatment should receive additional support during antiviral therapy. • HCV treatment can be considered also for patients actively using drugs if they wish to receive treatment and are able and willing to maintain regular appointments. Retreatment of non-sustained virological responders • Patients who failed on a regimen containing sofosbuvir as the only direct-acting antiviral can be retreated with a combination of sofosbuvir and simeprevir (HCV genotypes 1 or 4 only), or a combination of sofosbuvir and daclatasvir (all genotypes). • Patients who failed on a regimen containing simeprevir, telaprevir or boceprevir as the only direct-acting antiviral can be retreated with a combination of sofosbuvir and daclatasvir. • Patients who failed on a regimen containing daclatasvir as the only direct-acting antiviral can be retreated with a combination of sofosbuvir and simeprevir (HCV genotypes 1 or 4 only). • Patients who failed on a regimen containing sofosbuvir and simeprevir can be retreated with a combination of sofosbuvir and daclatasvir. • Patients who failed on a regimen containing sofosbuvir and daclatasvir can be retreated with a combination of sofosbuvir and simeprevir (HCV genotypes 1 or 4 only). • Alternatively, patients who failed on any of the new treatment regimens including sofosbuvir, simeprevir and/or daclatasvir can wait until new treatment combinations are available if they do not need urgent therapy. • The utility of HCV resistance testing prior to retreatment in patients who failed on any of the new treatment regimens including sofosbuvir, simeprevir and/or daclatasvir is unknown. Treatment of patients with severe liver disease • Patients with compensated cirrhosis should be treated, in the absence of contraindications, in order to prevent short- to mid-term complications; interferon-free regimens are preferred. • If a 12 to 24 week interferon-based direct-acting antiviral regimen is considered tolerable in patients with compensated cirrhosis and good liver function and without cytopenia, these patients can be treated as recommended above across genotypes. • Patients with cirrhosis should undergo regular surveillance for hepatocellular carcinoma, irrespective of SVR. Patients with an indication for liver transplantation • In patients awaiting liver transplantation, antiviral therapy is indicated, because it prevents graft infection if HCV RNA has been undetectable at least 30 days prior to transplantation. • Patients with conserved liver function (Child Pugh class A) in whom the indication for transplantation is hepatocellular carcinoma should be treated with sofosbuvir plus ribavirin until liver transplantation. • Patients with conserved liver function (Child Pugh class A) in whom the indication for transplantation is hepatocellular carcinoma can also be treated with sofosbuvir, peginterferon alfa and ribavirin for 12 weeks.

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	• In patients with conserved liver function (Child Pugh class A) in whom the indication for transplantation is hepatocellular carcinoma, the addition of another direct acting antiviral drug is likely to improve the prevention of HCV recurrence post-transplant; therefore, patients awaiting liver transplantation with genotype 1 to 4 infection can be treated with sofosbuvir, daclatasvir and ribavirin for 12 weeks prior to transplantation. • Patients with decompensated cirrhosis awaiting liver transplantation (Child Pugh class B and C) can be treated with sofosbuvir plus ribavirin until liver transplantation in experienced centers under close monitoring. Interferon alfa is contraindicated in these patients. • The addition of another direct-acting antiviral drug is likely to improve the prevention of HCV recurrence post-transplant; therefore, patients with decompensated cirrhosis awaiting liver transplantation (Child Pugh class B and C) with genotype 1 to 4 infection should be treated with sofosbuvir, daclatasvir and ribavirin until liver transplantation in experienced centers under close monitoring. • Patients with decompensated cirrhosis not on transplant waiting list should only be offered an interferon-free regimen within a clinical trial, an expanded access program or within experienced centers, because the efficacy, safety and outcomes have not yet been established for this group. <u>Post-liver transplantation recurrence</u> • Patients with post-transplant recurrence of HCV infection should be considered for therapy. • Patients with HCV genotype 2 infection must sofosbuvir plus ribavirin for 12 to 24 weeks, pending more data in this population. • Patients with HCV genotype 1, 3, 4, 5 or 6 infection can be treated with sofosbuvir plus daclatasvir for 12 to 24 weeks, with or without ribavirin, pending more data in this population. • Patients with HCV genotype 1 or 4 infection can be treated with sofosbuvir plus simeprevir for 12 to 24 weeks, with or without ribavirin, pending more data in this population. • No dose adjustment is required for tacrolimus or cyclosporine with any of the above combinations. Careful monitoring is important in the absence of safety data in this population. <u>Hepatitis B virus (HBV) co-infection</u> • Patients should be treated with the same regimens, following the same rules as HCV mono-infected patients. • If HBV replicates at significant levels before, during or after HCV clearance, concurrent HBV nucleoside/nucleotide analogue therapy is indicated. <u>Hemodialysis patients</u> • Hemodialysis patients, particularly those who are suitable candidates for renal transplantation, should be considered for antiviral therapy. • Hemodialysis patients should receive an interferon alfa-free and ribavirin-free regimen. • Due to the lack of safety and efficacy data, the need for dose adjustments for sofosbuvir, simeprevir and daclatasvir is unknown. • Given the lack of data, extreme caution is recommended and sofosbuvir should not be administered to patients with an estimated

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	glomerular filtration rate <30 mL/min/1.73 m^2 or with end-stage renal disease. Non-hepatic solid organ transplant recipients • HCV treatment before kidney transplantation may avoid liver-related mortality in the post-transplant patient, and may prevent HCV-specific causes of renal graft dysfunction. • Where possible, interferon-free and ribavirin-free antiviral regimen should be given to potential transplant recipients before listing for renal transplantation; however, no safety and efficacy data is available in this population. • Given the lack of data, extreme caution is recommended and sofosbuvir should not be administered to patients with an estimated glomerular filtration rate <30 mL/min/1.73 m^2 or with end-stage renal disease. • In non-hepatic solid organ transplant recipients, patients with an indication for anti-HCV therapy should receive an interferon-free regimen. • Patients with HCV genotype 2 infection must be treated with sofosbuvir plus ribavirin for 12 to 24 weeks, pending more data in this population. • Patients with HCV genotype 1, 3, 4, 5 or 6 infection can be treated with sofosbuvir plus daclatasvir for 12 to 24 weeks, with or without ribavirin, pending more safety data in this population. • Patients with HCV genotype 1 or 4 infection can be treated with sofosbuvir plus simeprevir for 12 to 24 weeks, with or without ribavirin, pending more data in this population. • No dose adjustment is required for tacrolimus or cyclosporine with any of these combinations. Careful monitoring is important in the absence of safety data in this population. Active drug addicts and patients on stable maintenance substitution • HCV treatment for people who inject drugs (PWIDs) should be considered on an individualized basis and delivered within a multidisciplinary team setting. • Sofosbuvir and simeprevir can be used in PWIDs on opioid substitution therapy. They do not require specific methadone and buprenorphine dose adjustment, but monitoring for signs of opioid toxicity or withdrawal should be undertaken. More data is needed with daclatasvir. • Consideration of interferon-containing or interferon-free therapy in PWIDs should be undertaken on an individualized basis, but those with early liver disease can be advised to await further data and/or potential development of improved therapies. • The regimens that can be used in PWIDs are the same as in non-PWIDs. • Awareness should be raised that liver transplantation is a therapeutic option in those with a history of injection drug use. • Opioid substitution therapy is not a contraindication for liver transplantation and individuals on opioid substitution should not be advised to reduce or stop therapy. Treatment of acute hepatitis C • Peginterferon alfa monotherapy for 24 weeks can be used in patients

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	with acute hepatitis C, who will achieve SVR in as many as 90% of cases. • Peginterferon alfa plus ribavirin for 24 weeks is recommended in patients with acute hepatitis C who are HIV-coinfection. • Although no data is available yet, interferon-free regimens can theoretically be used in patients with acute hepatitis C and are expected to achieve high SVR rates. • Note: Daclatasvir is not currently Food and Drug Administration-approved in the United States.
European Association for the Study of the Liver: **Management of Hepatitis C Virus Infection (2013)**[11]	Goals and endpoints of HCV therapy • The goal of therapy is to eradicate HCV infection. • The endpoint of therapy is SVR, defined by undetectable HCV RNA 24 weeks after the end of therapy; SVR usually equates to cure of infection in more than 99% of patients. • Undetectable HCV RNA at 12 weeks after the end of therapy (SVR 12) has been accepted in the US and Europe given concordance with SVR 24 is 99%; however, this concordance needs to be further validated in ongoing clinical trials. Indications for treatment • All treatment-naïve patients with compensated disease due to HCV should be considered for therapy. • Treatment should be scheduled, not deferred, for patients with significant fibrosis (F3 to F4). • In patients with less severe disease, indication for and timing of therapy can be individualized. First line treatment of chronic hepatitis C genotype 1 • Triple therapy with boceprevir or telaprevir added to peginterferon alfa and ribavirin is the approved standard of care for chronic hepatitis C genotype 1. There is no head-to-head comparison to allow recommendation of boceprevir or telaprevir as preferred therapy. • Patients with cirrhosis should never receive abbreviated treatment with boceprevir or telaprevir regimens. • Selected patients with high likelihood of SVR to peginterferon alfa and ribavirin or with contraindications to boceprevir or telaprevir can be treated with dual therapy. • When lead-in is used to identify patients with peginterferon alfa sensitive infection, the possibility of continuation of dual therapy should have been discussed with the patient prior to initiation of treatment. • Both peginterferon alfa-2a (180 µg/week) and peginterferon alfa-2b (1.5 µg/kg/week) can be used in dual or triple therapy. • Ribavirin should be dosed following the peginterferon alfa label for triple therapy. • Ribavirin should be administered at a weight-based dose of 15 mg/kg/day in dual therapy First line treatment of chronic hepatitis C genotypes 2, 3, 4, 5, and 6 • The combination of peginterferon alfa and ribavirin is the approved standard of care for chronic hepatitis C genotypes 2, 3, 4, 5, and 6. • Ribavirin should be administered at a weight-based dose of 15 mg/kg/day for genotypes 4, 5 and 6, and at a flat dose of 800 mg/day

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	for genotypes 2 and 3. • Patients with genotypes 2 and 3 with baseline factors suggesting low responsiveness should receive weight-based ribavirin at a dose of 15 mg/kg/day. <u>Treatment monitoring</u> • A real-time polymerase chain reaction-based assay with a lower limit of detection of <15 IU/mL should be used to monitor triple therapy. • During triple therapy in HCV genotype 1 patients, HCV RNA measurements should be performed at weeks four, eight, 12, 24, and end of treatment when administering boceprevir, and at weeks four, 12, 24, and end of treatment when administering telaprevir. • During dual therapy in any HCV genotype, HCV RNA levels should be assessed at baseline, weeks four, 12, 24 and end of treatment. • The end-of-treatment virological response and the SVR at 12 or 24 weeks after the end of treatment must be assessed. • Whether the baseline HCV RNA level is low or high may be a useful criterion to guide treatment decisions during dual therapy. The safest threshold level for discriminating low and high baseline HCV RNA is 400,000 IU/mL. • Dual therapy for all HCV genotypes should be stopped at week 12 if the HCV RNA decrease is <2 $\log_{10}$ IU/mL and at week 24 if HCV RNA is still detectable. • Triple therapy with boceprevir should be stopped if HCV RNA is >100 IU/mL at treatment week 12 or if HCV RNA is detectable at treatment week 24. • Triple therapy with telaprevir should be stopped if HCV RNA is >1,000 IU/mL at weeks four or 12 of therapy. • Dual therapy duration should be tailored to the on-treatment virological response at weeks four and 12. The likelihood of SVR is directly proportional to the rapidity of HCV RNA disappearance. • For patients receiving dual therapy who achieve an RVR and who have low baseline viral titre (<400,000 IU/mL), treatment for 24 weeks (genotype 1) or 16 weeks (genotype 2 or 3) can be considered. If negative predictors of response (i.e., advanced fibrosis/cirrhosis, metabolic syndrome, insulin resistance, hepatic steatosis) are present, published evidence for equal efficacy of shortened treatment is lacking. • Patients receiving dual therapy with genotypes 2 or 3, and with any adverse predictor of SVR, and who achieve an early virological response or a delayed virological response without an RVR, can be treated for 48 weeks. • Genotype 1 patients receiving dual therapy who demonstrate a delayed virological response can be treated for 72 weeks, provided that their HCV RNA is undetectable at week 24. <u>Treatment dose reductions and stopping rules</u> • The peginterferon alfa dose should be reduced if the absolute neutrophil count falls below 750/mm^3, or the platelet count falls below 50,000/mm^3. Peginterferon alfa should be stopped if the neutrophil count falls below 500/mm^3 or the platelet count falls below 25,000/mm^3 or if severe unmanageable depression develops. • If neutrophil or platelet counts rise, treatment can be restarted, but at a reduced peginterferon alfa dose. • If hemoglobin <10 g/dL occurs, the dose of ribavirin should be

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	adjusted downward by 200 mg at a time, and ribavirin should be stopped if hemoglobin falls below 8.5 g/dL. • Treatment should be stopped in case of a severe hepatitis flare or severe sepsis. • Boceprevir or telaprevir doses should not be reduced during therapy due to the risk of the development of antiviral resistance. If boceprevir or telaprevir have been stopped, they should never be reintroduced in the same course of treatment. Measures to improve treatment success rates • Full adherence to all antiviral drugs should be the aim in order to optimize SVR rates and to reduce the risk of emergence of specific drug resistance. • Body weight adversely influences the response to peginterferon alfa and ribavirin; therefore, a reduction of body weight in overweight patients prior to therapy may increase the likelihood of SVR. • Insulin resistance is associated with treatment failure for dual therapy; however, insulin sensitizers have no proven efficacy in improving SVR rates in these patients. • Counseling on abstaining from alcohol during antiviral therapy should be provided. • In dual therapy, recombinant erythropoietin can be administered when the hemoglobin level falls <10 g/dL in order to reduce the need for ribavirin dose reduction. • In patients receiving boceprevir or telaprevir-based triple therapy, ribavirin dose reduction should be the initial response to significant anemia. • There is no evidence that neutropenia during peginterferon alfa and ribavirin therapy is associated with more frequent infection episodes, or that the use of granulocyte colony stimulating factor reduces the rate of infections and/or improves SVR rates. • Patients with a history and/or signs of depression should be seen by a psychiatrist before therapy. Patients who develop depression during therapy should be treated with antidepressants. Preventative antidepressant therapy in selected patients may reduce the incidence of this condition during treatment, without any impact on SVR. Post treatment follow up of patients who achieve an SVR • Noncirrhotic patients with SVR should be retested for alanine transaminase and HCV RNA at 48 weeks post-treatment, and then discharged if alanine transaminase is normal and HCV RNA is negative. • Cirrhotic patients with SVR should undergo surveillance for hepatocellular carcinoma every six months by means of ultrasound. • If present, portal hypertension and esophageal varices should be managed, though index variceal bleed is seldom observed in low-risk patients after the achievement of SVR. • Patients with ongoing drug use should not be excluded from HCV treatment on the basis of perceived risk of reinfection. • Following SVR, monitoring for HCV reinfection through annual HCV RNA assessment should be undertaken on people who inject drugs with ongoing risk behavior. Retreatment of nonsustained virological responders to peginterferon alfa

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	and ribavirin • Patients infected with HCV genotype 1 who failed to eradicate HCV in prior therapy with peginterferon alfa and ribavirin should be considered for retreatment with the triple combination of peginterferon alfa, ribavirin and a protease inhibitor. • The previous response to interferon-based therapy is an important predictor of success of triple therapy. If the pattern of prior response to dual therapy is not clearly documented, the patient should not be treated with abbreviated response-guided therapy. • Patients with cirrhosis and prior null responders have a lower chance of cure and should not be treated with response-guided therapy with either boceprevir or telaprevir. • Patients infected with HCV genotypes other than 1 and who failed on prior therapy with non-pegylated interferon alfa, with or without ribavirin, can be re-treated with pegylated interferon alfa and ribavirin. Treatment of patients with severe liver disease • Patients with compensated cirrhosis should be treated, in the absence of contraindications, in order to prevent short to midterm complications. • Monitoring and management of side effects, especially those linked to portal hypertension, low platelet count, and low serum albumin should be done particularly carefully. Growth factors may be useful in this group. • Patients with cirrhosis should undergo regular surveillance for hepatocellular carcinoma, irrespective of SVR. • In patients awaiting liver transplantation, antiviral therapy, when feasible, prevents graft reinfection if an SVR is achieved. • Antiviral therapy may be started while awaiting liver transplantation, with the goal of achieving SVR or HCV RNA negativity before transplantation. • In patients with Child-Pugh B cirrhosis, antiviral therapy is offered on an individual basis in experienced centers, preferentially in patients with predictors of good response. • Patients with Child-Pugh C cirrhosis should not be treated with the current interferon alfa-based antiviral regimens due to a high risk of life-threatening complications. • Treatment can be started at low doses of peginterferon alfa and ribavirin, following a low accelerated dose regimen or at full doses. In the latter case, dose reductions and treatment interruptions are required in >50% of cases. • Patients with post-transplant recurrence of HCV infection should initiate therapy once chronic hepatitis is established and histologically proven. Significant fibrosis or portal hypertension one year after transplantation predicts rapid disease progression and graft loss and indicates urgent antiviral treatment. • For patients with HCV genotype 1, protease inhibitor-based therapy can be used, but frequent monitoring and dose adjustment of tacrolimus and cyclosporine are required. • Graft rejection is rare but may occur during peginterferon alfa treatment. A liver biopsy should be performed whenever liver tests worsen on antiviral therapy. Treatment of special groups

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	• Indications for HCV treatment in patients with HIV coinfection are identical to those in patients with HCV monoinfection. The same peginterferon alfa regimen should be used in HIV coinfected patients. Longer treatment duration may be considered for patients with genotype 2 and 3 who exhibit slow early viral kinetics. • Patients coinfected with HIV and HCV genotype 1 should be considered for telaprevir or boceprevir triple therapy regimen, but special care should be taken to minimize or avoid potential drug-drug interactions. • HIV patients with a diagnosis of acute HCV infection should be treated with peginterferon and ribavirin, with duration dependent on viral kinetics independent of HCV genotype. • Patients coinfected with hepatitis B should be treated with telaprevir or boceprevir triple therapy regimen, following the same rules as monoinfected patients. • If hepatitis B virus replicates at significant levels before, during or after HCV clearance, concurrent hepatitis B virus nucleoside/nucleotide analogue therapy is indicated. • Patients on hemodialysis, particularly those who are suitable candidates for renal transplantation, should be considered for antiviral therapy. • Antiviral treatment should comprise peginterferon alfa at an appropriately reduced dose. • Ribavirin can be used at very low doses, but with caution. • Boceprevir or telaprevir can be used with caution in patients with impaired creatinine clearance, and dose adjustment is probably unnecessary. • Patients with HCV and end stage renal disease scheduled for kidney transplantation should undergo antiviral therapy prior to transplantation due to the increased risk of acute transplant rejection. • Interferon alfa-based antiviral treatment is associated with a significant risk of renal graft rejection, and it should be avoided unless there is a powerful indication for antiviral treatment (e.g., aggressive cholestatic hepatitis). • Regular alcohol consumption should be strongly discouraged. • Treatment of patients with active illicit drug abuse has to be individualized. • Patients with hemoglobinopathies can be treated with combination therapy but need careful monitoring. <u>Follow up of untreated patients and of patients with treatment failure</u> • Untreated patients with chronic hepatitis C and those who failed prior treatment should be followed regularly. • Non-invasive methods for staging fibrosis are best suited for follow-up assessment at intervals. • Hepatocellular carcinoma screening must be continued indefinitely in patients with cirrhosis. <u>Treatment of acute hepatitis C</u> • Peginterferon alfa monotherapy for 24 weeks is recommended in patients with acute hepatitis C and achieves SVR in >90% of patients. • Patients failing to respond to monotherapy should be retreated according to the standard of care for chronic hepatitis C.

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World Health Organization: **Guidelines for the Screening, Care and Treatment of Persons with Hepatitis C Infection (2014)**[19]	Recommendations for treatment of HCV infection
	• All adults and children with chronic HCV infection, including people who inject drugs, should be assessed for antiviral treatment.
	• Peginterferon alfa in combination with ribavirin is recommended for the treatment of chronic HCV infection rather than standard non-peginterferon alfa with ribavirin.
	• Where access to treatment for HCV infection is limited, priority for treatment should be given to patients with advanced liver disease (F3 and F4).
	• Treatment with the direct-acting antivirals telaprevir or boceprevir, given in combination with peginterferon alfa and ribavirin, is suggested for genotype 1 chronic HCV infection rather than peginterferon alfa and ribavirin alone.
	• In high-income settings, HCV treatment with peginterferon alfa and ribavirin and with boceprevir or telaprevir plus peginterferon alfa and ribavirin has been evaluated as being cost–effective.
	• Sofosbuvir, given in combination with ribavirin with or without peginterferon alfa (depending on the HCV genotype), is recommended in genotypes 1, 2, 3 and 4 HCV infection rather than peginterferon alfa and ribavirin alone (or no treatment for persons who cannot tolerate peginterferon alfa); recommendation made without taking resource use into consideration.
	• Simeprevir, given in combination with peginterferon alfa and ribavirin, is recommended for persons with genotype 1b HCV infection and for persons with genotype 1a HCV infection without the Q80K polymorphism rather than peginterferon alfa and ribavirin alone; recommendation made without taking resource use into consideration.
	• Absolute contraindications to peginterferon alfa:
	  o Uncontrolled depression, psychosis, or epilepsy.
	  o Uncontrolled autoimmune disease.
	  o Decompensated cirrhosis (Child–Pugh ≥B7 or B6 in HCV/HIV coinfection).
	  o Pregnancy or unwillingness to use contraception.
	  o Breastfeeding women.
	  o Severe concurrent medical disease including severe infections.
	  o Poorly controlled hypertension, cardiac failure, or diabetes.
	  o Solid organ transplant (except liver transplant recipients).
	  o Chronic obstructive pulmonary disease.
	  o Age <2 years old.
	• Relative contraindications to peginterferon alfa:
	  o Abnormal hematological indices:
	  ▪ Hemoglobin <13 g/dL in men or <12 g/dL in women.
	  ▪ Neutrophil count $<1.5 \times 10^9$/L.
	  ▪ Platelet count $<90 \times 10^9$/L.
	  o Serum creatinine >1.5 mg/dL.
	  o Hemoglobinopathies (sickle cell disease or thalassemia).
	  o Significant coronary artery disease.
	  o Untreated thyroid disease.
	• Treatment for HCV infection is both efficacious and cost-effective in people who inject drugs and is therefore recommended.
	• Specialist care needs to address the additional needs of special populations of patients, including people who inject drugs, persons

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	coinfected with (or at risk for infection with) HIV, children and adolescents, and those with cirrhosis. • The decision to initiate treatment for HCV/HIV-coinfection is more complex than in those with HCV monoinfection, as response rates are lower, risk of potential toxicities is higher and treatment is complicated by a high pill burden, overlapping toxicities, and interactions between drugs used for treating HCV and HIV.

American Association for the Study of Liver Diseases: **An Update on Treatment of Genotype 1 Chronic Hepatitis C Virus Infection (2011)**[20]	• The optimal therapy for HCV genotype 1 is the use of boceprevir or telaprevir in combination with peginterferon alfa and ribavirin.
	• Boceprevir and telaprevir should not be used without peginterferon alfa and weight-based ribavirin.
	
	<u>Treatment-naïve patients</u>
	• The recommended dose of boceprevir is 800 mg three times daily (every seven to nine hours) with food plus peginterferon alfa and weight-based ribavirin for 24 to 44 weeks, preceded by four weeks of lead in peginterferon alfa plus ribavirin alone.
	  o Patients without cirrhosis treated with boceprevir, peginterferon alfa and ribavirin, whose HCV ribonucleic acid (RNA) levels at weeks eight and 24 is undetectable, may be considered for a shortened duration of treatment of 28 weeks in total (four weeks lead in of peginterferon alfa and ribavirin, followed by 24 weeks of triple therapy).
	  o Triple therapy should be stopped if the HCV RNA level is >100 IU/mL at treatment week 12 or detectable at treatment week 24.
	• The recommended dose of telaprevir is 750 mg three times daily (every seven to nine hours) with food (not low fat) plus peginterferon alfa and weight-based ribavirin for 12 weeks followed by an additional 12 to 36 weeks of peginterferon alfa plus ribavirin (without telaprevir).
	  o Patients without cirrhosis treated with telaprevir, peginterferon alfa and ribavirin, whose HCV RNA level at weeks four and 12 is undetectable should be considered for a shortened duration of therapy of 24 weeks.
	  o Triple therapy should be stopped if the HCV RNA levels is >1,000 IU/mL at treatment weeks four or 12 and/or detectable at treatment week 24.
	• Patients with cirrhosis treated with either boceprevir or telaprevir in combination with peginterferon alfa and ribavirin should receive therapy for a duration of 48 weeks.
	
	<u>Treatment-experienced patients</u>
	• Re-treatment with boceprevir or telaprevir, in combination with peginterferon alfa and weight-based ribavirin, can be recommended for patients who had virological relapse or were partial responders after a prior course of treatment with standard interferon alfa or peginterferon alfa and/or ribavirin.
	• Retreatment with telaprevir, in combination with peginterferon alfa and weight-based ribavirin, may be considered for prior null responders to a course of standard interferon alfa or peginterferon alfa and/or weight-based ribavirin.
	• Response-guided therapy of treatment-experienced patients using either a boceprevir- or telaprevir-based regimen can be considered for relapsers, may be considered for partial responders, but cannot be

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	recommended for null responders. • Patients re-treated with boceprevir plus peginterferon alfa and ribavirin who continue to have detectable HCV RNA >100 IU at week 12 should be withdrawn from all therapy because of the high likelihood of developing antiviral resistance. • Patients re-treated with telaprevir plus peginterferon alfa and ribavirin who continue to have detectable HCV RNA >1,000 IU at weeks four or 12 should be withdrawn from all therapy because of the high likelihood of developing antiviral resistance. <u>Adverse events</u> • Patients who develop anemia on protease inhibitor-based therapy for chronic hepatitis C should be managed by reducing the ribavirin dose. • Patients on protease inhibitor-based therapy should undergo close monitoring of HCV RNA levels and the protease inhibitors should be discontinued if virological breakthrough (greater than one log increase in serum HCV RNA above nadir) is observed. • Patients who fail to have a virological response, who experience virological breakthrough, or who relapse on one protease inhibitor should not be re-treated with other protease inhibitors. <u>Use and Interpretation of HCV RNA results during triple therapy</u> • An HCV assay with a lower limit of quantification of equal to or less than 25 IU/mL and a limit of HCV RNA detection of approximately 10 to 15 IU/mL should be used for monitoring response to therapy and decision making during triple therapy. • Response-guided therapy should only be considered when no virus is detected by a sensitive assay four weeks after initiation of the HCV protease inhibitor. <u>IL28B testing</u> • IL28B genotype is a robust pretreatment predictor of sustained virologic response (SVR) to peginterferon alfa and ribavirin as well as to protease inhibitor triple therapy in patients with chronic HCV genotype 1. Testing may be considered when the patient or provider wish additional information on the probability of treatment response or on the probable treatment needed.
American Gastroenterological Association: **Medical Position Statement on the Management of Hepatitis C (2006)**[21]	• Therapy is indicated for previously untreated patients with chronic hepatitis C, circulating HCV RNA, elevated aminotransferase levels, evidence on liver biopsy of moderate to severe hepatitis grade and stage, and compensated liver disease. • Patients with normal ALT activity are candidates for antiviral therapy or for monitoring without intervention, as determined on an individual basis and as influenced by patient factors such as motivation, genotype, histologic activity, and fibrosis. • Patients with compensated cirrhosis who can tolerate therapy are candidates for treatment. • The treatment of choice is pegylated interferon alfa plus ribavirin. • Patients with genotypes 1 and 4 require 48 weeks of therapy with pegylated interferon and high daily doses of ribavirin (1,000 to 1,200 mg, depending on weight). • Patients with genotypes 2 and 3 can be treated for only 24 weeks with pegylated interferon and with 800 mg of ribavirin daily, with the following exceptions:

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	o A longer duration of therapy may be considered on an individual patient basis taking into account factors such as elevated viral level, cirrhosis, or delayed response to therapy. o 12 weeks of therapy suffices in patients in whom HCV RNA levels are undetectable at week 4. o Patients with genotype 3, with high levels of HCV RNA or advanced fibrosis on liver biopsy, may require treatment for 48 weeks. • Therapy with peginterferon alfa and ribavirin should be strongly considered for patients who experienced a relapse after a course of standard interferon alfa/ribavirin combination therapy, while a longer duration of therapy in patients who experienced a relapse after 12 months of treatment with peginterferon alfa plus ribavirin is of unproven efficacy. • For children, the general principles of management are the same as those for adults, except that treatment is not recommended for children younger than 3 years. • For HIV-infected individuals, the optimal therapy consists of peginterferon alfa plus ribavirin for 48 weeks, regardless of genotype. Because of potential drug-drug interactions in patients on HIV treatment regimens that include didanosine, HIV regimens should be altered in those starting combination therapy for HCV infection. If didanosine is critical to the HIV regimen, ribavirin should be avoided.
National Institutes of Health, the Centers for Disease Control and Prevention, and the Human Immunodeficiency Virus Medicine Association of the Infectious Diseases Society of America: **Guidelines for Prevention and Treatment of Opportunistic Infections in Human Immunodeficiency Virus - Infected Adults and Adolescents (2013)**[22]	Aspergillosis • Voriconazole is the drug of choice but should be used cautiously with human immunodeficiency virus protease inhibitors and efavirenz. Amphotericin B deoxycholate at 1 mg/kg daily or lipid-formulation amphotericin B at 5 mg/kg daily are alternatives, as is caspofungin at 50 mg daily and posaconazole. • Other echinocandins, such as micafungin and anidulafungin, are reasonable alternatives. • For treatment failure (if voriconazole was used initially) substitution with amphotericin B, posaconazole, or echinocandins might be considered; the amphotericin B or echinocandins would be rational for those who began therapy with voriconazole or posaconazole. Candidiasis (mucocutaneous) • Oral fluconazole is as effective as topical therapy for oropharyngeal candidiasis and is considered the drug of choice. Initial episodes of oropharyngeal candidiasis can be adequately treated with topical therapy, including clotrimazole troches, nystatin suspension or pastilles, or miconazole mucoadhesive tablets. Itraconazole oral solution for seven to 14 days is as effective as oral fluconazole but less well tolerated. Posaconazole oral solution is also as effective as fluconazole and is generally better tolerated than itraconazole. Intravenous amphotericin B is usually effective and can be used among patients with refractory disease. Both conventional amphotericin B and lipid complex and liposomal amphotericin B have been used. • Systemic antifungals are required for effective treatment of esophageal candidiasis. A 14 to 21-day course of either fluconazole (oral or intravenous) or oral itraconazole solution is highly effective. Oral ketoconazole or itraconazole capsules are less effective than fluconazole because of variable absorption. Although intravenous caspofungin or intravenous voriconazole are effective in treating

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	esophageal candidiasis among human immunodeficiency virus -infected patients, oral or intravenous fluconazole remain the preferred therapies. Azole-refractory esophageal candidiasis can be treated with posaconazole, amphotericin B, anidulafungin, caspofungin, micafungin, or voriconazole. • Vulvovaginal candidiasis in human immunodeficiency virus -infected women is usually uncomplicated (90%) and responds readily to short-course oral or topical treatment with any of several therapies, including oral fluconazole, topical azoles, and itraconazole oral solution. Severe or recurrent episodes of vaginitis require oral fluconazole or topical antifungal therapy for ≥7 days. <u>Coccidioidomycosis</u> • For patients with clinically mild infection, such as focal pneumonia or a positive coccidioidal serologic test alone, initial therapy with a triazole antifungal is appropriate. • For patients with either diffuse pulmonary involvement or severely ill patients with extrathoracic disseminated disease, amphotericin B is the preferred initial therapy. Therapy with amphotericin B should continue until clinical improvement is observed. Some specialists would use a triazole antifungal concurrently with amphotericin B and continue the triazole once amphotericin B is stopped. <u>Cryptococcosis</u> • The recommended initial standard treatment is amphotericin B combined with flucytosine for ≥2 weeks for those with normal renal function. • The combination of amphotericin B with fluconazole is less effective than amphotericin B combined with flucytosine in terms of clearing *Cryptococcus* from the cerebrospinal fluid but is better than amphotericin B alone. • Fluconazole combined with flucytosine is an alternative to amphotericin B plus flucytosine, but is less effective than amphotericin B and is recommended only for persons unable to tolerate or unresponsive to standard treatment. • After at least a two-week period of successful induction therapy, amphotericin B and flucytosine may be discontinued and follow-up therapy initiated with fluconazole. This should continue for eight weeks. Itraconazole is an acceptable though less effective alternative. • The optimal therapy for those with treatment failure is not established. For those initially treated with fluconazole, therapy should be changed to amphotericin B, with or without flucytosine, and continued until a clinical response occurs. Liposomal amphotericin B may have improved efficacy over the deoxycholate formulation and should be considered in treatment failures. Higher doses of fluconazole in combination with flucytosine might also be useful. <u>Cryptosporidiosis</u> • In the setting of severe immunosuppression, antiretroviral therapy with immune restoration to a CD4+ count >100 cells/µL leads to resolution of clinical cryptosporidiosis and is the mainstay of treatment. • All patients with cryptosporidiosis should be offered antiretroviral therapy as part of the initial management of their infection. • Management should include symptomatic treatment of diarrhea.

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	Rehydration and repletion of electrolyte losses by either the oral or intravenous route are important. Severe diarrhea can exceed >10 L/day among patients with acquired immunodeficiency syndrome, often requiring intensive support. Aggressive efforts at oral rehydration should be made with oral rehydration solutions. Prevention of Cytomegalovirus • Cytomegalovirus end-organ disease is best prevented by using antiretroviral therapy to maintain the CD4+ count >100 cells/µL. • Although oral valganciclovir would likely prevent the occurrence of cytomegalovirus retinitis in patients with CD4+ counts <50 cells/µL, such therapy is not generally recommended because of the potential to induce cytomegalovirus resistance, the utility of treating disease when it occurs, and the lack of demonstrated survival advantage. Treatment of Cytomegalovirus disease • Oral valganciclovir, intravenous ganciclovir, intravenous ganciclovir followed by oral valganciclovir, intravenous foscarnet, and intravenous cidofovir are all effective treatments for cytomegalovirus retinitis. • The ganciclovir implant, a surgically-implanted reservoir of ganciclovir, which lasts approximately six months, also is very effective but it no longer is being manufactured. In its absence, some clinicians will use intravitreal injections of ganciclovir or foscarnet in conjunction with oral valganciclovir, at least initially, to provide immediate high intraocular levels of drug and presumably faster control of the retinitis. • Systemic therapy has been shown to reduce morbidity in the contralateral eye. This should be considered when choosing between the oral, intravenous, and local options. • The choice of initial therapy for cytomegalovirus retinitis should be individualized based on the location and severity of the lesion(s), the level of underlying immune suppression, and other factors such as concomitant medications and ability to adhere to treatment. • No one regimen has been proven in a clinical trial to have greater efficacy in terms of protecting vision, and thus clinical judgment must be used when choosing a regimen. • In studies conducted in the pre-antiretroviral therapy era, ganciclovir intraocular implant plus oral ganciclovir was superior to once-daily intravenous ganciclovir for treatment of cytomegalovirus retinitis; however, the implant is no longer manufactured. Assuming that this observation can be extended to other combinations of systemically and locally administered drugs, human immunodeficiency virus-specialists often recommend intravitreal ganciclovir or foscarnet injections plus oral valganciclovir as the preferred initial therapy for patients with immediate sight-threatening lesions. Intravitreal injections deliver high concentrations of the drug to the target organ immediately while steady-state concentrations in the eye are achieved with systemically delivered medications. For patients with small peripheral lesions, oral valganciclovir alone often is adequate. • After induction therapy, secondary prophylaxis (i.e., chronic maintenance therapy) should be continued until immune reconstitution occurs as a result of antiretroviral therapy. Regimens demonstrated to be effective for chronic suppression in randomized, controlled clinical trials include parenteral ganciclovir, oral valganciclovir, parenteral

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	foscarnet, combined parenteral ganciclovir and foscarnet, and parenteral cidofovir. Management of Cytomegalovirus retinitis treatment failures • When patients relapse while receiving maintenance therapy, induction with the same drug followed by reinstitution of maintenance therapy can control the retinitis, although for progressively shorter periods of time with each relapse. • Ganciclovir and foscarnet in combination appear to be superior in efficacy to either agent alone and should be considered for patients whose disease does not respond to single-drug therapy, and for patients with multiple relapses of retinitis. This drug combination, however, is associated with substantial toxicity. Treatment of Hepatitis B Virus coinfection in patients not receiving antiretroviral therapy • For patients with CD4+ counts >350 cells/µL who are not receiving antiretroviral therapy but meet criteria for hepatitis B virus treatment, adefovir or peginterferon alfa-2a monotherapy for 48 weeks might be considered, with close monitoring of hepatitis B virus deoxyribonucleic acid levels and follow-up to evaluate for hepatitis B e antigen seroconversion. However, early initiation of antiretroviral therapy should also be considered for human immunodeficiency virus/hepatitis B virus -coinfected persons with CD4+ counts >350 cells/µL. Treatment of Hepatitis B Virus coinfection in patients who require antiretroviral therapy • For human immunodeficiency virus-infected persons, some experts recommend combination therapy with two agents active against hepatitis B virus to reduce the risk of hepatitis B virus drug resistance; although, there are no results from controlled trials as yet to support this strategy. • Among patients infected with hepatitis B virus, hepatitis C virus, and human immunodeficiency virus, consideration of the need for antiretroviral therapy should be the first priority. If antiretroviral therapy is not required, interferon-based therapy, which suppresses both hepatitis C virus and hepatitis B virus, should be considered. If interferon-based therapy for hepatitis C virus has failed, treatment of chronic hepatitis B with nucleoside or nucleotide analogs is recommended. Treatment of Hepatitis C coinfection • Antiviral treatment for hepatitis C virus infection should be considered for all human immunodeficiency virus-infected persons with acute or chronic hepatitis C virus infection. • The combination of peginterferon alfa (PegIFN) plus ribavirin is the recommended backbone of therapy for HIV/HCV-co-infected patients regardless of HCV genotype. • Antiviral treatment with PegIFN is not recommended in patients with decompensated liver disease. • For HCV-genotype-1-infected patients who are not co-infected with HIV, a HCV NS3/4A protease inhibitor (PI), either boceprevir or telaprevir, in combination with PegIFN/ribavirin is recommended on

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	the basis of large clinical trials demonstrating significantly higher SVR rates with an acceptable safety/tolerability profile compared to PegIFN/ribavirin alone.
	• For HIV/HCV co-infected patients, preliminary data from small, ongoing clinical trials of boceprevir or telaprevir plus PegIFN/ribavirin for the treatment of HCV genotype 1 infection in HIV/HCV co-infected patients demonstrate greater efficacy than PegIFN/ribavirin alone, with a safety and tolerability profile similar to that observed in HCV monoinfected patients treated with boceprevir or telaprevir plus PegIFN/ribavirin. Preliminary recommendations are as follows:
	  o PegIFN is recommended for use for all HCV genotypes
	  o Ribavirin is recommended for use with PegIFN for all HCV genotypes.
	  o Boceprevir is approved for use in combination with PegIFN/ribavirin in HCV-genotype-1-monoinfected-patients. For HIV/HCV-co-infected patients, the regimen being evaluated is PegIFN/ribavirin administered for four weeks (lead-in phase) followed by boceprevir 800 mg orally every 7 to 9 hours (with a light snack) added to PegIFN/ribavirin for an additional 44 weeks.
	  o Telaprevir is approved for use in combination with PegIFN/ribavirin in HCV-genotype-1-monoinfected-patients. Dosing regimens lasting 48 weeks are being evaluated.
	• Patients with contraindications to the use of ribavirin can be treated with peginterferon alfa (2a or 2b) monotherapy. However, substantially lower sustained viral response rates are expected in persons not receiving ribavirin. HCV PIs should not be administered without ribavirin because of the high likelihood of virologic failure.
	
	<u>Treatment of herpes simplex virus disease</u>
	• Orolabial lesions can be treated with oral valacyclovir, famciclovir, or acyclovir for five to 10 days.
	• Severe mucocutaneous herpes simplex virus lesions are best treated initially with intravenous acyclovir. Patients may be switched to oral therapy after the lesions have begun to regress. Therapy should be continued until the lesions have completely healed.
	• Genital herpes simplex virus infection should be treated with oral valacyclovir, famciclovir, or acyclovir for five to 14 days. Short-course therapy (one, two, or three days) should not be used in patients with human immunodeficiency virus infection.
	• Most recurrences of genital herpes can be prevented by use of daily anti- herpes simplex virus therapy, and this is recommended for persons who have frequent or severe recurrences.
	• Suppressive therapy with oral acyclovir, valacyclovir, or famciclovir is effective in preventing recurrences. Suppressive therapy with valacyclovir should be 500 mg twice daily in human immunodeficiency virus -infected persons or twice-daily regimens with acyclovir or famciclovir should be used.
	
	<u>Management of herpes simplex virus treatment failure</u>
	• The treatment of choice for acyclovir-resistant herpes simplex virus is intravenous foscarnet. Topical trifluridine, cidofovir, and imiquimod also have been used successfully for lesions on external surfaces, although prolonged application for 21 to 28 days or longer might be

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	required. Histoplasmosis • Patients with moderately severe to severe disseminated histoplasmosis should be treated with an intravenous lipid formulation of amphotericin B for ≥2 weeks or until they clinically improve followed by oral itraconazole (200 mg three times daily for three days and then 200 mg twice daily for a total of ≥12 months). • In patients with less severe disseminated histoplasmosis, oral itraconazole at 200 mg three times daily for three days followed by 200 mg twice daily is appropriate initial therapy. Treatment of Isosporiasis (also known as Cystoisosporiasis) • Sulfamethoxazole-trimethoprim is the antimicrobial agent of choice for treatment of isosporiasis. It is the only agent whose use is supported by substantial published data and clinical experience. Therefore, potential alternative therapies should be reserved for patients with documented sulfa intolerance or in whom treatment fails. The traditional treatment regimen has been a 10-day course of Sulfamethoxazole-trimethoprim (800-160 mg) administered orally four times daily. • Intravenous administration of Sulfamethoxazole-trimethoprim should be considered for patients with potential or documented malabsorption. • Single-agent therapy with pyrimethamine has been used, with anecdotal success for treatment and prevention of isosporiasis. Pyrimethamine (50 to 75 mg/day) plus leucovorin (10 to 25 mg/day) to prevent myelosuppression may be an effective treatment alternative; it is the option for sulfa-intolerant patients. Leishmaniasis • Due to similar efficacy and a better toxicity profile, clinicians consider liposomal amphotericin B as the drug of choice for visceral leishmaniasis in human immunodeficiency virus-coinfected patients. The optimal amphotericin B dosage has not been determined. • Regimens with efficacy include conventional amphotericin B 0.5 to 1.0 mg/kg body weight/day intravenous to achieve a total dose of 1.5 to 2.0 g, or liposomal or lipid complex preparations of two to four mg/kg body weight administered on consecutive days or in an interrupted schedule (e.g., 4 mg/kg on Days 1 to 5, 10, 17, 24, 31, and 38) to achieve a total cumulative dose of 20 to 60 mg/kg body weight. A higher daily dosage is recommended for liposomal or lipid complex preparations than for conventional amphotericin B. Preventing disseminated *Mycobacterium avium* complex disease • Human immunodeficiency virus-infected adults and adolescents should receive chemoprophylaxis against disseminated *Mycobacterium avium* complex disease if they have a CD4+ count <50 cells/µL. • Azithromycin or clarithromycin are the preferred prophylactic agents. • The combination of clarithromycin and rifabutin is no more effective than clarithromycin alone for chemoprophylaxis, is associated with a higher rate of adverse effects than either drug alone, and should not be used. • The combination of azithromycin with rifabutin is more effective than

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	azithromycin alone; however, the additional cost, increased occurrence of adverse effects, potential for drug interactions, and absence of a survival difference compared to azithromycin alone do not warrant a routine recommendation for this regimen. • Azithromycin and clarithromycin also each confer protection against respiratory bacterial infections. • If azithromycin or clarithromycin cannot be tolerated, rifabutin is an alternative prophylactic agent for *Mycobacterium avium* complex disease, although drug interactions may make this agent difficult to use. • Primary *Mycobacterium avium* complex disease prophylaxis should be discontinued among adult and adolescent patients who have responded to antiretroviral therapy with an increase in CD4+ counts to >100 cells/µL for ≥3 months. Primary prophylaxis should be reintroduced if the CD4+ count decreases to <50 cells/µL. <u>Treatment of disseminated *Mycobacterium avium* Complex Disease</u> • Initial treatment of *Mycobacterium avium* complex disease should consist of two or more antimycobacterial drugs to prevent or delay the emergence of resistance. • Clarithromycin is the preferred first agent; however, azithromycin can be substituted for clarithromycin when drug interactions or clarithromycin intolerance preclude the use of clarithromycin. • Testing of *Mycobacterium avium* complex disease isolates for susceptibility to clarithromycin or azithromycin is recommended for all patients. <u>Treatment of Penicilliosis marneffei</u> • Penicilliosis is caused by the dimorphic fungus *Penicillium marneffei*, which is known to be endemic in Southeast Asia (especially Northern Thailand and Vietnam) and southern China. • The recommended treatment is liposomal amphotericin B, three to five mg/kg body weight/day intravenously for two weeks, followed by oral itraconazole, 400 mg/day for a subsequent duration of 10 weeks, followed by secondary prophylaxis. • Patients with mild disease can be initially treated with oral itraconazole 400 mg/day for eight weeks, followed by 200 mg/day for prevention of recurrence. • The alternative drug for primary treatment in the hospital is intravenous voriconazole, 6 mg/kg every 12 hours on day one and then 4 mg/kg every 12 hours for at least three days, followed by oral voriconazole, 200 mg twice daily for a maximum of 12 weeks. • Patients with mild disease can be initially treated with oral voriconazole 400 mg twice a day on day one, and then 200 mg twice daily for 12 weeks. The optimal dose of voriconazole for secondary prophylaxis after 12 weeks has not been studied. <u>Primary prophylaxis of *Pneumocystis (carinii) jiroveci* pneumonia</u> • Sulfamethoxazole-trimethoprim is the recommended prophylactic agent. One double-strength tablet daily is the preferred regimen. However, one single-strength tablet daily is also effective and might be better tolerated than one double-strength tablet daily. One double-strength tablet three times weekly is also effective. Sulfamethoxazole-

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	trimethoprim at a dose of one double-strength tablet daily confers cross-protection against toxoplasmosis and selected common respiratory bacterial infections. Lower doses of sulfamethoxazole-trimethoprim likely also confer such protection. • For patients who have an adverse reaction that is not life threatening, chemoprophylaxis with sulfamethoxazole-trimethoprim should be continued if clinically feasible; for those who have discontinued such therapy because of an adverse reaction, reinstituting sulfamethoxazole-trimethoprim should be strongly considered after the adverse event has resolved. Patients who have experienced adverse events, including fever and rash, might better tolerate reintroduction of the drug with a gradual increase in dose (i.e., desensitization), according to published regimens or reintroduction of sulfamethoxazole-trimethoprim at a reduced dose or frequency; as many as 70% of patients can tolerate such reinstitution of therapy. • If sulfamethoxazole-trimethoprim cannot be tolerated, alternative prophylactic regimens include dapsone, dapsone/pyrimethamine plus leucovorin, aerosolized pentamidine and atovaquone. • Primary *Pneumocystis (carinii) jiroveci* pneumonia prophylaxis should be discontinued for adult and adolescent patients who have responded to antiretroviral therapy with an increase in CD4+ counts to >200 cells/µL for >3 months. Prophylaxis should be reintroduced if the CD4+ count decreases to <200 cells/µL. Treatment of *Pneumocystis (carinii) jiroveci* pneumonia • Sulfamethoxazole-trimethoprim is the treatment of choice. The dose must be adjusted for abnormal renal function. Multiple randomized clinical trials indicate that sulfamethoxazole-trimethoprim is as effective as parenteral pentamidine and more effective than other regimens. Adding leucovorin to prevent myelosuppression during acute treatment is not recommended because of questionable efficacy and some evidence for a higher failure rate. Oral outpatient therapy of sulfamethoxazole-trimethoprim is highly effective among patients with mild-to-moderate disease. • Patients who have *Pneumocystis (carinii) jiroveci* despite sulfamethoxazole-trimethoprim prophylaxis are usually effectively treated with standard doses of sulfamethoxazole-trimethoprim. • Patients with documented or suspected *Pneumocystis (carinii) jiroveci* and moderate-to-severe disease, as defined by room air pO_2 <70 mm Hg or arterial-alveolar O_2 gradient >35 mm Hg, should receive adjunctive corticosteroids as early as possible, and certainly within 72 hours after starting specific *Pneumocystis (carinii) jiroveci* therapy. • The recommended duration of therapy for *Pneumocystis (carinii) jiroveci* is 21 days. • Patients who have a history of *Pneumocystis (carinii) jiroveci* should be administered chemoprophylaxis for life (i.e., secondary prophylaxis or chronic maintenance therapy) with sulfamethoxazole-trimethoprim unless immune reconstitution occurs as a result of antiretroviral therapy. • Secondary prophylaxis should be discontinued for adult and adolescent patients whose CD4+ count has increased from <200 cells/µL to >200 cells/µL for >3 months as a result of antiretroviral therapy. Prophylaxis should be reintroduced if the CD4+ count decreases to <200 cells/µL. If *Pneumocystis (carinii) jiroveci* recurs at a CD4+ count of ≥200

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	cells/µL, lifelong prophylaxis should be administered.
	
	Primary prophylaxis of *Toxoplasma* encephalitis
	• The double-strength tablet daily dose of sulfamethoxazole-trimethoprim recommended as the preferred regimen for *Pneumocystis (carinii) jiroveci* prophylaxis is effective against *Toxoplasma* encephalitis as well and is therefore recommended. Sulfamethoxazole-trimethoprim, one double-strength tablet three times weekly, is an alternative.
	• If patients cannot tolerate sulfamethoxazole-trimethoprim, the recommended alternative is dapsone-pyrimethamine plus leucovorin, which is also effective against *Pneumocystis (carinii) jiroveci* pneumonia.
	• Atovaquone with or without pyrimethamine/leucovorin can also be considered.
	• Prophylactic monotherapy with dapsone, pyrimethamine, azithromycin, or clarithromycin cannot be recommended on the basis of available data. Aerosolized pentamidine does not protect against *Toxoplasma* encephalitis and is not recommended.
	• Prophylaxis against *Toxoplasma* encephalitis should be discontinued among adult and adolescent patients who have responded to antiretroviral therapy with an increase in CD4+ counts to >200 cells/µL for >3 months. Prophylaxis for *Toxoplasma* encephalitis should be reintroduced if the CD4+ count decreases to <100–200 cells/µL.
	
	Treatment of *Toxoplasma* encephalitis
	• The initial therapy of choice for *Toxoplasma* encephalitis consists of the combination of pyrimethamine plus sulfadiazine plus leucovorin.
	• The preferred alternative regimen for patients with *Toxoplasma* encephalitis who are unable to tolerate or who fail to respond to first-line therapy is pyrimethamine plus clindamycin plus leucovorin.
	• Sulfamethoxazole-trimethoprim was reported in a small randomized trial to be effective and better tolerated than pyrimethamine-sulfadiazine. On the basis of less in vitro activity and less experience with sulfamethoxazole-trimethoprim, treatment with this drug may be considered an option.
	• Acute therapy for *Toxoplasma* encephalitis should be continued for at least six weeks, if there is clinical and radiologic improvement.
	
	Treatment of latent tuberculosis infection
	• Human immunodeficiency virus-infected persons, regardless of age, should be treated for latent tuberculosis infection if they have no evidence of active tuberculosis and:
	  o A positive diagnostic test for latent tuberculosis infection and no prior history of treatment for active or latent tuberculosis.
	  o A negative diagnostic test for latent tuberculosis infection but are close contacts of persons with infectious pulmonary tuberculosis.
	  o A history of untreated or inadequately treated healed tuberculosis (i.e., old fibrotic lesions on chest radiography) regardless of diagnostic tests for latent tuberculosis infection.
	• Treatment options for latent tuberculosis infection include isoniazid daily or twice weekly for nine months.

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	• Due to an increased risk of fatal and severe hepatotoxicity, a two-month regimen of daily rifampin and pyrazinamide is not recommended for latent tuberculosis infection treatment regardless of human immunodeficiency virus status. • Human immunodeficiency virus-infected persons receiving isoniazid should receive pyridoxine to minimize the risk of developing peripheral neuropathy. Alternatives for individuals who cannot take isoniazid or who have been exposed to a known isoniazid-resistant index case include either rifampin or rifabutin alone for four months. • For persons exposed to isoniazid- and/or rifampin-resistant tuberculosis, decisions to treat with one or two drugs other than isoniazid, rifampin, or rifabutin should be based on the relative risk of exposure to organisms broadly resistant to other antimycobacterial drugs and should be made in consultation with public health authorities. • Directly observed therapy should be used with intermittent dosing regimens when otherwise feasible to maximize regimen completion rates. • There is no evidence to suggest that latent tuberculosis infection treatment should be continued beyond the recommended duration in persons with human immunodeficiency virus infection. Therefore, latent tuberculosis infection treatment should be discontinued after completing the appropriate number of doses. <u>Treatment of active tuberculosis disease</u> • Recommendations for anti-tuberculosis treatment regimens in human immunodeficiency virus -infected adults follow the same principles as for adults without human immunodeficiency virus -infection. • Treatment of drug susceptible tuberculosis disease should include a six-month regimen with an initial phase of isoniazid, rifampin or rifabutin, pyrazinamide, and ethambutol administered for two months followed by isoniazid and rifampin (or rifabutin) for four additional months. • When drug-susceptibility testing confirms the absence of resistance to isoniazid, rifampin, and pyrazinamide, ethambutol may be discontinued before two months of treatment have been completed. • For patients with cavitary lung disease and cultures positive for *Mycobacterium tuberculosis* after completion of two months of therapy, treatment should be extended with isoniazid and rifampin for an additional three months for a total of nine months. • All human immunodeficiency virus-infected patients treated with isoniazid should receive pyridoxine supplementation. • For patients with extrapulmonary tuberculosis, a six- to nine-month regimen (two months of isoniazid, rifampin, pyrazinamide, and ethambutol followed by four to seven months of isoniazid and rifampin) is recommended. • Exceptions to the recommendation for a six- to nine-month regimen for extrapulmonary tuberculosis include central nervous system disease (tuberculoma or meningitis) and bone and joint tuberculosis, for which many experts recommend nine to 12 months. • Adjuvant corticosteroids should be added when treating central nervous system and pericardial disease. • Treatment with corticosteroids should be started intravenously as early as possible with change to oral therapy individualized according to

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	clinical improvement. • Recommended corticosteroid regimens are dexamethasone 0.3 to 0.4 mg/kg tapered over six to eight weeks or prednisone 1 mg/kg for three weeks, then tapered for three to five weeks. Treatment of varicella zoster virus disease • For uncomplicated varicella, the preferred treatment options are valacyclovir (1 gram orally three times daily), or famciclovir (500 mg orally three times daily) for five to seven days. Oral acyclovir (20 mg/kg body weight up to a maximum dose of 800 mg five times daily) can be an alternative. • Prompt antiviral therapy should be instituted in all human immunodeficiency virus-seropositive patients whose herpes zoster is diagnosed within one week of rash onset (or any time before full crusting of lesions). The recommended treatment options for acute localized dermatomal herpes zoster in human immunodeficiency virus-infected patients are oral valacyclovir, famciclovir, or acyclovir (doses as above) for seven to 10 days, although longer durations of therapy should be considered if lesions resolve slowly. Valacyclovir or famciclovir are preferred because of their improved pharmacokinetic properties and simplified dosing schedule. • If cutaneous lesions are extensive or if visceral involvement is suspected, intravenous acyclovir should be initiated and continued until clinical improvement is evident. A switch from intravenous acyclovir to oral antiviral therapy (to complete a 10 to 14 day treatment course) is reasonable when formation of new cutaneous lesions has ceased and the signs and symptoms of visceral varicella zoster virus infection are clearly improving. • Optimal antiviral therapy for progressive outer retinal necrosis remains undefined. Specific treatment should include systemic therapy with at least one intravenous drug (selected from acyclovir, ganciclovir, foscarnet, and cidofovir) coupled with injections of at least one intravitreal drug (selected from ganciclovir and foscarnet). Treatment regimens for progressive outer retinal necrosis recommended by certain specialists include a combination of intravenous ganciclovir and/or foscarnet plus intravitreal injections of ganciclovir and/or foscarnet. The prognosis for visual preservation in involved eyes is poor, despite aggressive antiviral therapy. • Other infectious disease states mentioned within these guidelines note that the treatment guidelines for that disease state should be utilized. • The guideline specifies that detailed recommendations for the treatment of human herpesvirus-8 and associated malignancies are beyond the scope of these guidelines. • Other excluded infectious disease states offer no specific therapy or utilize medications not licensed in the United States.

Centers for Disease Control and Prevention: **Sexually Transmitted Diseases Treatment Guidelines (2010)**[23]	Bacterial vaginosis
	• Recommended regimens:
	  o Metronidazole 500 mg orally twice a day for seven days.
	  o Metronidazole gel 0.75%, one full applicator (5 grams) intravaginally, once a day for five days.
	  o Clindamycin cream 2%, one full applicator (5 grams) intravaginally at bedtime for seven days.

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	• Alternative regimens:
	  o Tinidazole 2 grams orally once daily for two days.
	  o Tinidazole 1 gram orally once daily for five days.
	  o Clindamycin 300 mg orally twice daily for seven days.
	  o Clindamycin ovules 100 mg intravaginally once at bedtime for three days.
	
	<u>Cervicitis</u>
	• Recommended regimens for presumptive treatment:
	  o Azithromycin 1 gram orally in a single dose.
	  o Doxycycline 100 mg orally twice a day for seven days.
	
	<u>Chancroid</u>
	• Recommended regimens:
	  o Azithromycin 1 gram orally in a single dose.
	  o Ceftriaxone 250 mg intramuscular in a single dose.
	  o Ciprofloxacin 500 mg orally twice a day for three days.
	  o Erythromycin base 500 mg orally three times a day for seven days.
	
	<u>Chlamydial infections</u>
	• Recommended regimens:
	  o Azithromycin 1 gram orally in a single dose.
	  o Doxycycline 100 mg orally twice a day for seven days.
	• Alternative regimens:
	  o Erythromycin base 500 mg orally four times a day for seven days.
	  o Erythromycin ethylsuccinate 800 mg orally four times a day for seven days.
	  o Levofloxacin 500 mg orally once daily for seven days.
	  o Ofloxacin 300 mg orally twice a day for seven days.
	
	<u>Chlamydial infections among children</u>
	• Recommended regimen for children <45 kg:
	  o Erythromycin base or ethylsuccinate 50 mg/kg/day orally divided into four doses daily for 14 days.
	• Recommended regimen for children ≥45 kg and <8 years of age:
	  o Azithromycin 1 gram orally in a single dose.
	• Recommended regimens for children ≥8 years of age:
	  o Azithromycin 1 gram orally in a single dose.
	  o Doxycycline 100 mg orally twice a day for seven days.
	
	<u>Disseminated gonococcal infection</u>
	• Recommended regimen:
	  o Ceftriaxone 1 gram intramuscular or intravenous every 24 hours.
	• Alternative regimens:
	  o Cefotaxime 1 gram intravenous every eight hours.
	  o Ceftizoxime 1 gram intravenous every eight hours.
	
	<u>Epididymitis</u>
	• Recommended regimens:
	  o Ceftriaxone 250 mg intramuscular in a single dose plus doxycycline 100 mg orally twice a day for 10 days.

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	• For acute epididymitis most likely caused by enteric organisms:
	  o Levofloxacin 500 mg orally once daily for 10 days.
	  o Ofloxacin 300 mg orally twice a day for 10 days.
	
	<u>Genital herpes infection</u>
	• The use of systemic antivirals including valacyclovir, acyclovir, and famciclovir is encouraged for the treatment of primary and recurrent genital herpes. Topical therapy with antiviral drugs offers minimal clinical benefit, and their use is not recommended.
	• Systemic antiviral drugs partially control the symptoms and signs of herpes infection when used to treat first clinical episodes and recurrent episodes, or when used as daily suppressive therapy.
	• However, these drugs neither eradicate latent virus nor affect the risk, frequency, or severity of recurrences after the drug is discontinued.
	• Randomized trials have indicated that three antiviral medications provide clinical benefit for genital herpes: acyclovir, valacyclovir, and famciclovir.
	• Topical therapy with antiviral drugs offers minimal clinical benefit, and its use is discouraged.
	• Foscarnet is frequently effective for treatment of acyclovir-resistant genital herpes in immunocompromised individuals.
	• Recommended regimens for initial clinical episodes include:
	  o Acyclovir 400 mg three times a day for seven to 10 days or 200 mg five times a day for seven to 10 days.
	  o Famciclovir 250 mg three times a day for seven to 10 days.
	  o Valacyclovir 1 gram twice a day for seven to 10 days.
	• Recommended regimens for suppressive therapy in recurrent herpes (≥6 episodes/year) include:
	  o Acyclovir 400 mg twice daily.
	  o Famciclovir 250 mg twice daily.
	  o Valacyclovir 500 mg once daily or 1,000 mg once daily.
	• Recommended regimens for episodic therapy in recurrent herpes include:
	  o Acyclovir 400 mg three times a day for five days or 800 mg twice a day for five days or 800 mg three times a day for two days.
	  o Famciclovir 125 mg twice a day for five days or 1 gram twice a day for one day or 500 mg once then 250 mg twice a day for two days.
	  o Valacyclovir 500 mg twice a day for three days or 1 gram once a day for five days.
	• Recommended regimen for severe infections include:
	  o Intravenous acyclovir 5 to 10 mg/kg every eight hours for two to seven days or until clinical improvement is observed, followed by oral antiviral therapy to complete at least 10 days of total therapy.
	• Recommended regimens for suppressive therapy in patients with human immunodeficiency virus include:
	  o Acyclovir 400 to 800 mg twice to three times daily.
	  o Famciclovir 500 mg twice daily.
	  o Valacyclovir 500 mg twice daily.
	• Recommended regimens for episodic therapy in patients with human immunodeficiency virus include:
	  o Acyclovir 400 mg three times daily for five to 10 days.

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	o Famciclovir 500 mg twice daily for five to 10 days. o Valacyclovir 1 gram twice daily for five to 10 days. <u>Genital warts</u> • No evidence exists to identify one treatment as more efficacious than another and no treatment is ideal for all patients with genital warts. • Treatment selection may be based on wart size and number, anatomic site of wart, wart morphology, and adverse effects of treatment. • Interferon therapy is not recommended as a primary modality because of inconvenient routes of administration, frequent office visits, and the association between its use and a high frequency of adverse effects. <u>Granuloma inguinale (Donovanosis)</u> • Recommended regimen: o Doxycycline 100 mg orally twice a day for at least three weeks and until all lesions have completely healed. • Alternative regimens: o Azithromycin 1 gram orally once per week for at least three weeks and until all lesions have completely healed. o Ciprofloxacin 750 mg orally twice a day for at least three weeks and until all lesions have completely healed. o Erythromycin base 500 mg orally four times a day for at least three weeks and until all lesions have completely healed. o Sulfamethoxazole-trimethoprim one double-strength tablet orally twice a day for at least three weeks and until all lesions have completely healed. • The addition of an aminoglycoside (e.g., gentamicin 1 mg/kg IV every eight hours) to these regimens can be considered if improvement is not evident within the first few days of therapy. <u>Gonococcal conjunctivitis</u> • Recommended regimen: o Ceftriaxone 1 gram intramuscular in a single dose. <u>Gonococcal infections among children</u> • Recommended regimen for children >45 kg: o Treat with one of the regimens recommended for adults. • Recommended regimen for children who weigh ≤45 kg and who have uncomplicated gonococcal vulvovaginitis, cervicitis, urethritis, pharyngitis, or proctitis: o Ceftriaxone 125 mg intramuscular in a single dose. • Recommended regimen for children who weigh ≤45 kg and who have bacteremia or arthritis: o Ceftriaxone 50 mg/kg (maximum dose: 1 gram) intramuscular or intravenous in a single dose daily for seven days. • Recommended regimen for children who weigh >45 kg and who have bacteremia or arthritis: o Ceftriaxone 50 mg/kg intramuscular or intravenous in a single dose daily for seven days. <u>Gonococcal meningitis and endocarditis</u> • Recommended regimen: o Ceftriaxone 1 to 2 grams intravenous every 12 hours.

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	Hepatitis B
	• No specific therapy is available for persons with acute hepatitis B; treatment is supportive.
	• Persons with chronic hepatitis B virus infection should be referred for evaluation to a physician experienced in the management of chronic liver disease.
	• Therapeutic agents approved by Food and Drug Administration for treatment of chronic hepatitis B can achieve sustained suppression of hepatitis B virus replication and remission of liver disease in some persons.
	
	Hepatitis C
	• Combination therapy with pegylated interferon and ribavirin is the treatment of choice for patients with chronic hepatitis C.
	
	Lymphogranuloma venereum
	• Recommended regimen:
	  o Doxycycline 100 mg orally twice a day for 21 days.
	• Alternative regimen:
	  o Erythromycin base 500 mg orally four times a day for 21 days.
	
	Nongonococcal urethritis
	• Recommended regimens:
	  o Azithromycin 1 gram orally in a single dose.
	  o Doxycycline 100 mg orally twice a day for seven days.
	• Alternative regimens:
	  o Erythromycin base 500 mg orally four times a day for seven days.
	  o Erythromycin ethylsuccinate 800 mg orally four times a day for seven days.
	  o Levofloxacin 500 mg orally once daily for seven days.
	  o Ofloxacin 300 mg orally twice a day for seven days.
	
	Ophthalmia neonatorum caused by *Chlamydia trachomatis*
	• Recommended regimen:
	  o Erythromycin base or ethylsuccinate 50 mg/kg/day orally divided into four doses daily for 14 days.
	
	Pelvic inflammatory disease
	• Recommended parenteral regimen A:
	  o Cefotetan 2 grams intravenous every 12 hours.
	  o Cefoxitin 2 grams intravenous every six hours plus doxycycline 100 mg orally or intravenous every 12 hours.
	• Recommended parenteral regimen B:
	  o Clindamycin 900 mg intravenous every eight hours plus gentamicin loading dose intravenous or intramuscular (2 mg/kg of body weight), followed by a maintenance dose (1.5 mg/kg) every eight hours. Single daily dosing (3 to 5 mg/kg) can be substituted.
	• Alternative parenteral regimens:
	  o Ampicillin-sulbactam 3 grams IV every six hours plus doxycycline 100 mg orally or intravenous every 12 hours.
	• Recommended oral regimen:

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	o Ceftriaxone 250 mg intramuscular in a single dose plus doxycycline 100 mg orally twice a day for 14 days with or without metronidazole 500 mg orally twice a day for 14 days. o Cefoxitin 2 grams intramuscular in a single dose and probenecid, 1 gram orally administered concurrently in a single dose, plus doxycycline 100 mg orally twice a day for 14 days with or without metronidazole 500 mg orally twice a day for 14 days. o Other parenteral third-generation cephalosporin (e.g., ceftizoxime or cefotaxime) plus doxycycline 100 mg orally twice a day for 14 days with or without metronidazole 500 mg orally twice a day for 14 days. <u>Proctitis, proctocolitis, and enteritis</u> • Recommended regimen: o Ceftriaxone 250 mg intramuscular plus doxycycline 100 mg orally twice a day for seven days. <u>Recurrent and persistent urethritis</u> • Recommended regimens: o Metronidazole 2 grams orally in a single dose. o Tinidazole 2 grams orally in a single dose plus azithromycin 1 gram orally in a single dose (if not used for initial episode). <u>Sexual assault and sexually transmitted diseases</u> • Recommended regimen: ceftriaxone plus metronidazole plus azithromycin or doxycycline. <u>Primary and secondary syphilis</u> • Recommended regimen for adults: o Benzathine penicillin G 2.4 million units intramuscular in a single dose. • Recommended regimen for infants and children: o Benzathine penicillin G 50,000 units/kg intramuscular, up to the adult dose of 2.4 million units in a single dose. <u>Early latent syphilis</u> • Recommended regimens for adults: o Benzathine penicillin G 2.4 million units intramuscular in a single dose. • Recommended regimens for children: o Benzathine penicillin G 50,000 units/kg intramuscular, up to the adult dose of 2.4 million units in a single dose. <u>Late latent syphilis or latent syphilis of unknown duration</u> • Recommended regimens for adults: o Benzathine penicillin G 7.2 million units total, administered as three doses of 2.4 million units intramuscular each at one-week intervals. • Recommended regimens for children: o Benzathine penicillin G 50,000 units/kg intramuscular, up to the adult dose of 2.4 million units, administered as three doses at one-week intervals.

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	<u>Tertiary syphilis</u>
	• Recommended regimen:
	  o Benzathine penicillin G 7.2 million units total, administered as three doses of 2.4 million units intramuscular each at one-week intervals.
	
	<u>Neurosyphilis</u>
	• Recommended regimen:
	  o Aqueous crystalline penicillin G 18 to 24 million units per day, administered as 3 to 4 million units intravenous every four hours or continuous infusion, for 10 to 14 days.
	• Alternative regimen:
	  o Procaine penicillin 2.4 million units intramuscular once daily plus probenecid 500 mg orally four times a day, both for 10 to 14 days.
	
	<u>Trichomoniasis</u>
	• Recommended regimens: metronidazole 2 grams orally in a single dose or tinidazole 2 grams orally in a single dose.
	• Alternative regimen: metronidazole 500 mg orally twice a day for seven days.
	
	<u>Uncomplicated gonococcal infections of the cervix, urethra, and rectum</u>
	• Recommended regimens:
	  o Ceftriaxone 250 mg intramuscular in a single dose.
	  o Cefixime 400 mg orally in a single dose.
	  o Single-dose injectable cephalosporin regimens plus azithromycin 1 gram orally in a single dose or doxycycline 100 mg orally twice a day for seven days.
	
	<u>Uncomplicated gonococcal infections of the pharynx</u>
	• Recommended regimens:
	  o Ceftriaxone 250 mg intermuscular in a single dose plus azithromycin 1 gram orally in a single dose or doxycycline 100 mg orally twice a day for seven days.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the interferons are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Interferons[1-7]

Indication	Interferon Alfa-2b	Interferon Alfacon-1	Interferon Alfa-n3	Peginterferon Alfa-2a	Peginterferon Alfa-2b
Cancer					
Adjuvant to surgical treatment in patients with malignant melanoma who are free of disease but at high risk for systemic recurrence, within 56 days of surgery	✔				
Initial treatment of clinically aggressive follicular Non-Hodgkin's Lymphoma in conjunction with anthracycline-containing combination chemotherapy	✔				
Treatment of hairy cell leukemia	✔				
Treatment of selected patients with AIDS-related Kaposi's sarcoma	✔				
Condylomata Acuminata					
Intralesional treatment of selected patients with condylomata acuminata involving external surfaces of the genital and perianal areas	✔				
Intralesional treatment of refractory or recurring external condylomata acuminata			✔		
Hepatitis B					
Treatment of chronic hepatitis B in patients with compensated liver disease who have been serum HBsAg positive for at least 6 months and have evidence of HBV replication with elevated serum ALT	✔				
Treatment of patients with HBeAg positive and HBeAg negative chronic hepatitis B infection who have compensated liver disease and evidence of viral replication and liver inflammation				✔	
Hepatitis C					
Treatment of chronic hepatitis C in patients with compensated liver disease who have a history of blood or blood-product exposure and/or are HCV antibody positive	✔				
Treatment of chronic hepatitis C in patients with compensated liver disease		✔			
Treatment of chronic hepatitis C in patients with compensated liver disease who have not been previously treated with interferon alpha				✔	✔

IV. Pharmacokinetics

The pharmacokinetic parameters of the interferons are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Interferons[1-7]

Generic Name(s)	Bioavailability (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Interferon alfa-2b	>90	Kidney, extensive Liver, minor	Not reported	2 to 3
Interferon alfacon-1	83 to 100	Not reported	Renal	1.3 to 3.4
Interferon alfa-n3	Not reported	Kidney, extensive Liver, minor	Not reported	4.43 to 6.76
Peginterferon alfa-2a	>60	Liver	Renal	84 to 353
Peginterferon alfa-2b	Not reported	Liver	Renal	22 to 60

V. Drug Interactions

Significant drug interactions with the interferons are listed in Table 5.

Table 5. Significant Drug Interactions with the Interferons[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
None			

Significance level 1 = major severity, significance level 2 = moderate severity

VI. Adverse Drug Events

The most common adverse drug events reported with the interferons are listed in Table 6. The boxed warning for the interferons is listed in Table 7.

Table 6. Adverse Drug Events (%) Reported with the Interferons[1-7]

Adverse Events	Interferon Alfa-2b	Interferon Alfacon-1	Interferon Alfa-n3	Peginterferon Alfa-2a	Peginterferon Alfa-2b
Cardiovascular					
Arrhythmia	<5	✔	-	✔	✔
Cardiomyopathy	2	✔	-	✔	✔
Chest pain	-	5 to 13	10	<1	6 to 8
Flushing	-	4 to 13	1	-	4 to 6
Hypertension	-	-	-	✔	✔
Hypotension	<5	✔	6	-	✔
Myocardial infarction	✔	✔	-	✔	✔
Tachycardia	<5	✔	-	-	✔
Central Nervous System					
Abnormal thinking	-	8 to 20	-	-	-
Aggressive behavior	<5	✔	-	<1	✔
Agitation/irritability	1 to 22	17 to 21	-	19 to 33	14 to 47
Amnesia	1 to 14	2 to 10	-	-	-
Anxiety	1 to 9	9 to 19	-	✔	28 to 47
Apathy	-	✔	-	-	-
Ataxia	-	✔	-	-	-
Bipolar disorder	-	-	-	✔	✔
Concentration impaired	<1 to 14	-	1	8 to 10	10 to 17
Confusion	<1 to 12	4 to 5	-	-	-
Convulsions	-	✔	-	-	✔
Delusions	-	✔	-	-	-
Depression	3 to 40	18 to 26	2	18 to 20	29 to 59
Drowsiness	1 to 33	4 to 7	-	3 to 5	-
Dizziness	7 to 23	18 to 25	9	13 to 23	12 to 35
Fatigue	8 to 96	65 to 71	6 to 14	24 to 67	52 to 94
Gait abnormal	-	✔	-	-	-
Hallucinations	-	✔	-	✔	✔
Headache	21 to 62	78 to 82	10 to 31	27 to 60	56 to 70
Hemorrhagic cerebrovascular events	✔	✔	-	<1	✔
Homicidal ideation	✔	✔	-	-	✔
Insomnia	<1 to 12	24 to 39	2	19 to 30	23 to 40

Adverse Events	Interferon Alfa-2b	Interferon Alfacon-1	Interferon Alfa-n3	Peginterferon Alfa-2a	Peginterferon Alfa-2b
Ischemic cerebrovascular events	✔	✔	-	✔	✔
Lethargy	8 to 96	2 to 71	65	56 to 65	52 to 66
Loss of consciousness	-	✔	-	-	-
Malaise	8 to 96	2 to 11	65	56 to 65	4 to 7
Mania	-	-	-	✔	✔
Memory impairment	-	✔	-	-	✔
Migraine	-	-	-	-	✔
Nervousness	-	16 to 31	-	19 to 33	4 to 6
Paresthesia	1 to 21	9 to 13	1	-	21
Psychosis	-	-	-	<1	✔
Seizure	-	-	-	✔	-
Shivering	-	-	14 to 87	-	-
Somnolence	1 to 33	4 to 7	10	3 to 5	-
Speech disorder	-	✔	-	-	-
Suicidal behavior	<5	✔	-	<1	✔
Tremors	-	✔	-	-	-
Vertigo	-	-	-	-	✔
Dermatological					
Alopecia	8 to 38	10 to 14	-	18 to 28	22 to 36
Diaphoresis	-	11 to 13	2	6	6 to 11
Dry skin	-	2 to 6	-	4 to 10	11 to 24
Eczema	-	-	-	1 to 5	-
Erythema multiforme	✔	-	-	-	29
Exfoliative dermatitis	-	-	-	8 to 16	-
Herpes labialis	-	-	1	-	-
Phototoxicity	-	-	-	-	<1
Pruritus	-	10 to 14	2	12 to 19	12 to 29
Psoriasis	<5	-	✔	-	✔
Pyoderma gangrenosum	-	✔	-	-	-
Rash	-	10 to 13	1	5 to 8	6 to 24
Stevens-Johnson syndrome	✔	-	-	✔	✔
Toxic epidermal necrolysis	✔	✔	-	-	✔
Urticaria	-	-	-	-	<1
Vasculitis	-	-	-	-	<1
Endocrine and Metabolic					
Diabetes	<5	✔	-	<1	✔
Gynecomastia	<5	-	-	-	-

Adverse Events	Interferon Alfa-2b	Interferon Alfacon-1	Interferon Alfa-n3	Peginterferon Alfa-2a	Peginterferon Alfa-2b
Thyroid dysfunction	-	-	✔	-	-
Thyroiditis	-	-	-	✔	✔
Gastrointestinal					
Abdominal cramping	1 to 23	24 to 41	-	-	-
Abdominal discomfort	1 to 23	24 to 41	-	-	-
Abdominal pain	1 to 23	24 to 41	-	8 to 26	13 to 21
Anorexia	1 to 69	14 to 24	68	16 to 24	20 to 69
Constipation	<1 to 14	9 to 10	-	-	1 to 5
Diarrhea	2 to 45	22 to 29	6	11 to 31	18 to 37
Dry/painful mouth	-	-	6	4 to 6	6 to 12
Dyspepsia	-	10 to 21	3	49	6 to 9
Flatulence	-	5 to 8	3	-	-
Gastrointestinal bleeding	-	✔	-	<1	-
Hemorrhagic colitis	-	✔	-	<1	✔
Ischemic colitis	-	✔	-	<1	✔
Nausea	17 to 66	30 to 40	48	5 to 25	26 to 64
Pancreatitis	✔	✔	-	<1	<1
Taste alterations	<1 to 24	-	1	-	<1 to 38
Vomiting	66	11 to 13	3 to 29	5 to 25	7 to 26
Weight decrease	<1 to 10	16 to 22	-	4 to 16	11 to 29
Genitourinary					
Impaired spermatogenesis	✔	-	-	-	-
Interstitial nephritis	-	-	-	✔	✔
Menstrual cycle abnormalities	-	-	-	-	4 to 7
Nephrotic syndrome	✔	-	-	-	-
Polyuria	<5 to 10	-	-	-	-
Proteinuria	<5	-	-	-	7
Renal failure	✔	✔	-	-	✔
Renal insufficiency	✔	-	✔	-	✔
Hematological					
Anemia	<5	✔	7	2 to 14	11 to 12
Aplastic anemia	✔	✔	-	<1	-
Hematocrit decreased	-	✔	7	17 to 52	✔
Hemoglobin decreased	-	✔	7	17 to 52	✔
Hemolytic anemia	<5	30	-	-	-
Leukopenia	-	24 to 34	3	-	<1 to 10
Lymphopenia	-	✔	-	3 to 14	-

Adverse Events	Interferon Alfa-2b	Interferon Alfacon-1	Interferon Alfa-n3	Peginterferon Alfa-2a	Peginterferon Alfa-2b
Neutropenia	9 to 92	21 to 27	-	21 to 40	6 to 33
Platelets increased or decreased	-	✔	3	33 to 52	-
Pure red cell aplasia	-	-	-	✔	-
Thrombocytopenia	✔	18 to 19	-	5 to 8	5 to 7
Thrombocytopenic purpura	✔	✔	-	✔	✔
Hepatic					
Ascites	-	✔	-	-	-
Fatty liver	-	-	-	✔	-
Hepatic encephalopathy	✔	✔	-	-	-
Hepatomegaly	-	-	-	-	4 to 6
Hepatotoxicity	✔	✔	-	✔	-
Jaundice	<5	✔	-	-	-
Laboratory Test Abnormalities					
Albuminuria	<5	-	-	-	-
Alkaline phosphatase increased	-	-	8	-	23
Alanine aminotransferase increased	<5 to 63	✔	3	✔	10 to 77
Aspartate aminotransferase increased	<5 to 63	✔	3	✔	10 to 77
Bilirubin increased or decreased	<5	✔	4	-	-
Blood urea nitrogen increased	<5	-	-	-	-
Cholesterol increased	✔	✔	✔	20 to 36	✔
Hyperglycemia	<5	✔	✔	-	<1
Hyperkalemia	<5	-	✔	-	-
Hyperthyroidism	<5	✔	-	1 to 2	3
Hypocalcemia	<5	-	✔	-	-
Hypothyroidism	<5	✔	-	3 to 4	5
Lactate dehydrogenase increased	<5	-	-	-	-
Triglycerides increased	✔	✔	✔	20 to 36	✔
Uric acid increased	-	✔	-	-	33 to 38
Musculoskeletal					
Arthralgia	3 to 19	43 to 51	5 to 10	22 to 28	17 to 51
Arthritis	-	✔	-	-	-
Asthenia	5 to 63	7 to 10	-	-	-
Back pain	1 to 15	23 to 42	4	5 to 9	-
Bone pain	-	10 to 14	-	-	-
Limb pain	-	13 to 26	-	-	-
Myalgia	16 to 75	51 to 58	16 to 45	26 to 51	17 to 68
Myasthenia gravis	1 to 21	-	-	-	-

Adverse Events	Interferon Alfa-2b	Interferon Alfacon-1	Interferon Alfa-n3	Peginterferon Alfa-2a	Peginterferon Alfa-2b
Myositis	✔	✔	-	<1	✔
Neck pain	-	5 to 14	-	-	-
Pain	3 to 18	39 to 54	-	10 to 11	21 to 28
Rhabdomyolysis	✔	✔	-	✔	✔
Rigor	-	-	-	25 to 47	21 to 63
Respiratory					
Asthma	≤5	-	-	-	-
Bronchiolitis obliterans	✔	✔	-	-	-
Bronchitis	≤5 to 10	✔	-	-	-
Bronchoconstriction	✔	✔	-	-	-
Cough	<1 to 34	11 to 22	-	4 to 10	5 to 23
Dyspnea	<1 to 34	7 to 8	-	4 to 13	4 to 26
Epistaxis	<5 to 7	-	✔	-	-
Interstitial pneumonitis	✔	✔	-	✔	✔
Pharyngitis	<1 to 34	17 to 34	✔	-	10 to 12
Pneumonia	✔	✔	-	<5	✔
Pulmonary embolism	-	-	-	<1	-
Pulmonary hypertension	✔	✔	-	-	-
Pulmonary infiltrates	✔	✔	-	✔	-
Rhinitis	-	7 to 13	-	-	2 to 8
Sarcoidosis	✔	✔	-	-	-
Sinusitis	<1 to 34	12 to 17	-	-	6 to 7
Respiratory failure	✔	-	-	-	-
Respiratory tract infections	-	16 to 31	-	-	-
Special Senses					
Conjunctivitis	-	-	-	-	4
Decrease or loss of vision	✔	✔	6	✔	✔
Hearing impairment	-	-	-	✔	✔
Hearing loss	✔	✔	-	✔	✔
Macular edema	✔	✔	-	✔	✔
Optic edema	✔	3 to 9	-	✔	✔
Optic neuritis	✔	✔	-	✔	✔
Papilledema	✔	✔	-	✔	-
Retinal artery or vein thrombosis	✔	✔	-	✔	✔
Retinal detachment	✔	✔	-	✔	-
Retinal hemorrhages and cotton wool spots	✔	✔	-	✔	✔
Retinopathy	✔	✔	-	✔	✔

Adverse Events	Interferon Alfa-2b	Interferon Alfacon-1	Interferon Alfa-n3	Peginterferon Alfa-2a	Peginterferon Alfa-2b
Taste/smell disturbances	-	3 to 5	-	-	23
Visual disturbances	<5	3 to 5	1	4 to 5	2 to 5
Other					
Anaphylaxis	<5	3 to 7	-	✔	✔
Angioedema	✔	✔	-	-	✔
Bacterial, fungal and viral infections	✔	✔	✔	<5	✔
Chills	45 to 54	-	14 to 87	-	-
Drug addiction/overdose	✔	✔	-	-	✔
Fever	34 to 94	55 to 61	40 to 81	24 to 54	22 to 75
Flu-like syndrome	20 to 100	8 to 15	✔	✔	✔
Hypersensitivity reactions	✔	✔	-	✔	✔
Injection site reaction	✔	17 to 23	10	10 to 31	47 to 75
Lupus erythematosus	✔	-	-	-	-
Peripheral neuropathy	-	✔	-	✔	✔
Raynaud's phenomenon	✔	-	-	-	-
Rheumatoid arthritis	✔	-	-	-	✔
Sepsis	-	✔	-	<5	✔
Syndrome of inappropriate antidiuretic hormone secretion	<5	-	✔	-	-
Systemic lupus erythematosus	✔	-	-	✔	✔
Vasculitis	✔	-	-	-	-

✔ Percent not specified
- Event not reported

Table 7. Boxed Warning for the Interferons[1]

WARNING
Risk of serious disorders: May cause or aggravate fatal or life-threatening neuropsychiatric, autoimmune, ischemic, and infectious disorders. Monitor patients closely with periodic clinical and laboratory evaluations. Withdraw therapy in patients with persistently severe or worsening signs or symptoms of these conditions. In many, but not all cases, these disorders resolve after stopping therapy. **Use with ribavirin:** Ribavirin may cause birth defects and/or death of the unborn child. Extreme care must be taken to avoid pregnancy in female patients and in female partners of male patients. Ribavirin causes hemolytic anemia. The anemia associated with ribavirin therapy may result in a worsening of cardiac disease. Ribavirin is genotoxic and mutagenic and should be considered a potential carcinogen.

VII. Dosing and Administration

The usual dosing regimens for the interferons are listed in Table 8.

Table 8. Usual Dosing Regimens for the Interferons[1-7]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Interferon alfa-2b	Treatment of selected patients with AIDS-related Kaposi's sarcoma: Injection: 30 MIU/m^2 SC or IM TIW until disease progression or maximal response after 16 weeks Intralesional treatment of selected patients with condylomata acuminata involving external surfaces of the genital and perianal areas: Injection: 1.0 MIU/lesion TIW on alternative days for three weeks, for a maximum of five lesions in a single course. An additional course may be administered at 12 to 16 weeks Initial treatment of clinically aggressive follicular Non-Hodgkin's Lymphoma in conjunction with anthracycline-containing combination chemotherapy: Injection: 5 MIU SC TIW for up to 18 months Treatment of hairy cell leukemia: Injection: 2 MIU/m^2 IM or SC TIW for up to six months Treatment of chronic hepatitis B in patients with compensated liver disease who have been serum HBsAg positive for at least 6 months and have evidence of HBV	Treatment of chronic hepatitis B in patients with compensated liver disease who have been serum HBsAg positive for at least 6 months and have evidence of HBV replication with elevated serum ALT: Injection: ≥1 year of age, 3 MIU/m^2 SC TIW for one week, then 6 MIU/m^2 TIW for a total duration of 16 to 24 weeks	Injection: 6 MIU/mL 10 MIU/mL 18 MIU/mL 50 MIU/mL

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	replication with elevated serum ALT: Injection: 5 MIU daily or 10 MIU TIW SC or IM for 16 weeks Treatment of chronic hepatitis C in patients with compensated liver disease who have a history of blood or blood-product exposure and/or are HCV antibody positive: Injection: 3 MIU TIW SC or IM up to 18 to 24 months; patients who do not normalize their ALT after 16 weeks should be considered for treatment discontinuation Adjuvant to surgical treatment in patients with malignant melanoma who are free of disease but at high risk for systemic recurrence, within 56 days of surgery: Injection: induction, 20 MIU/m^2 IV daily for five consecutive days per week for four weeks; maintenance, 10 MIU/m^2 SC TIW for 48 weeks		
Interferon alfacon-1	Treatment of chronic hepatitis C in patients with compensated liver disease: Injection: monotherapy initial, 9 µg SC TIW for 24 weeks; if no response or relapse upon discontinuation, 15 µg SC TIW for up to 48 weeks; combination treatment with ribavirin, 15 µg SC once daily with ribavirin 500 to 600 mg twice daily for up to 48 weeks	Safety and efficacy in children have not been established	Injection: 9 µg/0.3 mL 15 µg/0.5 mL
Interferon alfa-n3	Intralesional treatment of refractory or recurring external condylomata acuminata: Injection: 0.05 mL/wart twice weekly for up to eight weeks	Safety and efficacy in children have not been established	Injection: 5 MIU/mL
Peginterferon alfa-2a	Treatment of patients with HBeAg positive and HBeAg negative chronic hepatitis B infection who have compensated liver disease and evidence of viral replication and liver inflammation: Injection: 180 µg SC once weekly for 48 weeks Treatment of chronic hepatitis C in patients with compensated liver disease who have not been previously treated with interferon alpha:	Treatment of chronic hepatitis C in patients with compensated liver disease who have not been previously treated with interferon alpha: Injection: ≥5 years of age, 180 µg/1.73 m^2 x BSA SC once weekly; maximum, 180 µg weekly	Injection: 180 µg/0.5 mL 180 µg/mL Kit: 180 µg/0.5 mL Pen injection: 135 µg/0.5 mL 180 µg/0.5 mL

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Injection: monotherapy, 180 µg SC once weekly for 48 weeks; combination treatment with ribavirin, 180 µg SC once weekly for 24 weeks (genotypes 2 and 3) or 48 weeks (genotypes 1 and 4)		
Peginterferon alfa-2b	Treatment of chronic hepatitis C in patients with compensated liver disease who have not been previously treated with interferon alpha: Injection: monotherapy, 1 µg/kg SC once weekly for one year; combination treatment with ribavirin, 1.5 µg/kg SC once weekly for 24 weeks (genotypes 2 and 3) or 48 weeks (genotype 1); treatment duration for patients who previously failed therapy is 48 weeks, regardless of HCV genotype	Hepatitis C (Chronic): Injection: ≥3 years of age, combination treatment with ribavirin, 60 µg/m^2 SC once weekly for 24 weeks (genotypes 2 and 3) or 48 weeks (genotype 1)	Kit: 50 µg/0.5 mL 80 µg/0.5 mL 120 µg/0.5 mL 150 µg/0.5 mL Pen injection kit: 50 µg/0.5 mL 80 µg/0.5 mL 120 µg/0.5 mL 150 µg/0.5 mL

Drug dosing abbreviations: AIDS=acquired immunodeficiency syndrome, ALT=alanine aminotransferase, BSA=body surface area, HBV=hepatitis B virus, HCV= hepatitis C virus, IM= intramuscularly, IV=intravenously, MIU=million international units, SC=subcutaneously, TIW= three times weekly

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the interferons are summarized in Table 9.

Table 9. Comparative Clinical Trials with the Interferons

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Hepatitis B				
Sun et al.[24] (2011) Peginterferon alfa-2a 180 µg/week x 48 weeks vs adefovir 10 mg daily x 72 weeks	OL, RCT Adult patients with chronic hepatitis B with lamivudine resistance	N=235 6 months posttreatment	Primary: Rate of HBeAg seroconversion at week 72 Secondary: Not reported	Primary: At six months posttreatment, significantly more patients in the peginterferon group achieved HBeAg seroconversion compared to adefovir (14.6 vs 3.8%; P=0.01). Overall, the response rate for all patients with lamivudine-resistant HBV was very low at any time period during the study. Patients taking peginterferon alfa-2a experienced a serious adverse event rate of 7.8% compared to 2.4% in the adefovir-treated group. Secondary: Not reported
Wong et al.[25] (2010) Peginterferon alfa-2b 1.5 µg/kg/week for 32 weeks plus lamivudine 100 mg daily for 52 to 104 weeks	2 RCTs (Pooled analysis) Adult Chinese patients with positive HBsAg for >6 months	N=85 5 years	Primary: Virological response at five years (defined as HBeAg seroconversion and HBV DNA reduction to <10,000 copies/mL) Secondary: Serum HBV DNA reduction to <10,000 copies/mL and undetectable level (<100 copies/mL),	Primary: Overall, 28 patients (33%) had a sustained virologic response at the end of the treatment period, and 25 (29%) has a sustained response at five years. At the end of the treatment period, 31 patients (37%) had achieved HBeAg seroconversion. At the five year period, this rate rose to 60% overall. Secondary: At the end of peginterferon treatment, 27 (32%) and 55 (65%) patients had HBV DNA levels undetectable and <10,000 copies/mL, respectively. At five years, these rates were 13 and 31% for undetectable and <10,000 copies/mL, respectively. Only two patients (2.4%) achieved HBsAg seroclearance during the study period. At five years, 48 (57%) patients had normal ALT levels.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			HBsAg seroclearance, normalization of ALT	
Cooksley et al.[26] (2003) Peginterferon alfa-2a 90, 180 or 270 µg/week for 24 weeks vs interferon alfa-2a 4.5 MIU TIW for 24 weeks	RCT Adult patients HBeAg-positive for >6 months	N=194 48 weeks	Primary: Loss of HBeAg after 48 weeks, suppression of HBV, ALT, and the combined response (HBeAg loss, HBV DNA suppression, and ALT normalization) Secondary: Not reported	Primary: After 48 weeks, HBeAg was cleared in 37% of patients taking peginterferon 90 µg, 35% of those taking peginterferon 180 µg, and 29% of those taking peginterferon 270 µg compared to 25% of patients on interferon. The difference between the four treatment groups was not significant (P=0.295). Suppression of HBV occurred in 43% taking peginterferon 90 µg, 39% taking peginterferon 180 µg, and 27% taking peginterferon 270 µg compared to 25% of patients on interferon. The difference between the four treatment groups was not significant (P=0.096). The proportion of normalized ALT occurred in 43% taking peginterferon 90 µg, 35% taking peginterferon 180 µg, and 31% taking peginterferon 270 µg compared to 26% of patients on interferon. The difference between the four treatment groups was not significant (P=0.096). The combined response (HBeAg loss, HBV DNA suppression, and ALT normalization) of all peginterferon alfa-2a doses was twice that achieved with conventional interferon alpha-2a (24 vs 12%; P=0.036). All treatment groups were similar with respect to frequency and severity of adverse events. Secondary: Not reported
Hepatitis C				
Brok et al.[27] (2005) Interferon monotherapy	MA Patients with hepatitis C patients without HIV who received interferon	N=9,991 (72 trials) Variable duration	Primary: Failure of SVR ≥6 months and liver-related morbidity plus all-cause mortality	Primary: Compared to monotherapy, combination therapy with ribavirin significantly reduced the number with failure of SVR (RR, 0.73; 95% CI, 0.71 to 0.75). For the combined total of all patients studied, combination therapy

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs interferon in combination with ribavirin	monotherapy or a combination of ribavirin and interferon		Secondary: Failure of end-of-treatment virologic response, failure of histological response, quality of life (QOL) and adverse events	significantly reduced morbidity and mortality (OR, 0.46; 95% CI, 0.22 to 0.96); however, morbidity and mortality were not significantly reduced compared to patients classified as naïve alone, nonresponders alone, or relapsers alone. Secondary: Combination therapy significantly reduced the number of patients with failure of virologic response at end-of-treatment (RR, 0.70; 95% CI, 0.67 to 0.72). Failure of histological response was significantly reduced with combination therapy, significantly reducing the number of patients with failure with grading (RR, 0.84; 95% CI, 0.80 to 0.87) and staging (RR, 0.95; 95% CI, 0.92 to 0.97). Where measured, combination therapy was found to significantly increase QOL, including measures of general health, social functioning and mental health. Anemia was reported in 22% of patients on combination therapy compared to 0.8% on monotherapy therapy (RR, 18.22; 95% CI, 12.92 to 25.70). Rates of leukopenia were significantly higher in patients treated with combination therapy (RR, 4.32; 95% CI, 1.56 to 11.90). Rates of dermatological and gastrointestinal adverse events also occurred significantly more often with combination therapy.
Chung et al.[28] (2004) Interferon alfa-2a 6 MIU TIW for 12 weeks, then 3 MIU for 36 weeks plus ribavirin vs peginterferon	RCT Adult HIV-infected patients with a confirmed diagnosis of hepatitis C not previously treated with interferon alfa	N=133 48 weeks	Primary: Virologic response at 24 weeks Secondary: SVR 24 weeks after treatment, virologic response at end of treatment, histologic response and changes in HIV control	Primary: At 24 weeks, 44% of patients on peginterferon had a virologic response compared to 15% on interferon (P<0.001). Secondary: SVR 24 weeks after treatment was reported in 27% of patients on peginterferon compared to 12% on interferon (P<0.03). At the end of treatment, 41% of patients on peginterferon had a virologic response compared to 12% on interferon (P<0.001). In patients without a virologic response, histologic response was reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
alfa-2a 180 µg/week for 48 weeks plus ribavirin				in 35% of patients on peginterferon and 36% on interferon. CD4 cell counts increased 3.5% in patients on peginterferon and 3.0% on interferon. Rates of influenza-like symptoms, depression, and decreases in hemoglobin occurred at comparable rates between treatment groups. Eight patients in each treatment group were withdrawn due to an adverse event or laboratory value abnormality.
Zeuzem et al.[29] (2000) Interferon alfa-2a 6 MIU TIW for 12 weeks, then 3 MIU for 36 weeks vs peginterferon alfa-2a 180 µg/week for 48 weeks	RCT Interferon naïve adult patients with a confirmed diagnosis of hepatitis C	N=531 72 weeks	Primary: Virologic response and ALT normalization at 72 weeks	Primary: At 72 weeks, 39% of patients on peginterferon had a virologic response compared to 19% on interferon (P=0.001). At 72 weeks, sustained normalization of ALT occurred in 45% of patients on peginterferon compared to 25% on interferon (P=0.001). The frequency and severity of drug-related adverse events were comparable between treatment groups. Depression occurred in 16% of those on peginterferon and 23% of those on interferon. Psychiatric disorders were reported in six patients on peginterferon and four of those on interferon.
Rasenack et al.[30] (2003) Interferon alfa-2a 6 MIU TIW for 12 weeks then 3 MIU for 36 weeks vs peginterferon alfa-2a 180 µg/week for 48 weeks	RCT Interferon naïve adult patients with a confirmed diagnosis of hepatitis C	N=531 24 weeks	Primary: Quality of life measured by 36–item Short-Form Health Survey (SF-36) and fatigue measured by the 10-item Fatigue Severity Scale (FSS) Secondary: Not reported	Primary: At weeks two and 12, a significantly higher quality of life score was observed with peginterferon compared to interferon (P<0.05). No significant difference was observed at weeks 24 or 48 between treatment groups. At weeks two, 12, and 24, significantly less disabling fatigue was observed with peginterferon compared to interferon (P<0.01). No significant difference was observed at week 48 between treatment groups. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Nevens et al.[31] (2010) Interferon alfa-2a 6 MIU TIW for 8 weeks, then 3 MIU TIW plus ribavirin vs peginterferon alfa-2a 180 µg/week plus ribavirin	MC, OL, RCT Adult patients with chronic hepatitis C	N=443 24 to 48 weeks	Primary: SVR rate as assessed by polymerase chain reaction 24 weeks after treatment Secondary: Sustained biochemical response rate (abnormal ALT) at 24 weeks after treatment; proportion of patients with undetectable HCV RNA at weeks 12, 24, and 48	Primary: After 24 weeks, SVR rates were significantly greater in the peginterferon group compared to the interferon group (52 vs 27%; P<0.001). Secondary: Sustained biochemical response rates were significantly greater in the peginterferon group compared to the interferon group (53 vs 34%; P<0.001). In respect to undetectable HCV RNA levels at weeks 12, 24, and 48, the peginterferon group had rates of 70, 84, and 87%, while the interferon group had rates of 42, 52, and 73%, respectively. A total of 190 patients (42.8%) discontinued therapy prematurely due to a lack of efficacy, adverse events, personal reasons, and lack of follow-up data. In the patients who did continue therapy, hematologic abnormalities were the most common adverse events with rates of anemia (29.7 vs 19.8%), thrombocytopenia (23.1 vs <10%), leucopenia (21.8 vs 10.4%) and neutropenia (18.3 vs <10%) for the peginterferon group compared to the interferon group.
McHutchison et al.[32] (1998) Interferon alfa-2b 3 MIU TIW for 24 to 48 weeks vs interferon alfa-2b 3 MIU TIW plus ribavirin 1,000 to 1,200 mg daily for 24 or 48 weeks	DB, PC, RCT Adult patients with hepatitis C	N=912 24 to 48 weeks	Primary: SVR 24 weeks after treatment Secondary: ALT and histologic improvement	Primary: SVR was significantly higher for all those on combination therapy (31 to 38%) compared to those receiving interferon alone (6 to 13%; P<0.001). Secondary: ALT levels normalized at the end of treatment in 58 to 65% of patients on combination therapy compared to 24 to 28% on monotherapy. Histologic improvement was significantly higher in patients on combination therapy (57 to 61%) compared to those on monotherapy (41 to 44%). Anemia necessitating a reduction in ribavirin dose occurred in 8% of patients on combination therapy. Dyspnea, pharyngitis, pruritus, rash, nausea, insomnia, and anorexia were more common with combination therapy than monotherapy. Dose reductions due to an adverse event occurred in 13 to 17% of patients on combination therapy compared to 9

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				to 12% in monotherapy.
Enriquez et al.[33] (2000) Interferon alfa-2b 3 MIU TIW plus ribavirin 1,000 to 1,200 mg daily for 24 weeks vs interferon alfa-2b 3 MIU TIW plus ribavirin 1,000 to 1,200 mg daily for 48 weeks	RCT Adult patients with hepatitis C who had previously received one or more courses of interferon alfa without achieving a sustained response	N=120 24 to 48 weeks	Primary: Virologic response at end of treatment and SVR at six months after treatment Secondary: Not reported	Primary: Virologic response at the end of therapy was 44.8% in those treated for 24 weeks and 46.8% in those treated for 48 weeks (P=0.85). SVR at six months was significantly higher in those treated for 48 weeks (37.1 vs 15.5%; P=0.013). Dose adjustments due to decreased hemoglobin levels occurred in 5% of patients treated for 48 weeks and 3% in those treated for 24 weeks. Influenza-like symptoms were reported in most patients for both treatment groups during the first two to four weeks. Secondary: Not reported
Poynard et al.[34] (1998) Interferon alfa-2b 3 MIU TIW plus ribavirin 1,000 to 1,200 mg daily for 24 weeks vs interferon alfa-2b 3 MIU TIW plus ribavirin 1,000 to 1,200 mg daily for 48 weeks vs interferon alfa-2b	MC, PC, RCT, Adult patients with compensated hepatitis C not previously treated	N=832 48 weeks	Primary: SVR at week 24 after treatment Secondary: ALT and histological improvement	Primary: SVR was significantly higher for both combination regimens compared to monotherapy (P<0.001). SVR was observed in 43% of combination therapy patients treated for 48 weeks and in 35% of those treated for 24 weeks compared to 19% with SVR among those treated with monotherapy. Secondary: ALT normalization was significantly higher with combination therapy patients treated for 48 weeks (50%) compared to those treated for 24 weeks (39%; P=0.02) and those on monotherapy (24%; P<0.001). Inflammation improvement was significantly higher in patients on 48 weeks of combination therapy (63%) compared to those on 24 weeks therapy (52%; P=0.05) and monotherapy (39%; P<0.001). Those on 24 weeks of combination therapy had significantly greater improvement in inflammation compared to monotherapy (52 vs 39%; P=0.007). Significantly more patients treated for 48 weeks (monotherapy and combination therapy) discontinued therapy due to an adverse reaction,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
3 MIU TIW plus placebo for 48 weeks				compared to those treated for 24 weeks.
Sjogren et al.[35] (2005) Interferon alfa-2b 3 MIU TIW plus ribavirin 1,000 mg/day vs interferon alfacon-1 15 µg TIW plus ribavirin 1,000 mg/day	RCT Adult patients with chronic hepatitis C	N=128 48 weeks	Primary: SVR at 24 weeks after treatment Secondary: Virologic response based on baseline viral load and response of those with genotype 1	Primary: Twenty-four weeks after treatment, 57% of patients on interferon alfacon-1 had SVR compared to 40% on interferon alfa-2b (P=0.052). Secondary: In patients with a high viral load, a virologic response was observed in 57% of patients on interferon alfacon-1 compared to 31% on interferon alfa-2b (P=0.025). In patients with genotype 1, a response was observed in 46% of patients on interferon alfacon-1 compared to 14% on interferon alfa-2b (P=0.019). Drug-related adverse events were comparable between treatment groups.
Manns et al.[36] (2001) Interferon alfa-2b 3 MIU TIW plus ribavirin 1,000 to 1,200 mg daily vs peginterferon alfa-2a 1.5 µg/kg/week plus ribavirin 800 mg daily vs peginterferon alfa-2a 1.5	RCT Adult patients with a confirmed diagnosis of hepatitis C not previously treated	N=1,530 48 weeks	Primary: SVR Secondary: SVR for genotype 1, 2, and 3	Primary: SVR rates were significantly higher for the high-dose peginterferon regimen (54%) compared to low-dose peginterferon (47%; P=0.01) and interferon (47%; P=0.01). Secondary: The SVR rate for genotype 1 was 42% for the high-dose peginterferon regimen compared to 34% for low-dose peginterferon and 33% for interferon (P=0.02 vs high-dose peginterferon). The SVR rates for genotype 2 and 3 were approximately 80% for all treatment groups. The side-effect profiles were comparable among treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
µg/kg/week for 4 weeks, then 0.5 µg/kg/week plus ribavirin 1,000 to 1,200 mg daily				
Carrat et al.[37] (2004) Interferon alfa-2b 3 MIU TIW plus ribavirin 800 mg daily for 48 weeks vs peginterferon alfa-2b 1.5 µg/kg/week plus ribavirin 800 mg daily for 48 weeks	RCT Adult HIV-infected patients with a confirmed diagnosis of hepatitis C not previously treated with interferon alfa	N=412 72 weeks	Primary: SVR at week 72 Secondary: Histological improvement, as measured by Metavir score and Ishak grade	Primary: SVR rates were significantly higher for the peginterferon regimen (27%) compared to interferon (20%; P=0.01). Secondary: Metavir scores decreased significantly with the peginterferon regimen (-0.19) compared to interferon (0.01; P=0.02). Mean changes in Ishak score were –0.57 for peginterferon and –0.26 with interferon (P=0.24). Doses of peginterferon were modified in 16% of patients due to clinical adverse events compared to 7% with interferon (P=0.004). Dose adjustments due to laboratory abnormalities occurred in 20% of patients on peginterferon and 7% with interferon (P=0.004). Treatment discontinuation due to an adverse event was comparable between treatment groups.
Lindsay et al.[38] (2001) Interferon alfa-2b 3 MIU TIW vs peginterferon alfa-2b 0.5, 1.0, or 1.5 µg/kg/week	RCT Adult patients with hepatitis C and compensated liver disease not previously treated	N=1,219 48 weeks	Primary: SVR 24 weeks after completion of therapy Secondary: Normalization of ALT and improvement of liver histology	Primary: For all three doses of peginterferon, SVR was significantly higher (P≤0.042) compared to interferon therapy. Secondary: At the end of therapy, normal ALT values were significantly higher for the 1 µg/kg (31%; P=0.002) and 1.5 µg/kg (33%; P<0.001) peginterferon groups compared to 20% with interferon. There were no significant differences in the 0.5 µg/kg peginterferon group and interferon. All three doses of peginterferon decreased liver inflammation to a greater extent compared to interferon therapy. The incidence and severity of adverse events were similar between treatment groups. Peginterferon regimens did demonstrate a higher incidence of injection site reactions.
Fried et al.[39]	RCT	N=1,121	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2002) Interferon alfa-2b 3 MIU TIW plus ribavirin 1,000 to 1,200 mg daily vs peginterferon alfa-2a 180 µg/week vs peginterferon alfa-2a 180 µg/week plus ribavirin 1,000 to 1,200 mg/day	Adult patients with a confirmed diagnosis of hepatitis C not previously treated with interferon alfa	48 weeks	SVR at 24 weeks after therapy Secondary: Virologic response at end of therapy and virologic response for genotype 1, 2, and 3	SVR rates 24 weeks after therapy were significantly higher for the peginterferon combination regimen (56%) compared to the interferon combination regimen (44%; P<0.001) and peginterferon monotherapy regimen (29%; P<0.001). Secondary: Virologic response rates at end of therapy were significantly higher for the peginterferon combination regimen (69%) compared to interferon (52%; P<0.001) and peginterferon monotherapy (59% P=0.01). SVR rates for genotype 1 were significantly higher for the peginterferon combination regimen (46%) compared to interferon (36%; P=0.01) and peginterferon monotherapy (21%; P<0.001). SVR rates for genotype 2 or 3 were significantly higher for the peginterferon combination regimen (76%) compared to interferon (61%; P=0.005) and peginterferon monotherapy (45%). Withdrawals due to adverse events were comparable between treatment groups. The most common reason for discontinuation was a psychiatric disorder. Both peginterferon regimens had a lower incidence of influenza-like symptoms and depression compared to interferon (P<0.05).
Swain et al.[40] (2010) Peginterferon alfa-2a 90 to 270 µg/week plus ribavirin 800 to 1,600 mg/day	9 RCTs (Pooled analysis) Patients with chronic hepatitis C	N=3,460 Variable duration	Primary: Percentage of patients with significant clinical events (death, liver transplant, decompensated liver disease, encephalopathy or ascites, hepatic malignancy); undetectable HCV RNA (<50 IU/mL) at last assessment in the primary trial	Primary: A total of 1.2% of patients reported a major clinical event during the follow-up period. The most common reported events were ascites, encephalopathy, and hepatic malignancy. A total of 89.1% of patients had undetectable HCV RNA at the last visit of their primary study and at least one HCV RNA assessment in the long-term follow-up period of the study. Of these patients, 98.7% continued to have an undetectable HCV RNA at a mean of four years after the end of their primary study. The main findings of this study showed that patients treated with peginterferon alfa-2a plus ribavirin do not require frequent follow-up laboratory assessment of their HCV RNA status.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: Not reported	Secondary: Not reported
Lam et al.[41] (2010) Peginterferon alfa-2a 180 µg/week plus ribavirin 800 to 1,200 mg daily for 24 weeks vs peginterferon alfa-2a 180 µg/week plus ribavirin 800 to 1,200 mg daily for 48 weeks	OL, MC, RCT Treatment-naïve adults with chronic hepatitis C genotype 6	N=60 24 to 48 weeks	Primary: SVR at the end of treatment period Secondary: Rapid virologic response (RVR), complete early virologic response (EVR), end of treatment response (ETR), biochemical response, and treatment adherence	Primary: At the end of the treatment period, there was no significant difference between the patients randomized to either 24 or 48 weeks of peginterferon for sustained virologic response (70% for 24 weeks vs 79% for 48 weeks; P=0.48). Secondary: Of the subgroup of patients who had HCV RNA polymerase chain reaction testing at week four of therapy, 85% in the 24 week group and 63% in the 48 week group achieved RVR (P=0.12). RVR was a significant predictor of SVR in the 48-week group and trending towards significance in the 24-week group: 82 and 83% of those with RVR achieved SVR compared to 33 and 29% for the 24-week and 48-week groups, respectively (P=0.07 and P=0.02). A similar percentage of patients in both the 24-week and 48-week groups achieved complete EVR (96 vs 97%; P=0.90) and ETR (89 vs 94%; P=0.48). Normalization of serum ALT levels six months after therapy was lower in the 24-week group compared to the 48-week group (78 vs 91%; P=0.16). Treatment adherence was 63% in the 24-week group compared to 79% for the 48-week group (P=0.18). There were no differences between the two treatment groups for rates of adverse events.
Ferenci et al.[42] (2010) Peginterferon alfa-2a 180 µg/week plus	RCT, MC Adult patients with chronic hepatitis C genotypes 1 and 4 who had early	N=517 24 weeks posttreatment	Primary: Relapse and SVR (defined as an undetectable HCV RNA at the end of the 24 week	Primary: The relapse rate was 33.6% in group A and 18.5% in group B (P=0.0115). The SVR rate was 51.1% in group A and 58.6% in group B (P>0.1). The overall SVR rate was 50.4%, including 115 of 150 patients with an

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ribavirin 1,000 to 1,200 mg/day for 48 weeks (group A) vs peginterferon alfa-2a 180 µg/week plus ribavirin 1,000 to 1,200 mg/day for 72 weeks (group B)	virologic response (undetectable HCV RNA at 24 weeks)		follow-up) Secondary: Not reported	RVR treated for 24 weeks and four of 78 patients without an EVR. There was no significant difference for rates of adverse events between the two treatment groups. Overall, there was a 17.3% adverse event rate in the 48 week group and 22.7% adverse event rate in the 72 week group. Secondary: Not reported
Katz et al.[43] (2012) Peginterferon (alfa-2a or alfa-2b) and ribavirin for 72 weeks vs peginterferon (alfa-2a or alfa-2b) and ribavirin for 48 weeks	MA Genotype 1 hepatitis C patients who are slow virological responders to peginterferon and ribavirin treatment (two definitions of slow responders: 1) patients with ≥2 log viral reduction but still detectable HCV RNA after 12 weeks of treatment and undetectable HCV RNA after 24 weeks of treatment; 2) patients with detectable HCV RNA after four weeks of treatment)	N=1369 (7 trials)	Primary: Mortality, liver-related morbidity Secondary: SVR24, relapse, adherence, adverse events	Primary: Overall mortality, HCV-related mortality, and liver-related morbidity were not reported by any of the included trials. Secondary: When pooling the results of the five trials which defined slow responders according to the first definition, a small but significant increase in the SVR proportion was seen after extending treatment to 72 weeks (RR, 1.43; 95% CI, 1.07 to 1.92; P=0.02, I^2=8%). In a meta-analysis of the three trials which defined the slow responders as patients without rapid virologic response, a statistically significant difference between the two groups (RR, 1.27; 95% CI, 1.07 to 1.50; P=0.006, I^2=38%) was also found. The end of treatment response was not significantly different between slow responders who were treated for 48 weeks and those treated for 72 weeks. This lack of difference was identified with both definitions of slow responders. The length of treatment did not affect the adherence proportion (RR, 0.95; 95% CI, 0.84 to 1.07; P=0.42, I^2=69%, 3 trials).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Di Bisceglie et al.[44] (2007) Peginterferon alfa-2a 180 µg/week plus ribavirin 1,000 to 1,200 mg/day for 12 weeks vs peginterferon alfa-2b 1.5 µg/kg/week plus ribavirin 1,000 to 1,200 mg/day for 12 weeks	OL, RCT Treatment-naïve adult patients with chronic hepatitis C genotype 1	N=341 12 weeks	Primary: Change in HCV-RNA concentration at week 12 Secondary: Incidence of adverse events	Primary: At the end of week 12, there was no significant difference between the two treatment groups for change in HCV-RNA concentration. There was also no significant difference at weeks four and eight. Secondary: There was no significant difference between the two treatment groups for rates of adverse events. However, there was an increase in the relative frequency of chills, fever, influenza-like illness, decreased appetite, rash, vomiting, and injection site reactions in the peginterferon alfa-2b group.
Escudero et al.[45] (2008) Peginterferon alfa-2a 180 µg/week plus ribavirin 800 to 1,200 mg/day vs peginterferon alfa-2b 1.5 µg/kg/week plus ribavirin 800 to 1,200 mg/day The duration of	OL Treatment-naïve adult patients with chronic hepatitis C	N=183 24 weeks posttreatment	Primary: SVR (defined by undetectable HCV RNA at week 72) Secondary: Rapid virological response at four weeks, early virological response at 12 weeks, transient virological response, adverse events	Primary: There was no significant difference between the two treatment groups for SVR (65.9% for PEG-INF alfa-2a group vs 62% for PEG-INF alfa-2b group; P=0.64). There were no differences in the percentage of patients with sustained virological response according to HCV genotype. In the subset of patients with HCV genotype 1, 50.8% of those treated with PEG-IFN alfa-2a plus ribavirin achieved sustained virological response compared to 46.6% for PEG-IFN alfa-2b plus ribavirin (P=0.713). The corresponding figures for HCV genotype 2/3 were 95 vs 89.3% (P=0.63) and for genotype 4 were 91.7 vs 83.3% (P=1.0). Other efficacy variables including rapid virological response at four weeks, early virological response at 12 weeks and transient virological response were also similar among patients in both treatment groups. There were similar rates of adverse events in both treatment groups as well

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
treatment was 24 weeks for patients with HCV genotypes 2 or 3, and 48 weeks for those with HCV genotypes 1 or 4.				as discontinuation of study drug due to adverse events (22 patients alfa-2a group vs 28 patients alfa-2b group, P=NS).
Scotto et al.[46] (2008) Peginterferon alfa-2a 180 µg/week plus ribavirin 15 mg/kg/day for 48 weeks vs peginterferon alfa-2b 1.5 µg/kg/week plus ribavirin 15 mg/kg/day for 48 weeks	OL, RCT Adult patients with chronic hepatitis C who were unresponsive to previous combined therapy (standard interferon alfa plus ribavirin for ≥3 months)	N=108 24 weeks posttreatment	Primary: SVR (defined by undetectable serum HCV RNA at 72 weeks) Secondary: Sustained biochemical response, adverse events	Primary: At the end of the 72-week period, there was no difference between the two treatment groups for SVR (20.4% for PEG-INF alfa-2a vs 18.5% for PEG-INF alfa-2b; P=NS). Secondary: There was no difference in normalization of ALT levels at the end of the 72-week period (22.2% PEG-INF alfa-2a group vs 24.1% PEG-INF alfa-2b group; P=NS). In terms of adverse events, there was no difference between the two groups.
Rumi et al.[47] (2010) Peginterferon alfa-2a 180 µg/week plus ribavirin 1,000 to 1,200 mg/day for 24 to 48 weeks (depending on genotype)	OL, RCT Treatment-naïve adult patients with chronic hepatitis C	N=431 24 weeks posttreatment	Primary: SVR (undetectable HCV-RNA 24 weeks after treatment), adverse events Secondary: Not reported	Primary: The overall SVR rate was higher in PEG-IFN alfa-2a group than in PEG-INF alfa-2b group (66 vs 54%, respectively; P=0.02). In patients with genotype 1 and 4, the SVR rates were 48 and 32% with PEG-IFN alfa-2a and PEG-IFN alfa-2b, respectively (P=0.04). In patients with genotype 2, the SVR rates were 96 and 82% with PEG-IFN alfa-2a and PEG-IFN alfa-2b, respectively (P=0.01). Rates of adverse events were similar between the two treatment groups. Eighteen patients in the peginterferon alfa-2a group compared to 23 in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs peginterferon alfa-2b 1.5 µg/kg/week plus ribavirin 800 to 1,200 mg/day for 24 to 48 weeks (depending on genotype)				alfa-2b group discontinued therapy due to adverse events. Secondary: Not reported
Ascione et al.[48] (2010) Peginterferon alfa-2a 180 µg/week plus ribavirin 1,000 to 1,200 mg/day for 48 weeks (genotype 1 or 4) or 24 weeks (genotype 2 or 3) (group A) vs peginterferon alfa-2b 1.5 µg/kg/week plus ribavirin 1,000 to 1,200 mg/day for 48 weeks (genotype 1 or 4) or 24 weeks (genotype 2 or 3) (group B)	RCT, OL Treatment-naïve adult patients with chronic hepatitis C	N=320 24 weeks posttreatment	Primary: SVR after 24 weeks of untreated follow-up Secondary: Not reported	Primary: SVR was achieved in 68.8% of patients treated with peginterferon alfa-2a compared to 54.4% of patients treated with peginterferon alfa-2b (P=0.008). Higher SVR rates were obtained in group A than group B among patients with genotype 1/4 (54.8 vs 39.8%; P=0.04), with genotype 2/3 (88.1 vs 74.6%; P=0.046), without cirrhosis (75.6 vs 55.9%; P=0.005), and with baseline levels HCV RNA >500,000 IU/mL (69 vs 46.2%; P=0.002). SVR rates in groups A and B were not statistically different among patients with baseline HCV RNA ≤500,000 IU/mL (68.4 vs 65.7%; P=0.727) or in patients with cirrhosis (42.4 vs 46.1%; P=0.774). Secondary: Not reported
Kamal et al.[49]	OL, RCT	N=213	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2011) Peginterferon alfa-2a 180 µg/week plus ribavirin 1,000 to 1,200 mg daily for 48 weeks vs peginterferon alfa-2b 1.5 µg/kg/week plus ribavirin 1,000 to 1,200 mg/day for 48 weeks	Treatment-naïve adult patients with chronic hepatitis C genotype 4	24 weeks posttreatment	SVR defined by undetectable HCV RNA 24 weeks after treatment Secondary: Biochemical response, histological response, quality of life, adverse events, adherence	Significantly more patients in the PEG-INF alfa-2a group had achieved SVR at the end of the study period compared to the PEG-INF alfa-2b group (70.6% PEG-INF alfa-2a vs 54.6% PEG-INF alfa-2b; P=0.0172). Significantly more patients in the PEG-INF alfa-2b group had relapse compared to the PEG-INF alfa-2a group (15.7 vs 5.1%; P=0.0019). Secondary: Among patients treated with PEG-IFN alfa-2a and ribavirin, 41.3% had undetectable HCV RNA after 4 weeks of therapy (RVR) compared to 27.78% of patients treated with PEG-IFN alfa-2b and ribavirin (P=0.0456). Among those who did not achieve RVR, 46.9 and 26.9% of patients in PEG-IFN alfa-2a and PEG-IFN alfa-2b groups, respectively, had undetectable HCV RNA at week 12 (P=0.1213). A total of 39.1 and 30.8% of patients in PEG-IFN alfa-2a and PEG-IFN alfa-2b groups, respectively, had a >2 $\log_{10}$ decline in HCV RNA (P=0.3754). Significantly more patients with RVR went on to achieve an SVR compared to their counterparts who lacked that response (97.3 vs 2.7%; P<0.0001). The mean time duration to aviremia was longer among patients receiving PEG-IFN alfa-2b than PEG-IFN alfa-2a (P=0.0283). Follow-up biopsies, performed on 42 patients showed that the rates of improvement in liver steatosis, liver grading scores and fibrosis scores at the end of the study period did not differ significantly between groups (P>0.05). The SF-36v2 and Chronic Liver Disease Questionnaire (CLDQ) were low during therapy and improved significantly after therapy successful therapy.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Overall, there was no significant difference between the two groups for rates of adverse events.
Brixner et al.[50] (2009) Peginterferon alfa-2a plus ribavirin (2a group) vs peginterferon alfa-2b plus ribavirin (2b group)	RETRO Adult patients with chronic hepatitis C	N=1783 Variable duration	Primary: Treatment persistence (duration of prescriptions filled after index date)	Primary: There was no significant difference in persistence rates for patients in the 2a group compared to the 2b group (median time to discontinuation: 245 vs 226 days, respectively; P=0.072).
Witthoeft et al.[51] (2010) Peginterferon alfa-2a plus ribavirin (group A) vs peginterferon alfa-2b plus ribavirin (group B) Dosing was up to discretion of treating physician.	RETRO Adult patients with chronic hepatitis C	N=3470 24 weeks	Primary: Early virologic response (≥2 $\log_{10}$ drop in HCV RNA or HCV RNA ≤50 IU/mL after 12 weeks), end of treatment response (EOT) and sustained virological response (SVR; HCV RNA ≤50 IU/mL or HCV RNA undetectable after 24 weeks) Secondary: Not reported	Primary: There was no significant difference in any of the virological response parameters measured between group A and group B. Overall, significantly fewer patients in group A discontinued therapy prior to the end of treatment compared to those in group B (21.8 vs 29.6%, P≤0.0001). Secondary: Not reported
Dogan et al.[52] (2013)	RCT	N=78	Primary: Rapid virological	Primary: The RVR (31 vs 26%), EVR (83 vs 81%), ETR (74 vs 63%), and SVR (46

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Peginterferon alfa (pegINFa)-2a 180 µg/week vs PegINFa-2b 1.5 µg/kg of body weight/week Both treatments were in combination with oral ribavirin (<75 kg, 1000 mg/day; ≥75 kg, 1200 mg/day)	Adult patients with chronic HCV genotype 1 infection with compensated liver disease and a detectable plasma HCV RNA level, and had not been treated previously for hepatitis C infection	Patients underwent treatment for up to 48 weeks and follow-up for 24 weeks	response (RVR), early virological response (EVR), end of treatment response (ETR), and SVR Secondary: Not reported	vs 51%) rates were similar for PegINFa-2a and PegINFa-2b groups, respectively. The overall SVR rate for these standard therapies was 48.7%. According to multivariable logistic regression analyses, virological responses were strongly related to baseline HCV viral load, but not degree of liver fibrosis. Secondary: Not reported
Flori et al.[53] (2013) Peginterferon alfa-2a vs peginterferon alfa-2b Both in combination with ribavirin	MA Adult patients with chronic hepatitis C without a history of liver transplantation or HIV	N=18,260 (26 studies) Variable duration	Primary: SVR Secondary: Adverse events	Primary: For studies using peginterferon alfa-2b at 1.5 µg/kg/week, the SVR was 44.5 % for the peginterferon alfa-2a and ribavirin group, and 38.6 % for the peginterferon alfa-2b and ribavirin group. The SVR was found to be significantly higher for the peginterferon alfa-2a and ribavirin group (OR, 1.24; 95% CI, 1.10 to 1.40; P<0.001, random-effects model). The analysis including all studies regardless of peginterferon alfa-2b dose remained significantly in favor of peginterferon alfa-2a (OR, 1.23; 95% CI, 1.10 to 1.37; P<0.001). Secondary: Adverse events leading to treatment discontinuation were reported in 12 studies. The frequency of adverse events was found to be similar in both groups: 11.2% for the peginterferon alfa-2a group and 10.2% for the peginterferon alfa-2b group (OR, 1.17; 95% CI, 0.98 to 1.38; P=0.08, fixed-effects model).
Van Vlierberghe et al.[54]	OL, OBS	N=219	Primary: SVR (defined by	Primary: A total of 49.3% of patients had an undetectable HCV RNA at the end of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2010) Peginterferon alfa-2b 1.5 µg/kg/week plus ribavirin 800 to 1,200 mg/day for 48 weeks	Treatment-naïve adult patients with chronic hepatitis C	48 weeks	undetectable HCV RNA 6 months after treatment completion) Secondary: Not reported	48 weeks of therapy. However, there was a fairly significant dropout rate and loss to follow-up (98 patients; 44.7%). A total of 41 patients discontinued therapy at various time points due to adverse events (n=23) or serious adverse events (n=18). The most common serious adverse events were anemia, fatigue/asthenia/malaise, and fever. Secondary: Not reported
Bruix et al.[55] (2011) Peginterferon alfa-2b 0.5 µg/kg/week vs no treatment	OL, RCT Adult patients with chronic hepatitis C who had failed previous interferon alfa plus ribavirin therapy	N=626 5 years	Primary: Time to development of first clinical event of liver decompensation, development of hepatocellular carcinoma, death, or liver transplantation Secondary: Not reported	Primary: There was no significant difference between the treatment groups for time to first clinical event (11 vs 9% for peginterferon and no treatment groups, respectively; P=0.144). There were significantly more adverse events in the treatment group compared to the no treatment group. Additionally, significantly more patients discontinued therapy in the treatment group compared to the no treatment group. Secondary: Not reported
Buti et al.[56] (2010) Peginterferon alfa-2b 1.5 µg/kg/week plus ribavirin 800 to 1,400 mg/day for 48 weeks (group A) vs	OL, MC, RCT Adult patients with chronic hepatitis C genotype 1	N=1,428 48 to 72 weeks	Primary: SVR at the end of the treatment period Secondary: End-of-treatment virologic response, relapse rates, adverse events	Primary: At the end of the treatment period, there was no difference in the rates of SVR between the two treatment groups (43 vs 48%, P=0.644). Secondary: End-of-treatment response was 83 and 70% in groups A and B, respectively. Relapse rates were similar in slow responders treated for 48 or 72 weeks (47 vs 33%; P=0.169). There was no significant difference between the two groups when comparing adverse events; however the raw rates of adverse events in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
peginterferon alfa-2b 1.5 µg/kg/week plus ribavirin 800 to 1,400 mg/day for 72 weeks (group B)				group receiving 72 weeks of treatment were higher and may represent a clinical significance (3.5 vs 8.2%).
Brady et al.[57] (2010) Peginterferon alfa-2b 3.0 µg/kg/week for 12 weeks, then 1.5 µg/kg/week for 36 weeks, plus ribavirin 11 to 15 mg/kg/day for 48 weeks (induction group) vs peginterferon alfa-2b 1.5 µg/kg/week plus ribavirin 11 to 15 mg/kg/day for 48 weeks (SOC)	RCT, OL Treatment-naïve adult patients with chronic hepatitis C genotype 1 or 4	N=610 6 months	Primary: SVR defined as persistent loss of HCV RNA at 6 months of follow-up evaluation after completion of 48 weeks of treatment Secondary: Early virologic response (virus-negative at week 12); subgroup analysis of SVR response in African American and Hispanic populations	Primary: Complete early virologic response was 62.6 vs 57.7% in induction vs SOC (P=NS). Overall SVR was 32% in the induction group vs 29% in SOC group (P=0.434). Secondary: A total of 48.8% of patients from the induction group and 42.8% of patients from the SOC group discontinued therapy before 48 weeks (P=0.2). Overall SVR in African Americans was similar in the patients receiving induction therapy (35%) vs SOC (32%; P=0.9). Overall SVR for Hispanic patients was similar in patients receiving induction therapy (36.1%) vs SOC (22.5%; P=0.292). As shown in other studies with peginterferon alfa-2b combined with ribavirin, there was a large portion of patients experience adverse events. There were no significant life-threatening adverse events reported in any study group. There were also no significant differences between the two study groups for rates of adverse events.
McHutchison et al.[58] (2009) Peginterferon alfa-2b 1.5 µg/kg/week plus	RCT, DB, MC Patients ≥18 years of age with compensated liver disease due to chronic HCV	N=3,070 24 weeks posttreatment	Primary: Sustained virologic response (defined as undetectable HCV RNA levels 24 weeks after the completion of	Primary: The rates of sustained virologic response did not differ significantly among the three treatment groups, with a rate of 39.8% (95% CI, 36.8 to 42.8) for standard-dose peginterferon alfa-2b, 38.0% (95% CI, 35.0 to 41.0) for low-dose peginterferon alfa-2b, and 40.9% (95% CI, 37.9 to 43.9%) for peginterferon alfa-2a, (P=0.20 for standard-dose vs low-dose peginterferon alfa-2b; P=0.57 for standard-dose peginterferon alfa-2b vs

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ribavirin 800 to 1,400 mg/day for 48 weeks (standard-dose arm) vs peginterferon alfa-2b 1.0 µg/kg/week plus ribavirin 800 to 1,400 mg/day for 48 weeks (low-dose arm) vs peginterferon alfa-2a 180 µg/week plus ribavirin 1,000 to 1,200 mg/day for 48 weeks	genotype 1 infection and a detectable plasma HCV RNA level who had not been previously treated for hepatitis C infection		therapy) Secondary: Rates of virologic response during the treatment phase and relapse (defined as an undetectable HCV RNA level at the end of the treatment phase, with a detectable HCV RNA level during the follow-up period)	peginterferon alfa-2a). Secondary: Response rates at the end of the treatment phase were higher with peginterferon alfa-2a than with either peginterferon alfa-2b regimen, however the virologic relapse rate was also higher. HCV RNA suppression at treatment weeks four and 12 was strongly associated with achievement of sustained virologic response in all three treatment groups. Fewer than 5% of patients who had a reduction from the baseline HCV RNA level of less than 1 $\log_{10}$ IU/mL at week four also had a sustained virologic response. A prolonged time (>12 weeks of therapy) to undetectable HCV RNA level was associated with a higher likelihood of relapse after treatment. Rates of sustained virologic response were similar among the three treatment groups, within the subgroups of patients receiving the same dose of ribavirin. Relapse rates were 23.5% for standard-dose peginterferon alfa-2b, 20.0% for low-dose peginterferon alfa-2b, and 31.5% for peginterferon alfa-2a (95% CI, –13.2 to –2.8 for the standard dose regimens; 95% CI, –1.6 to 8.6% for standard-dose peginterferon alfa-2b vs low-dose peginterferon alfa-2b). The types and frequencies of adverse events were similar among the three groups. The most common adverse events included influenza-like symptoms, depression, and the hematologic events of anemia and neutropenia. The proportion of patients with neutropenia was 21.1% in patients receiving peginterferon alfa-2a, 19.4% in patients receiving standard-dose peginterferon alfa-2b, and 12.5% in patients receiving low-dose peginterferon alfa-2b. Most psychiatric adverse events were mild or moderate and were not treatment-limiting.
Marcellin et al.[59] (2011) Peginterferon alfa-	MC, OL, RCT Patients 18 to 65 years of age with	N=161 72 weeks	Primary: SVR, viral breakthrough, relapse	Primary: Rapid virologic response (RVR) was 80.0, 69.0, 82.5, and 66.7% in the q8h alfa-2a, q8h alfa-2b, q12h alfa-2a, and q12h alfa-2b groups, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
2a 180 µg/week, ribavirin 1,000 to 1,200 mg/day, and telaprevir 750 mg 3 times daily (q8h alfa-2a) vs peginterferon alfa-2b 1.5 µg/kg/week, ribavirin 800 to 1,200 mg/day and telaprevir 750 mg 3 times daily (q8h alfa-2b) vs peginterferon alfa-2a 180 µg/week, ribavirin 1,000 to 1,200 mg/day and telaprevir 1,125 mg every 12 hours (q12h alfa-2a) vs peginterferon alfa-2b 1.5 µg/kg/week, ribavirin 800 to 1,200 mg/day and telaprevir 1,125 mg every 12 hours (q12h alfa-	chronic HCV genotype 1 infection who were treatment-naïve		Secondary: Not reported	RVR in the pooled q8h group was similar to that in the pooled q12h group (74.4 vs 74.7%). RVR rate in the pooled peginterferon alfa-2a group was higher than in the pooled peginterferon alfa-2b group (81.3 vs 67.9%). At week 12, the percentage of patients with undetectable HCV RNA increased to 92.5, 92.9, 82.5, and 84.6%, in the q8h alfa-2a, q8h alfa-2b, q12h alfa-2a, and q12h alfa-2b groups, respectively. SVR was similar in all four treatment groups: 85.0, 81.0, 82.5, and 82.1% in the q8h alfa-2a, q8h alfa-2b, q12h alfa-2a, and q12h alfa-2b groups, respectively. SVR rate was 82.9% in the pooled telaprevir q8h group and 82.3% in the pooled telaprevir q12h group. SVR rate was 83.8% in the pooled peginterferon alfa-2a group and 81.5% in the pooled peginterferon alfa-2b group. Relapse was observed in nine patients: three, two, three, and one in the q8h alfa-2a, q8h alfa-2b, q12h alfa-2a, and q12h alfa-2b groups, respectively. A total of 8.7% of viral breakthroughs were observed in one, six, three, and four patients in the q8h alfa-2a, q8h alfa-2b, q12h alfa-2a, and q12h alfa-2b groups, respectively. There were no significant adverse events or deaths during the study. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
2b) Patients received 12 weeks of treatment with telaprevir and peginterferon alfa/ribavirin, followed by peginterferon alfa/ribavirin alone for 12 or 36 weeks, based on on-treatment virologic response criteria. Patients with undetectable plasma HCV RNA at week 4 through week 20 were scheduled to receive a total of 24 weeks of therapy. Patients not meeting this criterion were assigned to receive a total of 48 weeks of treatment.				
Gane et al.[60] (2013) Group 1: Sofosbuvir 400 mg and ribavirin 1,000 mg/day (weight <75 kg) or 1,200	OL Patients19 years of age or older, who had chronic HCV infection without cirrhosis	N=95	Primary: Serum HCV RNA levels, safety Secondary: Not reported	Primary: Viral suppression was rapid in all patients, regardless of genotype, status with respect to previous treatment, baseline viral load, race or ethnic group, IL28B status, and presence or absence of interferon in the regimen. All 95 patients had an undetectable level of HCV RNA by week four, with viral suppression sustained through the end of treatment. All 40 patients with HCV genotype 2 or 3 infection who received

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/day (weight ≥75 kg) for 12 weeks Group 2: Group 1 treatment plus 4 weeks of concomitant peginterferon alfa-2a 180 µg once weekly Group 3: Group 1 treatment plus 8 weeks of concomitant peginterferon alfa-2a 180 µg once weekly Group 4: Group 1 treatment plus 8 weeks of concomitant peginterferon alfa-2a 180 µg once weekly (additional groups amended): Group 5: Sofosbuvir 400 mg daily monotherapy for 12 weeks Group 6:				sofosbuvir and ribavirin for 12 weeks had an undetectable level of serum HCV RNA at two, four, eight, 12, 24, and 48 weeks after treatment. The presence or absence of peginterferon alfa-2a appeared to have no effect on viral kinetics or rate of sustained virologic response. Six of the 10 patients in the sofosbuvir monotherapy group had a sustained virologic response at 12 and 24 weeks after treatment. All 95 patients completed treatment. The most common adverse events were headache, fatigue, insomnia, nausea, rash, and anemia. Hematologic abnormalities were more common among patients who received interferon than among those who did not. Neutropenia and thrombocytopenia were not observed in the groups that did not receive interferon. However, sofosbuvir monotherapy was associated with a modest decrease in the hemoglobin level. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Sofosbuvir plus peginterferon and ribavirin for 8 weeks				
Hairy Cell Leukemia				
Grever et al.[61] (1995) Interferon alfa-2a 3 MIU TIW vs pentostatin 4 mg/m^2 IV every 2 weeks	RCT Patients diagnosed with hairy cell leukemia that were previously untreated for this condition	N=313 Mean 57 months	Primary: Rates of complete and partial to complete remission Secondary: Not reported	Primary: Complete and partial remission was significantly higher with pentostatin compared to interferon (P<0.05). Complete remission was achieved in 11% on interferon compared to 76% on pentostatin. Partial-to-complete remission was achieved in 38% of patients on interferon compared to 79% in patients on pentostatin. Myelosuppression was significantly more frequent with pentostatin (P=0.013). Secondary: Not reported
Federico et al.[62] (1994) Interferon alfa (either alfa-2a, alfa-2b or alfa-n1*) 3 MIU daily Patients with a partial response may be randomly selected to undergo splenectomy.	RCT Adult patients with histologically confirmed hairy cell leukemia not previously treated.	N=177 38 months	Primary: Rates of remission (complete, partial or minor), overall response rate (complete, partial and minor remission) Secondary: Survival after splenectomy	Primary: Treatment with interferon alfa resulted in complete remission in 16.9%, partial remission in 62.0% and minor remission in 16%. Response rate was 92.7% for interferon alfa-2a, 97.2% for interferon alfa-2b and 95.3% for interferon alfa-n1. Secondary: Four-year progression-free survival for patients that had undergone a splenectomy after a partial response on interferon was 53%, compared to 22% of patients assigned to observation (P=0.116).

Drug regimen abbreviations: IV=intravenously, MIU=million international units, TIW= three times weekly
Study abbreviations: DB=double-blind, CI=confidence interval, MA=meta-analysis, MC=multicenter, OBS=observational study, OL=open label, PC=placebo-controlled, QOL=quality of life, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, SF-36=Short-Form Health Survey
Other abbreviations: ALT=alanine aminotransferase, DNA=deoxyribonucleic acid, HBeAg=hepatitis B e antigen, HBV=hepatitis B virus, HCV=hepatitis C virus, HIV=human immunodeficiency virus, RNA=ribonucleic acid, SVR=sustained virologic response
*Not commercially available in the US

Additional Evidence

Dose Simplification
Several trials have determined that longer treatment durations with combination interferon therapy (48 weeks) are more effective than shorter treatment regimens (24 weeks).[33-34] Bernstein et al. conducted a meta-analysis of three trials comparing peginterferon alfa-2a and interferon alfa-2a to measure the impact of interferon therapy on quality of life and treatment adherence in patients with hepatitis C.[63] Peginterferon was found to provide a significantly higher sustained virologic response, and was associated with an improvement in quality of life and less fatigue (P<0.01).

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
Perrillo et al. evaluated the effects of interferon treatment on quality of life and health care utilization in patients with hepatitis C.[64] Patients received treatment interferon alfa-2b three times weekly or peginterferon alfa-2a once weekly. After 24 and 48 weeks, patients receiving peginterferon experienced significantly less impairment of quality of life compared to patients receiving interferon (P<0.05). Fewer patients treated with peginterferon required prescription medications to treat adverse events related to HCV therapy as compared to interferon therapy (56.9 vs 70.2%, respectively; P=0.007). There were no significant differences between the treatment groups in other areas of healthcare resource utilization.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 10. Relative Cost of the Interferons

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Interferon alfa-2b	injection	Intron® A	$$$$$	N/A
Interferon alfacon-1	injection	Infergen®	$$$$$	N/A
Interferon alfa-n3	injection	Alferon N®	$$$$$	N/A
Peginterferon alfa-2a	injection	Pegasys®	$$$$$	N/A
Peginterferon alfa-2b	injection	PegIntron®	$$$$$	N/A

N/A=Not available

X. Conclusions

Interferons are naturally occurring proteins with antiviral, antiproliferative and immunoregulatory properties.[1-7] The Food and Drug Administration (FDA)-approved indications vary among the products; however, the interferons are primarily used for the treatment of chronic hepatitis B and chronic hepatitis C. None of the interferons are available in a generic formulation.

Guidelines recommend the use of peginterferon alfa as one of several initial treatment options for patients with chronic hepatitis B.[14,22] Interferon alfa-2a and peginterferon alfa-2a were shown to be equally effective following 48 weeks of treatment.[26]

For the treatment of chronic hepatitis C genotype 1, guidelines recommend the use of peginterferon alfa in combination with sofosbuvir and ribavirin for 12 weeks. However, interferon-free regimens are becoming more prevalent, as they avoid the toxicity associated with interferon use.[15-16,18-19] Guidelines do not give preference to one pegylated product over another. The peginterferon alfa products have both been shown to be more effective than standard interferon alfa products for the treatment of chronic hepatitis C.[28-29,31,36-39] Studies directly comparing the peginterferon alfa products have demonstrated mixed results.[44-45,47-49,52,58] The largest trial was conducted by McHutchison et al. and included over 3,000 patients with chronic hepatitis C genotype 1 infection. The investigators demonstrated similar sustained virologic response rates, relapse rates and adverse events with peginterferon alfa-2a and peginterferon alfa-2b.[58]

Interferon alfa-2b and interferon alfa-n3 are approved for the treatment of condylomata acuminata. However, the interferons are considered a second-line treatment option by the CDC and there are no published clinical trials which directly compare these agents.[23] Interferon alfa-2b is also approved for the treatment of selected patients with AIDS-related Kaposi's sarcoma, hairy cell leukemia, follicular Non-Hodgkin's lymphoma, and as an adjuvant to surgical treatment in patients with malignant melanoma. Due to the limited usage anticipated for most of these indications, the interferon alfa products should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand interferon alfa products within the class reviewed are comparable to each other and to the generics in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use. Peginterferon alfa-2a (Pegasys®) and peginterferon alfa-2b (PegIntron®) offer significant clinical advantages in general use over the other brands, generics, and OTC products in the same class (if applicable) but are comparable to each other.

XI. Recommendations

No brand interferon alfa product is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

Alabama Medicaid should work with manufacturers on cost proposals so that at least one brand peginterferon alfa product is selected as a preferred agent.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Neuraminidase Inhibitors
AHFS Class 081828
November 12, 2014

I. Overview

Influenza A viruses (primarily H1N1 and H3N2) and influenza B viruses circulate worldwide. Influenza epidemics occur nearly every year making this disease a major cause of respiratory illness in the United States.[1-3] The majority of complications, hospitalizations, and deaths from seasonal influenza occur in persons over 65 years of age, children younger than two years of age, and persons of any age with certain underlying health conditions. The most effective way to minimize the negative impact of influenza is through annual vaccination.[1-3]

Antiviral medications are an important adjunct to vaccination for the control and prevention of influenza disease. The neuraminidase inhibitors block the viral release mechanisms during the replication cycles of influenza A and B.[4-7] Neuraminidase is an enzyme that is necessary for release of daughter virions from infected cells. Without the action of neuraminidase, the new virions are tethered to the cellular membrane glycoproteins of their parent cells and therefore, the virus will remain aggregated at the cell surface and cannot spread to other cells.[1-7] Because the peak range for influenza virus replication is 24 to 72 hours after the onset of illness, oseltamivir and zanamivir should be administered as early as possible.[1-7]

The neuraminidase inhibitors that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. There are no generic products available. This class was last reviewed in May 2012.

Table 1. Neuraminidase Inhibitors Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Oseltamivir	capsule, suspension	Tamiflu®	Tamiflu®†
Zanamivir	powder for inhalation	Relenza®	Relenza®†

†The preferred status of this product is contingent upon statewide influenza epidemiology status as reported by the CDC.
PDL=Preferred Drug List.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the neuraminidase inhibitors are summarized in Table 2.

Table 2. Treatment Guidelines Using the Neuraminidase Inhibitors

Clinical Guideline	Recommendation(s)
Centers for Disease Control and Prevention Morbidity and Mortality Weekly Report: **Antiviral Agents for the Treatment and Chemoprophylaxis of Influenza: Recommendations of the Advisory Committee on Immunization Practices (2011)[1]**	• Annual influenza vaccination is the most effective method for preventing seasonal influenza virus infection and its complications. • Antiviral treatment is recommended as soon as possible for: o Patients with confirmed or suspected influenza who have severe, complicated, or progressive illness or who require hospitalization. o Outpatients with confirmed or suspected influenza who are at higher risk for influenza complications on the basis of their age or underlying medical conditions. • Persons at higher risk for influenza complications recommended for antiviral treatment include: o Children less than two years of age. o Adults aged ≥65 years. o Persons with chronic pulmonary (including asthma), cardiovascular (except hypertension alone), renal, hepatic, hematological (including sickle cell disease), metabolic disorders (including diabetes mellitus), or neurologic and neurodevelopment conditions (including disorders of the brain, spinal cord, peripheral nerve, and

Clinical Guideline	Recommendation(s)
	muscle such as cerebral palsy, epilepsy [seizure disorders], stroke, intellectual disability [mental retardation], moderate to severe developmental delay, muscular dystrophy, or spinal cord injury). o Persons with immunosuppression, including that caused by medications or by human immunodeficiency virus infection. o Women who are pregnant or postpartum (within two weeks after delivery). o Persons aged <19 years who are receiving long-term aspirin therapy. o American Indians/Alaska Natives. o Persons who are morbidly obese (i.e., body-mass index ≥40). o Residents of nursing homes and other chronic-care facilities. • Four licensed prescription influenza antiviral agents are available in the United States: amantadine, rimantadine, zanamivir, and oseltamivir. Oseltamivir and zanamivir, neuraminidase inhibitors are active against both influenza A and B. Rimantadine and amantadine are only active against influenza A. • Recommended antiviral medications include oseltamivir and zanamivir. Greater than 99% of currently circulating influenza virus strains are sensitive to these medications. Amantadine and rimantadine should not be used because of the high levels of resistance to these drugs. Local antiviral resistance surveillance data should be monitored. Currently circulating influenza A (H3N2) and 2009 H1N1 viruses are resistant to adamantanes. These medications are not recommended for use against influenza A virus infections. • Oseltamivir may be used for treatment or chemoprophylaxis of influenza among infants less than one year of age when indicated. • Antiviral treatment is recommended as soon as possible for all persons with suspected or confirmed influenza requiring hospitalization or who have progressive, severe or complicated illness regardless of previous health or vaccination status. The greatest benefit is when initiated within 48 hours of influenza onset. However, it may be beneficial in those with severe, complicated, or progressive illness and in hospitalized patients if administered >48 hours from onset. Health-care providers and patients should make this decision on an individual basis. • Randomized, controlled trials conducted primarily among persons with mild illness in outpatient settings have demonstrated that zanamivir or oseltamivir can reduce the duration of uncomplicated influenza A and B illness by approximately one day when administered within 48 hours of illness onset compared to placebo. • Data are limited about the effectiveness of zanamivir and oseltamivir treatment in preventing serious influenza-related complications. • Chemoprophylaxis with antiviral medications is not a substitute for influenza vaccination when influenza vaccine is available. • Post-exposure chemoprophylaxis lowers but does not eliminate the risk for influenza. Susceptibility to influenza returns once the antiviral medication is stopped, and influenza vaccination is recommended. Duration should be for a total of no more than 10 days after the most recent known exposure to a close contact known to have influenza. • Pre-exposure chemoprophylaxis must be administered for the duration of time when exposure might occur and should only be used for persons who are at very high risk for influenza-related complications who cannot otherwise be protected during times when a high risk for exposure exists. The duration of pre-exposure chemoprophylaxis based on potential exposure in the community depends on the duration of community influenza activity. • Zanamivir is approved for treatment of adults with uncomplicated acute

Clinical Guideline	Recommendation(s)

	illness caused by influenza A or B virus, and for chemoprophylaxis of influenza among adults. It is also approved for treatment of influenza among children seven years of age and older and for chemoprophylaxis of influenza among children five years of age and older.
	• Oseltamivir is approved for treatment of adults with uncomplicated acute illness caused by influenza A or B virus and for chemoprophylaxis of influenza among adults. It is also approved for the treatment and chemoprophylaxis of influenza among children one year of age and older.
	• Rimantadine is Food and Drug Administration (FDA) approved for children one year of age and older and for treatment and chemoprophylaxis of only influenza A virus infections among adults. Use of rimantadine among children less than one year of age has not been evaluated adequately.
	• Oseltamivir, zanamivir, and rimantadine are "Pregnancy Category C" medications. Oseltamivir is preferred for treatment of pregnant women.
	
	<u>2009 Influenza A (H1N1)</u>
	• In the post-pandemic period, 2009 H1N1 virus strains now are considered to be the predominant seasonal influenza A (H1N1) virus strains.
	• Reverse transcription polymerase chain reaction is the most accurate and sensitive test for detecting influenza viruses, including the 2009 H1N1 virus.
	• Epidemiologic studies of seasonal influenza or 2009 H1N1 suggest that persons at higher risk for influenza complications include:
	  o Children less than five years of age (especially those less than two years of age).
	  o Adults aged ≥65 years.
	  o Persons with chronic pulmonary (including asthma), cardiovascular (except hypertension alone), renal, hepatic, hematologic (including sickle cell disease), metabolic disorders (including diabetes mellitus) or neurologic and neurodevelopment conditions (including disorders of the brain, spinal cord, peripheral nerve, and muscle such as cerebral palsy, epilepsy (seizure disorders), stroke, intellectual disability (mental retardation), moderate to severe developmental delay, muscular dystrophy, or spinal cord injury).
	  o Persons with immunosuppression, including that caused by medications or by human immunodeficiency virus infection.
	  o Women who are pregnant or postpartum (within two weeks after delivery).
	  o Persons aged ≤18 years who are receiving long-term aspirin therapy.
	  o American Indians/Alaska Natives.
	  o Persons who are morbidly obese (i.e., body mass index ≥40).
	  o Residents of nursing homes and other chronic-care facilities.
	• Studies conducted during the 2009 influenza A (H1N1) pandemic indicate that viral shedding, clinical illness, and transmissibility in a household setting are similar compared to seasonal influenza.
	• During the 2009 H1N1 pandemic, the clinical syndrome most likely to be the cause of hospitalization was diffuse viral pneumonitis, which in some instances led to shock and respiratory failure.
	• Influenza complications among children during the 2009 influenza A (H1N1) pandemic were generally similar to those observed among children with seasonal influenza. However, much higher rates of illness among children observed during the 2009 H1N1 pandemic compared to most influenza seasons resulted in much higher rates of children hospitalized with complications.
	• Circulating 2009 H1N1 virus strains are resistant to adamantanes. These are not recommended for treatment or prophylaxis.

Clinical Guideline	Recommendation(s)
	• The World Health Organization has recommended empiric neuraminidase inhibitor treatment for all persons with suspected or confirmed 2009 H1N1 virus infection that are at increased risk for influenza complications. • Similar recommendations were made by Centers for Disease Control and Prevention during the 2009 H1N1 pandemic and the subsequent 2009-2010 influenza season. • Oseltamivir or zanamivir is recommended for antiviral chemoprophylaxis of 2009 H1N1. • Those with a potential exposure to a person with laboratory-confirmed 2009 H1N1 should receive chemoprophylaxis. • Sporadic oseltamivir-resistant 2009 H1N1 virus infections have been identified. • Transmission of oseltamivir-resistant influenza B virus strains or 2009 H1N1 virus strains acquired from persons treated with oseltamivir is rare but has been documented. • Nearly all sporadic cases of oseltamivir-resistant 2009 H1N1 virus infections identified to date also have been associated with the H275Y mutation in neuraminidase; these oseltamivir-resistant H275Y virus infections are susceptible to zanamivir. • Intravenous zanamivir is the recommended antiviral treatment for severely ill patients with highly suspected or confirmed oseltamivir-resistant 2009 H1N1 virus infection. • As of December 2010, no evidence existed of ongoing transmission of oseltamivir-resistant 2009 H1N1 virus strains worldwide. • During the 2009 H1N1 pandemic, recommendations for oseltamivir dosing of children less than one year of age were developed, on the basis of very limited pharmacokinetic data. • The Emergency Use Authorization issued during the 2009 H1N1 pandemic for this indication expired on June 23, 2010, but recommendations on dosing for children less than one year of age are available. • Centers for Disease Control and Prevention recommends that clinicians who treat children aged three to 11 months administer 3 mg/kg/dose twice per day for treatment, and 3 mg/kg/dose once per day for chemoprophylaxis. • Infants less than three months of age are recommended to receive 3 mg/kg/dose twice per day for treatment. However, chemoprophylaxis for infants less than three months of age is not recommended unless the exposure situation was judged to be critical, because of a lack of data on use of oseltamivir on this age group. • World Health Organization subsequently recommended that children aged <14 days who are being treated for suspected or confirmed influenza receive 3 mg/kg/dose once daily. Lower doses should be considered for infants who are not receiving regular oral feedings or those who have substantially reduced renal function.

American Academy of Pediatrics: **Recommendations for Prevention and Control of Influenza in Children, 2013-2014 (2013)**[2]	• Seasonal influenza immunization is recommended for all children six months and older.
	• Healthy children two years and older can receive either inactivated influenza vaccines or live-attenuated influenza vaccine.
	• Particular focus should be on the administration of inactivated influenza vaccines for all children and adolescents with underlying medical conditions associated with an increased risk of complications from influenza, including the following:
	  o Asthma or other chronic pulmonary diseases, including cystic fibrosis.
	  o Hemodynamically significant cardiac disease.
	  o Immunosuppressive disorders or therapy.

Clinical Guideline	Recommendation(s)
	o Human immunodeficiency virus infection. o Sickle cell anemia and other hemoglobinopathies. o Diseases that require long-term aspirin therapy, including juvenile idiopathic arthritis or Kawasaki disease. o Chronic renal dysfunction. o Chronic metabolic disease, including diabetes mellitus. o Any condition that can compromise respiratory function or handling of secretions or can increase the risk of aspiration, such as neurodevelopmental disorders, spinal cord injuries, seizure disorders, or neuromuscular abnormalities. • Although universal immunization for all people six months and older is recommended for the 2013–2014 influenza season, particular immunization efforts with either inactivated influenza vaccine or live-attenuated influenza vaccine should be made for the following groups to prevent transmission of influenza to those at risk, unless contraindicated: o Household contacts and out-of home care providers of children younger than five years of age and at-risk children of all ages (healthy contacts two through 49 years of age can receive either inactivated influenza vaccines or live-attenuated influenza vaccine). o Any woman who is pregnant, is considering pregnancy, has recently delivered, or is breastfeeding during the influenza season (inactivated influenza vaccines only). Studies have shown that infants born to immunized women have better influenza-related health outcomes. However, according to Internet panel surveys conducted by the Centers for Disease Control and Prevention, only 47% of pregnant women reported receiving an influenza vaccine during the 2011–2012 season, even though both pregnant women and their infants are at higher risk of complications. In addition, data from some studies suggest that influenza vaccination in pregnancy may decrease the risk of preterm birth as well as giving birth to infants who are small for gestational age. Pregnant women can safely receive the influenza vaccine during any trimester. o Children and adolescents of American Indian/Alaskan Native heritage. o Health care professionals or health care volunteers. Despite the recent American Academy of Pediatrics recommendation for mandatory influenza immunization for all health care professionals, many health care professionals remain unvaccinated. As of November 2012, the Centers for Disease Control and Prevention estimated that only 62.9% of health care professionals received the seasonal influenza vaccine. The American Academy of Pediatrics recommends mandatory vaccination of health care professionals, because they frequently come into contact with patients at high risk of influenza illness in their clinical settings. o Close contacts of immunosuppressed people. <u>Use of antiviral medications</u> • Oseltamivir remains the antiviral drug of choice for the management of influenza infections. Zanamivir is an acceptable alternative but is more difficult to administer. • Treatment should be offered for the following: o Any child hospitalized with presumed influenza or with severe, complicated, or progressive illness attributable to influenza, regardless of influenza immunization status. o Influenza infection of any severity in children at high risk of complications of influenza infection.

Clinical Guideline	Recommendation(s)

	• Treatment should be considered for the following:
	  o Any otherwise healthy child with influenza infection for whom a decrease in duration of clinical symptoms is felt to be warranted by his or her pediatrician; the greatest impact on outcome will occur if treatment can be initiated within 48 hours of illness onset.
	• Although immunization is the preferred approach to prevention of infection, chemoprophylaxis during an influenza outbreak, as defined by the Center for Disease Control and Prevention, is recommended:
	  o For children at high risk of complications from influenza for whom influenza vaccine is contraindicated.
	  o For children at high risk during the two weeks after influenza immunization.
	  o For family members or health care professionals who are unimmunized and are likely to have ongoing, close exposure to unimmunized children at high risk; or unimmunized infants and toddlers who are younger than 24 months.
	  o For control of influenza outbreaks for unimmunized staff and children in a closed institutional setting with children at high risk (e.g., extended-care facilities).
	  o As a supplement to immunization among children at high risk, including children who are immunocompromised and may not respond to vaccine.
	  o As postexposure prophylaxis for family members and close contacts of an infected person if those people are at high risk of complications from influenza.
	  o For children at high risk and their family members and close contacts, as well as health care professional, when circulating strains of influenza virus in the community are not matched with seasonal influenza vaccine strains, on the basis of current data from the Centers for Disease Control and Prevention and local health departments.
	• Amantadine and rimantadine should not be used because circulating influenza A viruses have sustained high levels of resistance to these drugs, and they are not effective against influenza B viruses.

Infectious Diseases Society of America:
Seasonal Influenza in Adults and Children-Diagnosis, Treatment, Chemoprophylaxis, and Institutional Outbreak Management: Clinical Practices Guidelines of the Infectious Diseases Society of America (2009)[3]
	<u>Antivirals for treatment</u>
	• Treatment is recommended for adults and children with influenza virus infection who meet the following criteria:
	  o Patients with laboratory-confirmed or highly susceptible influenza virus infection at high risk for developing complications within 48 hours after symptom onset. Treatment is recommended regardless of influenza vaccination status and severity of illness.
	  o Patients requiring hospitalization for laboratory-confirmed or highly suspected influenza illness, regardless of underlying illness or influenza vaccination status, if treatment can be initiated within 48 hours after onset of symptoms.
	• Treatment should be considered for adults and children with influenza virus infection who meet the following criteria:
	  o Outpatients at high risk of complications, with illness that is not improving and with a positive influenza test result from a specimen obtained >48 hours after symptom onset.
	  o Outpatients with laboratory-confirmed or highly suspected influenza virus infection who are not at increased risk for complications, whose symptom onset is <48 hours before presentation and who wish to shorten the duration of illness and to further reduce their relatively low risk of complications or who are in close contact with persons at high risk of complications

Clinical Guideline	Recommendation(s)

	secondary to influenza infection.
	• Patients at high risk for complications from influenza include:
	  o Unvaccinated infants 12 to 24 months old.
	  o Patients with asthma or other chronic pulmonary diseases.
	  o Patients with hemodynamically significant cardiac disease.
	  o Patients who have immunosuppressive disorders or who are receiving immunosuppressive therapy.
	  o Human immunodeficiency virus infected patients.
	  o Patients with sickle cell anemia and other hemoglobinopathies.
	  o Patients with diseases requiring long term aspirin therapy.
	  o Patients with chronic renal dysfunction.
	  o Patients with cancer.
	  o Patients with chronic metabolic disease.
	  o Patients with neuromuscular disorders, seizure disorders or cognitive dysfunction that may compromise the handling of respiratory secretions.
	  o Patients ≥65 years old.
	  o Residents of any age in nursing homes or other long term care institutions.
	• On the basis of antiviral susceptibility patterns current as of March 2009:
	  o Influenza A (H1N1) virus infections should be treated with either zanamivir or an adamantine (preferably rimantadine due to a more tolerable adverse event profile). Oseltamivir should not be used.
	  o Influenza A (H3N2) virus infections should be treated with oseltamivir or zanamivir. The adamantanes should not be used.
	  o If subtype information is unavailable, influenza A should be treated with either zanamivir or combination oseltamivir and rimantadine therapy.
	  o Influenza B virus infection should be treated with oseltamivir or zanamivir.
	
	<u>Antivirals for chemoprophylaxis</u>
	• Antiviral chemoprophylaxis is not a substitute for influenza vaccination, which is the primary tool to prevent influenza.
	• When influenza viruses are circulating in the community, chemoprophylaxis can be considered for high risk patients during the two weeks after vaccination before an adequate immune response to inactivated vaccine develops.
	• Antiviral chemoprophylaxis should be considered for adults and children at least one year old who are at high risk of developing complications from influenza for whom influenza vaccination is contraindicated, unavailable or expected to have low effectiveness.
	• Antiviral chemoprophylaxis, in conjunction with prompt administration of the inactivated vaccine, should be considered for adults and children at least one year old who are at high risk of developing complications from influenza virus infection and have not yet received influenza vaccine when influenza activity has already been detected in the community.
	• Antiviral chemoprophylaxis may be considered for unvaccinated adults, including health care workers, and for children at least one year old who are in close contact with patients at high risk of developing influenza complications during periods of influenza activity.
	• Antiviral chemoprophylaxis is recommended for all residents, vaccinated and unvaccinated, in institutions (i.e., nursing homes, long term care facilities) that are experiencing influenza outbreaks.
	• The strongest consideration for use of antiviral chemoprophylaxis should be given to patients at the highest risk of influenza-associated complications.

Clinical Guideline	Recommendation(s)

	• Antiviral chemoprophylaxis should be considered for patients at high risk of developing complications from influenza if influenza vaccine is not available due to a shortage.
	• Antiviral chemoprophylaxis can be considered for high risk patients in situations where there is documented low influenza vaccine clinical effectiveness because of the circulation of influenza virus strains that are antigenically distant from the vaccine strains.
	• Antiviral chemoprophylaxis should be initiated at the onset of sustained community influenza activity in patients at high risk of complications who are not adequately protected as a result of poor immune response, lack of influenza vaccination or ineffective vaccine.
	• Antiviral chemoprophylaxis use for appropriate persons within households should be initiated when one family member develops suspected or confirmed influenza and any other family member is at high risk of complications secondary to infection, including infants less than six months old.
	  o In this setting, all non-infected family members should receive antiviral chemoprophylaxis.
	  o All eligible family members in these settings should be vaccinated, making chemoprophylaxis unnecessary.
	• Antiviral chemoprophylaxis and other control measures should be initiated in institutions when an influenza outbreak is detected or when influenza is strongly suspected but the etiology of the outbreak is unknown.
	• If inactivated influenza vaccine is administered, antiviral chemoprophylaxis can generally be stopped after two weeks for patients in non-institutional settings. At least six weeks of chemoprophylaxis will be required for children less than nine years of age.
	• When antiviral chemoprophylaxis is used in a household after the diagnosis of influenza in one family member, chemoprophylaxis should be continued for 10 days.
	• In patients at high risk for complications from influenza for whom influenza vaccination is contraindicated, unavailable or expected to have low effectiveness, chemoprophylaxis should continue for the duration that influenza viruses are circulating in the community during influenza season.
	• On the basis of antiviral susceptibility patterns current as of March 2009:
	  o For influenza A (H1N1), zanamivir or an adamantine (preferably rimantadine due to a more tolerable adverse event profile) should be used for chemoprophylaxis. Oseltamivir should not be used.
	  o For influenza A (H3N2), oseltamivir or zanamivir should be used for chemoprophylaxis. The adamantanes should not be used.
	  o If subtype information is unavailable, either zanamivir or combination oseltamivir and rimantadine therapy should be used for influenza A chemoprophylaxis.
	  o Oseltamivir or zanamivir should be used for influenza B chemoprophylaxis.
	
	<u>Outbreak management in institutional settings</u>
	• All residents with laboratory-confirmed influenza virus infection should be treated with an appropriate influenza antiviral medication.
	• After one case of laboratory-confirmed influenza, all patients in the facility subsequently developing influenza-like illness should be considered for treatment.
	• During documented outbreaks of influenza in long term care facilities, all resident should receive influenza antiviral chemoprophylaxis, regardless of influenza vaccination status.

Clinical Guideline	Recommendation(s)
	• For all institutional employees who are unable to receive influenza vaccine or for whom vaccine is contraindicated or expected to be ineffective, antiviral chemoprophylaxis should be administered. • Antiviral chemoprophylaxis should be continued for 14 days or for seven days after the onset of symptoms in the last person infected, whichever is longer.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the neuraminidase inhibitors are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Neuraminidase Inhibitors[4-7]

Indication	Oseltamivir	Zanamivir
Prophylaxis of influenza in patients aged five years and older		✔ *‡
Treatment of influenza in patients aged seven years and older who have been symptomatic for no more than two days		✔ *†
Prophylaxis of influenza in patients one year and older	✔ §	
Treatment of acute, uncomplicated influenza in patients two weeks of age and older who have been symptomatic for no more than two days	✔ §	

*Not recommended for the treatment or prophylaxis of influenza in individuals with underlying airways disease.
†Not proven effective for treatment of influenza in individuals with underlying airways disease.
‡Not proven effective for prophylaxis of influenza in the nursing home setting.
§Efficacy not established in patients who begin therapy after 48 hours of symptoms.

IV. Pharmacokinetics

The pharmacokinetic parameters of the neuraminidase inhibitors are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Neuraminidase Inhibitors[4-7]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Oseltamivir	>75	3 to 42	Liver	Renal (>99) Feces (<20)	6 to 10
Zanamivir	4 to 17	<10	Minimal to none	Renal	2.5 to 5.1

V. Drug Interactions

Significant drug interactions with the neuraminidase inhibitors are listed in Table 5.

Table 5. Significant Drug Interactions with the Neuraminidase Inhibitors[4]

Generic Name(s)	Significance Level	Interaction	Mechanism
Neuraminidase inhibitors	2	Influenza virus vaccine	Neuraminidase inhibitors may inhibit the replication of live vaccine virus thereby decreasing the production of influenza strain-specific antibodies.

Significance level 1=major severity; significance level 2=moderate severity

VI. Adverse Drug Events

The most common adverse drug events reported with the neuraminidase inhibitors are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with the Neuraminidase Inhibitors[4-7]

Adverse Events	Oseltamivir	Zanamivir
Cardiovascular		
Angina	<1	-
Arrhythmia	✔	✔
Syncope	-	✔
Central Nervous System		
Abnormal behavior	✔	✔
Agitation	✔	✔
Anxiety	✔	✔
Confusion	✔	-
Consciousness altered	✔	✔
Delirium	✔	✔
Delusions	✔	✔
Dizziness	1 to 2	1 to 2
Fatigue	1 to 8	1 to 8
Fever/chills	<1	1 to 9
Hallucination	✔	✔
Headache	2 to 18	2 to 24
Hypothermia	✔	-
Insomnia	1	-
Malaise	-	1 to 8
Neuropsychiatric events	<1	-
Nightmares	✔	✔
Seizure	✔	✔
Vertigo	≤1	-
Dermatological		
Dermatitis	✔	-
Eczema	✔	-
Erythema multiforme	✔	✔
Rash	✔	✔
Stevens-Johnson syndrome	✔	✔
Toxic epidermal necrolysis	✔	✔
Urticaria	✔	<2
Gastrointestinal		
Abdominal pain	2 to 5	<2
Anorexia/appetite decreased	-	2 to 4
Appetite increased	-	2 to 4
Gastrointestinal bleeding	✔	-
Diarrhea	1 to 3	2 to 3
Hemorrhagic colitis	✔	-
Nausea	4 to 10	≤3
Pseudomembranous colitis	<1	-
Throat/tonsil discomfort/pain	-	8 to 19
Vomiting	2 to 15	1 to 2
Hepatic		
Hepatitis	✔	-
Liver function test abnormalities	✔	-
Musculoskeletal		
Arthralgia/articular rheumatism	-	≤2
Muscle pain	-	3 to 8

Adverse Events	Oseltamivir	Zanamivir
Myalgia	-	<2
Respiratory		
Asthma	-	<1
Bronchitis	1 to 2	2
Bronchospasm	-	✔
Cough	1 to 5	≤2 to 17
Dyspnea	-	✔
Ear, nose, and throat infections	-	<5
Epistaxis	1	-
Infection (ear/nose/throat)	-	1 to 5
Nasal inflammation	-	1
Nasal signs and symptoms	-	2 to 20
Sinusitis	-	3
Other		
Allergy	<1	-
Allergic or allergic-like reaction	-	✔
Anaphylactic/anaphylactoid reactions	✔	-
Conjunctivitis	1	-
Diabetes aggravation	✔	-
Facial edema	-	✔
Fracture	<1	-
Hemorrhage (ear/nose/throat)	-	<1
Oropharyngeal edema	-	✔
Swelling of face or tongue	✔	-
Viral infection	-	3 to 13

✔ Percent not specified.
- Event not reported or incidence <1%.

VII. Dosing and Administration

The usual dosing regimens for the neuraminidase inhibitors are listed in Table 7.

Table 7. Usual Dosing Regimens for the Neuraminidase Inhibitors[4-7]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Oseltamivir	Prophylaxis of influenza in patients one year and older: Capsule, suspension: 75 mg once daily for ≥10 days; patients may take up to six weeks for community outbreak Treatment of acute, uncomplicated influenza in patients two weeks of age and older who have been symptomatic for no more than two days: Capsule, suspension: 75 mg twice daily for five days	Prophylaxis of influenza in patients one year and older: Capsule, suspension: ≤15 kg, 30 mg twice daily for ≥10 days; 15.1 to 23.0 kg, 45 mg twice daily for ≥10 days; 23.1 to 40 kg, 60 mg twice daily for ≥10 days; ≥40.1 kg, 75 mg twice daily for ≥10 days; ; patients may take up to six weeks for community outbreak Treatment of acute, uncomplicated influenza in patients one to 12 years of age who have been symptomatic for no more than two days: Capsule, suspension: ≤15 kg, 30 mg twice daily for five days; 15.1 to 23.0 kg, 45 mg twice	Capsule: 30 mg 45 mg 75 mg Suspension: 6 mg/mL

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		daily for five days; 23.1 to 40 kg, 60 mg twice daily for five days; ≥40.1 kg, 75 mg twice daily for five days Treatment of acute, uncomplicated influenza in patients two weeks to <1 year of age who have been symptomatic for no more than two days: Capsule, suspension: 3 mg/kg twice daily	
Zanamivir	Prophylaxis of influenza in patients aged five years and older (household setting): Inhalation powder: 10 mg once daily for 10 days Prophylaxis of influenza in patients aged five years and older (community outbreak): Inhalation powder: 10 mg once daily for 28 days Treatment of influenza in patients aged seven years and older who have been symptomatic for no more than two days: Inhalation powder: 10 mg twice daily for five days	Prophylaxis of influenza in patients aged five years and older (household setting): Inhalation powder: 10 mg once daily for 10 days Prophylaxis of influenza in patients aged five years and older (community outbreak): Inhalation powder: 10 mg once daily for 28 days Treatment of influenza in patients aged seven years and older who have been symptomatic for no more than two days: Inhalation powder: 10 mg twice daily for five days	Inhalation powder: 5 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the neuraminidase inhibitors are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Neuraminidase Inhibitors

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Prophylaxis of Influenza				
Chik et al.[8] (2004) Oseltamivir 75 mg daily for 8 weeks (for prophylaxis)	OL, OS, PRO Patients with a mean age of 14, immuno-compromised through chemo-therapy or bone marrow transplantation	N=32 12 weeks	Primary: Diagnosis of influenza Secondary: Not reported	Primary: Throughout the study period there were no laboratory confirmed cases of influenza infection. Secondary: Not reported
Peters et al.[9] (2001) Oseltamivir 75 mg daily for 6 weeks beginning when influenza was detected locally vs placebo	DB, MC, PC, PG, RCT Frail older occupants (mean age 81, >80% vaccinated) in residential homes across the United States and Europe	N=548 1998 to 1999 influenza season	Primary: Laboratory-confirmed clinical influenza Secondary: Adverse events	Primary: Oseltamivir resulted in a 92% reduction in the incidence of laboratory-confirmed clinical influenza compared to placebo (0.4 vs 4.4%; P=0.002). Of subjects vaccinated against influenza, oseltamivir was 91% effective in preventing laboratory-confirmed clinical influenza compared to placebo (0.5 vs 5.0%; P=0.003). Oseltamivir was associated with a significant reduction in the incidence of secondary complications compared to placebo (0.4 vs 2.6%; P=0.037). Secondary: A similar incidence of adverse events, including gastrointestinal events, occurred in both groups.
Welliver et al.[10] (2001) Oseltamivir 75 mg daily for 7 days	DB, PC, RCT Households with an index contact of any age, and	N=962 (377 households) 7 days	Primary: Proportion of contacts of an influenza-positive index	Primary: For household contacts of infected index contacts, the incidence of laboratory-confirmed clinical influenza for those receiving oseltamivir during the seven-day prophylaxis period was 0.8 vs 12.9% for those receiving placebo. This was calculated as a protective efficacy rate of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	with 2 to 8 other contacts >12 years of age; within <48 hours of symptom onset in the index contact		contact with laboratory-confirmed clinical influenza during the dosing period; proportion of influenza cases in the test population as a whole Secondary: Number of households with additional influenza-related illnesses	89% (95% CI, 67 to 97; P<0.001). For households with infected index contacts, the proportion of households with at least one subsequently infected contact were 3.6% for the oseltamivir group compared to 22.8% for the placebo group. This was calculated as a protective efficacy rate of 84% (95% CI, 49 to 95; P<0.001). Data was also collected in cases where the index contact was not influenza as confirmed by laboratory tests, and in this group 0.4% of individuals taking oseltamivir came down with influenza from exposure in the community compared to 3.1% of individuals receiving placebo. Protective efficacy for these individuals exposed to influenza outside the household was calculated at 89% (95% CI, 10 to 99; P=0.009). Twenty-one of the clinical cases among the placebo recipients were infected with influenza A and 13 with influenza B. None of the clinical cases in the group of oseltamivir-treated contacts was infected with influenza A, so protective efficacy was not calculated. The protective efficacy against influenza B in contacts of all index contacts was calculated at 78.5% (P=0.02). Secondary: Frequency of individuals shedding virus and therefore more likely to transmit to others was significantly reduced in oseltamivir recipients compared to placebo recipients. The protective efficacy in contacts of an influenza positive index contact was calculated at 84% (95% CI, 57 to 95; P<0.001).
Hayden et al.[11] (1999) Oseltamivir 75 mg daily for six weeks or	DB, MC, PC, RCT Healthy, nonimmunized adults 18 to 65 years of age	N=1,559 1997 to 1998 influenza season	Primary: Laboratory-confirmed influenza-like illness Secondary:	Primary: The risk of influenza among subjects assigned to either QD or BID oseltamivir (1.2 and 1.3%, respectively) was lower than that among subjects assigned to placebo (4.8%; P<0.001 and P=0.001 for the comparison with QD and BID oseltamivir, respectively). The protective efficacy of oseltamivir in the two active-treatment groups

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
oseltamivir 75 mg BID for six weeks vs placebo			Adverse events	combined was 74% (95% CI, 53 to 88) at all the sites and 82% (95% CI, 60 to 93) at sites in Virginia, where the rate of influenza infection was higher than the overall rate. For culture-proven influenza, the rate of protective efficacy in the two oseltamivir groups combined was 87% (95% CI, 65 to 96). The rate of laboratory-confirmed influenza infection was lower with oseltamivir than with placebo (5.3 vs 10.6%; P<0.001). Secondary: Oseltamivir was well tolerated but was associated with a greater frequency of nausea (12.1 and 14.6% in the QD and BID groups, respectively) and vomiting (2.5 and 2.7%, respectively) than was placebo (nausea, 7.1%; vomiting, 0.8%). The frequency of premature discontinuation of drug or placebo was similar among the three groups (3.1 to 4.0%).
Hayden et al.[12] (2004) Oseltamivir 75 mg BID for 10 days (postexposure prophylaxis[PEP]) vs oseltamivir 75 mg BID for 5 days at the time of developing illness (expectant treatment)	PG, PRO, RCT Household contacts of index cases presenting with an influenza-like illness ≥1 year of age	N=812 2000 to 2001 influenza season	Primary: Secondary spread of influenza Secondary: Not reported	Primary: PEP provided a protective efficacy of 58.5% (95% CI, 15.6 to 79.6; P=0.0114) for households against proven influenza and 68.0% (95% CI, 34.9 to 84.2; P=0.0017) for individual contacts, compared to treatment of index cases alone. No oseltamivir-resistant variants were detected in treated index cases or contacts. Secondary: Not reported
Hayden et al.[13] (2000) Zanamivir 10 mg	DB, PC Families with two to five members	N=1,158 1998 to1999 influenza	Primary: The proportion of families with at least one	Primary: The proportion of families with at least one initially healthy household contact in whom influenza developed was smaller in the zanamivir group than in the placebo group (four vs 19%; P<0.001); the difference

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
inhaled daily for 10 days in household contacts as prophylaxis vs placebo If an influenza-like illness developed in one member, the family was randomly assigned to receive either inhaled zanamivir or placebo. Infected family members (index) were treated with either 10 mg of inhaled zanamivir or placebo.	and at least one child who was 5 years of age or older	season	household contact with symptomatic, laboratory-confirmed influenza Secondary: Zanamivir-resistant variants and the median duration of symptoms in the index cases	represented a 79% reduction in the proportion of families with at least one affected contact. Secondary: Zanamivir provided protection against both influenza A and influenza B. A neuraminidase-inhibition assay and sequencing of the neuraminidase and hemagglutinin genes revealed no zanamivir-resistant variants. Among the subjects with index cases of laboratory-confirmed influenza, the median duration of symptoms was 2.5 days shorter in the zanamivir group than in the placebo group (5.0 vs 7.5 days; P=0.01).
Monto et al.[14] (2002) Zanamivir 10 mg inhaled daily for 10 days in household contacts as prophylaxis vs placebo	DB, MC, PC, RCT Once a person with a suspected case of influenza was identified (index patient), treatment of all other household members (contacts) ≥5 years old was	N=1,778 11 months	Primary: Household contacts that developed symptomatic, laboratory-confirmed influenza Secondary: Not reported	Primary: Four percent of zanamivir-treated households and 19% of placebo-treated households had at least one contact who developed symptomatic, laboratory-confirmed influenza (P<0.001), representing 81% protective efficacy (95% CI, 64 to 90). Protective efficacy was similarly high for individuals (82%) and against both influenza types A and B (78 and 85%, respectively, for households). Zanamivir was well tolerated and was effective in preventing influenza types A and B within households where the index patient was not treated. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Index patients received relief medication only.	initiated; eligible households were composed of 2 to 5 members, with at least 1 adult >18 years of age and 1 child 5 to17 years of age			
Monto et al.[15] (1999) Zanamivir 10 mg inhaled daily for 4 weeks vs placebo	DB, PC, RCT Healthy adults 18 to 69 years of age	N=1,107 1997 to1998 influenza season	Primary: Laboratory-confirmed clinical influenza occurrence Secondary: Adverse events	Primary: Zanamivir was 67% efficacious (95% CI, 39 to 83; P<0.001) in preventing laboratory-confirmed clinical influenza meeting the case definition and 84% efficacious (95% CI, 55 to 94; P=0.001) in preventing laboratory-confirmed illnesses with fever. All influenza infections occurring during the season, with or without symptoms, were prevented with an efficacy of 31% (95% CI, 4 to 50; P=0.03). Secondary: The nature and incidence of adverse events in the zanamivir group did not differ from the placebo group. Adverse events thought by the investigators to be potentially drug-related were observed in 27 (5%) patients in the placebo group and 30 (5%) patients in the zanamivir group. Potential adverse events that were considered severe were seen in one (<1%) patient in the placebo group and one (<1%) patient in the zanamivir group.
LaForce et al.[16] (2007) Zanamivir 10 mg inhaled QD for 28 days vs placebo	DB, MC, PC, RCT Community-dwelling patients aged ≥12 years who were at high risk (defined as age ≥65 years or the presence of	N=3,363 36 to 49 days	Primary: Proportion of patients who developed symptomatic influenza A or B infection during prophylaxis as confirmed by culture and/or serology	Primary: Four (0.2%) of 1678 zanamivir-treated subjects developed symptomatic culture/serology-confirmed influenza between day one and day 28, compared to 23(1.4%) of 1,685 placebo recipients (RR, 0.17; 95% CI, 0.07-0.44; P<0.001). Secondary: A significant difference in the incidence of symptomatic, laboratory-confirmed influenza in favor of zanamivir was seen in the per-protocol population (P=0.014), as well as in subjects who developed symptomatic, laboratory-confirmed influenza between days two and 28

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	chronic disorders of the pulmonary or cardiovascular system or diabetes mellitus) for developing complications of influenza		Secondary: Patients with culture/serology-confirmed influenza who developed symptomatic influenza A or B during prophylaxis, with symptoms beginning on day 2/3 or later, fever, complication of influenza, patients who developed influenza like illness, and patients who had laboratory-confirmed influenza regardless of symptoms	(P<0.001) and days three and 28(P=0.001). These results represented protective efficacies of 75, 81, and 80%, respectively. Significantly fewer zanamivir-treated subjects than placebo recipients developed laboratory-confirmed influenza with recorded fever (6/1678 vs 16/1685, respectively; P=0.050; RR, 0.37; 95% CI, 0.15 to 0.92).This result represented a protective efficacy of 63%. Confirmed influenza with complications occurred in1 of 1,678 subjects in the zanamivir group and eight of 1,685 subjects in the placebo group (RR, 0.12; 95% CI, 0.02 to 0.73; P=0.042). This result represented a protective efficacy of 88%. The numbers of zanamivir recipients (9%) and placebo recipients (10%) who developed symptomatic influenza like illness regardless of laboratory confirmation did not differ significantly (RR, 0.86; 95% CI, 0.70 to 1.06). There was no significant difference in the numbers of zanamivir and placebo recipients who developed laboratory-confirmed infection regardless of symptoms (2 and 3%, respectively; RR, 0.76; 95% CI, 0.50 to 1.15).
Halloran et al.[17] (2007) Neuraminidase inhibitors for postexposure prophylaxis	MA Individuals >1 year of age who were household contacts of an individual diagnosed with	N=3,902 14 days or more	Primary: Efficacy in preventing illness, reduction in infectiousness, reduction in pathogenicity	Primary: Efficacy against illness was demonstrated with zanamivir (75%; 95% CI, 54 to 86) and oseltamivir (81%; 95% CI, 35 to 94). In zanamivir-treated patients, the effect on reducing infectiousness vs placebo treated patients was 19% (95% CI, -160 to 75) compared to 80% (95% CI, 43 to 93) for oseltamivir vs placebo.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	influenza		Secondary: Not reported	In reducing the pathogenicity, the efficacy of zanamivir was 52% (95% CI, 19 to 72) and 56% (95% CI, 14 to 77) in two studies, compared to 56% (95% CI, 10 to 73) and 79% (95% CI, 45 to 92) for two other studies with oseltamivir. Secondary: Not reported
Jefferson et al.[18] (2009) Oseltamivir vs zanamivir vs placebo, control antivirals, or no intervention	MA Healthy people exposed to naturally occurring influenza	20 trials Variable duration	Primary: Influenza or influenza-like illness Secondary: Not reported	Primary: Evidence was insufficient to support or refute the effect of neuraminidase inhibitors on prophylaxis of influenza-like illness (RR, 1.28; 95% CI, 0.45 to 3.66 for oseltamivir; RR, 1.51; 95% CI, 0.77 to 2.95 for zanamivir). Zanamivir reduced the chance of symptomatic laboratory confirmed influenza (RR, 0.38; 95% CI, 0.17 to 0.85 for 10 mg daily). Oseltamivir was similarly efficacious (RR, 0.39; 95% CI, 0.18 to 0.85 for 75 mg daily). Neither protected against asymptomatic influenza. Two zanamivir trials reported significant protection for households (RR, 0.1930 and RR, 0.219) and two oseltamivir trials reported similar results (RR, 0.1634 and RR, 0.4218). There was evidence of benefit in shortening the duration of influenza-like illness for zanamivir (HR, 1.24; 95% CI, 1.13 to 1.36) and for oseltamivir (HR, 1.20; 95% CI, 1.06 to 1.35) if taken within 48 hours of the onset of symptoms. Oseltamivir induced nausea (OR, 1.79; 95% CI, 1.10 to 2.93). Secondary: Not reported
Jackson et al.[19] (2011) Amantadine	MA Patients who received antiviral	20 trials Variable duration	Primary: Prevention of symptomatic laboratory-	Primary: Oseltamivir was efficacious in seasonal prophylaxis against (RR, 0.24; 95% CI, 0.09 to 0.54). A protective effect of oseltamivir in seasonal prophylaxis was found in one study which included the frail elderly

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs oseltamivir vs zanamivir vs placebo or no treatment	agents for the prevention of influenza		confirmed influenza Secondary: Complications prevented, hospitalizations prevented, length of influenza illness and time to return to normal activities	living in residential care (RR, 0.08; 95% CI, 0.01 to 0.63). Oseltamivir was effective in preventing the transmission of symptomatic laboratory-confirmed influenza in households of mixed composition (RR, 0.19; 95% CI, 0.08 to 0.45). Oseltamivir have a preventative effect against symptomatic laboratory-confirmed influenza when employed as post-exposure prophylaxis in pediatric contacts (≥1 year of age; RR, 0.36; 95% CI, 0.15 to 0.84). Zanamivir demonstrated a protective efficacy of 68% for seasonal prophylaxis in adults (RR, 0.32; 95% CI, 0.17 to 0.63) and at-risk adolescents/adults (RR, 0.17; 95% CI, 0.07 to 0.44). There was no significant different in older people with zanamivir. Zanamivir was effective in preventing the transmission of symptomatic laboratory-confirmed influenza in households of mixed composition (RR, 0.21; 95% CI, 0.13 to 0.33). There was no significant difference in the elderly in long-term care (RR, 0.68; 95% CI, 0.33 to 1.27). Evidence for the use of amantadine against symptomatic laboratory-confirmed influenza in seasonal prophylaxis was limited. One trial demonstrated a non-significant preventative effect among healthy adults in seasonal prophylaxis (RR, 0.40; 95% CI, 0.08 to 2.03). Amantadine was effective in preventing symptomatic laboratory-confirmed influenza in healthy adolescents (RR, 0.10; 95% CI, 0.03 to 0.34). Secondary: Oseltamivir seasonal prophylaxis was associated with a non-significant 78% reduction in secondary complications among at-risk elderly patients with laboratory-confirmed influenza (P=1.14). In a study of post-exposure prophylaxis, the proportion of contacts with laboratory-confirmed influenza with at least one secondary complication

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				was equivalent among patients who received oseltamivir and those in the control arm who received expectant treatment upon the onset of influenza-like illness (7 vs 5%). However, the more severe respiratory complications occurred among the expectant treatment group. The median duration of illness in contacts was shorter in the oseltamivir post-exposure prophylaxis group vs those receiving treatment on influenza onset (5.5 vs 39.8 hours; P=0.103). Fewer contacts with laboratory-confirmed influenza in the oseltamivir post-exposure prophylaxis group were bedbound compared to patients in those receiving treatment on influenza onset (7 vs 28%). Significantly less work absence was reported among patients who received zanamivir as seasonal prophylaxis vs control group patients (mean hours lost 0.6 vs 1.4; P=0.001). Total productive time lost was also less in the zanamivir group (1.8 vs 3.0 hours; P=0.001). Significantly fewer households who received zanamivir post-exposure prophylaxis reported a contact developing a complication of laboratory-confirmed influenza (2 vs 6%; P=0.01). Complications of symptomatic laboratory-confirmed influenza during the first 28 days following postexposure prophylaxis initiation were lower among the zanamivir-treated patients vs placebo (5 vs 6%; P=0.653). The proportion of cases with complications requiring antibiotics was marginally lower among patients receiving zanamivir post-exposure prophylaxis compared to placebo (5 vs 8%). Among household contacts with laboratory-confirmed influenza, the median time to alleviation of symptoms without use of medication was 5.5 days in the prophylaxis and 8.0 days in the placebo groups. Mean duration of significant influenza-like symptoms was shorter in the zanamivir post-exposure prophylaxis vs placebo group (0.2 vs 0.6 days; P=0.016). No secondary outcomes were described relating to the use of amantadine in seasonal prophylaxis. Limited evidence was identified for milder influenza illness of shorter

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				duration as a result of the use of amantadine in post-exposure prophylaxis. The severity of symptoms was reported as 56.0% mild and 9.0% severe in the amantadine group, and 38.0% mild and 19.0% severe in the placebo group (P<0.01 for severe symptoms, P<0.001 for mild symptoms). Mean duration of illness was found to be shorter in the amantadine group vs the placebo group (P<0.05).
Treatment of Influenza				
Aoki et al.[20] (2003) Oseltamivir 75 mg BID for 5 days	MC, OL Patients (12 to 70 years of age) presenting within 48 hours of the onset of influenza symptoms	N=1,426 1999 to 2000 influenza season	Primary: Illness duration Secondary: Duration of fever, severity of symptoms, time to return to baseline activity	Primary: Earlier intervention was associated with shorter illness duration (P<0.0001). Initiation of therapy within the first 12 hours after fever onset reduced the total median illness duration by 74.6 hours (3.1 days; 41.0%) more than intervention at 48 hours. Secondary: The early administration of oseltamivir further reduced the duration of fever (P=0.0115), severity of symptoms (P=0.0023) and the times to return to baseline activity (P=0.001).
Machado et al.[21] (2004) Oseltamivir 75 mg BID for 5 days	OL, PRO Patients with a proven upper or lower respiratory tract influenza infection detected by direct immuno-fluorescence assay	N=66 1 year	Primary: Complications of influenza Secondary: Not reported	Primary: The percent of patients who developed influenza-related pneumonia after the initiation of oseltamivir within 48 hours of symptoms appearing was 5.1% and no patients died of influenza. Secondary: Not reported
Singh et al.[22] (2003) Oseltamivir 75 mg BID vs	MA Individuals 13 to 97 years of age presenting within 36 hours of onset of influenza	N=2,413 Specific duration varied	Primary: Alleviation of illness, return to normal health status, ability to perform usual activities, normal	Primary: When compared to placebo, the time to alleviation of illness was reduced by 19% (median duration, 100.6; 95% CI, 94.8 to 104.7 vs 124.5 hours; 95% CI, 117.7 to 132.3; P<0.00010). When compared to placebo individuals who received oseltamivir returned to normal health status, regained ability to perform usual

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	symptoms		sleep patterns, symptom improvement, duration of illness Secondary: Not reported	activities and regained normal sleep patterns significantly faster (P values not reported). When compared to placebo, treatment with oseltamivir significantly reduced fatigue by 29% and myalgia by 26% (P<0.0001). More placebo- than oseltamivir-treated patients (57%) remained febrile after 48 hours of treatment (no P value reported). The median duration of acute febrile illness was significantly shortened by use of oseltamivir when compared to placebo use in patients with cardiac disease (44.0 vs 64.7 hours; P=0.026) and chronic obstructive pulmonary disease (37.9 vs 53.8 hours; P=0.004). Secondary: Not reported
Kawai et al.[23] (2006) Oseltamivir 75 mg BID for 5 days vs placebo	MC, PRO Patients who reported influenza-like illness	N=1,818 (influenza A) N=1,485 (influenza B) 5 days	Primary: Duration of fever Secondary: Not reported	Primary: Patients with influenza A and influenza B who were treated with oseltamivir had a significantly shorter duration of fever compared to patients who were not treated with oseltamivir (P<0.001). The duration of fever was significantly longer among oseltamivir-treated patients who had influenza B compared to influenza A, respectively (65.4 vs 47.9 hours; P<0.001). For patients with influenza B compared to patients with influenza A, the duration of fever, measured from the time at which the first dose of oseltamivir was administered, was significantly longer at all-time points (P<0.001). For patients with influenza B compared to patients with influenza A, the duration of fever from the time at which the first dose of oseltamivir was administered was significantly longer in all age groups (P<0.001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Kaiser et al.[24] (2003) Oseltamivir 75 mg BID for 5 days vs placebo	MA Patients 13 to 97 years of age with influenza like illnesses	N=3,564 28 days	Primary: The occurrence of lower respiratory tract complications, requiring intervention Secondary: Hospitalizations, upper respiratory tract complications, overall antibiotic use	Primary: Among influenza-infected patients, oseltamivir reduced the incidence of lower respiratory tract complications leading to antibiotic intervention by 55% compared to placebo (4.6 vs 10.3%; P<0.001). Secondary: The overall percentage of patients hospitalized for any cause was 1.7% in the placebo group compared to 0.7% in the oseltamivir group (59% reduction; P=0.02). A reduction of 50% in overall hospitalizations was seen in the oseltamivir-treated, influenza-infected at-risk patients compared to placebo treated, influenza-infected at-risk patients (1.6 vs 3.2%; P=0.17). The overall incidence of respiratory events following influenza infection was reduced by 28% in the oseltamivir group when compared to the placebo group (11.9 vs 16.9%; P=0.001). No difference was observed in physician diagnosed upper respiratory tract complications leading to antibiotic use between the two treatment groups (P value not reported).
Fry et al.[25] (2014) Oseltamivir BID for 5 days vs placebo	DB, RCT Patients median age of 5 with a positive rapid influenza test identified by surveillance of households	N=1,190 Duration varied	Primary: Duration of clinical illness and viral shedding in patients treated less than and more than 48 hours since illness onset and the frequency of oseltamivir resistance during	Primary: The median duration of symptoms was shorter in the oseltamivir group (three days) than in the placebo group (four days; P=0.01). When stratified by timing of treatment initiation, in participants enrolled 48 hours or longer since illness onset, the median duration of symptoms was similar in both groups (oseltamivir, three days; placebo, three days; P=0.04). The median duration of symptoms was reduced by one day in the group given oseltamivir who were enrolled less than 48 hours since symptom onset compared with those given placebo, but this difference was NS. In those with all swab specimens (n=1,134), oseltamivir significantly

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			treatment Secondary: Not reported	reduced virus isolation on days two (placebo, 374 [66%] vs oseltamivir, 321 [56%]; difference, 15.2%; 95% CI, 9.5 to 20.8; P=0.0004), four (241 [43%] vs 174 [30%]; difference, 30.2%; 95% CI, 24.6 yo 35.8; P<0.0001), and seven (68 [12%] vs 36 [6%]; difference, 47.5%; 95% CI, 44.2 to 50.8; P=0.0009). In participants enrolled 48 hours or longer since illness onset, oseltamivir treatment significantly reduced virus isolation on days two and four, but not day seven. In participants enrolled less than 48 hours since illness onset, oseltamivir treatment significantly reduced virus isolation on days two, four, and seven. The emergency of resistance to oseltamivir during treatment was rare overall (<1%) and in influenza A H1N1 viruses (3.9%). Secondary: Not reported
Ebell et al.[26] (2013) Oseltamivir vs placebo	MA Adults with suspected or confirmed influenza	N=4,769 Duration not reported	Primary: Mean duration of symptoms, likelihood of complications and likelihood of hospitalization Secondary: Not reported	Primary: Treatment with oseltamivir was associated with a mean reduction in the duration of symptoms by 20.7 hours in the intent to treat population (95% CI, 13.3 to 28.0). The mean reduction in the duration of symptoms was 25.4 hours for the intention-to-treat infected population (95% CI, 17.2 to 33.5). There was no significant difference between the oseltamivir and placebo treatment groups regarding the likelihood of any hospitalization in the intention-to-treat population (RD, 0.1%; 95% CI, -0.5 to 0.6). Moreover, no difference between groups were reported in the intention-to-treat population with regard to hospitalizations due to respiratory complications, sepsis or dehydration (RD, 0.0%; 95% CI, -0.5 to 0.4). Pneumonia was less common among patients receiving oseltamivir compared to placebo in the intention-to-treat infected population (RD, -

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				0.9%; 95% CI, -1.7 to -0.1); however, a significant reduction in the likelihood of pneumonia was not observed among patients in the intention-to-treat population (RD, -0.6%; 95% CI, -1.7 to 0.4). The composite outcome of otitis media, sinusitis, pneumonia and bronchitis was significantly less frequent among patients receiving oseltamivir compared to placebo in the intention-to-treat infected population (RD, -2.8%; 95% CI, -4.9 to -0.6). If acute bronchitis is excluded, there was no difference between groups in the likelihood of the combined outcome (RD, -0.1%; 95% CI, -1.7 to 1.5). Data were not reported for these outcomes in the intention-to-treat population. Secondary: Not reported
Jefferson et al.[27] (2014) Oseltamivir	MA PC, RCTs, on adults and children who had confirmed or suspected exposure to natural influenza	N=43 trials Duration varied	Primary: Time to first alleviation of symptoms, influenza outcomes, complications, admissions to hospital, and adverse events Secondary: Not reported	Primary: In treatment trials on adults, oseltamivir reduced the time to first alleviation of symptoms by 16.8 hours (95% CI, 8.4 to 25.1; P<0.001). There was no effect in children with asthma, but there was an effect in otherwise healthy children (mean difference, 29 hours, 95% CI, 12 to 47; P=0.001). In treatment trials there was no difference in admissions to hospital in adults (risk difference, 0.15%; 95% CI, -0.91 to 0.78; P=0.84) and sparse data in children and for prophylaxis. In adult treatment trials, oseltamivir reduced investigator mediated unverified pneumonia (risk difference, 1.00%; 0.22 to 1.49; number needed to treat to benefit, 100; 95% CI, 67 to 451). The effect was not statistically significant in the five trials that used a more detailed diagnostic form for "pneumonia," and no clinical study reports reported laboratory or diagnostic confirmation of "pneumonia." The effect on unverified pneumonia in children and for prophylaxis was NS. There was no significant reduction in risk of unverified bronchitis,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				otitis media, sinusitis, or any complication classified as serious or that led to study withdrawal. Oseltamivir in the treatment of adults increased the risk of nausea (risk difference, 3.66%; 0.90 to 7.39; number needed to treat to harm, 28; 95% CI, 14 to 112) and vomiting (4.56%, 2.39 to 7.58; 22, 14 to 42). In treatment of children, oseltamivir induced vomiting (5.34%, 1.75 to 10.29; 19, 10 to 57). In prophylaxis trials, oseltamivir reduced symptomatic influenza in participants by 55% (3.05%, 1.83 to 3.88; number needed to treat to benefit, 33; 26 to 55) and households (13.6%, 9.52 to 15.47; number needed to treat to benefit, 7; 6 to 11) based on one study, but there was no significant effect on asymptomatic influenza and no evidence of a reduction in transmission. In prophylaxis studies, oseltamivir increased the risk of psychiatric adverse events during the combined "on-treatment" and "off-treatment" periods (risk difference, 1.06%; 0.07 to 2.76; number needed to treat to harm, 94; 36 to 1,538) and there was a dose-response effect on psychiatric events in two "pivotal" treatment trials of oseltamivir, at 75 mg (standard dose) and 150 mg (high dose) BID (P=0.038). In prophylaxis studies, oseltamivir increased the risk of headaches on-treatment (risk difference, 3.15%; 0.88 to 5.78; number needed to treat to harm, 32; 18 to 115), renal events with treatment (0.67%, -0.01 to 2.93), and nausea while receiving treatment (4.15%, 0.86 to 9.51; number needed to treat to harm, 25; 11 to 116). Secondary: Not reported
Lin et al.[28] (2006) Oseltamivir 75 mg	OL, RCT Chinese patients at high risk	N=56 5 days of treatment,	Primary: Duration and severity of illness	Primary: The duration and severity of influenza symptoms was significantly reduced in the oseltamivir group, by 36.8% (P=0.0479) and 43.1% (P=0.0002) respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
BID for 5 days vs symptomatic treatment	initiating treatment within 48 hours after symptom onset	follow-up varied	Secondary: Incidence of complications, antibiotic use, hospitalizations	Secondary: The duration of fever was significantly reduced in the oseltamivir group by 45.2% (P=0.0051), as was the proportion that returned to baseline health status within five days (11 vs 45%; P=0.0011). In the oseltamivir group, the incidence rates of complications (11 vs 45%; P=0.0053) and antibiotic use (37 vs 69%; P=0.0167) were significantly lower.
Lee et al.[29] (2010) Oseltamivir 75 mg BID for 5 days vs no antiviral treatment	PRO Hospitalized patients ≥18 years of age with laboratory-confirmed seasonal influenza infection	N=754 Variable duration	Primary: Clinical outcomes Secondary: Not reported	Primary: Supplemental oxygen and ventilatory support was required in 53.2% and 5.4% of patients, respectively. A total of 5.2% of patients died, which were due to pneumonia, respiratory failure and sepsis. A total of 52% of patients received oseltamivir treatment. Omission of antiviral treatment was associated with delayed presentation or negative antigen detection results. The mortality rate was 4.56 and 7.42 per 1,000 patient-days in the treated and untreated patients, respectively. Antiviral use was associated with reduced risk of death (HR, 0.27; 95% CI, 0.13 to 0.55; P<0.001). Improved survival was observed with treatment started within 4 days from onset. Earlier hospital discharge (HR, 1.28; 95% CI, 1.04 to 1.57; P=0.019) and faster discontinuation of oxygen therapy (HR, 1.30; 95% CI, 1.01 to 1.69; P=0.043) was associated with early treatment within two days. Secondary: Not reported
Ng et al.[30] (2010)	OL	N=384 (index	Primary: Clinical	Primary: Index patients who had taken oseltamivir within 24 hours of symptom

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Oseltamivir vs no therapy	Patients who reported ≥2 symptoms of acute respiratory illness with symptom onset within 48 hours and lived with at least 2 other individuals, none of whom had reported acute respiratory illness symptoms during the previous 14 days	patients and household contacts) 7-10 days	outcomes Secondary: Not reported	onset experienced a 44% reduction in time to alleviation of all signs and symptoms, with an adjusted acceleration factor of alleviation of 0.56 (95% CI, 0.42 to 0.76) compared to index patients who did not take any antiviral. Results were similar for time to alleviation of fever and time to alleviation of respiratory symptoms. The median duration of viral shedding after symptom onset was six days, and viral shedding resolved sooner in individuals prescribed oseltamivir within 24 hours of onset. Index patients who took oseltamivir within 48 hours of onset had a non-significant reduction in duration of viral shedding in year 2007 (acceleration factor, 0.76; 95% CI, 0.51 to 1.14) and 2008 (acceleration factor, 0.99; 95% CI, 0.83 to 1.17) compared to index patients who did not take any antiviral medication. Household contacts of index patients who took oseltamivir within 24 hours of first symptoms had a non-significant lower risk of developing influenza virus infection confirmed by RT-PCR or viral culture (adjusted OR, 0.54; 95% CI, 0.11 to 2.57), clinical influenza (adjusted OR, 0.52; 95% CI, 0.25 to 1.08), and clinical influenza confirmed by RT-PCR or viral culture (adjusted OR, 0.47; 95% CI, 0.05 to 4.03). The risk reduction was attenuated for the contacts of index patients who had taken oseltamivir later than 24 hours after symptom onset (P=0.09 for laboratory-confirmed influenza and P=0.41 for clinical influenza). Household contacts were at lower risk of illness from influenza virus infection if they had been vaccinated, if they were older, or if their corresponding index patient was older.
Bueno et al.[31] (2013) Oseltamivir	MC, RETRO Children admitted to the hospitals with confirmed	N=287 Duration varied	Primary: Fever duration, oxygen support, antibiotics administration,	Primary: There were no significant differences between treated and untreated patients in days of fever after admission (1.7+2.0, 2.1+2.9; P>0.05), length of stay (5.2+3.6, 5.5+3.4; P>0.05), days of hypoxia (1.6+2.3, 2.1+2.9; P>0.05), diagnosis of bacterial pneumonia (10%, 17%; P>0.05),

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs no treatment	influenza infections		length of hospital stay, intensive care admission and bacterial complications Secondary: Not reported	intensive care admission (6.5%, 1.5%; P>0.05) or antibiotic prescription (44%, 51%; P>0.05). There were no differences when the population was stratified by age (below or over one year) or by the presence or absence of asthma. Secondary: Not reported
Sugaya et al.[32] (2007) Oseltamivir BID for 5 days (weight-based dosing) vs control	OL Children aged 1 to 15 years of age presenting to outpatient clinics within 48 hours of onset of symptoms	N=127 (influenza A) N=362 (influenza B) 5 days	Primary: Total febrile period, duration of fever, effectiveness according to age, effectiveness and history of vaccination, virus shedding Secondary: Not reported	Primary: When comparing the study participants with influenza A to those with influenza B, there was a significant difference in the mean duration of febrile period (2.19 vs 4.44 days; P<0.001). In patients with influenza B, the mean duration of febrile period significantly differed between the patients treated with oseltamivir and the control patients (2.98 vs 5.55 days; P<0.001). The mean duration of fever after the initiation of therapy was 1.31 days with influenza A patients compared to 2.18 days with influenza B patients (P<0.001). For patients with influenza B, the duration of fever was significantly longer in children one to five years of age (2.37 days) than in children six to 10 years of age (1.97 days; P=0.013) and 11 to 15 years of age (1.54 days; P=0.006). The difference between children six to 10 and 11 to 15 years of age was NS (P=0.14). There was a significant difference in the duration of fever in the two younger groups of children between the patients with influenza A and B (children one to five, 1.42 vs 2.37 days; P<0.001 and children six to 10, 1.23 vs 1.97 days; P<0.001). There was no significant difference in duration of fever with influenza A vs influenza B in the group of children aged 11 to 15 (P=0.54). There was no significant difference either for the total population or for

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				the subgroups by age in the duration of fever between patients with influenza A who had been vaccinated and those who had not (1.36 vs 1.36 days). There was a significant difference in mean virus titers two days after the start of oseltamivir between the influenza A and influenza B groups (0.61 vs 2.84; P<0.001). Secondary: Not reported
Whitley et al.[33] (2001) Oseltamivir liquid 2 mg/kg/dose BID for 5 days vs placebo	DB, PC, RCT Children 1 through 12 years of age with fever and a history of cough or coryza <48 hours duration	N=695 1998 to 1999 influenza season	Primary: Time to resolution of illness including mild/absent cough and coryza, return to normal activity and euthermia Secondary: Adverse events	Primary: Among infected children, the median duration of illness was reduced by 36 hours (26%) in oseltamivir recipients compared to placebo recipients (101; 95% CI, 89 to 118 vs 137 hours; 95% CI, 125 to 150; P<0.0001). Oseltamivir treatment also reduced cough, coryza and duration of fever. New diagnoses of otitis media were reduced by 44% (12 vs 21%). The incidence of physician-prescribed antibiotics was significantly lower in influenza-infected oseltamivir (68 of 217, 31%) than placebo (97 of 235, 41%; P=0.03) recipients. Secondary: Oseltamivir therapy was generally well-tolerated, although associated with an excess frequency of emesis (5.8%). Discontinuation because of adverse events was low in both groups (1.8% with oseltamivir vs 1.1% with placebo).
Hiba et al[34] (2011) Oseltamivir 75 mg BID for 5 days (early treatment) vs	OS, RETRO All adults with laboratory-confirmed pandemic 2009 influenza A (H1N1) in three hospitals in	N=449 5 days	Primary: Influenza complications with early vs late oseltamivir treatment (pulmonary infiltrates visualized on	Primary: Early treatment with oseltamivir was associated with fewer complications as defined by the primary outcome (35.4 vs 157.7% late; P<0.001). On multivariable analysis, late initiation of oseltamivir remained significantly associated with complications (OR, 2.37; 95% CI, 1.52 to 3.70).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
oseltamivir 75 mg BID for 5 days (late treatment, initiation later than 48 hours after symptom onset)	central Israel between 22 July 2009 and the end of the influenza pandemic in January 2010		chest X-ray or CT scan, documentation of hypoxia [arterial saturation, 90%], mechanical ventilation, intensive care unit admission, need for hemodynamic support, or in-hospital death) Secondary: Events occurring only after initiation of oseltamivir and those presenting after admission	Secondary: Early oseltamivir was associated with a lower rate of all secondary outcomes. Any complication developing after admission occurred in 15 (7.9%) of the early oseltamivir treated patients compared to 42 (16.2%) of the late treated patients (P=0.010). Any complication developing after the start of oseltamivir occurred in 13 (6.9%) of the early oseltamivir treated patients compared to 33 (12.7%) of the late treated patients (P=0.045). In the adjusted analysis, initiation of oseltamivir >48 hours after admission was significantly associated with complications developing after admission (OR, 4.09; 95% CI, 1.55 to 10.80). Early oseltamivir was also associated with a lower rate of most individual components of the composite primary outcome, including in-hospital mortality (1/180 [0.5%] patients in the early oseltamivir treated patients compared to 13/260 [5.0%] in the late treated patients [P=0.006]). Other individual components of the composite primary endpoint include: pneumonia, 22.2% early oseltamivir vs 46.9% late oseltamivir (P<0.001); hypoxemia, 20.1% early oseltamivir vs 28.1% late oseltamivir (P=0.053); intensive care unit admission, 3.2% early oseltamivir vs 9.2% late oseltamivir (P=0.011); mechanical ventilation, 3.2% early oseltamivir vs 8.1% late oseltamivir (P=0.031); and number of hospitalization days for patients discharged alive, five early oseltamivir vs seven late oseltamivir (P=0.001).
Nicholson et al.[35] (2000) Oseltamivir 75 mg BID for 5 days vs	RCT Adults with naturally acquired laboratory-confirmed influenza with febrile influenza-	N=726 3 months	Primary: Time to resolution of illness Secondary: Symptom scores, viral shedding,	Primary: Duration of illness was significantly shorter by 29 hours (25% reduction, median duration 87.4 hours; 95% CI, 73.3 to 104.7; P=0.02) with oseltamivir 75 mg and by 35 hours (30% reduction, 81.8 hours; 95% CI, 68.2 to 100.0; P=0.01) with oseltamivir 150 mg, both in comparison to placebo (116.5 hours; 95% CI, 101.5 to 137.8). The effect of oseltamivir was apparent within 24 hours of the start of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
oseltamivir 150 mg BID for 5 days vs placebo	like illness of up to 36 hours duration		health, activity, sleep quality, and tolerability	treatment. In patients treated within 24 hours of symptom onset, symptoms were alleviated 43 hours (37% reduction) and 47 hours (40% reduction) earlier with oseltamivir 75 and 150 mg, respectively, compared to placebo (for 75 mg, time to symptom alleviation was 74.5 hours; 95% CI, 68.2 to 98.0; P=0.02, for 150 mg, time to symptom alleviation was 70.7 hours; 95% CI, 54.0 to 89.4; P=0.01, for placebo, time to symptom alleviation was 117.5 hours; 95% CI, 103.0 to 143.8). Secondary: Oseltamivir was associated with lower symptom scores, less viral shedding, and improved health, activity, and sleep quality, and was well tolerated.
Treanor et al.[36] (2000) Oseltamivir 75 mg BID for 5 days vs oseltamivir 150 mg BID for 5 days vs placebo for 5 days	DB, MC, RCT Adults aged 18 to 65 years presenting within 36 hours of onset of influenza symptoms; patients presented with oral temperature 38ºC or higher plus 1 or more respiratory symptom including cough, sore throat or nasal symptoms; 1 or more constitutional symptom including headache, malaise, myalgia,	N=629 21 days	Primary: Duration of illness, defined as the time to the beginning of the first 24-hour period in which all influenza symptoms were rated as mild or less Secondary: Duration and severity of individual symptoms, incidence of secondary complications, quantity of viral shedding	Primary: The median durations of illness were 103.3 hours (4.3 days) in the placebo group, and 71.5 hours (3.0 days) and 69.9 hours (2.9 days) in the 75 and 150 mg oseltamivir groups, respectively. Treatment with oseltamivir at either 75 or 150 mg BID resulted in statistically significant reductions (P<0.001 and P=0.006, respectively) in the area under the curve analysis of total symptom scores which reflects the severity and duration of illness. There were no differences between the two doses of oseltamivir with regard to effects. The 75 and 150 mg doses of oseltamivir reduced the severity of illness compared to placebo by 38 and 35%, respectively (P<0.001 for both). Secondary: Duration of cough was reduced from a median of 55 hours in the placebo group to 31 hours (43% reduction) in the 75 mg group and to 40 hours (27% reduction) in the 150 mg group. The duration of myalgia was also reduced, from a median of 28 hours in the placebo group to 16 hours (42% reduction) in the 75 mg group and 19 hours (32% reduction) in the 150 mg group. After 24 hours of treatment, median viral titers had decreased by 1.2 logs

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	sweats and/or chills or fatigue			in the placebo group vs 1.7 and 2.0 logs in the 75 and 150 mg oseltamivir groups, respectively. These differences were not statistically significant. Nausea and vomiting occurred more frequently in both the oseltamivir groups compared to the placebo group (P<0.001).
MIST Study Group[37] (1998) Zanamivir 10 mg inhaled BID for 5 days vs placebo	DB, MC, RCT Healthy individuals 12 years of age or older presenting with influenza-like illness of 36 hours duration or less	N=455 28 days	Primary: Length of time to alleviation of clinically important symptoms including absence of fever, mild headache, cough, myalgia and sore throat for 24 hours Secondary: Length of time to return to normal activities, mean symptom scores, sleep distur-bance, use of relief medications, rate of complications and associated use of antibiotics	Primary: Zanamivir significantly shortened the time to alleviation of symptoms in the intention-to-treat population compared to placebo (5.0 vs 6.5 days; P=0.011). This 1.5 day benefit was also seen for influenza-positive patients (4.5 vs 6.0 days; P=0.004). In patients who were febrile and received zanamivir, symptoms were decreased two days earlier than in those who received placebo (P<0.001) in the intention-to-treat and influenza-positive patient groups. Influenza-positive patients treated with zanamivir had significantly less severe symptoms overall on days one to14 than those on placebo (P<0.05). High-risk patients had significantly fewer complications than those on placebo (P=0.004) and fewer high risk patients needed antibiotic medication to treat those complications (P=0.025). Secondary: When zanamivir recipients were compared to patients on placebo, return to normal activities, sleep disturbances, complication rates, and associated use of antibiotics were all less in the intention-to-treat and influenza-positive populations, but the differences were NS.
Hedrick et al.[38] (2000) Zanamivir 10 mg	DB, MC, PC, PG, RCT Children 5 to 12	N=471 1998 to 1999 influenza	Primary: Alleviation of symptoms	Primary: A total of 346 (73%) patients were influenza-positive by culture, serology or polymerase chain reaction (65% influenza A, 35% influenza B). Zanamivir reduced the median time to symptom alleviation by 1.25

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
inhaled BID for 5 days vs placebo	years of age with influenza-like symptoms for ≤36 hours	season	Secondary: Return to normal activities, use of relief medications, adverse events	days compared to placebo among patients with confirmed influenza infection (P<0.001). Secondary: Zanamivir-treated patients returned to normal activities significantly faster than placebo treated patients (influenza-positive population; P=0.022, intent-to-treat population; P=0.019). The zanamivir-treated patients also took significantly fewer relief medications than those treated with placebo in the influenza-positive (P=0.005) and intent-to-treat (P=0.016) populations. Zanamivir was well-tolerated, demonstrating adverse event profiles similar to those of placebo and no clinically significant changes in laboratory findings. Adverse events were reported during treatment for 21% for patients in the zanamivir group and 26% of patients in the placebo group.
Lalezari et al.[39] (2001) Zanamivir 10 mg BID for 5 days vs placebo	MA High risk patients with confirmed influenza	N=321 21 to 28 days	Primary: Time to return to normal activities, median time to alleviation of symptoms Secondary: Not reported	Primary: A treatment benefit of 2.5 days was seen with the zanamivir-treated high risk patients compared to the placebo-treated high risk patients (P=0.015). Patients returned to normal activities three days earlier (P=0.022) and had an 11% reduction (P=0.0.9) in the median total symptom score over one to five days of treatment with zanamivir compared to treatment with placebo. The incidence of complications requiring antibiotic use was reduced by 43% with treatment with zanamivir compared to treatment with placebo (P=0.045). Adverse events were similar between the treatment groups (P value not reported). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Hayden et al.[40] (1997) Zanamivir 6.4 mg by intranasal spray* plus 10 mg by inhalation BID for 5 days vs zanamivir 10 mg by inhalation plus placebo spray BID for 5 days vs placebo by both routes BID for 5 days	DB, RCT Adults with acute influenza of ≤48 hours duration	N=417 1994 to 1995 influenza season	Primary: Length of time to alleviation of all major symptoms Secondary: Not reported	Primary: Of 262 patients with confirmed influenza-virus infection (63% of all patients), the median length of time to the alleviation of all major symptoms was one day shorter (four vs five days) in the 88 patients given inhaled and intranasal zanamivir (P=0.02) and the 85 patients given inhaled zanamivir alone (P=0.05) than in the 89 patients given placebo. Among the infected patients who were febrile at enrollment and among those who began treatment within 30 hours after the onset of symptoms, the median time to the alleviation of major symptoms was four days in both zanamivir groups and seven days in the placebo group (P≤0.01). Secondary: Not reported
Monto et al.[41] (1999) Zanamivir 10 mg inhaled BID for 5 days vs zanamivir 10 mg inhaled 4 times a day for 5 days vs placebo	DB, MC, PG, RCT Healthy persons ≥13 years of age who presented with symptoms of influenza ≤48 hours of duration	N=1,256 1995-1996 influenza season	Primary: Alleviation of all major symptoms Secondary: Nights of disturbed sleep, time to resumption of normal activities, use of symptom relief medications	Primary: In the overall population with or without influenza infection, zanamivir reduced the median number of days to alleviate all major symptoms by one day (P=0.012 two BID vs placebo; P=0.014 QID vs placebo). The reduction was greater in patients treated within 30 hours of symptom onset, febrile at study entry, and in defined high-risk groups. Secondary: Zanamivir reduced nights of disturbed sleep (P=0.013, zanamivir QID vs placebo; P=0.026), time to resumption of normal activities (P=0.005, zanamivir QID vs placebo; P<0.001), and use of symptom relief medications (P<0.001, zanamivir QID vs placebo; P=0.007).
Louie et al.[42]	RETRO	N=748	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2013) Neuraminidase inhibitor therapy	Patients 0 to 17 years of age hospitalized in intensive care units with laboratory-confirmed influenza from April 3, 2009, through September 30, 2012	Duration varied	Mortality Secondary: Not reported	Of neuraminidase inhibitor-treated cases, 38 (6%) died compared with 11 (8%) of 131 untreated cases (OR, 0.67; 95% CI, 0.34 to 1.36). In a multivariate model that included receipt of mechanical ventilation and other factors associated with disease severity, the estimated risk of death was reduced in neuraminidase inhibitor-treated cases (OR, 0.36; 95% CI, 0.16 to 0.83). Treatment within 48 hours of illness onset was significantly associated with survival (P=0.04). Cases with neuraminidase inhibitor treatment initiated earlier in illness were less likely to die. Secondary: Not reported
Kawai et al.[43] (2009) Oseltamivir 75 mg for adults and 2 mg/kg for children <37.5 kg BID for 5 days vs zanamivir 10 mg BID for 5 days	OL Patients with H1N1 or H3N2 virus infection	N=373 5 days	Primary: Efficacy and safety Secondary: Not reported	Primary: The duration of fever after the start of oseltamivir therapy was significantly longer for patients with H1N1 virus infection during the 2008–2009 season than it was for those with infection during the 2007–2008 season (P<0.001) and for patients with H3N2 virus during the 2008–2009 season (P<0.01). No significant difference was found in the duration of fever after the start of zanamivir therapy among the three groups with H1N1 virus infection during the 2007–2008 season, H1N1 virus infection during the 2008–2009 season, or H3N2 virus infection during the 2008–2009 season. The duration of fever after the start of oseltamivir therapy for patients in the ≤15-year-old and >15-year-old age groups was significantly longer for patients of both groups in 2008– 2009 than in patients with H1N1 virus in 2007–2008. The duration of oseltamivir therapy in the 2008–2009 season was significantly longer than that of zanamivir therapy in each age group in the 2008–2009 season (P<0.001 and P<0.01, respectively). The duration of fever after onset of symptoms was significantly longer

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				for patients with H1N1 virus infection in the 2008–2009 season than for patients with H1N1 virus infection in the 2007–2008 season and for patients with H3N2 virus infection in the 2008– 2009 season. A significant difference was found between oseltamivir and zanamivir therapy for patients with H1N1 virus infection in the 2008–2009 season (P<0.001). The duration of fever for patients treated with oseltamivir was significantly longer during the 2008–2009 season than it was during the 2007–2008 season for patients ≤15 years old (P<0.01) but was not statistically significant for patients >15 years old. The duration of zanamivir therapy was significantly shorter than the duration of oseltamivir therapy in both age groups in the 2008–2009 season. The percentages of febrile patients at 48 and 72 hours after oseltamivir therapy were significantly higher in the H1N1 virus infection group during 2008–2009 than in the H1N1 virus infection group during 2007–2008 or the H3N2 virus group during the 2008–2009 season in all age groups. The percentage of febrile patients at 48 and 72 hours after oseltamivir therapy for the H1N1 virus infection group during the 2008–2009 season was also significantly higher than for the H1N1 virus group during 2007–2008 for children <10 years old. Secondary: Not reported
Sugaya et al.[44] (2008) Oseltamivir (weight-based dosing) BID for 5 days vs zanamivir 20 mg/day given BID for 5 days	OL Children with influenza A (H1N1) virus, influenza A (H3N2) virus, and influenza B virus infections	N=162 5 days	Primary: Total febrile period and the duration of fever after the start of treatment Secondary: Not reported	Primary: In patients with influenza A (H3N2), there was no significant difference in total febrile period or duration of fever after the start of treatment with oseltamivir and zanamivir (mean duration of febrile period, 2.40 vs 2.39 days; mean duration of fever after the start of treatment, 1.35 vs 1.40 days). The total febrile period was shortened by ~2 days with oseltamivir (P<0.05) and zanamivir (P<0.05). There were no significant differences in the body temperature among the groups. In patients with influenza A (H1N1), there was no significant difference in total febrile period or the duration of fever after the start of treatment between the treatment groups (mean duration of febrile period, 2.60 vs

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				2.46 days; mean duration of fever after the start of treatment, 1.79 vs 1.54 days). There were no significant differences in the body temperature among the groups. In patients with influenza B, there was no significant difference in total febrile period or duration of fever after the start of treatment between the treatment groups (mean duration of febrile period, 2.95 vs 2.84 days; mean duration of fever after the start of treatment, 1.86 vs 1.67 days). The total febrile period was shortened by ~1 day with oseltamivir (P<0.05) and with zanamivir (P<0.05). There were no significant differences in the body temperature among the groups. Secondary: Not reported
Tuna et al.[45] (2012) Oseltamivir vs zanamivir	RCT Patients diagnosed with influenza during the influenza season between October 1, 2009 and February 1, 2010	N=80 Duration varied	Primary: Efficacy and safety Secondary: Not reported	Primary: There was no significant difference in efficacy for the two drugs (P>0.05). Temperature normalization was significantly faster in patients taking zanamivir (P=0.0157). Drowsiness was the most frequent adverse event for both drugs (38% for the oseltamivir group, and 22% for the zanamivir group). Respiratory distress was observed in five patients in the zanamivir group, whereas it was not observed in patients in the oseltamivir group (P<0.05). One patient had to discontinue therapy in the zanamivir group due to respiratory distress. Secondary: Not reported
Shun-Shin et al.[46] (2009) Oseltamivir vs	MA Children ≤12 years of age with influenza	N=2,629 (7 trials) Variable duration	Primary: Time to resolution of illness and incidence of influenza in children living in	Primary: Treatment with zanamivir and oseltamivir provided a median reduction in time to resolution of symptoms of between 0.5 and 1.5 days. A 10 day course of prophylaxis with either zanamivir or oseltamivir was associated with an 8% reduction in the risk of developing confirmed symptomatic influenza after the introduction of an index case of clinical

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zanamivir			households with index cases of influenza Secondary: Not reported	influenza into the household (P<0.001). This equates to a number needed to treat of 13 to prevent one additional household case of symptomatic influenza. Oseltamivir did not reduce asthma exacerbations or improve peak flow in children with asthma in on trial. Treatment was not associated with reduction in overall use of antibiotics. Zanamivir was well tolerated, but oseltamivir was associated with an increased risk of vomiting (number needed to harm=20). Secondary: Not reported
Duval et al.[47] (2010) Oseltamivir 75 mg BID plus zanamivir 10 mg by inhalation BID (OZ) vs oseltamivir 75 mg BID plus inhaled placebo (O) vs zanamivir 10 mg by inhalation BID plus oral placebo (Z)	DB, PC, RCT French adults 18 years of age and older who consulted their general practitioner within 36 hours of influenza symptoms, with a temperature ≥38°C, one or more respiratory symptoms, one or more general symptoms, and a positive nasal rapid test for influenza A	N=541 7 days	Primary: Proportion of patients with nasal influenza reverse transcription-PCR below 200 copies genome equivalent/µL at day two Secondary: Decrease of log10 viral load between days zero and two, time to resolution of illness, number of patients with alleviation of	Primary: The proportion of patients with a reverse transcriptase-PCR, 200 copies genome equivalent/µL on day two of treatment was 52.6% for OZ, 62.5% for O (P=0.055, for the OZ vs O comparison, treatment effect comparison, 29.9%; 95% CI, 219.9 to 0.2), and 40.5% for Z (P=0.020, for the OZ vs Z comparison; treatment effect comparison, 12.1%; 95% CI, 2.02 to 22.3). The O vs Z comparison was 22%; 95% CI, 12.1 to 32.0. Secondary: The day two to day zero decrease of log10 viral load was 2.14 log10 copies genome equivalent/µL for OZ, 2.49 log10 copies genome equivalent/µL for O, (P=0.060 for the OZ vs O comparison; treatment effect comparison, 20.35; 95% CI, 20.8 to 0.07), and 1.68 log10 copies genome equivalent/mL for Z (P=0.016 for the OZ vs Z comparison; treatment effect comparison, 0.46; 95% CI, 0.03 to 0.9). The median time to resolution of illness was 3.5 days for OZ, 3.0 days for O (P=0.015 for the OZ vs O comparison; treatment effect comparison, 0.5%; 95% CI, 0.0 to 1.5), and 4.0 days for Z (P=0.78 for the OZ vs Z comparison; treatment effect comparison, 20.5; 95% CI,

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			symptoms at the end of treatment (day five), symptoms score at the end of treatment, incidence of secondary complications of influenza, occurrence of adverse events in all participants having received at least one dose	21.0 to 0.5). The O vs Z comparison was -1.0; 95% CI, -1.5 to -0.5. The number of patients with alleviation of symptoms at the end of treatment (day five) was 26 (13.5%) for OZ, 15 (8.5%) for O (P=0.014 for the OZ vs O comparison; treatment effect comparison, 5%; 95% CI, -1.3 to 11.4), and 23 (13.3%) for Z (P=0.93 for the OZ vs Z comparison; treatment effect comparison, 1.0; 95% CI, -6.7 to 7.2). The O vs Z comparison was 11.5%; 95% CI, 1.7 to 21.3. The median symptoms score at day five (end of treatment) was three for OZ, two for O (P=0.013 for the OZ vs O comparison; treatment effect comparison, 1; 95% CI, 0.0 to 1.0), and three for Z (P=0.93 for the OZ vs Z comparison; treatment effect comparison, 0.0; 95% CI, 21.0 to 0.0). The O vs Z comparison was -1.0; 95% CI, -2.0 to -1.0. The percentage of patients with clinical event during treatment was 26 (13.5%) for OZ, 15 (8.5%) for O (P=0.14 for the OZ vs O comparison; treatment effect comparison, 5.0%; 95% CI, 21.3 to 11.4, and 23 (13.3%) for Z (P=1.00 for the OZ vs Z comparison; treatment effect, 0.3%; 95% CI, 26.7 to 7.2). The O vs Z comparison was -4.8%; 95% CI, -11.2 to 1.6. Nausea and/or vomiting tended to be more frequent in the combination arm (OZ, 13; O, 4; and Z, 5 patients, respectively).
Kawai et al.[48] (2008) Zanamivir 10 mg (adults and children aged ≥5 years) BID for five days vs oseltamivir	MC, PRO Patients 5 years of age and older who reported to any of 27 clinics throughout Japan with influenza-like illness and received a	N=1,113 5 days	Primary: Duration of fever from onset, duration of fever after administration of first dose of oseltamivir or zanamivir, percentage of patients afebrile	Primary: The duration of fever from its onset was significantly shorter for patients with influenza A treated with zanamivir compared to those treated with oseltamivir (31.8 and 35.5 hours, respectively; P<0.05). The duration of fever after starting zanamivir was significantly shorter compared to oseltamivir for influenza B (35.8 and 52.7 hours, respectively; P<0.001). No statistically significant differences in the percentage of patients afebrile at 24 or 48 hours after the first dose of drug were shown

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(75 mg for adults and children >37.5 kg;2 mg/kg for children <37.5 kg) orally BID for five days vs no treatment Antipyretics were not administered, and in the case of emergency, acetaminophen was used temporally.	diagnosis of influenza A or B based on the results of commercial antigen detection kits		at 24 and 48 hours after the first dose of zanamivir or oseltamivir, virus isolation before and after zanamivir therapy Secondary: Not reported	between zanamivir and oseltamivir therapy in patients with influenza A (P value not reported). The percentage of patients afebrile at 24 or 48 hours after the first dose of drug was significantly higher in the zanamivir group compared to the oseltamivir group in patients with influenza B (P<0.001). No significant difference was observed in zanamivir patients with influenza A or influenza B (P value not reported). The percentage of patients afebrile 24 and 48 hours after starting oseltamivir was significantly higher for influenza A compared to influenza B (P<0.001). In patients five to 10 years of age, there was no significant difference in the re-isolation rate between influenza A (A/H3N2 or A/H1N1, 47.1%) and influenza B (36.1%). The re-isolation rate in patients >10 years of age and in all patients was significantly higher for influenza B (20.0 and 25.5%) than for influenza A (6.3 and 12.5%, respectively; P<0.01 and P<0.05, respectively). The re-isolation rate was significantly higher in patients five to 10 years of age than in patients >10 years of age for influenza A (P<0.001). Secondary: Not reported
Kawai et al.[49] (2005) Amantadine 50 mg for adults and 1.5 to 2.5 mg/kg for children was administered BID for 5 days to patients with influenza A (Group 3) vs	OL Patients diagnosed with influenza who received oseltamivir or amantadine therapy within 48 hours after symptom onset	N=2,163 5 days	Primary: Time from onset of symptoms to start of treatment, duration of fever, impact of age on outcome Secondary: Not reported	Primary: For all three groups the duration of fever was significantly shorter in patients who received the medication within 12 hours after the onset of symptoms compared to greater than 12 hours after the honest of symptoms (P<0.001). For patients in group 2 the duration of fever was significantly longer when compared to groups 1 and 3, however there was no significant differences between groups 1 and 3 (P<0.01 to <0.05). The duration of fever was significantly longer for patients in groups 2 and 3 aged 0 to six years when compared to those aged seven to 15 and 16 to 64; P<0.001 to 0.01). The duration of fever of patients 0 to six in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
oseltamivir 75 mg for adults and 2 mg/kg for children (<37.5 kg) given BID for 5 days to patients with either influenza A (Group 1) or influenza B (Group 2)				group 1 was significantly shorter than for those same aged patients in group 2 (P<0.01). For patients aged 16 to 64 and >65 there was no significant difference found between groups in duration of fever (P=NS).
Kimberlin et al.[50] (2010) Amantadine vs rimantadine vs oseltamivir	RETRO Children <12 months of age with influenza	N=180 Variable duration	Primary: Frequency of neurologic adverse events and all adverse events Secondary: Not reported	Primary: Abnormalities that potentially reflected neurologic involvement were consistent with influenza disease, related to preexisting underlying neurologic conditions, or explainable by a concomitant medication. Two patients had possible seizures or seizure-like movements during therapy with no preexisting history of such events, but in both cases the seizures were not thought to be related to antiviral therapy. Only 33% of the patients had Glasgow Coma Score information available in their medical records. The end-of-treatment ranked verbal score was slightly lower for oseltamivir treated patients (P=0.04). Total scores were identical between the two therapies (P=0.40). One death occurred within 30 days following initiation of the influenza antiviral medications. Secondary: Not reported
Treatment and Prophylaxis of Influenza				
Nordstrom et al.[51] (2005) <u>Group 1</u> Oseltamivir with a diagnosed influenza-like illness	Cohort, RETRO Patients receiving oseltamivir or with a diagnosis of influenza-like illness	N=11,632 (Group 1) N=60,427 (Group 2) N=17,133	Primary: Diagnosis of pneumonia, hospitalization for any cause, dispensing of an antibiotic	Primary: When comparing influenza-like illness with oseltamivir to influenza-like illness with no antivirals, the adjusted HR for pneumonia was 0.72 (95% CI, 0.60 to 0.86), for antibiotic dispensing the adjusted HR for pneumonia was 0.89 (95% CI, 0.86 to 0.93), and for hospitalization the adjusted HR for pneumonia was 0.74 (95% CI, 0.61 to 0.90).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs Group 2 oseltamivir with no diagnosis of influenza-like illness vs Group 3 no antiviral therapy and diagnosed with influenza-like illness		(Group 3) December 1, 1999 to March 31, 2002	Secondary: Not reported	Secondary: Not reported
Johny et al.[52] (2002) Zanamivir 10 mg BID until excretion of virus ceased	OL Patients post allograft with diagnosed influenza	N=7 5 to 44 days	Primary: Toxicity, morbidity Secondary: Not reported	Primary: With the administration of zanamivir there were no toxicity attributes noted and there was no mortality seen in the seven patients (P value not reported). Secondary; Not reported
Jefferson et al.[53] (2006) Neuraminidase inhibitors as prophylaxis and/or treatment for influenza or influenza-like illness vs placebo	MA Individuals with known pre-existing chronic pathology known to aggravate the course of influenza	N=1,014 patients received a neuraminidase inhibitor 22 to 49 days	Primary: Efficacy (distribution and/or severity of influenza), viral load, adverse events Secondary: Not reported	Primary: Neuraminidase inhibitors did not demonstrate an effect against influenza like illness when used as prophylaxis when compared to placebo (RR, 1.28; 95% CI, 0.45 to 3.66 for oseltamivir and RR, 1.51; 95% CI, 0.77 to 2.95 for zanamivir). Against symptomatic influenza, the efficacy of oseltamivir was 61% (RR, 0.39; 95% CI, 0.18 to 0.85) at the 75 mg dose and 73% (RR, 0.27; 95% CI, 0.11 to 0.67) at the 150 mg dose. Zanamivir was calculated to be 62% efficacious (RR, 0.38; 95% CI, 0.17 to 0.85). There was no significant effect from either NI on asymptomatic influenza (P value not reported).

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				Nausea was associated with oseltamivir (OR, 1.79; 95% CI, 1.10 to 2.93). In the treatment of post-exposure prophylaxis, oseltamivir was found to have an efficacy rate of 58.5% (95% CI, 15.6 to 79.6) for households and 68.0% (95% CI, 34.9 to 84.2) to 89.0% in contacts of index cases; similar findings were reported for zanamivir (P value not reported). Results for alleviation of influenza symptoms favored the treatment groups (HR, 1.33; 95% CI, 1.29 to 1.37 for zanamivir and HR, 1.30; 95% CI, 1.13 to 1.50 for oseltamivir). Both neuraminidase inhibitors significantly diminished nasal titers (no P value reported). The use of oseltamivir was associated with lower respiratory tract complications (OR, 0.32; 95% CI, 0.18 to 0.57). Secondary: Not reported
Cooper et al.[54] (2003) Neuraminidase inhibitors as prophylaxis and/or treatment for influenza vs placebo or standard care	MA Children, healthy adults, and adults at high risk	N=>1,000 (exact number not specified) 21 to 28 days	Primary: Duration of symptoms in days Secondary: Not reported	Primary: In the intent-to treat-population with zanamivir, the median duration of symptoms in days was reduced by 1.0 (95% CI, 0.5 to 1.5) in the treatment of children, 0.8 (95% CI, 0.3 to 1.3) in otherwise healthy individuals, and 0.9 (95% CI, -0.1 to 1.9) for high risk individuals. In the intent-to-treat population with oseltamivir, the median duration of symptoms in days was reduced by 0.9 (95% CI, 0.3 to 1.5) in the treatment of children, 0.9 (95% CI, 0.3 to 1.4) in otherwise healthy individuals, and 0.4 (95% CI, -0.7 to 1.4) for high risk individuals. A relative reduction of 70 to 90% in the odds of developing influenza was associated with the prophylactic use of zanamivir or oseltamivir (P values not reported).

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				Some studies did not present the vaccination status of the individuals; for the ones that did, the percentage of patients vaccinated ranged from 0 to 80%. Secondary: Not reported
Matheson et al.[55] (2007) Neuraminidase inhibitors as prophylaxis and/or treatment for influenza vs placebo or other antiviral drugs	MA Healthy and at-risk children less than 12 years of age	N=1,500 Variable duration	Primary: Time to resolution of symptoms, secondary household attacks, confirmed influenza or influenza-like disease, adverse events Secondary: Not reported	Primary: The median duration of illness was reduced by oseltamivir by 26% (36 hours) in healthy children with laboratory-confirmed influenza (P<0.0001). In comparison the reduction was only 7.7% (10 hours) in "at risk" (asthmatic) children (P=0.54). The median duration of illness was reduced by zanamivir by 24% (1.25 days) in healthy children with laboratory-confirmed influenza (P<0.001), and no information was available concerning "at risk" (asthmatic) children. A significant reduction in the complications of influenza (otitis media) was seen with oseltamivir, although a trend was seen with zanamivir. Vomiting was more common in children receiving placebo, while there was no difference between placebo and zanamivir in terms of adverse events. Secondary: Not reported
Turner et al.[56] (2003) Neuraminidase inhibitors) as prophylaxis and/or treatment for influenza vs	MA Children, healthy adults, and adults at high risk	N=29 studies Duration varied up to 28 days	Primary: Median duration of symptoms, risk of infection Secondary: Not reported	Primary: For influenza-positive patients, treatment with oseltamivir reduced the median duration of symptoms in the influenza positive group by 1.38 days (95% CI, 0.80 to 1.96) for otherwise healthy adults; by 0.50 days (95% CI, -0.96 to 1.88) for the high-risk population, and by 1.50 days (95% CI, 0.8 to 2.2) for the group of children. Prophylaxis with oseltamivir resulted in a RR reduction of 75 to 90% depending on the strategy used and the patient population studied (no P

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				value reported). For influenza-positive patients, treatment with zanamivir reduced the median duration of symptoms in the influenza positive group by 1.26 days (95% CI, 0.59 to 1.93) for otherwise healthy adults; by 1.99 days (95% CI, 0.90 to 3.08) for the high-risk population, and by 1.30 days (95% CI, 0.3 to 2.0) for the group of children. Prophylaxis with zanamivir resulted in a relative-risk reduction of 70 to 90% depending on the strategy used and the patient population studied (P value not reported). Secondary: Not reported
Wang et al.[57] (2012) Neuraminidase inhibitors (oseltamivir, zanamivir, peramivir and laninamivir*) vs placebo or other antiviral drugs	SR Healthy and at-risk children <12 years of age	N=2,356 Duration not specified	Primary: Time to resolution of illness, return to normal activity or school, resolution of symptoms, complications, discontinuation/ withdrawal and systemic events Secondary: Symptom scores, highest daily temperature, sleep disturbance, rescue medication,	Primary: *Time to resolution of illness (i.e. resolution of symptoms and return to usual activities)* In one study, treatment with oseltamivir reduced the median duration of illness by 1.5 days (26%, P<0.0001), from 5.7 to 4.2 days in the intention-to-treat infected population. A small but significant reduction of 0.88 days was seen in the intention-to-treat population (a 17% reduction, from 5.3 to 4.4 days; P=0.0002). In a study evaluating oseltamivir in children with asthma, there was no significant reduction in the median duration of illness compared to placebo (from 5.60 to 5.16 days; P=0.54) in the intention-to-treat infected population. *Time to resolution of influenza symptoms* Zanamivir treatment reduced the median time to the resolution of symptoms by 1.25 days (from 5.25 to 4.00 days; P<0.001) in the intention-to-treat infected population, with a smaller improvement of 0.5 days (from 5.0 to 4.5 days; P=0.001) in the intention-to-treat population. In another study, zanamivir treatment reduced the median time to resolution of symptoms by 0.5 days (from 5.5 to 5.0 days; P<0.0377) in the intention-to-treat population.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			antibiotic use and hospital admissions	Treatment with oseltamivir significantly reduced the median time to the resolution of all symptoms by 36 hours (from 100 to 63 hours; P<0.0001) in the intention-to-treat infected population. In two studies, treatment with oseltamivir did not significantly reduce in the median time to alleviation of all symptoms (115.6 to 90.4 hours; P=0.1197) in the intention-to-treat infected population. Results from one study reported that oseltamivir treatment reduced the median duration of symptoms by 2.8 days in children with laboratory-confirmed influenza A or B (P<0.001). Treatment with laninamivir octanoate 20 mg reduced duration of influenza symptoms by 31 hours compared to oseltamivir in children with influenza diagnosed on rapid near-patient testing (36%; P=0.009); however, no statistically significant difference was reported with laninamivir octanoate 40mg in these children (P=0.059). *Time to return to normal activities* Zanamivir treatment reduced the median time to return to normal activity by one day in both the intention-to-treat infected (P=0.022) and the intention-to-treat populations (P=0.019). After the five-day observation period, 36.0% of participants who received zanamivir and 28.1% of the placebo group returned to school in the intention-to-treat population (P=0.19). Treatment with oseltamivir reduced the median time to return to normal activity by 1.9 days (40%; P<0.0001) in the intention-to-treat infected population. No data were available for the intention-to-treat population. There was a nonsignificant trend towards benefit with oseltamivir in asthmatic children with laboratory-confirmed influenza, with a reduction in median time to return to normal activity of 12.6 hours (11%; P=0.46). There was no data available for the intention-to-treat population. Children treated with oseltamivir returned to daycare two days sooner than children in the placebo (P=0.01). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Other secondary outcome measures Zanamivir reduced time to resolution of illness (no further use of relief medication) by 1.5 days in the intention-to-treat infected population (from 6.5 to 5.0 days; P<0.001) and 1.0 days in the intention-to-treat population (from 6.0 to 5.0 days; P=0.002). There was no significant difference between patients treated with zanamivir or placebo with regard to the time to resolution of cough (P=0.1960). Oseltamivir treatment reduced the median time to resolution of fever by 1.0 days (from 2.8 to 1.8 days; P<0.0001), time to return to normal health and activity by 0.53 days (from 4.75 to 4.23 days; P=0.4555) and time to alleviation of all symptoms by 1.05 days (from 4.82 to 3.77 days; P=0.1197). The mean number of doses of antipyretics and/or analgesics was significantly decreased in children with laboratory-confirmed influenza treated with oseltamivir (P=0.01) in children with influenza A; however, no difference was observed in children with influenza B (P=0.88). No children in the intention-to-treat infected population were diagnosed with pneumonia or hospitalized during the treatment period. Treatment with oseltamivir was associated with a small reduction in the incidence of otitis media in children aged one to five years with laboratory-confirmed influenza (RD, -0.14; 95% CI, -0.24 to -0.04). Results of one trial with zanamivir did not demonstrate any difference in the incidence of otitis media between children treated with zanamivir or placebo. Overall, treatment with neuraminidase inhibitors did not significantly reduce antibiotic use (RD, -0.07; 95% CI, -0.15 to 0.01).
Jefferson et al.[58] (2006) Amantadine, rimantadine, or neuraminidase inhibitors as	MA Healthy individuals 16 to 65 years of age	52 trials Variable duration	Primary: Prophylactic efficacy, duration of nasal shedding, time to alleviate symptoms,	Primary: For the prophylaxis of influenza A and influenza-like illness, amantadine prevented 61% (95% CI, 35 to 76) and 25% (95% CI, 13 to 36) of cases respectively. The use of amantadine was associated with nausea (OR, 2.56; 95% CI, 1.37 to 4.79), insomnia and hallucinations (2.54; 95% CI, 1.50 to 4.31).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
prophylaxis and/or treatment for influenza vs placebo, no intervention, or symptomatic medication			adverse events, lower respiratory tract complications Secondary: Not reported	The duration of fever in days was significantly shortened with amantadine compared to placebo (0.99; 95% CI, –1.26 to -0.71); in comparison with nasal shedding of influenza A, there were no significant difference was seen (0.93; 95% CI, 0.71 to 1.21). Compared to placebo when used for prophylaxis, neuraminidase inhibitors have no significant effect on influenza-like illness (1.28; 95% CI, 0.45 to 3.66 for oseltamivir 75 mg a day and 1.51; 95% CI, 0.77 to 2.95 for zanamivir 10 mg a day). Against symptomatic influenza, oseltamivir was 61 or 73% (75 and 150 mg doses) effective, while zanamivir was 62% efficacious. Nausea was associated with the use of oseltamivir (OR, 1.79; 95% CI, 1.10 to 2.93). The protective efficacy of oseltamivir was 58.8% from household contacts and from 68 to 89% in contacts of index cases. Compared to placebo the HRs for the time-to-alleviate symptoms were 1.33 (95% CI, 1.29 to 1.37) for zanamivir and 1.30 (95% CI, 1.13 to 1.50) for oseltamivir, when the medications were started within 48 hours of onset of symptoms. In preventing lower respiratory tract complications in influenza cases, oseltamivir 150 mg a day was judged to be effective (OR, 0.32; 95% CI, 0.18 to 0.57). Secondary: Not reported
Hsu et al.[59] (2012) Antiviral drugs (amantadine,	MA Patients receiving any of the antiviral drugs for	N=Not reported Duration not reported	Primary: Mortality, hospitalization, intensive care unit admission,	Primary: There was a reduction in mortality with oseltamivir treatment compared to no antiviral therapy (OR, 0.23; 95% CI, 0.13 to 0.43). The overall grade for the quality of evidence was low. A pooled estimate of unadjusted effects from nine studies resulted in a more modest reduction

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
oseltamivir, rimantadine, zanamivir) vs placebo	the treatment of laboratory-confirmed influenza or influenza-like illness (not confirmed)		mechanical ventilation and respiratory failure, duration of hospitalization, duration of signs and symptoms, time to return to normal activity, complications, critical adverse events (major psychotic disorders, encephalitis, stroke, or seizure), important adverse events (pain in extremities, clonic twitching, body weakness, or dermatologic changes), influenza viral shedding and emergence of antiviral resistance Secondary: Not reported	in mortality (OR, 0.51; 95% CI, 0.23 to 1.14). Treatment with oseltamivir reduced hospitalizations in outpatients compared to patients treated with placebo (OR, 0.75; 95% CI, 0.66 to 0.89). Oseltamivir reduces the duration of fever by approximately 33 hours (95% CI, 21 to 45 hours) from onset of symptoms compared to no antiviral therapy (standardized mean difference, -0.91; 95% CI, -1.25 to -0.57). Oseltamivir may be associated with fewer adverse events compared to no antiviral therapy (RR, 0.76; 95% CI, 0.70 to 0.81). At six months, one study found a reduction in risk for stroke and transient ischemic attacks in patients <65 years who received oseltamivir (HR, 0.66; 95% CI, 0.56 to 0.77). Oseltamivir was not associated with fewer complications, such as pneumonia (OR, 0.83; 95% CI, 0.59 to 1.16) or any recurrent cardiovascular outcome (OR, 0.58; 95% CI, 0.31 to 1.10); however, there was a reduction in otitis media (OR, 0.75; 95% CI, 0.64 to 0.87). The incidence of resistance to oseltamivir treatment across five studies was 30 per 1000 patients (95% CI, 10 to 60) and influenza virus was detectable in 330 per 1000 patients (95% CI, 280 to 370) approximately five days after treatment with oseltamivir. No study compared the persistence of influenza virus between patients who received oseltamivir and those who did not. There was no significant reduction in hospitalization following inhaled zanamivir treatment compared to those who receive no antiviral therapy (OR, 0.66; 95% CI, 0.37 to 1.18). Zanamivir reduced the duration of symptoms by approximately 23 hours (95% CI, 17 to 28) on the basis of a large standardized mean difference (-0.94; 9% CI, -1.21 to -0.66).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was no increased risk of including otitis media (OR, 1.19; 95% CI, 0.67 to 2.14), respiratory disease (OR, 1.17; 95% CI, 0.98 to 1.39). The combined results of five Japanese studies in patients with confirmed influenza suggest that inhaled zanamivir may be associated with slightly shorter symptom duration than oseltamivir (difference, 7 hours; 95% CI, 2 to 12). There was no statistically significant difference between oseltamivir and inhaled zanamivir with regard to hospitalizations (OR, 1.40; 95% CI, 0.45 to 4.35) or intensive care unit admissions (OR, 0.58; 95% CI, 0.16 to 2.18) in pregnant women. The results of another study demonstrated no statistically significant difference in influenza viral detection after five days between the treatments (OR, 3.05; 95% CI, 0.78 to 11.96). The results of one study reported that amantadine may reduce mortality (OR, 0.04; 95% CI, 0.00 to 0.73) and pneumonia (OR, 0.76; CI, 0.38 to 1.53) compared to no antiviral therapy; however, time to alleviation of symptoms did not significantly between treatments. No studies that compared rimantadine with no antiviral therapy. Secondary: Not reported

*Not commercially available in the United States.
Drug regimen abbreviations: BID=twice daily, QID=four times daily
Study abbreviations: CI=confidence interval, DB=double blind, HR=hazard ratio, MA=meta-analysis, MC=multicenter, NS=not significant, OL=open label, OR=odds ratio, OS=observational study, PC=placebo controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RD=risk difference, RR=relative risk, SR=systematic review

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 9. Relative Cost of the Neuraminidase Inhibitors

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Oseltamivir	capsule, suspension	Tamiflu®	$$$$	N/A
Zanamivir	powder for oral inhalation	Relenza®	$$$	N/A

N/A=Not available.

X. Conclusions

The neuraminidase inhibitors are approved for the treatment and prophylaxis of influenza A and influenza B virus infections. Guidelines recommend the use of either oseltamivir or zanamivir for the treatment and chemoprophylaxis of all influenza subtypes.[1-3] Due to the emergence of resistance, the adamantanes are not effective. Although rare, development of resistance to zanamivir and oseltamivir has been identified during treatment of seasonal influenza.[1-3]

Several clinical trials have demonstrated that the prophylactic use of oseltamivir and zanamivir reduces the risk of developing symptomatic influenza infections.[8-16,19] Studies have also shown the neuraminidase inhibitors reduce the duration and severity of illness, as well as complications compared to placebo.[20-24,28,32-33,35-41] There are relatively few studies that directly compare the efficacy and safety of oseltamivir and zanamivir. Guidelines do not that one agent is clinically more efficacious over another.[1-3]

Therefore, oseltamivir (Tamiflu®) and zanamivir (Relenza®) offer significant clinical advantages in general use over the other brands and to the generic products in the class (if applicable).

XI. Recommendations

Oseltamivir (Tamiflu®) and zanamivir (Relenza®) are recommended for preferred status contingent upon statewide influenza epidemiology status as reported by the Centers for Disease Control and Prevention.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Nucleosides and Nucleotides
AHFS Class 081832
November 12, 2014

I. Overview

The nucleosides and nucleotides are approved for the treatment of infections caused by herpes simplex virus, varicella-zoster virus, and cytomegalovirus, as well as for the treatment of chronic hepatitis B, chronic hepatitis C, and respiratory syncytial virus.[1-15] They possess antiviral activity due to their structural similarity to the basic building blocks of ribonucleic acid (RNA) and deoxyribonucleic acid (DNA).[16] Many of these agents inhibit viral DNA or RNA polymerase, the enzymes necessary for viral replication. In addition, these agents may also be incorporated into viral DNA during synthesis, acting as a chain terminator of DNA synthesis.

There are nearly 100 Herpesviridae known; however, only eight human Herpesviruses (HHV) have been identified.[17] These eight viruses are classified into three subfamilies: alpha-herpesvirus which includes herpes simplex virus types 1 and 2 (HSV-1 and HSV-2, respectively) and varicella-zoster virus (VZV); beta-herpesvirus which includes cytomegalovirus (CMV) and roseolovirus; and gamma-herpesvirus which includes Epstein-Barr virus (EBV) and Kaposi's sarcoma-associated herpesvirus (KSHV).

Infection with HSV is associated with chronic, life-long infections.[18] The two most common manifestations are genital herpes and labial herpes. Genital herpes typically results from infection with HSV-2; however, either HSV type can lead to genital ulcers.[18-19] Initial primary genital HSV infections tend to be more severe with lesions persisting for several weeks. Clinical manifestations include painful genital ulcers, itching, dysuria, headache, fever, malaise and lymphadenopathy.[20] Recurrent episodes are generally shorter and produce mainly localized vesicles which progress through ulcerated and crusted stages for up to 10 days. Labial herpes typically results from infection with HSV-1.[21-22] Initial primary episodes can be widespread and associated with severe discomfort; however, recurrent episodes tend to be more localized.[19] Before skin lesions appear, there is often a prodrome phase consisting of pain, itching, tingling, and burning.[19,22] Papules then present on the lip and infrequently on the palate, chin or the oral mucosa. This is then followed by progression through ulcerated, crusted, and healing stages within five days (for recurrent episodes).[22]

Infection with VZV is a common cause of chickenpox in children and herpes zoster (shingles) in adults.[23] Chickenpox is a highly contagious disease that is characterized by an exanthematous vesicular rash. Following resolution of the rash, the virus remains dormant in the dorsal root ganglia until reactivation, which then causes herpes zoster. The factors that lead to reactivation are unknown; however, the elderly and immunocompromised are most often affected. Herpes zoster is characterized by a unilateral painful dermatomal vesicular rash with vesicular eruptions. It is also associated with acute neuritis and postherpetic neuralgia. There are vaccines currently available for the prevention of chickenpox and herpes zoster.

CMV is a common virus that infects most people worldwide. Immunocompetent individuals are often asymptomatic; however CMV may cause severe disease in immunocompromised individuals, including pneumonia, retinitis, hepatitis, gastritis, colitis, Guillain-Barre syndrome, myocarditis, thrombocytopenia, hemolytic anemia, and meningoencephalitis.[23]

The hepatitis B virus (HBV) is a DNA virus that is transmitted through exposure with infected blood and body fluids and is a leading cause of death from liver disease.[25-26] Acute infection occurs following HBV exposure and the infection generally clears after one to three months in immunocompetent individuals. However, chronic infections (≥6 months) are increased in immunocompromised patients and patients who are exposed early in life.[26] Treatment of acute infections is generally supportive and antiviral treatment is not indicated.[25] Treatment of chronic hepatitis B is determined by evidence of viral replication and liver injury.[25] The hepatitis C virus (HCV) is an enveloped RNA virus that is transmitted through exposure with infected blood. HCV infection is one of the main causes of chronic liver disease worldwide, and the long-term impact of infection is highly variable, from minimal changes to extensive fibrosis and cirrhosis with or without hepatocellular carcinoma.[27] There are seven genotypes of HCV (genotypes 1 to 7), with genotype 1 being the most common in the United States, followed by

genotypes 2 and 3.[27-28] Genotype 1 is associated with a lower response to therapy and a longer duration of therapy is required.

RSV is the leading cause of lower respiratory tract infections in children younger than one year.[29] Nearly all children will be infected with RSV by age two. In most patients, RSV infection will cause a low-grade fever, cough, and wheezing that resolves after several days and only requires symptomatic treatment. In high-risk patients, such as those with chronic lung disease, those born premature, and those with congenital heart disease, RSV exposure may lead to more severe symptoms such as hypoxemia and cyanosis, and may necessitate hospitalization.

Several of the nucleoside and nucleotide analogues have been modified and formulated into prodrugs to improve their pharmacokinetic profile. Valacyclovir and valganciclovir are the L-valyl ester of acyclovir and ganciclovir, respectively.[3,13-14] These modifications increase the bioavailability of the parent compound. Famciclovir is a diacetyl ester of penciclovir, which is an antiviral agent that is only used topically due to its low bioavailability.[8] To obtain the therapeutic effect of penciclovir, famciclovir must be orally administered and metabolized to penciclovir.

The nucleosides and nucleotides that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. The majority of products in this review are available in a generic formulation. This class was last reviewed in May 2012.

Table 1. Nucleosides and Nucleotides Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Acyclovir	buccal tablet, capsule, injection, suspension, tablet	Zovirax®*, Sitavig®	acyclovir
Adefovir	tablet	Hepsera®*	adefovir
Cidofovir	injection	Vistide®*	cidofovir
Entecavir	solution, tablet	Baraclude®*	entecavir
Famciclovir	tablet	Famvir®*	famciclovir
Ganciclovir	injection	Cytovene®*	ganciclovir
Ribavirin	capsule, inhalation solution, solution, tablet	Copegus®*, Rebetol®*, Virazole®	ribavirin
Telbivudine	tablet	Tyzeka®	none
Valacyclovir	tablet	Valtrex®*	valacyclovir
Valganciclovir	solution, tablet	Valcyte®	none

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the nucleosides and nucleotides are summarized in Table 2.

Table 2. Treatment Guidelines Using the Nucleosides and Nucleotides

Clinical Guideline	Recommendation(s)

Infectious Diseases Society of America: **Clinical Practice Guidelines: Management of Encephalitis (2008)**[30]
 	
Reviewed and deemed current as of July 2011
	• Herpes simplex virus
	  o Acyclovir is the treatment of choice. The dosage of acyclovir in patients with normal renal function is 10 mg/kg intravenously every eight hours for 14 to 21 days.
	• Varicella-zoster virus
	  o Acyclovir (10 to 15 mg/kg intravenously every eight hours for 10 to 14 days) is the drug of choice.
	  o Ganciclovir can be considered as an alternative agent.
	  o Adjunctive corticosteroids can be considered, but reliable data is lacking.
	• Cytomegalovirus

Clinical Guideline	Recommendation(s)
	o The combination of ganciclovir (5 mg/kg intravenously every 12 hours) and foscarnet (60 mg/kg intravenously every eight hours or 90 mg/kg intravenously every 12 hours) for three weeks, followed by maintenance therapy, is recommended. o Cidofovir is not recommended because its ability to penetrate the blood-brain barrier has been poorly studied. • Human herpesvirus 6 o Ganciclovir or foscarnet alone or in combination is currently the best treatment option in immunocompromised patients. o Use of these agents in immunocompetent patients can be considered, but the data is unclear on their effectiveness. • B virus o Valacyclovir (1 gram orally every eight hours for 14 days) is recommended for prophylactic and acute therapy. o Alternative agents are ganciclovir and acyclovir. • Measles virus o Ribavirin may decrease the severity and duration of measles in normal adults and immunocompromised children with life-threatening disease. o Intraventricular ribavirin can be considered in patients with subacute sclerosing panencephalitis. • Nipah virus o Ribavirin can be considered.
American Association for the Study of Liver Diseases: **Chronic Hepatitis B Update (2009)**[31]	General information • The aims of treatment of chronic hepatitis B virus (HBV) are to achieve sustained suppression of HBV replication and remission of liver disease. The ultimate goal is to prevent cirrhosis, hepatic failure and hepatocellular carcinoma. • Parameters used to assess treatment response include normalization of serum alanine aminotransferase (ALT), decrease in serum HBV DNA level, loss of hepatitis B e antigen (HBeAg) with or without detection of anti-HBe, and improvement in liver histology. • Responses to antiviral therapy of chronic hepatitis B are categorized as biochemical (BR), virologic (VR), or histologic (HR), and as on-therapy or sustained off therapy. • Seven therapeutic agents have been approved for the treatment of adults with chronic hepatitis B in the United States. While interferons are administered for predefined durations, the nucleoside/nucleotide analogues (NAs) are usually administered until specific endpoints are achieved. The difference in approach is related to the additional immune modulatory effects of the interferons. General treatment recommendations • Patients with HBeAg-positive chronic hepatitis B with ALT >2 times normal or moderate/severe hepatitis on biopsy and HBV DNA >20,000 IU/mL should be considered for treatment. o Treatment should be delayed for three to six months in persons with compensated liver disease to determine if spontaneous HBeAg seroconversion occurs. o Patients with icteric ALT flares should be promptly treated. o Treatment may be initiated with any of the seven approved antiviral medications, but peginterferon alfa, tenofovir, or entecavir are preferred. o Clinical trials suggest that the efficacy of peginterferon alfa is similar to or slightly better than standard interferon alfa. • Patients with HBeAg-positive chronic hepatitis B and ALT persistently

Clinical Guideline	Recommendation(s)

	normal or minimally elevated (<2 times normal) generally should not be initiated on treatment.
	• Children with elevated ALT >2 times normal should be considered for treatment if ALT levels remain elevated at this level for longer than six months.
	  o Treatment may be initiated with interferon alfa or lamivudine.
	• Patients with HBeAg-negative chronic hepatitis B (serum HBV DNA >20,000 IU/mL and elevated ALT>2 times normal) should be considered for treatment.
	  o Liver biopsy may be considered for HBeAg-negative patients with lower HBV DNA levels (2,000 to 20,000 IU/mL) and borderline normal or minimally elevated ALT levels.
	  o Treatment may be initiated if there is moderate/severe inflammation or significant fibrosis on biopsy.
	  o Treatment may be initiated with any of the seven approved antiviral medications, but peginterferon alfa, tenofovir, or entecavir are preferred in view of the need for long-term treatment.
	• Patients who failed to respond to prior interferon alfa (standard or pegylated) therapy may be retreated with nucleoside/nucleotide analogues (NA).
	• Patients who failed to achieve primary response as evidenced by <2 log decrease in serum HBV DNA level after at least six months of NA therapy should be switched to an alternative treatment or receive additional treatment.
	• In patients with inactive HBsAg carrier state, antiviral treatment is not indicated, but these patients should be monitored.
	
	<u>Patients who develop breakthrough infection while receiving NA therapy</u>
	• All patients with virologic breakthrough should be considered for rescue therapy.
	• For patients in whom there was no clear indication for hepatitis B treatment and who continue to have compensated liver disease, withdrawal of therapy may be considered but these patients need to be closely monitored and treatment reinitiated if they experience severe hepatitis flares.
	
	<u>Treatment of patients with lamivudine (or telbivudine)-resistant HBV</u>
	• If adefovir is used, lamivudine (or telbivudine) should be continued indefinitely to decrease the risk of hepatitis flares during the transition period and to reduce the risk of subsequent adefovir resistance.
	• If tenofovir is used, continuation of lamivudine (or telbivudine) is recommended to decrease the risk of subsequent antiviral resistance.
	• If entecavir is used, lamivudine or telbivudine should be stopped as continued presence of lamivudine- (or telbivudine-) resistant mutations will increase the risk of entecavir resistance. Entecavir is not an optimal therapy because of increasing risk of resistance to entecavir over time.
	
	<u>Treatment of patients with adefovir-resistant HBV</u>
	• In patients with no prior exposure to other NA, lamivudine, telbivudine, or entecavir may be added. Alternatively, adefovir may be stopped and tenofovir plus lamivudine or emtricitabine may be used.
	• In patients with prior lamivudine resistance in whom lamivudine had been stopped when treatment was switched to adefovir, adefovir may

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	be stopped and tenofovir plus lamivudine, emtricitabine, or entecavir may be used but the durability of response to this combination is unknown. <u>Treatment of patients with entecavir-resistant HBV</u> • Adefovir or tenofovir can be used as it has been shown to have activity against entecavir-resistant HBV in *in vitro* studies, but clinical data are lacking. <u>Treatment of patients with compensated cirrhosis</u> • Treatment should be considered for patients with ALT >2 times normal, and for patients with normal or minimally elevated ALT if serum HBV DNA levels are high (>2,000 IU/mL). • Patients with compensated cirrhosis are best treated with NAs because of the risk of hepatic decompensation associated with interferon alfa–related flares of hepatitis. In view of the need for long-term therapy, tenofovir or entecavir is preferred. <u>Treatment of patients with decompensated cirrhosis</u> • Treatment should be promptly initiated with a NA that can produce rapid viral suppression with low risk of drug resistance. • Lamivudine or telbivudine may be used as initial treatment in combination with adefovir or tenofovir to reduce the risk of drug resistance. • Entecavir or tenofovir alone would be an appropriate treatment in this setting but clinical data documenting their safety and efficacy in patients with decompensated cirrhosis are lacking. • Treatment should be coordinated with a transplant center. • Interferon alfa or peginterferon alfa should not be used in patients with decompensated cirrhosis. <u>Treatment duration</u> • The recommended treatment duration for HBeAg-positive chronic hepatitis B is 16 weeks for standard interferon alfa and 48 weeks for peginterferon alfa. • The recommended treatment duration for HBeAg-negative chronic hepatitis B is 48 weeks for both standard and peginterferon alfa. • Treatment with NAs should be continued until the patient has achieved HBeAg seroconversion and undetectable serum HBV (for patients with HBeAg-positive chronic hepatitis B). For patients with HBeAg-negative chronic hepatitis B, treatment should be continued until the patient has achieved HBsAg clearance. For patients with compensated cirrhosis, treatment should be received long-term. However, treatment may be stopped in HBeAg-positive patients if they have confirmed HBeAg seroconversion and have completed at least six months of consolidation therapy and in HBeAg-negative patients if they have confirmed HBsAg clearance. For patients with decompensated cirrhosis and recurrent hepatitis B post–liver transplantation, life-long treatment is recommended. <u>Recommendations for treatment of patients with HBV/HIV coinfection</u> • Patients who meet criteria for chronic hepatitis B should be treated. • Patients who are not on highly active antiretroviral therapy (HAART) and are not anticipated to require HAART in the near future should be treated with an antiviral therapy that does not target HIV, such as

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	peginterferon alfa or adefovir. Although telbivudine does not target HIV, it should not be used in this circumstance. • Patients in whom treatment for both HBV and HIV is planned should receive therapies that are effective against both viruses: lamivudine plus tenofovir or emtricitabine plus tenofovir are preferred. • Patients who are already on effective HAART that does not include a drug active against HBV may be treated with peginterferon alfa or adefovir. • In patients with lamivudine resistance, tenofovir should be added. <u>Recommendations for treatment of hepatitis B carriers who require immunosuppressive or cytotoxic therapy</u> • Prophylactic antiviral therapy is recommended for HBV carriers at the onset of cancer chemotherapy or of a finite course of immunosuppressive therapy. • Patients with baseline HBV DNA<2,000 IU/mL level should continue treatment for six months after completion of chemotherapy or immunosuppressive therapy. • Patients with high baseline HBV DNA (>2,000 IU/mL) level should continue treatment until they reach treatment endpoints as in immunocompetent patients. • Lamivudine or telbivudine can be used if the anticipated duration of treatment is short (<12 months) and baseline serum HBV DNA is not detectable. • Tenofovir or entecavir is preferred if longer duration of treatment is anticipated. • Interferon alfa should be avoided in view of the bone marrow suppressive effect. <u>Recommendations for treatment of patients with acute symptomatic hepatitis B</u> • Treatment is only indicated for patients with fulminant hepatitis B and those with protracted, severe acute hepatitis B. • Lamivudine or telbivudine may be used when the anticipated duration of treatment is short; otherwise, entecavir is preferred. • Treatment should be continued until HBsAg clearance is confirmed or indefinitely in those who undergo liver transplantation. • Interferon alfa therapy is contraindicated.

American Association for the Study of Liver Diseases, Infectious Diseases Society of America, and International Antiviral Society-USA: **Recommendations for testing, managing, and treating hepatitis C (2014)**[32]	• It may be advisable to delay treatment for some patients with documented early fibrosis stage (F0 to 2), because waiting for future highly effective, pangenotypic, direct-acting antiviral combinations in interferon-free regimens may be prudent. Potential advantages of waiting to begin treatment will be provided in a future consensus guideline update.
	• A regimen is classified as either "recommended" when it is favored for most patients or "alternative" when optimal in a particular subset of patients in that category. When a treatment is clearly inferior or is deemed harmful, it is classified as "not recommended."
	• Recommendations for peginterferon alfa and ribavirin relapsers are the same as for treatment-naïve persons as described below.
	• Interferon ineligible criteria:
	  o Intolerance to interferon alfa.
	  o Autoimmune hepatitis and other autoimmune disorders.
	  o Hypersensitivity to peginterferon alfa or any of its components.

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	o Decompensated hepatic disease. o Major uncontrolled depressive illness. o A baseline neutrophil count below 1,500/µL, a baseline platelet count below 90,000/µL, or baseline hemoglobin below 10 g/dL. o A history of preexisting cardiac disease. <u>When and in whom to initiate HCV therapy</u> • Treatment is recommended for patients with chronic HCV infection. • Liver-related complications in which HCV treatment is most likely to provide the most immediate and impactful benefits are assigned "highest" and "high" priorities. • Highest priority due to highest risk for severe complications: o Advanced fibrosis (F3) or compensated cirrhosis (F4) o Organ transplant recipients o Severe extrahepatic hepatitis C (type 2 or 3 essential mixed cryoglobulinemia with end-organ manifestations e.g., vasculitis) o Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis • High priority due to high risk for complications: o Fibrosis (F2) o Human immunodeficiency virus (HIV) or hepatitis B virus (HBV)-coinfection o Other coexistent liver disease (e.g., non-alcoholic steatohepatitis) o Debilitating fatigue o Type 2 Diabetes mellitus (insulin resistant) o Porphyria cutanea tarda • Persons whose risk of HCV transmission is high and in whom HCV treatment may yield transmission reduction benefits: o Men who have sex with men with high-risk sexual practices o Active injection drug users o Incarcerated persons o Persons on long-term hemodialysis • Factors associated with accelerated fibrosis progression: o Fibrosis stage o Inflammation grade o Older age at time of infection o Male sex o Organ transplant o Alcohol consumption o Nonalcoholic fatty liver disease o Obesity o Insulin resistance o Genotype 3 o HIV or HBV-coinfection <u>Treatment of HCV genotype 1 in treatment-naïve patients and relapsers with prior peginterferon alfa and ribavirin</u> • Recommended treatments: o Interferon eligible: sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. o Interferon ineligible: sofosbuvir plus simeprevir with or without ribavirin for 12 weeks. • Alternative treatments:

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	o Interferon eligible: simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks (for genotype 1a, baseline resistance testing for Q80K should be performed and alternative treatments considered if this mutation is present). o Interferon ineligible: sofosbuvir plus ribavirin for 24 weeks. • Treatments that are not recommended: o Boceprevir or telaprevir plus peginterferon alfa and ribavirin for 24 or 48 weeks. o Peginterferon alfa and ribavirin for 48 weeks. o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. <u>Treatment of HCV genotype 2 in treatment-naïve patients and relapsers with prior peginterferon alfa and ribavirin</u> • Recommended treatments: o Sofosbuvir plus ribavirin for 12 weeks. • Alternative treatments: o None. • Treatments that are not recommended: o Peginterferon alfa and ribavirin for 24 weeks. o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. o Any regimen with boceprevir, telaprevir, or simeprevir. <u>Treatment of HCV genotype 3 in treatment-naïve patients and relapsers with prior peginterferon alfa and ribavirin</u> • Recommended treatments: o Sofosbuvir plus ribavirin for 24 weeks. • Alternative treatments: o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Treatments that are not recommended: o Peginterferon alfa and ribavirin for 24 to 48 weeks. o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. o Any regimen with boceprevir, telaprevir, or simeprevir. <u>Treatment of HCV genotype 4 in treatment-naïve patients and relapsers with prior peginterferon alfa and ribavirin</u> • Recommended treatments: o Interferon eligible: sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. o Interferon ineligible: sofosbuvir plus ribavirin for 24 weeks. • Alternative treatments: o Simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 to 48 weeks. • Treatments that are not recommended: o Peginterferon alfa and ribavirin for 48 weeks. o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. o Any regimen with boceprevir or telaprevir. <u>Treatment of HCV genotype 5 or 6 in treatment-naïve patients and relapsers with prior peginterferon alfa and ribavirin</u> • Recommended treatments: o Interferon eligible: sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks.

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	• Alternative treatments:
	  o Peginterferon alfa and ribavirin for 48 weeks.
	• Treatments that are not recommended:
	  o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral.
	  o Any regimen with boceprevir or telaprevir.
	
	Recommendations for patients with HCV genotype 1 with prior null or partial response to peginterferon alfa and ribavirin
	• Recommended treatments:
	  o Sofosbuvir plus simeprevir with or without ribavirin for 12 weeks.
	• Alternative treatments:
	  o Sofosbuvir for 12 weeks plus peginterferon alfa and ribavirin for 12 to 24 weeks.
	  o Sofosbuvir plus ribavirin for 24 weeks.
	  o Simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks (for genotype 1a, baseline resistance testing for Q80K should be performed and alternative treatments considered if this mutation is present).
	• Treatments that are not recommended:
	  o Boceprevir or telaprevir plus peginterferon alfa and ribavirin.
	  o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral.
	
	Recommendations for patients with HCV genotype 1 with prior null or partial response to peginterferon alfa and ribavirin plus either boceprevir or telaprevir
	• Recommended treatments:
	  o Sofosbuvir for 12 weeks plus peginterferon alfa and ribavirin for 12 to 24 weeks.
	• Alternative treatments:
	  o Interferon eligible: Sofosbuvir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks.
	  o Interferon ineligible: Sofosbuvir plus ribavirin for 24 weeks.
	• Treatments that are not recommended:
	  o Boceprevir, simeprevir, or telaprevir plus peginterferon alfa and ribavirin.
	  o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral.
	  o A recommendation for simeprevir use for patients with previous telaprevir or boceprevir exposure has not been provided due to potential risk of preexistent resistance to protease inhibitor treatment.
	
	Recommendations for patients with HCV genotype 2 with prior null or partial response to peginterferon alfa and ribavirin
	• Recommended treatments:
	  o Sofosbuvir plus ribavirin for 12 weeks;
	  ▪ In treatment-experienced cirrhotics only, the decision to extend therapy to 16 weeks should be made on a case-by-case basis.
	• Alternative treatments:
	  o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks (cirrhotics only)
	• Treatments that are not recommended:

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	o Boceprevir or telaprevir plus peginterferon alfa and ribavirin. o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. <u>Recommendations for patients with HCV genotype 3 with prior null or partial response to peginterferon alfa and ribavirin</u> • Recommended treatments: o Sofosbuvir plus ribavirin for 24 weeks. • Alternative treatments: o Sofosbuvir plus ribavirin for 16 weeks (cirrhotics only). o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Treatments that are not recommended: o Peginterferon alfa and ribavirin with or without protease inhibitor. o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. <u>Recommendations for patients with HCV genotype 4 with prior null or partial response to peginterferon alfa and ribavirin</u> • Recommended treatments: o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Alternative treatments: o Sofosbuvir plus ribavirin for 24 weeks. • Treatments that are not recommended: o Peginterferon alfa and ribavirin with or without protease inhibitor o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. <u>Recommendations for patients with HCV genotype 5 or 6 with prior null or partial response to peginterferon alfa and ribavirin</u> • Recommended treatments: o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Alternative treatments: o None. • Treatments that are not recommended: o Peginterferon alfa and ribavirin with or without protease inhibitor. o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. <u>Initial treatment of human immunodeficiency virus (HIV)/HCV co-infected patients with HCV genotype 1 who are treatment-naïve or prior peginterferon alfa and ribavirin relapsers</u> • Recommended treatments: o Interferon eligible: sofosbuvir plus peginterferon and ribavirin for 12 weeks. o Interferon ineligible: ▪ Sofosbuvir plus ribavirin for 24 weeks. ▪ Sofosbuvir plus simeprevir with or without ribavirin for 12 weeks. • Alternative treatments: o Interferon eligible: simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks (for genotype 1a, baseline resistance testing for Q80K should be performed and alternative treatments considered if this mutation is present).

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	o Interferon ineligible: none. • Treatments that are not recommended: o Boceprevir or telaprevir plus peginterferon alfa and ribavirin for 24 or 48 weeks. o Peginterferon alfa and ribavirin for 48 weeks. o Simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 48 weeks. • Allowable antiretroviral therapy: o For sofosbuvir use: all except didanosine, zidovudine, or tipranavir. o For simeprevir use: limited to raltegravir, rilpivirine, maraviroc, enfuvirtide, tenofovir, emtricitabine, lamivudine, abacavir. <u>Recommendations for HIV/HCV co-infected patients with HCV genotype 1 with prior null or partial response to peginterferon alfa and ribavirin</u> • Recommended treatments: o Sofosbuvir plus simeprevir with or without ribavirin for 12 weeks. • Alternative treatments: o Interferon eligible: sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. o Interferon ineligible: sofosbuvir plus ribavirin for 24 weeks. • Treatments that are not recommended: same as for treatment-naïve or prior peginterferon alfa and ribavirin relapsers above. • Allowable antiretroviral therapy: same as for treatment-naïve or prior peginterferon alfa and ribavirin relapsers above. <u>Treatment of HIV/HCV co-infected patients with HCV genotype 2</u> • Recommended treatments (regardless of treatment history): o Sofosbuvir plus ribavirin for 12 weeks. • Alternative treatments: o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks (only in prior nonresponders to peginterferon alfa and ribavirin eligible for peginterferon alfa). • Treatments that are not recommended: o Peginterferon alfa and ribavirin for 24 to 48 weeks. o Any regimen with boceprevir, telaprevir, or simeprevir. o Allowable antiretroviral therapy: same as above. <u>Treatment of HIV/HCV co-infected patients with HCV genotype 3</u> • Recommended treatments (regardless of treatment history): o Sofosbuvir plus ribavirin for 24 weeks. • Alternative treatments: o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks (only in prior nonresponders to peginterferon alfa and ribavirin eligible for peginterferon alfa). • Treatments that are not recommended: o Peginterferon alfa and ribavirin for 24 to 48 weeks. o Any regimen with boceprevir, telaprevir, or simeprevir. o Allowable antiretroviral therapy: same as above. <u>Treatment of HIV/HCV co-infected patients with HCV genotype 4</u> • Recommended treatments (regardless of treatment history): o Interferon eligible: sofosbuvir plus peginterferon alfa and

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	ribavirin for 12 weeks. o Interferon ineligible: sofosbuvir plus ribavirin for 24 weeks. • Alternative treatments: o None. • Treatments that are not recommended: o Peginterferon alfa and ribavirin for 48 weeks. o Any regimen with boceprevir, telaprevir, or simeprevir. o Allowable antiretroviral therapy: same as above. <u>Treatment of HIV/HCV co-infected patients with HCV genotype 5 or 6</u> • Recommended treatments (regardless of treatment history): o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Alternative treatments: o None. • Treatments that are not recommended: o Peginterferon alfa and ribavirin for 48 weeks. o Any regimen with boceprevir, telaprevir, or simeprevir. o Allowable antiretroviral therapy: same as above. <u>Treatment of patients with cirrhosis</u> • Treatment-naive patients with compensated cirrhosis, including those with hepatocellular carcinoma, should receive the same treatment as recommended for patients without cirrhosis. • Patients with decompensated cirrhosis (moderate or severe hepatic impairment; Child Turcotte Pugh class B or C) should be referred to a medical practitioner with expertise in that condition (ideally in a liver transplant center). • Recommended regimen for patients with any HCV genotype who have decompensated cirrhosis (moderate or severe hepatic impairment; Child Turcotte Pugh class B or C) who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma. o Sofosbuvir plus weight-based ribavirin (with consideration of the patient's creatinine clearance and hemoglobin level) for up to 48 weeks. o This regimen should be used only by highly experienced HCV provider. • The following regimens are not recommended for patients with decompensated cirrhosis (moderate or severe hepatic impairment; Child Turcotte Pugh class B or C): o Any interferon-based therapy. o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. o Telaprevir, boceprevir, or simeprevir-based regimens. <u>Treatment of patients who develop recurrent HCV infection post-liver transplant</u> • Recommended regimen for treatment-naive patients with HCV genotype 1 in the allograft liver, including those with compensated cirrhosis. o Sofosbuvir plus simeprevir with or without dose-adjusted ribavirin for 12 to 24 weeks. • Alternate regimen for treatment-naive patients with genotype 1 HCV in the allograft liver, including those with compensated cirrhosis. o Sofosbuvir and dose-adjusted ribavirin (with consideration of the patient's creatinine clearance and hemoglobin level), with or without peginterferon alfa, for 24 weeks.

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	• Recommended regimen for treatment-naive patients with HCV genotype 2 or 3 in the allograft liver, including those with compensated cirrhosis. o Sofosbuvir plus dose-adjusted ribavirin (with consideration for creatinine clearance and hemoglobin level) for 24 weeks. • Treatment-naive patients with decompensated allograft HCV infection should receive the same treatment as recommended for patients with decompensated cirrhosis (moderate or severe hepatic impairment; Child Turcotte Pugh class B or C).

Department of Veterans Affairs National Hepatitis C Resource Center Program and the Office of Public Health:
HCV Infection: Treatment Considerations (2014)[33]
	Treatment considerations
	• The urgency of treating HCV should be based on the risk of developing decompensated cirrhosis or dying from liver or liver-related disease, and prolonging graft survival in liver transplant recipients.
	• Urgent treatment should be considered in patients with advanced cirrhosis, selected patients with hepatocellular carcinoma awaiting liver transplant, post-transplant recipients with cirrhosis, and patients with serious extra-hepatic manifestations of HCV.
	• Patients with mild liver disease (F0 to F2) may consider waiting until newer therapies are available that may improve the chance of treatment success and reduce treatment-related adverse effects; approval is anticipated over the next 12 to 24 months.
	• Factors that may complicate adherence, such as active substance abuse, neurocognitive disorders, and lack of social support, should be addressed before initiating medications.
	• Sofosbuvir or simeprevir should not be used as monotherapy or in reduced dosages; neither drug should be restarted if discontinued.
	• Interferon ineligible or intolerant criteria:
	  o Platelet count <75,000/mm^3.
	  o Decompensated liver cirrhosis (Child Turcotte Pugh class B or C).
	  o Severe mental health conditions that may be exacerbated by interferon or may respond poorly to medical therapy.
	  o Autoimmune diseases that may be exacerbated by interferon-mediated immune modulation.
	  o Inability to complete a prior treatment course due to documented interferon-related adverse effects.
	• Treatment of patients with HCV/HIV co-infection is similar to that of HCV mono-infected patients. Drug-drug interactions must be carefully considered.
	
	Treatment of HCV genotype 1 in treatment-naïve, non-cirrhotic or cirrhotic interferon eligible patients
	• Preferred regimen:
	  o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks.
	• Alternative regimen:
	  o Simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks (do not use in genotype 1a with Q80K polymorphism).
	
	Treatment of HCV genotype 1 in treatment-naïve, non-cirrhotic interferon ineligible patients
	• Preferred regimens:
	  o Sofosbuvir plus ribavirin for 24 weeks.
	  o Sofosbuvir plus simeprevir with or without ribavirin for 12

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	weeks. • Alternative regimen: o None. Treatment of HCV genotype 1 in treatment-naïve, cirrhotic interferon ineligible patients • Preferred regimen: o Sofosbuvir plus simeprevir with or without ribavirin for 12 weeks. • Alternative regimen: o None. Treatment of HCV genotype 1 in treatment-experienced, non-cirrhotic interferon eligible patients • Preferred regimen: o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Alternative regimen: o Simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks (relapsers) or 48 weeks (prior partial or null responders); do not use in genotype 1a with Q80K polymorphism or previous failure of boceprevir- or telaprevir-based therapy. Treatment of HCV genotype 1 in treatment-experienced, cirrhotic interferon eligible patients • Preferred regimen: o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Alternative regimen (peginterferon alfa and ribavirin null responders only): o Sofosbuvir plus simeprevir with or without ribavirin for 12 weeks. Treatment of HCV genotype 1 in treatment-experienced, non-cirrhotic or cirrhotic interferon ineligible patients • Preferred regimen: o Sofosbuvir plus simeprevir with or without ribavirin for 12 weeks. • Alternative regimen: o None. Treatment of HCV genotype 2 in treatment-naïve patients • Preferred regimen: o Sofosbuvir plus ribavirin for 12 weeks. • Alternative regimen: o None. Treatment of HCV genotype 2 in treatment-experienced patients • Preferred regimens: o Sofosbuvir plus ribavirin for 12 to 16 weeks. o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks (interferon eligible only). • Alternative regimen: o None. Treatment of HCV genotype 3 in treatment-naïve patients

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	• Preferred regimens:
	  o Sofosbuvir plus ribavirin for 24 weeks.
	• Alternative regimen:
	  o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks (interferon eligible only).
	
	Treatment of HCV genotype 3 in treatment-experienced cirrhotic patients
	• Preferred regimens:
	  o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks (interferon eligible only).
	• Alternative regimen:
	  o Sofosbuvir plus ribavirin for 24 weeks (interferon ineligible only).
	
	Treatment of HCV genotype 1, 2, 3, or 4 in patients with hepatocellular carcinoma
	• Preferred regimens:
	  o Sofosbuvir plus ribavirin for 24 to 48 weeks or until liver transplant, whichever occurs first.
	• Alternative regimen:
	  o None.
	
	Treatment of patients with HCV genotype 1, 2, 3, or 4 infection post-liver transplant
	• Sofosbuvir plus ribavirin with or without peginterferon for 24 weeks
	
	Treatment of patients with HCV genotype 1, 2, 3, or 4 infection post-other solid organ transplant (kidney, heart, or lung)
	• Discuss with transplant center. Do not use peginterferon-containing regimens. Sofosbuvir has not been studied in non-liver transplant recipients.
	
	Discontinuing HCV treatment based on lack of virologic response
	• Patients receiving sofosbuvir-based regimen should have HCV ribonucleic acid (RNA) assessed at week 4 of treatment; if the HCV RNA is detectable at week 4 or at any time point thereafter, reassess HCV RNA in 2 weeks. If the repeated HCV RNA increased (i.e., >1 $\log_{10}$ IU/mL from nadir) or if the HCV RNA is ≥25 IU/mL at week 8 of therapy, discontinuation of all treatment should be strongly considered.
	• Patients receiving simeprevir plus peginterferon and ribavirin regimen should have HCV RNA levels assessed at week 4, 12, and 24; if the HCV RNA is ≥25 IU/mL at any of these time points, all treatment should be discontinued.
	
	Use in renal insufficiency
	• Sofosbuvir use is not recommended if creatinine clearance <30 mL/min or end-stage renal disease due to insufficient safety and efficacy data.
	• No simeprevir dose adjustment is needed if creatinine clearance <30 mL/min.
	• Peginterferon alfa-2a dosage should be reduced to 135 µg/week once weekly for creatinine clearance <30 mL/min, including hemodialysis.
	• Peginterferon alfa-2b dosage should be reduced by 25% for creatinine clearance 30 to 50 mL/min and by 50% for creatinine clearance <30

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	mL/min, including hemodialysis. • Ribavirin should be dosed at 200 mg daily alternating with 400 mg daily for creatinine clearance 30 to 50 mL/min and 200 mg daily for creatinine clearance <30 mL/min, including hemodialysis. Use in hepatic impairment • No simeprevir dosage recommendation can be provided in moderate to severe hepatic impairment (Turcotte Pugh Class B or C) due to higher simeprevir exposures. • No sofosbuvir dosage adjustment in required for patients with any degree of renal impairment. • Peginterferon alfa use is not recommended in patients with moderate or severe hepatic impairment (Turcotte Pugh Class B or C). Mental health and substance-use disorders • Patients with severe mental health conditions (e.g., psychotic disorders, bipolar disorder, major depression, posttraumatic stress disorder) who are engaged in mental health treatment should be considered for therapy on a case-by-case basis; interferon use may worsen these conditions. Substance or alcohol use • The presence of current heavy alcohol use (>14 drinks per week for men or >7 drinks per week for women), binge alcohol use (>4 drinks per occasion at least once per month), or active injection drug use warrants referral to an addiction specialist before treatment initiation. • There are no published data supporting minimal length of abstinence as an inclusion criterion for HCV antiviral treatment. • Patients with active substance- or alcohol-use disorders should be considered for therapy on a case-by-case basis and care should be coordinated with substance-use treatment specialist.
Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program Office: **Update on the management and treatment of hepatitis C virus infection (2012)**[34]	Recommendations in patients being considered for HCV therapy • All patients with chronic HCV infection should be evaluated for HCV antiviral treatment. • Patients should be counseled on their likelihood of achieving SVR, based upon individual factors such as body mass index, genotype, race, stage of fibrosis, and viral load before initiating therapy. • IL28B genotype testing can be performed before peginterferon-ribavirin therapy with or without a protease inhibitor, if the results would alter treatment decisions. Recommendations for treatment-naïve patients with genotype 1 infection • Peginterferon alfa and ribavirin, in combination with boceprevir (800 mg three times daily with food) or telaprevir (750 mg three times daily with 20 grams of fat), is the standard of care for most treatment-naïve genotype 1-infected patients. • If a telaprevir-containing regimen is used in treatment-naïve noncirrhotic patients who achieve an extended rapid virologic response (eRVR), telaprevir should be discontinued at week 12 and peginterferon-ribavirin should be continued for an additional 12 weeks. If HCV RNA is detectable at week four, but <1,000 IU/mL and remains <1,000 IU/mL or becomes undetectable at week 12, telaprevir should be discontinued at week 12, and peginterferon-ribavirin can be continued for another 36 weeks. • If a telaprevir-containing regimen is used in treatment-naïve cirrhotics

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	who achieve an HCV RNA that is undetectable or <1,000 IU/mL at treatment weeks four and 12, telaprevir should be discontinued at week 12, and peginterferon-ribavirin can be continued for 36 more weeks. • If a boceprevir-containing regimen is used in treatment-naïve noncirrhotics, if HCV RNA declines by ≥1 $\log_{10}$ during the four-week lead-in, and HCV RNA is undetectable at weeks eight to 24, treatment with boceprevir-peginterferon-ribavirin for 24 weeks is sufficient. If HCV RNA is detectable at week eight, but <100 IU/mL at week 12, and negative at week 24, boceprevir-peginterferon-ribavirin should be continued until week 36, followed by peginterferon-ribavirin alone for 12 more weeks. If HCV RNA declines by <1 $\log_{10}$ during the lead-in, boceprevir-peginterferon-ribavirin can be continued for 44 weeks. • If a boceprevir-containing regimen is used in treatment-naïve cirrhotics, 44 weeks of boceprevir-peginterferon-ribavirin is required after the four-week lead-in. <u>Recommendations for treatment of nonresponders and relapsers with genotype 1 infection</u> • For patients who previously failed peginterferon-ribavirin, retreatment with boceprevir or ribavirin and peginterferon-ribavirin may be considered, particularly in patients who were relapsers. • If a boceprevir-containing regimen is used for retreatment of noncirrhotic prior partial responders or relapsers, the treatment duration is 36 weeks if HCV RNA is undetectable from weeks eight to 24. If HCV RNA is detectable at week 12, but <100 IU / mL and is undetectable from weeks 24 to 36, boceprevir can be discontinued at week 36 and peginterferon-ribavirin can be continued for an additional 12 weeks. • If a boceprevir-containing regimen is used for re-treatment in cirrhotics, the treatment duration is 48 weeks if HCV RNA is detectable at week 12, but <100 IU/mL, and becomes undetectable from weeks 24 to 36. • If a boceprevir-containing regimen is used for retreatment of prior null responders, the treatment duration is 48 weeks if HCV RNA is detectable at week 12, but <100 IU/mL, and becomes undetectable from weeks 24 to 36. • If a telaprevir-containing regimen is used for retreatment of prior relapsers, and HCV RNA is undetectable from weeks four and 12, telaprevir should be discontinued at week 12 and peginterferon-ribavirin should be continued for an additional 12 weeks. If HCV RNA is detectable, but <1,000 IU/mL at week four and/or 12, telaprevir can be discontinued at week 12, and peginterferon-ribavirin can be continued for an additional 36 weeks. • If a telaprevir-containing regimen is used for re-treatment of prior partial responders or null responders, and HCV RNA is <1,000 IU/mL at weeks four and 12, telaprevir should be discontinued at week 12 and peginterferon-ribavirin should be continued for an additional 36 weeks. <u>Recommendations for dose modification</u> • Peginterferon alfa and ribavirin doses should be reduced in response to decreases in white blood cells, neutrophils, hemoglobin or platelets. • If ribavirin is stopped for seven or more days in patients concomitantly receiving boceprevir or telaprevir, then the protease inhibitor should also be permanently discontinued. The protease inhibitors should be either continued at full dose or discontinued. • A ribavirin dose reduction should be used as initial management of

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	HCV treatment-related anemia in a symptomatic patient with a hemoglobin <10 g/dL. Erythropoietin may be administered in patients with symptomatic anemia related to peginterferon-ribavirin therapy with or without protease inhibitors to limit anemia-related ribavirin dose reductions or dose discontinuations.
	• A peginterferon dose reduction should be used as initial management of HCV treatment-related neutropenia (an absolute neutrophil count of <750, or as clinically indicated). Granulocyte colony-stimulating factor should not be given as primary therapy to prevent peginterferon alfa dose reductions.
	
	<u>Recommendations for treatment monitoring</u>
	• Patients should be monitored for treatment-related adverse effects at least every two weeks early in the course of therapy, and every one to two months during treatment as clinically indicated.
	• Assessment of treatment adherence and screening for depression, suicidal ideation, alcohol, and illicit drug use should be performed at every visit.
	• Patients should be counseled about avoiding pregnancy through the use of two forms of contraception during treatment and for six months posttreatment. If a patient is receiving a boceprevir- or telaprevir-containing regimen, two alternative effective methods of contraception, such as intrauterine devices and barrier methods, should be used in at-risk patients and partners during and for at least six months after treatment.
	• In patients receiving telaprevir-peginterferon-ribavirin, all treatment should be stopped if any of the following occur:
	  o HCV RNA level >1,000 IU/mL at week four or 12.
	  o Detectable HCV RNA levels at week 24 or at any time point thereafter.
	  o HCV RNA rebounds at any time point (≥1 $\log_{10}$ increase from the nadir HCV RNA).
	• In patients receiving boceprevir-peginterferon-ribavirin, all treatment should be stopped if any of the following occur:
	  o HCV RNA level ≥100 IU/mL at week 12 with a boceprevir-containing regimen.
	  o Detectable HCV RNA levels at week 24 or at any time point thereafter.
	  o HCV RNA rebounds at any time point (≥1 $\log_{10}$ increase from the nadir HCV RNA).
	• Do not switch to the other protease inhibitor if virologic failure occurs with one protease inhibitor.
	
	<u>Recommendations for groups with special considerations for therapy</u>
	• Peginterferon alfa monotherapy may be used to treat patients with contraindications to ribavirin.
	• For patients who achieve RVR and have a low baseline viral load (HCV RNA <400,000 IU/mL), 24-weeks of treatment with peginterferon-ribavirin may be sufficient.
	• Treatment can be deferred in patients with minimal inflammation and/or minimal portal fibrosis on liver biopsy.
	• HCV genotype 1-infected patients with compensated cirrhosis (Child-Pugh Class <7), adequate neutrophils (>1.5 k/mm^3), and adequate platelet counts (>75 k/mm^3) should be considered for treatment with boceprevir (for 44 weeks) or telaprevir (for 12 weeks) combined with peginterferon-ribavirin at standard doses for 48 weeks.

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	• Patients with cirrhosis continue to be at risk for hepatocellular carcinoma and should undergo routine screening regardless of viral clearance status. Recommendations for treatment-naïve and -experienced patients with genotype 2 or 3 infection • Treatment-naïve patients should be treated with peginterferon-ribavirin for 24 weeks. • For patients with low viral load (HCV RNA <600,000 IU/mL) and mild fibrosis who achieve a RVR, 12 to 18 weeks of treatment may be sufficient. • For patients with genotype 3 infection and a high HCV RNA (>600,000 IU/mL), steatosis or advanced fibrosis, treatment beyond 24 weeks may improve response. • Retreatment duration is 48 weeks. Recommendations in patients with genotype 4 infection • Appropriate candidates with HCV genotype 4 infections should be treated with peginterferon alfa-2a 180 µg per week or peginterferon alfa-2b 1.5 µg / kg per week, plus ribavirin up to 1,400 mg per day for 48 weeks. Recommendations in patients with decompensated cirrhosis • Liver transplantation is the treatment of choice in patients with decompensated cirrhosis. • Antiviral therapy is contraindicated in most patients with decompensated cirrhosis. • Interferon-based therapy in combination with ribavirin can be considered for patients awaiting liver transplantation if they have a Child-Pugh score <7 and a Model for End-Stage Liver Disease score ≤18. • If beginning antiviral therapy, the interferon dose should be reduced and growth factors may be used to for treatment-associated cytopenias. Recommendations in patients following solid organ transplantation • Interferon-based antiviral therapy is contraindicated in patients who have received a heart, lung or kidney transplant. • In patients with biopsy-proven chronic HCV disease following liver transplantation, peginterferon-ribavirin for 48 weeks may be considered. • Monitor antiviral therapy in post-liver transplant patients on antiviral therapy and discontinue if rejection is documented. Pre-emptive antiviral therapy early post-transplantation in patients without histological recurrence should be avoided. Recommendations in patients with renal disease • Considered modified doses of antiviral therapy with interferon (standard or pegylated). • Antiviral therapy for HCV treatment is not recommended in patients following renal transplant; however, it may be considered if patients develop fibrosing cholestatic hepatitis. Recommendations in patients with comorbid conditions • Antiviral therapy is not recommended in patients with a limited life expectancy. In addition, peginterferon-ribavirin, treatment should be

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	avoided in comorbid conditions that may be exacerbated by treatment. Recommendations for patients on methadone • Antiviral therapy should be offered to patients enrolled in a methadone maintenance program who meet criteria for therapy. Coordinated HCV treatment between providers and substance abuse specialists should occur. Recommendations in patients with ongoing alcohol use • Encourage patients to decrease alcohol consumption or to abstain, and refer for behavioral intervention to reduce alcohol use. Antiviral therapy may be used in patients who are otherwise appropriate candidates, regardless of prior alcohol use. Alcohol reduces adherence and treatment response. Recommendations in obese patients and those with hepatic steatosis • Patients with a body mass index >30 should be considered for antiviral treatment. Control comorbid conditions prior to initiation of antiviral therapy. Recommendations in patients with human immunodeficiency virus (HIV)/HCV coinfection • Patients with controlled HIV infection and evidence of liver disease on biopsy should be considered for HCV antiviral therapy. Treatment should consist of peginterferon-ribavirin at doses similar to those with HCV for a duration of 48 weeks. Recommendations in patients with acute HCV infection • Observe patients for eight to 20 weeks from time of initial exposure to monitor for spontaneous resolution of infection. • In patients who fail to resolve infection spontaneously, treatment with peginterferon alfa, with or without ribavirin for 24 to 48 weeks should be used, based on genotype and HCV RNA response during therapy.
European Association for the Study of the Liver: **Treatment of Hepatitis (2014)**[35]	Goals and endpoints of HCV therapy • The goal of therapy is to eradicate HCV infection, to prevent hepatic cirrhosis, decompensation of cirrhosis, hepatocellular carcinoma, and death. • The endpoint of therapy is SVR, defined by undetectable HCV RNA 12 and 24 weeks after the end of treatment; SVR usually equates to cure of infection in more than 99% of patients. • Both SVR 12 and SVR 24 have been accepted in the US and Europe, given that their concordance is 99%. Indications for treatment • All treatment-naïve and -experienced patients with compensated disease due to HCV should be considered for therapy. • Treatment should be prioritized for patients with significant fibrosis (F3 to F4). • Treatment is justified in patients with moderate fibrosis (F2). • In patients with no or mild disease (F0 to F1), the indication for and timing of therapy can be individualized. • Patients with decompensated cirrhosis who are on the transplant list should be considered for interferon-free, ideally ribavirin-free therapy. Treatment considerations for HIV/HCV-coinfection

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	• Indications for HCV treatment and treatment regimens in HCV/HIV co-infected persons are identical to those in patients with HCV mono-infection.
	• The use of cobicistat-based regimens, efavirenz, delavirdine, etravirine, nevirapine, ritonavir, and any HIV protease inhibitor, boosted or not by ritonavir, is not recommended in HIV-infected patients receiving simeprevir.
	• Daclatasvir dose should be adjusted to 30 mg daily in HIV-infected patients receiving atazanavir/ritonavir and to 90 mg daily in those receiving efavirenz.
	• No drug-drug interaction has been reported between sofosbuvir and antiretroviral drugs.
	
	<u>Treatment options for HCV genotype 1 infection</u>
	• Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks.
	  o The most efficacious and the easiest to use interferon alfa-containing option, without the risk of selecting resistant viruses in case of treatment failure.
	• Simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks (in treatment-naïve and prior relapsers, including cirrhotics) or 48 weeks (in prior partial and null responders, including cirrhotics).
	  o Not recommended for HCV genotype 1a with Q80K polymorphism.
	  o HCV RNA levels should be monitored on treatment. Treatment should be stopped if HCV RNA level is ≥25 IU/mL at week four, 12, or 24.
	• Daclatasvir plus peginterferon alfa and ribavirin for 24 weeks (HCV genotype 1b only).
	  o Not recommended for HCV genotype 1a given the preliminary data available, pending results of on-going large-scale studies.
	  o Daclatasvir should be given for 12 weeks in combination with peginterferon alfa and ribavirin. Daclatasvir, in combination with peginterferon alfa and ribavirin, should be continued for an additional 12 weeks (24 weeks total) in patients who do not achieve an HCV RNA level <25 IU/mL at week 4 and undetectable at week 10. Peginterferon alfa and ribavirin should be continued alone between week 12 and 24 (24 weeks total) in patients who achieve an HCV RNA level <25 IU/mL at week 4 and undetectable at week 10.
	• Sofosbuvir plus ribavirin for 24 weeks.
	  o Due to suboptimal SVR rates, reserve for interferon alfa ineligible patients when no other interferon-free option is available.
	• Sofosbuvir plus simeprevir for 12 weeks.
	  o The addition of ribavirin should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis.
	• Sofosbuvir plus daclatasvir for 12 weeks (treatment-naïve) or 24 weeks (treatment-experienced, including prior telaprevir or boceprevir failures).
	  o The addition of ribavirin should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis.
	
	<u>Treatment options for HCV genotype 2 infection</u>

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	• Sofosbuvir plus ribavirin for 12 weeks (or 16 to 20 weeks in cirrhotics, especially treatment-experienced).
	• Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks is an option for cirrhotic and/or treatment-experienced patients.
	
	Treatment options for HCV genotype 3 infection
	• Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks
	• Sofosbuvir plus ribavirin for 24 weeks
	  o Suboptimal in treatment-experienced cirrhotics, who should be proposed an alternative treatment option.
	• Sofosbuvir plus daclatasvir for 12 weeks (treatment-naïve) or 24 weeks (treatment-experienced, pending data with 12 weeks of therapy).
	  o The addition of ribavirin should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis.
	
	Treatment options for HCV genotype 4 infection
	• Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks.
	• Simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks (in treatment-naïve and prior relapsers, including cirrhotics) or 48 weeks (in prior partial and null responders, including cirrhotics).
	  o HCV RNA levels should be monitored on treatment. Treatment should be stopped if HCV RNA level is ≥25 IU/mL at week four, 12, or 24.
	• Daclatasvir plus peginterferon alfa and ribavirin for 24 weeks.
	  o Daclatasvir should be given for 12 weeks in combination with peginterferon alfa and ribavirin. Daclatasvir, in combination with peginterferon alfa and ribavirin, should be continued for an additional 12 weeks (24 weeks total) in patients who do not achieve an HCV RNA level <25 IU/mL at week four and undetectable at week 10. Peginterferon alfa and ribavirin should be continued alone between week 12 and 24 (24 weeks total) in patients who achieve an HCV RNA level <25 IU/mL at week four and undetectable at week 10.
	• Sofosbuvir plus ribavirin for 24 weeks.
	  o Should be reserved for interferon alfa intolerant or -ineligible patients.
	• Sofosbuvir plus simeprevir for 12 weeks.
	  o The addition of ribavirin should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis.
	• Sofosbuvir plus daclatasvir for 12 weeks (treatment-naïve) or 24 weeks (treatment-experienced).
	  o The addition of ribavirin should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis.
	
	Treatment options for HCV genotype 5 or 6 infection
	• Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks.
	• Sofosbuvir plus ribavirin for 24 weeks.
	  o Should be reserved for interferon alfa intolerant or -ineligible patients.
	
	Treatment monitoring
	• A real-time polymerase chain reaction-based assay with a lower limit

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	of detection of <15 IU/mL should be used to monitor HCV RNA levels during and after therapy. • In patients treated with sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks, HCV RNA should be measured at baseline and at weeks 4, 12, and 12 or 24 weeks after the end of therapy. • In patients treated with simeprevir for 12 weeks plus peginterferon alfa and ribavirin for an additional 24 or 48 weeks, HCV RNA should be measured at baseline, week four, 12, 24 (end of treatment in treatment-naïve and prior relapsers), week 48 (end of treatment in prior partial and null responders), and 12 or 24 weeks after the end of therapy. • In patients treated with daclatasvir for 12 to 24 weeks plus peginterferon alfa and ribavirin for 24 weeks, HCV RNA should be measured at baseline, week four, 10, and 24 (end of treatment), and 12 or 24 weeks after the end of therapy. • In patients treated with sofosbuvir plus simeprevir with or without ribavirin for 12 weeks; sofosbuvir plus daclatasvir with or without ribavirin for 12 or 24 weeks; and sofosbuvir plus ribavirin 12 or 24 weeks, HCV RNA should be measured at baseline, week 2 (assessment of adherence), week four, week 12 or 24 (end of treatment), and 12 or 24 weeks after the end of therapy. <u>Stopping (futility) rules</u> • Treatment with simeprevir plus peginterferon alfa and ribavirin should be stopped if HCV RNA level is ≥25 IU/mL at treatment week four, 12 or 24. • No futility rules have been defined for other treatment regimens. <u>Virological response-guided triple therapy</u> • With the triple combination of daclatasvir plus peginterferon alfa and ribavirin, patients who do not achieve an HCV RNA level <25 IU/mL at week 4 and undetectable at week 10 should receive the three drugs for 24 weeks. • Patients who achieve an HCV RNA level <25 IU/mL at week four and undetectable at week 10 should stop daclatasvir at week 12 and continue with peginterferon alfa and ribavirin dual therapy until week 24. • No response-guided therapy is used in other treatment regimens. <u>Measures to improve treatment adherence</u> • HCV treatment should be delivered within a multidisciplinary team setting, with experience in HCV assessment and therapy. • Counseling on the importance of adherence is recommended. • In persons who actively inject drugs, access to harm reduction programs is mandatory. • Patients should be counseled to abstain from alcohol during antiviral therapy; patients with on-going alcohol consumption during treatment should receive additional support during antiviral therapy. • HCV treatment can be considered also for patients actively using drugs if they wish to receive treatment and are able and willing to maintain regular appointments. <u>Retreatment of non-sustained virological responders</u> • Patients who failed on a regimen containing sofosbuvir as the only direct-acting antiviral can be retreated with a combination of sofosbuvir and simeprevir (HCV genotypes 1 or 4 only), or a

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	combination of sofosbuvir and daclatasvir (all genotypes). • Patients who failed on a regimen containing simeprevir, telaprevir or boceprevir as the only direct-acting antiviral can be retreated with a combination of sofosbuvir and daclatasvir. • Patients who failed on a regimen containing daclatasvir as the only direct-acting antiviral can be retreated with a combination of sofosbuvir and simeprevir (HCV genotypes 1 or 4 only). • Patients who failed on a regimen containing sofosbuvir and simeprevir can be retreated with a combination of sofosbuvir and daclatasvir. • Patients who failed on a regimen containing sofosbuvir and daclatasvir can be retreated with a combination of sofosbuvir and simeprevir (HCV genotypes 1 or 4 only). • Alternatively, patients who failed on any of the new treatment regimens including sofosbuvir, simeprevir and/or daclatasvir can wait until new treatment combinations are available if they do not need urgent therapy. • The utility of HCV resistance testing prior to retreatment in patients who failed on any of the new treatment regimens including sofosbuvir, simeprevir and/or daclatasvir is unknown. <u>Treatment of patients with severe liver disease</u> • Patients with compensated cirrhosis should be treated, in the absence of contraindications, in order to prevent short- to mid-term complications; interferon-free regimens are preferred. • If a 12 to 24 week interferon-based direct-acting antiviral regimen is considered tolerable in patients with compensated cirrhosis and good liver function and without cytopenia, these patients can be treated as recommended above across genotypes. • Patients with cirrhosis should undergo regular surveillance for hepatocellular carcinoma, irrespective of SVR. <u>Patients with an indication for liver transplantation</u> • In patients awaiting liver transplantation, antiviral therapy is indicated, because it prevents graft infection if HCV RNA has been undetectable at least 30 days prior to transplantation. • Patients with conserved liver function (Child Pugh class A) in whom the indication for transplantation is hepatocellular carcinoma should be treated with sofosbuvir plus ribavirin until liver transplantation. • Patients with conserved liver function (Child Pugh class A) in whom the indication for transplantation is hepatocellular carcinoma can also be treated with sofosbuvir, peginterferon alfa and ribavirin for 12 weeks. • In patients with conserved liver function (Child Pugh class A) in whom the indication for transplantation is hepatocellular carcinoma, the addition of another direct acting antiviral drug is likely to improve the prevention of HCV recurrence post-transplant; therefore, patients awaiting liver transplantation with genotype 1 to 4 infection can be treated with sofosbuvir, daclatasvir and ribavirin for 12 weeks prior to transplantation. • Patients with decompensated cirrhosis awaiting liver transplantation (Child Pugh class B and C) can be treated with sofosbuvir plus ribavirin until liver transplantation in experienced centers under close monitoring. Interferon alfa is contraindicated in these patients. • The addition of another direct-acting antiviral drug is likely to improve the prevention of HCV recurrence post-transplant; therefore, patients

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	with decompensated cirrhosis awaiting liver transplantation (Child Pugh class B and C) with genotype 1 to 4 infection should be treated with sofosbuvir, daclatasvir and ribavirin until liver transplantation in experienced centers under close monitoring. • Patients with decompensated cirrhosis not on transplant waiting list should only be offered an interferon-free regimen within a clinical trial, an expanded access program or within experienced centers, because the efficacy, safety and outcomes have not yet been established for this group. Post-liver transplantation recurrence • Patients with post-transplant recurrence of HCV infection should be considered for therapy. • Patients with HCV genotype 2 infection must sofosbuvir plus ribavirin for 12 to 24 weeks, pending more data in this population. • Patients with HCV genotype 1, 3, 4, 5 or 6 infection can be treated with sofosbuvir plus daclatasvir for 12 to 24 weeks, with or without ribavirin, pending more data in this population. • Patients with HCV genotype 1 or 4 infection can be treated with sofosbuvir plus simeprevir for 12 to 24 weeks, with or without ribavirin, pending more data in this population. • No dose adjustment is required for tacrolimus or cyclosporine with any of the above combinations. Careful monitoring is important in the absence of safety data in this population. Hepatitis B virus (HBV) co-infection • Patients should be treated with the same regimens, following the same rules as HCV mono-infected patients. • If HBV replicates at significant levels before, during or after HCV clearance, concurrent HBV nucleoside/nucleotide analogue therapy is indicated. Hemodialysis patients • Hemodialysis patients, particularly those who are suitable candidates for renal transplantation, should be considered for antiviral therapy. • Hemodialysis patients should receive an interferon alfa-free and ribavirin-free regimen. • Due to the lack of safety and efficacy data, the need for dose adjustments for sofosbuvir, simeprevir and daclatasvir is unknown. • Given the lack of data, extreme caution is recommended and sofosbuvir should not be administered to patients with an estimated glomerular filtration rate <30 mL/min/1.73 m^2 or with end-stage renal disease. Non-hepatic solid organ transplant recipients • HCV treatment before kidney transplantation may avoid liver-related mortality in the post-transplant patient, and may prevent HCV-specific causes of renal graft dysfunction. • Where possible, interferon-free and ribavirin-free antiviral regimen should be given to potential transplant recipients before listing for renal transplantation; however, no safety and efficacy data is available in this population. • Given the lack of data, extreme caution is recommended and sofosbuvir should not be administered to patients with an estimated glomerular filtration rate <30 mL/min/1.73 m^2 or with end-stage renal

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	disease. • In non-hepatic solid organ transplant recipients, patients with an indication for anti-HCV therapy should receive an interferon-free regimen. • Patients with HCV genotype 2 infection must be treated with sofosbuvir plus ribavirin for 12 to 24 weeks, pending more data in this population. • Patients with HCV genotype 1, 3, 4, 5 or 6 infection can be treated with sofosbuvir plus daclatasvir for 12 to 24 weeks, with or without ribavirin, pending more safety data in this population. • Patients with HCV genotype 1 or 4 infection can be treated with sofosbuvir plus simeprevir for 12 to 24 weeks, with or without ribavirin, pending more data in this population. • No dose adjustment is required for tacrolimus or cyclosporine with any of these combinations. Careful monitoring is important in the absence of safety data in this population. Active drug addicts and patients on stable maintenance substitution • HCV treatment for people who inject drugs (PWIDs) should be considered on an individualized basis and delivered within a multidisciplinary team setting. • Sofosbuvir and simeprevir can be used in PWIDs on opioid substitution therapy. They do not require specific methadone and buprenorphine dose adjustment, but monitoring for signs of opioid toxicity or withdrawal should be undertaken. More data is needed with daclatasvir. • Consideration of interferon-containing or interferon-free therapy in PWIDs should be undertaken on an individualized basis, but those with early liver disease can be advised to await further data and/or potential development of improved therapies. • The regimens that can be used in PWIDs are the same as in non-PWIDs. • Awareness should be raised that liver transplantation is a therapeutic option in those with a history of injection drug use. • Opioid substitution therapy is not a contraindication for liver transplantation and individuals on opioid substitution should not be advised to reduce or stop therapy. Treatment of acute hepatitis C • Peginterferon alfa monotherapy for 24 weeks can be used in patients with acute hepatitis C, who will achieve SVR in as many as 90% of cases. • Peginterferon alfa plus ribavirin for 24 weeks is recommended in patients with acute hepatitis C who are HIV-coinfection. • Although no data is available yet, interferon-free regimens can theoretically be used in patients with acute hepatitis C and are expected to achieve high SVR rates. • Note: Daclatasvir is not currently Food and Drug Administration-approved in the United States.
European Association for the Study of the Liver: **Management of Hepatitis C Virus Infection (2013)**[27]	Goals and endpoints of HCV therapy • The goal of therapy is to eradicate HCV infection. • The endpoint of therapy is SVR, defined by undetectable HCV RNA 24 weeks after the end of therapy; SVR usually equates to cure of infection in more than 99% of patients.

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	• Undetectable HCV RNA at 12 weeks after the end of therapy (SVR 12) has been accepted in the US and Europe given concordance with SVR 24 is 99%; however, this concordance needs to be further validated in ongoing clinical trials. Indications for treatment • All treatment-naïve patients with compensated disease due to HCV should be considered for therapy. • Treatment should be scheduled, not deferred, for patients with significant fibrosis (F3 to F4). • In patients with less severe disease, indication for and timing of therapy can be individualized. First line treatment of chronic hepatitis C genotype 1 • Triple therapy with boceprevir or telaprevir added to peginterferon alfa and ribavirin is the approved standard of care for chronic hepatitis C genotype 1. There is no head-to-head comparison to allow recommendation of boceprevir or telaprevir as preferred therapy. • Patients with cirrhosis should never receive abbreviated treatment with boceprevir or telaprevir regimens. • Selected patients with high likelihood of SVR to peginterferon alfa and ribavirin or with contraindications to boceprevir or telaprevir can be treated with dual therapy. • When lead-in is used to identify patients with peginterferon alfa sensitive infection, the possibility of continuation of dual therapy should have been discussed with the patient prior to initiation of treatment. • Both peginterferon alfa-2a (180 µg/week) and peginterferon alfa-2b (1.5 µg/kg/week) can be used in dual or triple therapy. • Ribavirin should be dosed following the peginterferon alfa label for triple therapy. • Ribavirin should be administered at a weight-based dose of 15 mg/kg/day in dual therapy First line treatment of chronic hepatitis C genotypes 2, 3, 4, 5, and 6 • The combination of peginterferon alfa and ribavirin is the approved standard of care for chronic hepatitis C genotypes 2, 3, 4, 5, and 6. • Ribavirin should be administered at a weight-based dose of 15 mg/kg/day for genotypes 4, 5 and 6, and at a flat dose of 800 mg/day for genotypes 2 and 3. • Patients with genotypes 2 and 3 with baseline factors suggesting low responsiveness should receive weight-based ribavirin at a dose of 15 mg/kg/day. Treatment monitoring • A real-time polymerase chain reaction-based assay with a lower limit of detection of <15 IU/mL should be used to monitor triple therapy. • During triple therapy in HCV genotype 1 patients, HCV RNA measurements should be performed at weeks four, eight, 12, 24, and end of treatment when administering boceprevir, and at weeks four, 12, 24, and end of treatment when administering telaprevir. • During dual therapy in any HCV genotype, HCV RNA levels should be assessed at baseline, weeks four, 12, 24 and end of treatment. • The end-of-treatment virological response and the SVR at 12 or 24 weeks after the end of treatment must be assessed.

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	• Whether the baseline HCV RNA level is low or high may be a useful criterion to guide treatment decisions during dual therapy. The safest threshold level for discriminating low and high baseline HCV RNA is 400,000 IU/mL. • Dual therapy for all HCV genotypes should be stopped at week 12 if the HCV RNA decrease is <2 $\log_{10}$ IU/mL and at week 24 if HCV RNA is still detectable. • Triple therapy with boceprevir should be stopped if HCV RNA is >100 IU/mL at treatment week 12 or if HCV RNA is detectable at treatment week 24. • Triple therapy with telaprevir should be stopped if HCV RNA is >1,000 IU/mL at weeks four or 12 of therapy. • Dual therapy duration should be tailored to the on-treatment virological response at weeks four and 12. The likelihood of SVR is directly proportional to the rapidity of HCV RNA disappearance. • For patients receiving dual therapy who achieve an RVR and who have low baseline viral titre (<400,000 IU/mL), treatment for 24 weeks (genotype 1) or 16 weeks (genotype 2 or 3) can be considered. If negative predictors of response (i.e., advanced fibrosis/cirrhosis, metabolic syndrome, insulin resistance, hepatic steatosis) are present, published evidence for equal efficacy of shortened treatment is lacking. • Patients receiving dual therapy with genotypes 2 or 3, and with any adverse predictor of SVR, and who achieve an early virological response or a delayed virological response without an RVR, can be treated for 48 weeks. • Genotype 1 patients receiving dual therapy who demonstrate a delayed virological response can be treated for 72 weeks, provided that their HCV RNA is undetectable at week 24. <u>Treatment dose reductions and stopping rules</u> • The peginterferon alfa dose should be reduced if the absolute neutrophil count falls below 750/mm^3, or the platelet count falls below 50,000/mm^3. Peginterferon alfa should be stopped if the neutrophil count falls below 500/mm^3 or the platelet count falls below 25,000/mm^3 or if severe unmanageable depression develops. • If neutrophil or platelet counts rise, treatment can be restarted, but at a reduced peginterferon alfa dose. • If hemoglobin <10 g/dL occurs, the dose of ribavirin should be adjusted downward by 200 mg at a time, and ribavirin should be stopped if hemoglobin falls below 8.5 g/dL. • Treatment should be stopped in case of a severe hepatitis flare or severe sepsis. • Boceprevir or telaprevir doses should not be reduced during therapy due to the risk of the development of antiviral resistance. If boceprevir or telaprevir have been stopped, they should never be reintroduced in the same course of treatment. <u>Measures to improve treatment success rates</u> • Full adherence to all antiviral drugs should be the aim in order to optimize SVR rates and to reduce the risk of emergence of specific drug resistance. • Body weight adversely influences the response to peginterferon alfa and ribavirin; therefore, a reduction of body weight in overweight patients prior to therapy may increase the likelihood of SVR. • Insulin resistance is associated with treatment failure for dual therapy;

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	however, insulin sensitizers have no proven efficacy in improving SVR rates in these patients. • Counseling on abstaining from alcohol during antiviral therapy should be provided. • In dual therapy, recombinant erythropoietin can be administered when the hemoglobin level falls <10 g/dL in order to reduce the need for ribavirin dose reduction. • In patients receiving boceprevir or telaprevir-based triple therapy, ribavirin dose reduction should be the initial response to significant anemia. • There is no evidence that neutropenia during peginterferon alfa and ribavirin therapy is associated with more frequent infection episodes, or that the use of granulocyte colony stimulating factor reduces the rate of infections and/or improves SVR rates. • Patients with a history and/or signs of depression should be seen by a psychiatrist before therapy. Patients who develop depression during therapy should be treated with antidepressants. Preventative antidepressant therapy in selected patients may reduce the incidence of this condition during treatment, without any impact on SVR. <u>Post treatment follow up of patients who achieve an SVR</u> • Noncirrhotic patients with SVR should be retested for alanine transaminase and HCV RNA at 48 weeks post-treatment, and then discharged if alanine transaminase is normal and HCV RNA is negative. • Cirrhotic patients with SVR should undergo surveillance for hepatocellular carcinoma every six months by means of ultrasound. • If present, portal hypertension and esophageal varices should be managed, though index variceal bleed is seldom observed in low-risk patients after the achievement of SVR. • Patients with ongoing drug use should not be excluded from HCV treatment on the basis of perceived risk of reinfection. • Following SVR, monitoring for HCV reinfection through annual HCV RNA assessment should be undertaken on people who inject drugs with ongoing risk behavior. <u>Retreatment of nonsustained virological responders to peginterferon alfa and ribavirin</u> • Patients infected with HCV genotype 1 who failed to eradicate HCV in prior therapy with peginterferon alfa and ribavirin should be considered for retreatment with the triple combination of peginterferon alfa, ribavirin and a protease inhibitor. • The previous response to interferon-based therapy is an important predictor of success of triple therapy. If the pattern of prior response to dual therapy is not clearly documented, the patient should not be treated with abbreviated response-guided therapy. • Patients with cirrhosis and prior null responders have a lower chance of cure and should not be treated with response-guided therapy with either boceprevir or telaprevir. • Patients infected with HCV genotypes other than 1 and who failed on prior therapy with non-pegylated interferon alfa, with or without ribavirin, can be re-treated with pegylated interferon alfa and ribavirin. <u>Treatment of patients with severe liver disease</u> • Patients with compensated cirrhosis should be treated, in the absence

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	of contraindications, in order to prevent short to midterm complications. • Monitoring and management of side effects, especially those linked to portal hypertension, low platelet count, and low serum albumin should be done particularly carefully. Growth factors may be useful in this group. • Patients with cirrhosis should undergo regular surveillance for hepatocellular carcinoma, irrespective of SVR. • In patients awaiting liver transplantation, antiviral therapy, when feasible, prevents graft reinfection if an SVR is achieved. • Antiviral therapy may be started while awaiting liver transplantation, with the goal of achieving SVR or HCV RNA negativity before transplantation. • In patients with Child-Pugh B cirrhosis, antiviral therapy is offered on an individual basis in experienced centers, preferentially in patients with predictors of good response. • Patients with Child-Pugh C cirrhosis should not be treated with the current interferon alfa-based antiviral regimens due to a high risk of life-threatening complications. • Treatment can be started at low doses of peginterferon alfa and ribavirin, following a low accelerated dose regimen or at full doses. In the latter case, dose reductions and treatment interruptions are required in >50% of cases. • Patients with post-transplant recurrence of HCV infection should initiate therapy once chronic hepatitis is established and histologically proven. Significant fibrosis or portal hypertension one year after transplantation predicts rapid disease progression and graft loss and indicates urgent antiviral treatment. • For patients with HCV genotype 1, protease inhibitor-based therapy can be used, but frequent monitoring and dose adjustment of tacrolimus and cyclosporine are required. • Graft rejection is rare but may occur during peginterferon alfa treatment. A liver biopsy should be performed whenever liver tests worsen on antiviral therapy. <u>Treatment of special groups</u> • Indications for HCV treatment in patients with HIV coinfection are identical to those in patients with HCV monoinfection. The same peginterferon alfa regimen should be used in HIV coinfected patients. Longer treatment duration may be considered for patients with genotype 2 and 3 who exhibit slow early viral kinetics. • Patients coinfected with HIV and HCV genotype 1 should be considered for telaprevir or boceprevir triple therapy regimen, but special care should be taken to minimize or avoid potential drug-drug interactions. • HIV patients with a diagnosis of acute HCV infection should be treated with peginterferon and ribavirin, with duration dependent on viral kinetics independent of HCV genotype. • Patients coinfected with hepatitis B should be treated with telaprevir or boceprevir triple therapy regimen, following the same rules as monoinfected patients. • If hepatitis B virus replicates at significant levels before, during or after HCV clearance, concurrent hepatitis B virus nucleoside/nucleotide analogue therapy is indicated. • Patients on hemodialysis, particularly those who are suitable

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	candidates for renal transplantation, should be considered for antiviral therapy. • Antiviral treatment should comprise peginterferon alfa at an appropriately reduced dose. • Ribavirin can be used at very low doses, but with caution. • Boceprevir or telaprevir can be used with caution in patients with impaired creatinine clearance, and dose adjustment is probably unnecessary. • Patients with HCV and end stage renal disease scheduled for kidney transplantation should undergo antiviral therapy prior to transplantation due to the increased risk of acute transplant rejection. • Interferon alfa-based antiviral treatment is associated with a significant risk of renal graft rejection, and it should be avoided unless there is a powerful indication for antiviral treatment (e.g., aggressive cholestatic hepatitis). • Regular alcohol consumption should be strongly discouraged. • Treatment of patients with active illicit drug abuse has to be individualized. • Patients with hemoglobinopathies can be treated with combination therapy but need careful monitoring. <u>Follow up of untreated patients and of patients with treatment failure</u> • Untreated patients with chronic hepatitis C and those who failed prior treatment should be followed regularly. • Non-invasive methods for staging fibrosis are best suited for follow-up assessment at intervals. • Hepatocellular carcinoma screening must be continued indefinitely in patients with cirrhosis. <u>Treatment of acute hepatitis C</u> • Peginterferon alfa monotherapy for 24 weeks is recommended in patients with acute hepatitis C and achieves SVR in >90% of patients. • Patients failing to respond to monotherapy should be retreated according to the standard of care for chronic hepatitis C.
World Health Organization: **Guidelines for the Screening, Care and Treatment of Persons with Hepatitis C Infection (2014)**[36]	<u>Recommendations for treatment of HCV infection</u> • All adults and children with chronic HCV infection, including people who inject drugs, should be assessed for antiviral treatment. • Peginterferon alfa in combination with ribavirin is recommended for the treatment of chronic HCV infection rather than standard non-peginterferon alfa with ribavirin. • Where access to treatment for HCV infection is limited, priority for treatment should be given to patients with advanced liver disease (F3 and F4). • Treatment with the direct-acting antivirals telaprevir or boceprevir, given in combination with peginterferon alfa and ribavirin, is suggested for genotype 1 chronic HCV infection rather than peginterferon alfa and ribavirin alone. • In high-income settings, HCV treatment with peginterferon alfa and ribavirin and with boceprevir or telaprevir plus peginterferon alfa and ribavirin has been evaluated as being cost–effective. • Sofosbuvir, given in combination with ribavirin with or without peginterferon alfa (depending on the HCV genotype), is recommended in genotypes 1, 2, 3 and 4 HCV infection rather than peginterferon alfa and ribavirin alone (or no treatment for persons who cannot tolerate peginterferon alfa); recommendation made without taking resource use

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	into consideration. • Simeprevir, given in combination with peginterferon alfa and ribavirin, is recommended for persons with genotype 1b HCV infection and for persons with genotype 1a HCV infection without the Q80K polymorphism rather than peginterferon alfa and ribavirin alone; recommendation made without taking resource use into consideration. • Absolute contraindications to peginterferon alfa: o Uncontrolled depression, psychosis, or epilepsy. o Uncontrolled autoimmune disease. o Decompensated cirrhosis (Child–Pugh ≥B7 or B6 in HCV/HIV coinfection). o Pregnancy or unwillingness to use contraception. o Breastfeeding women. o Severe concurrent medical disease including severe infections. o Poorly controlled hypertension, cardiac failure, or diabetes. o Solid organ transplant (except liver transplant recipients). o Chronic obstructive pulmonary disease. o Age <2 years old. • Relative contraindications to peginterferon alfa: o Abnormal hematological indices: ▪ Hemoglobin <13 g/dL in men or <12 g/dL in women. ▪ Neutrophil count $<1.5 \times 10^9$/L. ▪ Platelet count $<90 \times 10^9$/L. o Serum creatinine >1.5 mg/dL. o Hemoglobinopathies (sickle cell disease or thalassemia). o Significant coronary artery disease. o Untreated thyroid disease. • Treatment for HCV infection is both efficacious and cost-effective in people who inject drugs and is therefore recommended. • Specialist care needs to address the additional needs of special populations of patients, including people who inject drugs, persons coinfected with (or at risk for infection with) HIV, children and adolescents, and those with cirrhosis. • The decision to initiate treatment for HCV/HIV-coinfection is more complex than in those with HCV monoinfection, as response rates are lower, risk of potential toxicities is higher and treatment is complicated by a high pill burden, overlapping toxicities, and interactions between drugs used for treating HCV and HIV.
American Association for the Study of Liver Diseases: **An Update on Treatment of Genotype 1 Chronic Hepatitis C Virus Infection (2011)**[37]	• The optimal therapy for HCV genotype 1 is the use of boceprevir or telaprevir in combination with peginterferon alfa and ribavirin. • Boceprevir and telaprevir should not be used without peginterferon alfa and weight-based ribavirin. <u>Treatment-naïve patients</u> • The recommended dose of boceprevir is 800 mg three times daily (every seven to nine hours) with food plus peginterferon alfa and weight-based ribavirin for 24 to 44 weeks, preceded by four weeks of lead in peginterferon alfa plus ribavirin alone. o Patients without cirrhosis treated with boceprevir, peginterferon alfa and ribavirin, whose HCV ribonucleic acid (RNA) levels at weeks eight and 24 is undetectable, may be considered for a shortened duration of treatment of 28 weeks in total (four weeks lead in of peginterferon alfa and ribavirin, followed by 24 weeks of triple therapy).

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	o Triple therapy should be stopped if the HCV RNA level is >100 IU/mL at treatment week 12 or detectable at treatment week 24. • The recommended dose of telaprevir is 750 mg three times daily (every seven to nine hours) with food (not low fat) plus peginterferon alfa and weight-based ribavirin for 12 weeks followed by an additional 12 to 36 weeks of peginterferon alfa plus ribavirin (without telaprevir). o Patients without cirrhosis treated with telaprevir, peginterferon alfa and ribavirin, whose HCV RNA level at weeks four and 12 is undetectable should be considered for a shortened duration of therapy of 24 weeks. o Triple therapy should be stopped if the HCV RNA levels is >1,000 IU/mL at treatment weeks four or 12 and/or detectable at treatment week 24. • Patients with cirrhosis treated with either boceprevir or telaprevir in combination with peginterferon alfa and ribavirin should receive therapy for a duration of 48 weeks. <u>Treatment-experienced patients</u> • Re-treatment with boceprevir or telaprevir, in combination with peginterferon alfa and weight-based ribavirin, can be recommended for patients who had virological relapse or were partial responders after a prior course of treatment with standard interferon alfa or peginterferon alfa and/or ribavirin. • Retreatment with telaprevir, in combination with peginterferon alfa and weight-based ribavirin, may be considered for prior null responders to a course of standard interferon alfa or peginterferon alfa and/or weight-based ribavirin. • Response-guided therapy of treatment-experienced patients using either a boceprevir- or telaprevir-based regimen can be considered for relapsers, may be considered for partial responders, but cannot be recommended for null responders. • Patients re-treated with boceprevir plus peginterferon alfa and ribavirin who continue to have detectable HCV RNA >100 IU at week 12 should be withdrawn from all therapy because of the high likelihood of developing antiviral resistance. • Patients re-treated with telaprevir plus peginterferon alfa and ribavirin who continue to have detectable HCV RNA >1,000 IU at weeks four or 12 should be withdrawn from all therapy because of the high likelihood of developing antiviral resistance. <u>Adverse events</u> • Patients who develop anemia on protease inhibitor-based therapy for chronic hepatitis C should be managed by reducing the ribavirin dose. • Patients on protease inhibitor-based therapy should undergo close monitoring of HCV RNA levels and the protease inhibitors should be discontinued if virological breakthrough (greater than one log increase in serum HCV RNA above nadir) is observed. • Patients who fail to have a virological response, who experience virological breakthrough, or who relapse on one protease inhibitor should not be re-treated with other protease inhibitors. <u>Use and Interpretation of HCV RNA results during triple therapy</u> • An HCV assay with a lower limit of quantification of equal to or less than 25 IU/mL and a limit of HCV RNA detection of approximately 10 to 15 IU/mL should be used for monitoring response to therapy and

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	decision making during triple therapy. • Response-guided therapy should only be considered when no virus is detected by a sensitive assay four weeks after initiation of the HCV protease inhibitor. <u>IL28B testing</u> • IL28B genotype is a robust pretreatment predictor of sustained virologic response (SVR) to peginterferon alfa and ribavirin as well as to protease inhibitor triple therapy in patients with chronic HCV genotype 1. Testing may be considered when the patient or provider wish additional information on the probability of treatment response or on the probable treatment needed.

American Gastroenterological Association: **Medical Position Statement on the Management of Hepatitis C (2006)**[38]	• Therapy is indicated for previously untreated patients with chronic hepatitis C, circulating HCV RNA, elevated aminotransferase levels, evidence on liver biopsy of moderate to severe hepatitis grade and stage, and compensated liver disease.
	• Patients with normal ALT activity are candidates for antiviral therapy or for monitoring without intervention, as determined on an individual basis and as influenced by patient factors such as motivation, genotype, histologic activity, and fibrosis.
	• Patients with compensated cirrhosis who can tolerate therapy are candidates for treatment.
	• The treatment of choice is pegylated interferon alfa plus ribavirin.
	• Patients with genotypes 1 and 4 require 48 weeks of therapy with pegylated interferon and high daily doses of ribavirin (1,000 to 1,200 mg, depending on weight).
	• Patients with genotypes 2 and 3 can be treated for only 24 weeks with pegylated interferon and with 800 mg of ribavirin daily, with the following exceptions:
	  o A longer duration of therapy may be considered on an individual patient basis taking into account factors such as elevated viral level, cirrhosis, or delayed response to therapy.
	  o 12 weeks of therapy suffices in patients in whom HCV RNA levels are undetectable at week 4.
	  o Patients with genotype 3, with high levels of HCV RNA or advanced fibrosis on liver biopsy, may require treatment for 48 weeks.
	• Therapy with peginterferon alfa and ribavirin should be strongly considered for patients who experienced a relapse after a course of standard interferon alfa/ribavirin combination therapy, while a longer duration of therapy in patients who experienced a relapse after 12 months of treatment with peginterferon alfa plus ribavirin is of unproven efficacy.
	• For children, the general principles of management are the same as those for adults, except that treatment is not recommended for children younger than 3 years.
	• For HIV-infected individuals, the optimal therapy consists of peginterferon alfa plus ribavirin for 48 weeks, regardless of genotype. Because of potential drug-drug interactions in patients on HIV treatment regimens that include didanosine, HIV regimens should be altered in those starting combination therapy for HCV infection. If didanosine is critical to the HIV regimen, ribavirin should be avoided.

Centers for Disease Control and Prevention: **Sexually Transmitted Diseases**	<u>Bacterial vaginosis</u> • Recommended regimens: o Metronidazole 500 mg orally twice a day for seven days.

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Treatment Guidelines (2010)[18]	o Metronidazole gel 0.75%, one full applicator (5 grams) intravaginally, once a day for five days. o Clindamycin cream 2%, one full applicator (5 grams) intravaginally at bedtime for seven days. • Alternative regimens: o Tinidazole 2 grams orally once daily for two days. o Tinidazole 1 gram orally once daily for five days. o Clindamycin 300 mg orally twice daily for seven days. o Clindamycin ovules 100 mg intravaginally once at bedtime for three days. <u>Cervicitis</u> • Recommended regimens for presumptive treatment: o Azithromycin 1 gram orally in a single dose. o Doxycycline 100 mg orally twice a day for seven days. <u>Chancroid</u> • Recommended regimens: o Azithromycin 1 gram orally in a single dose. o Ceftriaxone 250 mg intramuscular in a single dose. o Ciprofloxacin 500 mg orally twice a day for three days. o Erythromycin base 500 mg orally three times a day for seven days. <u>Chlamydial infections</u> • Recommended regimens: o Azithromycin 1 gram orally in a single dose. o Doxycycline 100 mg orally twice a day for seven days. • Alternative regimens: o Erythromycin base 500 mg orally four times a day for seven days. o Erythromycin ethylsuccinate 800 mg orally four times a day for seven days. o Levofloxacin 500 mg orally once daily for seven days. o Ofloxacin 300 mg orally twice a day for seven days. <u>Chlamydial infections among children</u> • Recommended regimen for children <45 kg: o Erythromycin base or ethylsuccinate 50 mg/kg/day orally divided into four doses daily for 14 days. • Recommended regimen for children ≥45 kg and <8 years of age: o Azithromycin 1 gram orally in a single dose. • Recommended regimens for children ≥8 years of age: o Azithromycin 1 gram orally in a single dose. o Doxycycline 100 mg orally twice a day for seven days. <u>Disseminated gonococcal infection</u> • Recommended regimen: o Ceftriaxone 1 gram intramuscular or intravenous every 24 hours. • Alternative regimens: o Cefotaxime 1 gram intravenous every eight hours. o Ceftizoxime 1 gram intravenous every eight hours. <u>Epididymitis</u> • Recommended regimens:

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	o Ceftriaxone 250 mg intramuscular in a single dose plus doxycycline 100 mg orally twice a day for 10 days. • For acute epididymitis most likely caused by enteric organisms: o Levofloxacin 500 mg orally once daily for 10 days. o Ofloxacin 300 mg orally twice a day for 10 days. <u>Genital herpes infection</u> • The use of systemic antivirals including valacyclovir, acyclovir, and famciclovir is encouraged for the treatment of primary and recurrent genital herpes. Topical therapy with antiviral drugs offers minimal clinical benefit, and their use is not recommended. • Systemic antiviral drugs partially control the symptoms and signs of herpes infection when used to treat first clinical episodes and recurrent episodes, or when used as daily suppressive therapy. • However, these drugs neither eradicate latent virus nor affect the risk, frequency, or severity of recurrences after the drug is discontinued. • Randomized trials have indicated that three antiviral medications provide clinical benefit for genital herpes: acyclovir, valacyclovir, and famciclovir. • Topical therapy with antiviral drugs offers minimal clinical benefit, and its use is discouraged. • Foscarnet is frequently effective for treatment of acyclovir-resistant genital herpes in immunocompromised individuals. • Recommended regimens for initial clinical episodes include: o Acyclovir 400 mg three times a day for seven to 10 days or 200 mg five times a day for seven to 10 days. o Famciclovir 250 mg three times a day for seven to 10 days. o Valacyclovir 1 gram twice a day for seven to 10 days. • Recommended regimens for suppressive therapy in recurrent herpes (≥6 episodes/year) include: o Acyclovir 400 mg twice daily. o Famciclovir 250 mg twice daily. o Valacyclovir 500 mg once daily or 1,000 mg once daily. • Recommended regimens for episodic therapy in recurrent herpes include: o Acyclovir 400 mg three times a day for five days or 800 mg twice a day for five days or 800 mg three times a day for two days. o Famciclovir 125 mg twice a day for five days or 1 gram twice a day for one day or 500 mg once then 250 mg twice a day for two days. o Valacyclovir 500 mg twice a day for three days or 1 gram once a day for five days. • Recommended regimen for severe infections include: o Intravenous acyclovir 5 to 10 mg/kg every eight hours for two to seven days or until clinical improvement is observed, followed by oral antiviral therapy to complete at least 10 days of total therapy. • Recommended regimens for suppressive therapy in patients with human immunodeficiency virus include: o Acyclovir 400 to 800 mg twice to three times daily. o Famciclovir 500 mg twice daily. o Valacyclovir 500 mg twice daily. • Recommended regimens for episodic therapy in patients with human immunodeficiency virus include:

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	o Acyclovir 400 mg three times daily for five to 10 days. o Famciclovir 500 mg twice daily for five to 10 days. o Valacyclovir 1 gram twice daily for five to 10 days. <u>Genital warts</u> • No evidence exists to identify one treatment as more efficacious than another and no treatment is ideal for all patients with genital warts. • Treatment selection may be based on wart size and number, anatomic site of wart, wart morphology, and adverse effects of treatment. • Interferon therapy is not recommended as a primary modality because of inconvenient routes of administration, frequent office visits, and the association between its use and a high frequency of adverse effects. <u>Granuloma inguinale (Donovanosis)</u> • Recommended regimen: o Doxycycline 100 mg orally twice a day for at least three weeks and until all lesions have completely healed. • Alternative regimens: o Azithromycin 1 gram orally once per week for at least three weeks and until all lesions have completely healed. o Ciprofloxacin 750 mg orally twice a day for at least three weeks and until all lesions have completely healed. o Erythromycin base 500 mg orally four times a day for at least three weeks and until all lesions have completely healed. o Sulfamethoxazole-trimethoprim one double-strength tablet orally twice a day for at least three weeks and until all lesions have completely healed. • The addition of an aminoglycoside (e.g., gentamicin 1 mg/kg IV every eight hours) to these regimens can be considered if improvement is not evident within the first few days of therapy. <u>Gonococcal conjunctivitis</u> • Recommended regimen: o Ceftriaxone 1 gram intramuscular in a single dose. <u>Gonococcal infections among children</u> • Recommended regimen for children >45 kg: o Treat with one of the regimens recommended for adults. • Recommended regimen for children who weigh ≤45 kg and who have uncomplicated gonococcal vulvovaginitis, cervicitis, urethritis, pharyngitis, or proctitis: o Ceftriaxone 125 mg intramuscular in a single dose. • Recommended regimen for children who weigh ≤45 kg and who have bacteremia or arthritis: o Ceftriaxone 50 mg/kg (maximum dose: 1 gram) intramuscular or intravenous in a single dose daily for seven days. • Recommended regimen for children who weigh >45 kg and who have bacteremia or arthritis: o Ceftriaxone 50 mg/kg intramuscular or intravenous in a single dose daily for seven days. <u>Gonococcal meningitis and endocarditis</u> • Recommended regimen: o Ceftriaxone 1 to 2 grams intravenous every 12 hours.

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	Hepatitis B
	• No specific therapy is available for persons with acute hepatitis B; treatment is supportive.
	• Persons with chronic hepatitis B virus infection should be referred for evaluation to a physician experienced in the management of chronic liver disease.
	• Therapeutic agents approved by Food and Drug Administration for treatment of chronic hepatitis B can achieve sustained suppression of hepatitis B virus replication and remission of liver disease in some persons.
	
	Hepatitis C
	• Combination therapy with pegylated interferon and ribavirin is the treatment of choice for patients with chronic hepatitis C.
	
	Lymphogranuloma venereum
	• Recommended regimen:
	  o Doxycycline 100 mg orally twice a day for 21 days.
	• Alternative regimen:
	  o Erythromycin base 500 mg orally four times a day for 21 days.
	
	Nongonococcal urethritis
	• Recommended regimens:
	  o Azithromycin 1 gram orally in a single dose.
	  o Doxycycline 100 mg orally twice a day for seven days.
	• Alternative regimens:
	  o Erythromycin base 500 mg orally four times a day for seven days.
	  o Erythromycin ethylsuccinate 800 mg orally four times a day for seven days.
	  o Levofloxacin 500 mg orally once daily for seven days.
	  o Ofloxacin 300 mg orally twice a day for seven days.
	
	Ophthalmia neonatorum caused by *Chlamydia trachomatis*
	• Recommended regimen:
	  o Erythromycin base or ethylsuccinate 50 mg/kg/day orally divided into four doses daily for 14 days.
	
	Pelvic inflammatory disease
	• Recommended parenteral regimen A:
	  o Cefotetan 2 grams intravenous every 12 hours.
	  o Cefoxitin 2 grams intravenous every six hours plus doxycycline 100 mg orally or intravenous every 12 hours.
	• Recommended parenteral regimen B:
	  o Clindamycin 900 mg intravenous every eight hours plus gentamicin loading dose intravenous or intramuscular (2 mg/kg of body weight), followed by a maintenance dose (1.5 mg/kg) every eight hours. Single daily dosing (3 to 5 mg/kg) can be substituted.
	• Alternative parenteral regimens:
	  o Ampicillin-sulbactam 3 grams IV every six hours plus doxycycline 100 mg orally or intravenous every 12 hours.
	• Recommended oral regimen:
	  o Ceftriaxone 250 mg intramuscular in a single dose plus

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	doxycycline 100 mg orally twice a day for 14 days with or without metronidazole 500 mg orally twice a day for 14 days. o Cefoxitin 2 grams intramuscular in a single dose and probenecid, 1 gram orally administered concurrently in a single dose, plus doxycycline 100 mg orally twice a day for 14 days with or without metronidazole 500 mg orally twice a day for 14 days. o Other parenteral third-generation cephalosporin (e.g., ceftizoxime or cefotaxime) plus doxycycline 100 mg orally twice a day for 14 days with or without metronidazole 500 mg orally twice a day for 14 days. <u>Proctitis, proctocolitis, and enteritis</u> • Recommended regimen: o Ceftriaxone 250 mg intramuscular plus doxycycline 100 mg orally twice a day for seven days. <u>Recurrent and persistent urethritis</u> • Recommended regimens: o Metronidazole 2 grams orally in a single dose. o Tinidazole 2 grams orally in a single dose plus azithromycin 1 gram orally in a single dose (if not used for initial episode). <u>Sexual assault and sexually transmitted diseases</u> • Recommended regimen: ceftriaxone plus metronidazole plus azithromycin or doxycycline. <u>Primary and secondary syphilis</u> • Recommended regimen for adults: o Benzathine penicillin G 2.4 million units intramuscular in a single dose. • Recommended regimen for infants and children: o Benzathine penicillin G 50,000 units/kg intramuscular, up to the adult dose of 2.4 million units in a single dose. <u>Early latent syphilis</u> • Recommended regimens for adults: o Benzathine penicillin G 2.4 million units intramuscular in a single dose. • Recommended regimens for children: o Benzathine penicillin G 50,000 units/kg intramuscular, up to the adult dose of 2.4 million units in a single dose. <u>Late latent syphilis or latent syphilis of unknown duration</u> • Recommended regimens for adults: o Benzathine penicillin G 7.2 million units total, administered as three doses of 2.4 million units intramuscular each at one-week intervals. • Recommended regimens for children: o Benzathine penicillin G 50,000 units/kg intramuscular, up to the adult dose of 2.4 million units, administered as three doses at one-week intervals. <u>Tertiary syphilis</u> • Recommended regimen: o Benzathine penicillin G 7.2 million units total, administered

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	as three doses of 2.4 million units intramuscular each at one-week intervals.
	
	<u>Neurosyphilis</u>
	• Recommended regimen:
	  o Aqueous crystalline penicillin G 18 to 24 million units per day, administered as 3 to 4 million units intravenous every four hours or continuous infusion, for 10 to 14 days.
	• Alternative regimen:
	  o Procaine penicillin 2.4 million units intramuscular once daily plus probenecid 500 mg orally four times a day, both for 10 to 14 days.
	
	<u>Trichomoniasis</u>
	• Recommended regimens: metronidazole 2 grams orally in a single dose or tinidazole 2 grams orally in a single dose.
	• Alternative regimen: metronidazole 500 mg orally twice a day for seven days.
	
	<u>Uncomplicated gonococcal infections of the cervix, urethra, and rectum</u>
	• Recommended regimens:
	  o Ceftriaxone 250 mg intramuscular in a single dose.
	  o Cefixime 400 mg orally in a single dose.
	  o Single-dose injectable cephalosporin regimens plus azithromycin 1 gram orally in a single dose or doxycycline 100 mg orally twice a day for seven days.
	
	<u>Uncomplicated gonococcal infections of the pharynx</u>
	• Recommended regimens:
	  o Ceftriaxone 250 mg intermuscular in a single dose plus azithromycin 1 gram orally in a single dose or doxycycline 100 mg orally twice a day for seven days.

American College of Obstetricians and Gynecologists: **Herpes Simplex Virus Infections (2004)**[39] **(Reviewed and deemed current as of 2009)**	• Acyclovir, valacyclovir, and famciclovir are antiviral drugs approved for treatment of genital herpes. • Comparative trials of these medications suggest they have compatible clinical efficacy and result in comparable decrease in viral shedding. • Treatment should be offered for first episode, even if they appear to be mild initially. • Treatment of first episodes decreases lesions, viral shedding, and symptoms, but does not affect the long-term natural history of infection. • Newly acquired HSV infections can have a prolonged course with systemic and neurologic involvement that can be substantially ameliorated by using antiviral therapy. Oral therapy is recommended, except in severe cases in which a woman is unable to tolerate oral intake or has prominent neurologic involvement. Such patients should be hospitalized and treated with intravenous acyclovir. • Recurrent episodes of genital herpes can be managed effectively either with daily suppressive or episodic antiviral drugs. • Episodic therapy decreases the duration of the episode (lesion, pain, and viral shedding) and is most effective when the patient initiates the therapy at prodrome or at the beginning of the episode. This form of therapy is most effective for a patient with infrequent symptomatic recurrences. • Topical antiviral medication is not effective therapy and does not add

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	to the benefit of the oral medication; its use is discouraged.
World Health Organization: **Guidelines for the Management of Sexually Transmitted Infections (2003)**[40]	Genital Herpes Infection • The first clinical episode should be treated with acyclovir, valacyclovir, or famciclovir, all for seven days. • Recurrent infections should be treated with acyclovir, valacyclovir, or famciclovir, all for five days. • Suppressive therapy may include acyclovir, valacyclovir, or famciclovir continuously. • Severe disease should be treated with intravenous acyclovir. • Treatment during pregnancy should be with acyclovir. • Patients who are co-infected with human immunodeficiency virus should be treated with acyclovir. • Neonates should be treated with intravenous acyclovir.

Centers for Disease Control and Prevention: **Prevention of Herpes Zoster– Recommendations of the Advisory Committee on Immunization Practices (2008)**[41]	Vaccination
	• Zoster vaccine is recommended for all persons aged ≥60 years who have no contraindications, including persons who report a previous episode of zoster or who have chronic medical conditions. Zoster vaccination is not indicated to treat acute zoster, to prevent persons with acute zoster from developing postherpetic neuralgia (PHN), or to treat ongoing PHN.
	• Before routine administration of zoster vaccine, it is not necessary to ask patients about their history of varicella (chickenpox) or to conduct serologic testing for varicella immunity.
	
	Treatment
	• Acyclovir, famciclovir, and valacyclovir are approved by the FDA for treatment of zoster in immunocompetent patients. All three are nucleoside analogs that inhibit replication of human herpes viruses, including varicella zoster virus.
	• Clinical trials have indicated that acyclovir, famciclovir, and valacyclovir reduce the duration of viral shedding and lesion formation, reduce the time to rash healing, and decrease the severity and duration of acute pain from zoster and the risk for progression to PHN.
	• Because all three antiviral agents are safe and well tolerated, many experts recommend that treatment should be considered for all eligible patients with zoster, and specifically recommend treatment for persons:
	  o Aged ≥50 years
	  o Moderate or severe pain
	  o Moderate or severe rash
	  o Involvement of non-truncal dermatomes
	• In clinical trials, treatment has been initiated within 72 hours of rash onset, a biologically arbitrary time point that often is not feasible in clinical practice. The benefits of later treatment have not been studied. If treatment cannot be initiated within 72 hours of rash onset, experts recommend that it should be initiated as soon as possible, particularly in the presence of new vesicle formation or of complications.

Infectious Diseases Society of America: **Recommendations for the Management of Herpes Zoster (2007)**[42]	• Topical antiviral therapy lacks efficacy in patients with herpes zoster (HZ) and is not recommended.
	• Systemic antiviral therapy is strongly recommended as first-line treatment for all immunocompetent patients with HZ who fulfill any of the following criteria:
	  o >50 years of age
	  o Moderate or severe pain
	  o Moderate or severe rash

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	o Non-truncal involvement • In patients who have a low risk for complications of HZ (those who are younger with mild acute pain and rash and truncal involvement) the potential benefits of treatment are unknown but may be meaningful because such patients can still develop postherpetic neuralgia (PHN). • Antiviral therapy should be considered even for patients whose risk of developing PHN and other complications of HZ is likely to be low. • There are no systematic data addressing the effectiveness of antiviral therapy administered outside of the clinical trial setting. In clinical practice, brivudin, famciclovir, and valacyclovir can be expected to have greater overall effectiveness than acyclovir on the basis of their potentially greater efficacy and higher and more reliable levels of antiviral activity in blood. • In patients presenting >72 hours after rash onset, the potential benefits of initiating antiviral therapy are unknown but might be meaningful, given the minimal risks of treatment with acyclovir, famciclovir, and valacyclovir. • The initiation of antiviral therapy can be considered for patients presenting >72 hours after rash onset with continued new vesicle formation or when there are cutaneous, motor, neurologic, or ocular complications. Advanced age and severe pain (which are potent risk factors for PHN) are additional factors that can prompt consideration of initiating antiviral therapy >72 hours after rash onset. • In patients who still have new vesicles forming or who have cutaneous, motor, neurologic, or ocular complications after seven days of antiviral therapy, it is recommended that consideration be given to extending the duration of antiviral therapy for greater than seven days for these patients. • When rash healing has not occurred in a normal fashion in an immunocompetent patient with HZ, further evaluation by an infectious diseases specialist is recommended. Infection with varicella zoster virus resistant to acyclovir (mediated by absent or altered expression of thymidine kinase) has been reported in immunocompromised but not in immunocompetent patients.
American Academy of Pediatrics: **Varicella-Zoster Infections (2009)**[43]	• The decision to use antiviral therapy and the route and duration of therapy should be determined by specific host factors, extent of infection, and initial response to therapy. • Antiviral drugs have a limited window of opportunity to affect the outcome of varicella zoster virus infection. In immunocompetent hosts, most virus replication has stopped by 72 hours after onset of rash; the duration of replication may be extended in immunocompromised hosts. • Oral acyclovir is not recommended for routine use in otherwise healthy children with varicella. Administration within 24 hours of onset of rash results in only a modest decrease in symptoms. • Oral acyclovir should be considered for otherwise healthy people at increased risk of moderate to severe varicella, such as people older than 12 years of age, people with chronic cutaneous or pulmonary disorders, people receiving long-term salicylate therapy, and people receiving short, intermittent, or aerosolized courses of corticosteroids. • Some experts also recommend use of oral acyclovir for secondary household cases in which the disease usually is more severe than in the primary case. • Intravenous antiviral therapy is recommended for immunocompromised patients, including patients being treated with chronic corticosteroids. Therapy initiated early in the course of the

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	illness, especially within 24 hours of rash onset, maximizes efficacy. Oral acyclovir should not be used to treat immunocompromised children with varicella because of poor oral bioavailability. Some experts have used high-dose oral acyclovir, valacyclovir, or famciclovir in selected immunocompromised patients perceived to be at lower risk of developing severe varicella, such as HIV-infected patients with relatively normal concentrations of CD4+ T-lymphocytes and children with leukemia in whom careful follow-up is ensured. • Famciclovir is converted to penciclovir, which has an extended half-life in infected cells. Valacyclovir is converted to acyclovir and produces four-fold greater serum concentrations than those produced by oral acyclovir. No pediatric formulation is available for either medication, and insufficient data exist on the use or dose of these drugs in children to support therapeutic recommendations.
American Academy of Pediatrics: **Respiratory Syncytial Virus[44] (2012)**	• Primary treatment is supportive and should include hydration, careful clinical assessment of respiratory status, including measurement of oxygen saturation, use of supplemental oxygen, suction of the upper airway, and if necessary, intubation and mechanical ventilation. • Ribavirin has in vitro antiviral activity against respiratory syncytial virus (RSV), and aerosolized ribavirin therapy has been associated with a small but statistically significant increase in oxygen saturation during the acute infection in several small studies. However, a consistent decrease in need for mechanical ventilation, decrease in length of stay in the pediatric intensive care unit, or reduction in days of hospitalization among ribavirin recipients has not been demonstrated. • The aerosol route of administration, concern about potential toxic effects among exposed health care professionals, and conflicting results of efficacy trials have led to decreasing use of this drug. • Ribavirin is not recommended for routine use but may be considered for use in select patients with documented, potentially life-threatening RSV infection.
National Institutes of Health, the Centers for Disease Control and Prevention, and the Human Immunodeficiency Virus Medicine Association of the Infectious Diseases Society of America: **Guidelines for Prevention and Treatment of Opportunistic Infections in Human Immunodeficiency Virus - Infected Adults and Adolescents (2013)[45]**	<u>Aspergillosis</u> • Voriconazole is the drug of choice but should be used cautiously with human immunodeficiency virus protease inhibitors and efavirenz. Amphotericin B deoxycholate at 1 mg/kg daily or lipid-formulation amphotericin B at 5 mg/kg daily are alternatives, as is caspofungin at 50 mg daily and posaconazole. • Other echinocandins, such as micafungin and anidulafungin, are reasonable alternatives. • For treatment failure (if voriconazole was used initially) substitution with amphotericin B, posaconazole, or echinocandins might be considered; the amphotericin B or echinocandins would be rational for those who began therapy with voriconazole or posaconazole. <u>Candidiasis (mucocutaneous)</u> • Oral fluconazole is as effective as topical therapy for oropharyngeal candidiasis and is considered the drug of choice. Initial episodes of oropharyngeal candidiasis can be adequately treated with topical therapy, including clotrimazole troches, nystatin suspension or pastilles, or miconazole mucoadhesive tablets. Itraconazole oral solution for seven to 14 days is as effective as oral fluconazole but less well tolerated. Posaconazole oral solution is also as effective as fluconazole and is generally better tolerated than itraconazole. Intravenous amphotericin B is usually effective and can be used among patients with refractory disease. Both conventional amphotericin B and lipid complex and liposomal amphotericin B have been used.

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	• Systemic antifungals are required for effective treatment of esophageal candidiasis. A 14 to 21-day course of either fluconazole (oral or intravenous) or oral itraconazole solution is highly effective. Oral ketoconazole or itraconazole capsules are less effective than fluconazole because of variable absorption. Although intravenous caspofungin or intravenous voriconazole are effective in treating esophageal candidiasis among human immunodeficiency virus -infected patients, oral or intravenous fluconazole remain the preferred therapies. Azole-refractory esophageal candidiasis can be treated with posaconazole, amphotericin B, anidulafungin, caspofungin, micafungin, or voriconazole. • Vulvovaginal candidiasis in human immunodeficiency virus -infected women is usually uncomplicated (90%) and responds readily to short-course oral or topical treatment with any of several therapies, including oral fluconazole, topical azoles, and itraconazole oral solution. Severe or recurrent episodes of vaginitis require oral fluconazole or topical antifungal therapy for ≥7 days. <u>Coccidioidomycosis</u> • For patients with clinically mild infection, such as focal pneumonia or a positive coccidioidal serologic test alone, initial therapy with a triazole antifungal is appropriate. • For patients with either diffuse pulmonary involvement or severely ill patients with extrathoracic disseminated disease, amphotericin B is the preferred initial therapy. Therapy with amphotericin B should continue until clinical improvement is observed. Some specialists would use a triazole antifungal concurrently with amphotericin B and continue the triazole once amphotericin B is stopped. <u>Cryptococcosis</u> • The recommended initial standard treatment is amphotericin B combined with flucytosine for ≥2 weeks for those with normal renal function. • The combination of amphotericin B with fluconazole is less effective than amphotericin B combined with flucytosine in terms of clearing *Cryptococcus* from the cerebrospinal fluid but is better than amphotericin B alone. • Fluconazole combined with flucytosine is an alternative to amphotericin B plus flucytosine, but is less effective than amphotericin B and is recommended only for persons unable to tolerate or unresponsive to standard treatment. • After at least a two-week period of successful induction therapy, amphotericin B and flucytosine may be discontinued and follow-up therapy initiated with fluconazole. This should continue for eight weeks. Itraconazole is an acceptable though less effective alternative. • The optimal therapy for those with treatment failure is not established. For those initially treated with fluconazole, therapy should be changed to amphotericin B, with or without flucytosine, and continued until a clinical response occurs. Liposomal amphotericin B may have improved efficacy over the deoxycholate formulation and should be considered in treatment failures. Higher doses of fluconazole in combination with flucytosine might also be useful. <u>Cryptosporidiosis</u> • In the setting of severe immunosuppression, antiretroviral therapy with immune restoration to a CD4+ count >100 cells/μL leads to resolution

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	of clinical cryptosporidiosis and is the mainstay of treatment. • All patients with cryptosporidiosis should be offered antiretroviral therapy as part of the initial management of their infection. • Management should include symptomatic treatment of diarrhea. Rehydration and repletion of electrolyte losses by either the oral or intravenous route are important. Severe diarrhea can exceed >10 L/day among patients with acquired immunodeficiency syndrome, often requiring intensive support. Aggressive efforts at oral rehydration should be made with oral rehydration solutions. <u>Prevention of Cytomegalovirus</u> • Cytomegalovirus end-organ disease is best prevented by using antiretroviral therapy to maintain the CD4+ count >100 cells/µL. • Although oral valganciclovir would likely prevent the occurrence of cytomegalovirus retinitis in patients with CD4+ counts <50 cells/µL, such therapy is not generally recommended because of the potential to induce cytomegalovirus resistance, the utility of treating disease when it occurs, and the lack of demonstrated survival advantage. <u>Treatment of Cytomegalovirus disease</u> • Oral valganciclovir, intravenous ganciclovir, intravenous ganciclovir followed by oral valganciclovir, intravenous foscarnet, and intravenous cidofovir are all effective treatments for cytomegalovirus retinitis. • The ganciclovir implant, a surgically-implanted reservoir of ganciclovir, which lasts approximately six months, also is very effective but it no longer is being manufactured. In its absence, some clinicians will use intravitreal injections of ganciclovir or foscarnet in conjunction with oral valganciclovir, at least initially, to provide immediate high intraocular levels of drug and presumably faster control of the retinitis. • Systemic therapy has been shown to reduce morbidity in the contralateral eye. This should be considered when choosing between the oral, intravenous, and local options. • The choice of initial therapy for cytomegalovirus retinitis should be individualized based on the location and severity of the lesion(s), the level of underlying immune suppression, and other factors such as concomitant medications and ability to adhere to treatment. • No one regimen has been proven in a clinical trial to have greater efficacy in terms of protecting vision, and thus clinical judgment must be used when choosing a regimen. • In studies conducted in the pre-antiretroviral therapy era, ganciclovir intraocular implant plus oral ganciclovir was superior to once-daily intravenous ganciclovir for treatment of cytomegalovirus retinitis; however, the implant is no longer manufactured. Assuming that this observation can be extended to other combinations of systemically and locally administered drugs, human immunodeficiency virus-specialists often recommend intravitreal ganciclovir or foscarnet injections plus oral valganciclovir as the preferred initial therapy for patients with immediate sight-threatening lesions. Intravitreal injections deliver high concentrations of the drug to the target organ immediately while steady-state concentrations in the eye are achieved with systemically delivered medications. For patients with small peripheral lesions, oral valganciclovir alone often is adequate. • After induction therapy, secondary prophylaxis (i.e., chronic maintenance therapy) should be continued until immune reconstitution occurs as a result of antiretroviral therapy. Regimens demonstrated to

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	be effective for chronic suppression in randomized, controlled clinical trials include parenteral ganciclovir, oral valganciclovir, parenteral foscarnet, combined parenteral ganciclovir and foscarnet, and parenteral cidofovir. Management of Cytomegalovirus retinitis treatment failures • When patients relapse while receiving maintenance therapy, induction with the same drug followed by reinstitution of maintenance therapy can control the retinitis, although for progressively shorter periods of time with each relapse. • Ganciclovir and foscarnet in combination appear to be superior in efficacy to either agent alone and should be considered for patients whose disease does not respond to single-drug therapy, and for patients with multiple relapses of retinitis. This drug combination, however, is associated with substantial toxicity. Treatment of Hepatitis B Virus coinfection in patients not receiving antiretroviral therapy • For patients with CD4+ counts >350 cells/µL who are not receiving antiretroviral therapy but meet criteria for hepatitis B virus treatment, adefovir or peginterferon alfa-2a monotherapy for 48 weeks might be considered, with close monitoring of hepatitis B virus deoxyribonucleic acid levels and follow-up to evaluate for hepatitis B e antigen seroconversion. However, early initiation of antiretroviral therapy should also be considered for human immunodeficiency virus/hepatitis B virus -coinfected persons with CD4+ counts >350 cells/µL. Treatment of Hepatitis B Virus coinfection in patients who require antiretroviral therapy • For human immunodeficiency virus-infected persons, some experts recommend combination therapy with two agents active against hepatitis B virus to reduce the risk of hepatitis B virus drug resistance; although, there are no results from controlled trials as yet to support this strategy. • Among patients infected with hepatitis B virus, hepatitis C virus, and human immunodeficiency virus, consideration of the need for antiretroviral therapy should be the first priority. If antiretroviral therapy is not required, interferon-based therapy, which suppresses both hepatitis C virus and hepatitis B virus, should be considered. If interferon-based therapy for hepatitis C virus has failed, treatment of chronic hepatitis B with nucleoside or nucleotide analogs is recommended. Treatment of Hepatitis C coinfection • Antiviral treatment for hepatitis C virus infection should be considered for all human immunodeficiency virus-infected persons with acute or chronic hepatitis C virus infection. • The combination of peginterferon alfa (PegIFN) plus ribavirin is the recommended backbone of therapy for HIV/HCV-co-infected patients regardless of HCV genotype. • Antiviral treatment with PegIFN is not recommended in patients with decompensated liver disease. • For HCV-genotype-1-infected patients who are not co-infected with HIV, a HCV NS3/4A protease inhibitor (PI), either boceprevir or telaprevir, in combination with PegIFN/ribavirin is recommended on

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	the basis of large clinical trials demonstrating significantly higher SVR rates with an acceptable safety/tolerability profile compared to PegIFN/ribavirin alone.
	• For HIV/HCV co-infected patients, preliminary data from small, ongoing clinical trials of boceprevir or telaprevir plus PegIFN/ribavirin for the treatment of HCV genotype 1 infection in HIV/HCV co-infected patients demonstrate greater efficacy than PegIFN/ribavirin alone, with a safety and tolerability profile similar to that observed in HCV monoinfected patients treated with boceprevir or telaprevir plus PegIFN/ribavirin. Preliminary recommendations are as follows:
	  o PegIFN is recommended for use for all HCV genotypes
	  o Ribavirin is recommended for use with PegIFN for all HCV genotypes.
	  o Boceprevir is approved for use in combination with PegIFN/ribavirin in HCV-genotype-1-monoinfected-patients. For HIV/HCV-co-infected patients, the regimen being evaluated is PegIFN/ribavirin administered for four weeks (lead-in phase) followed by boceprevir 800 mg orally every 7 to 9 hours (with a light snack) added to PegIFN/ribavirin for an additional 44 weeks.
	  o Telaprevir is approved for use in combination with PegIFN/ribavirin in HCV-genotype-1-monoinfected-patients. Dosing regimens lasting 48 weeks are being evaluated.
	• Patients with contraindications to the use of ribavirin can be treated with peginterferon alfa (2a or 2b) monotherapy. However, substantially lower sustained viral response rates are expected in persons not receiving ribavirin. HCV PIs should not be administered without ribavirin because of the high likelihood of virologic failure.
	
	<u>Treatment of herpes simplex virus disease</u>
	• Orolabial lesions can be treated with oral valacyclovir, famciclovir, or acyclovir for five to 10 days.
	• Severe mucocutaneous herpes simplex virus lesions are best treated initially with intravenous acyclovir. Patients may be switched to oral therapy after the lesions have begun to regress. Therapy should be continued until the lesions have completely healed.
	• Genital herpes simplex virus infection should be treated with oral valacyclovir, famciclovir, or acyclovir for five to 14 days. Short-course therapy (one, two, or three days) should not be used in patients with human immunodeficiency virus infection.
	• Most recurrences of genital herpes can be prevented by use of daily anti- herpes simplex virus therapy, and this is recommended for persons who have frequent or severe recurrences.
	• Suppressive therapy with oral acyclovir, valacyclovir, or famciclovir is effective in preventing recurrences. Suppressive therapy with valacyclovir should be 500 mg twice daily in human immunodeficiency virus -infected persons or twice-daily regimens with acyclovir or famciclovir should be used.
	
	<u>Management of herpes simplex virus treatment failure</u>
	• The treatment of choice for acyclovir-resistant herpes simplex virus is intravenous foscarnet. Topical trifluridine, cidofovir, and imiquimod also have been used successfully for lesions on external surfaces, although prolonged application for 21 to 28 days or longer might be required.

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	Histoplasmosis • Patients with moderately severe to severe disseminated histoplasmosis should be treated with an intravenous lipid formulation of amphotericin B for ≥2 weeks or until they clinically improve followed by oral itraconazole (200 mg three times daily for three days and then 200 mg twice daily for a total of ≥12 months). • In patients with less severe disseminated histoplasmosis, oral itraconazole at 200 mg three times daily for three days followed by 200 mg twice daily is appropriate initial therapy. Treatment of Isosporiasis (also known as Cystoisosporiasis) • Sulfamethoxazole-trimethoprim is the antimicrobial agent of choice for treatment of isosporiasis. It is the only agent whose use is supported by substantial published data and clinical experience. Therefore, potential alternative therapies should be reserved for patients with documented sulfa intolerance or in whom treatment fails. The traditional treatment regimen has been a 10-day course of Sulfamethoxazole-trimethoprim (800-160 mg) administered orally four times daily. • Intravenous administration of Sulfamethoxazole-trimethoprim should be considered for patients with potential or documented malabsorption. • Single-agent therapy with pyrimethamine has been used, with anecdotal success for treatment and prevention of isosporiasis. Pyrimethamine (50 to 75 mg/day) plus leucovorin (10 to 25 mg/day) to prevent myelosuppression may be an effective treatment alternative; it is the option for sulfa-intolerant patients. Leishmaniasis • Due to similar efficacy and a better toxicity profile, clinicians consider liposomal amphotericin B as the drug of choice for visceral leishmaniasis in human immunodeficiency virus-coinfected patients. The optimal amphotericin B dosage has not been determined. • Regimens with efficacy include conventional amphotericin B 0.5 to 1.0 mg/kg body weight/day intravenous to achieve a total dose of 1.5 to 2.0 g, or liposomal or lipid complex preparations of two to four mg/kg body weight administered on consecutive days or in an interrupted schedule (e.g., 4 mg/kg on Days 1 to 5, 10, 17, 24, 31, and 38) to achieve a total cumulative dose of 20 to 60 mg/kg body weight. A higher daily dosage is recommended for liposomal or lipid complex preparations than for conventional amphotericin B. Preventing disseminated *Mycobacterium avium* complex disease • Human immunodeficiency virus-infected adults and adolescents should receive chemoprophylaxis against disseminated *Mycobacterium avium* complex disease if they have a CD4+ count <50 cells/µL. • Azithromycin or clarithromycin are the preferred prophylactic agents. • The combination of clarithromycin and rifabutin is no more effective than clarithromycin alone for chemoprophylaxis, is associated with a higher rate of adverse effects than either drug alone, and should not be used. • The combination of azithromycin with rifabutin is more effective than azithromycin alone; however, the additional cost, increased occurrence of adverse effects, potential for drug interactions, and absence of a survival difference compared to azithromycin alone do not warrant a routine recommendation for this regimen.

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	• Azithromycin and clarithromycin also each confer protection against respiratory bacterial infections.
	• If azithromycin or clarithromycin cannot be tolerated, rifabutin is an alternative prophylactic agent for *Mycobacterium avium* complex disease, although drug interactions may make this agent difficult to use.
	• Primary *Mycobacterium avium* complex disease prophylaxis should be discontinued among adult and adolescent patients who have responded to antiretroviral therapy with an increase in CD4+ counts to >100 cells/µL for ≥3 months. Primary prophylaxis should be reintroduced if the CD4+ count decreases to <50 cells/µL.
	
	<u>Treatment of disseminated *Mycobacterium avium* Complex Disease</u>
	• Initial treatment of *Mycobacterium avium* complex disease should consist of two or more antimycobacterial drugs to prevent or delay the emergence of resistance.
	• Clarithromycin is the preferred first agent; however, azithromycin can be substituted for clarithromycin when drug interactions or clarithromycin intolerance preclude the use of clarithromycin.
	• Testing of *Mycobacterium avium* complex disease isolates for susceptibility to clarithromycin or azithromycin is recommended for all patients.
	
	<u>Treatment of Penicilliosis marneffei</u>
	  • Penicilliosis is caused by the dimorphic fungus *Penicillium marneffei*, which is known to be endemic in Southeast Asia (especially Northern Thailand and Vietnam) and southern China.
	  • The recommended treatment is liposomal amphotericin B, three to five mg/kg body weight/day intravenously for two weeks, followed by oral itraconazole, 400 mg/day for a subsequent duration of 10 weeks, followed by secondary prophylaxis.
	  • Patients with mild disease can be initially treated with oral itraconazole 400 mg/day for eight weeks, followed by 200 mg/day for prevention of recurrence.
	  • The alternative drug for primary treatment in the hospital is intravenous voriconazole, 6 mg/kg every 12 hours on day one and then 4 mg/kg every 12 hours for at least three days, followed by oral voriconazole, 200 mg twice daily for a maximum of 12 weeks.
	  • Patients with mild disease can be initially treated with oral voriconazole 400 mg twice a day on day one, and then 200 mg twice daily for 12 weeks. The optimal dose of voriconazole for secondary prophylaxis after 12 weeks has not been studied.
	
	<u>Primary prophylaxis of *Pneumocystis (carinii) jiroveci* pneumonia</u>
	• Sulfamethoxazole-trimethoprim is the recommended prophylactic agent. One double-strength tablet daily is the preferred regimen. However, one single-strength tablet daily is also effective and might be better tolerated than one double-strength tablet daily. One double-strength tablet three times weekly is also effective. Sulfamethoxazole-trimethoprim at a dose of one double-strength tablet daily confers cross-protection against toxoplasmosis and selected common respiratory bacterial infections. Lower doses of sulfamethoxazole-trimethoprim likely also confer such protection.
	• For patients who have an adverse reaction that is not life threatening,

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	chemoprophylaxis with sulfamethoxazole-trimethoprim should be continued if clinically feasible; for those who have discontinued such therapy because of an adverse reaction, reinstituting sulfamethoxazole-trimethoprim should be strongly considered after the adverse event has resolved. Patients who have experienced adverse events, including fever and rash, might better tolerate reintroduction of the drug with a gradual increase in dose (i.e., desensitization), according to published regimens or reintroduction of sulfamethoxazole-trimethoprim at a reduced dose or frequency; as many as 70% of patients can tolerate such reinstitution of therapy. • If sulfamethoxazole-trimethoprim cannot be tolerated, alternative prophylactic regimens include dapsone, dapsone/pyrimethamine plus leucovorin, aerosolized pentamidine and atovaquone. • Primary *Pneumocystis (carinii) jiroveci* pneumonia prophylaxis should be discontinued for adult and adolescent patients who have responded to antiretroviral therapy with an increase in CD4+ counts to >200 cells/µL for >3 months. Prophylaxis should be reintroduced if the CD4+ count decreases to <200 cells/µL. <u>Treatment of *Pneumocystis (carinii) jiroveci* pneumonia</u> • Sulfamethoxazole-trimethoprim is the treatment of choice. The dose must be adjusted for abnormal renal function. Multiple randomized clinical trials indicate that sulfamethoxazole-trimethoprim is as effective as parenteral pentamidine and more effective than other regimens. Adding leucovorin to prevent myelosuppression during acute treatment is not recommended because of questionable efficacy and some evidence for a higher failure rate. Oral outpatient therapy of sulfamethoxazole-trimethoprim is highly effective among patients with mild-to-moderate disease. • Patients who have *Pneumocystis (carinii) jiroveci* despite sulfamethoxazole-trimethoprim prophylaxis are usually effectively treated with standard doses of sulfamethoxazole-trimethoprim. • Patients with documented or suspected *Pneumocystis (carinii) jiroveci* and moderate-to-severe disease, as defined by room air pO_2 <70 mm Hg or arterial-alveolar O_2 gradient >35 mm Hg, should receive adjunctive corticosteroids as early as possible, and certainly within 72 hours after starting specific *Pneumocystis (carinii) jiroveci* therapy. • The recommended duration of therapy for *Pneumocystis (carinii) jiroveci* is 21 days. • Patients who have a history of *Pneumocystis (carinii) jiroveci* should be administered chemoprophylaxis for life (i.e., secondary prophylaxis or chronic maintenance therapy) with sulfamethoxazole-trimethoprim unless immune reconstitution occurs as a result of antiretroviral therapy. • Secondary prophylaxis should be discontinued for adult and adolescent patients whose CD4+ count has increased from <200 cells/µL to >200 cells/µL for >3 months as a result of antiretroviral therapy. Prophylaxis should be reintroduced if the CD4+ count decreases to <200 cells/µL. If *Pneumocystis (carinii) jiroveci* recurs at a CD4+ count of ≥200 cells/µL, lifelong prophylaxis should be administered. <u>Primary prophylaxis of *Toxoplasma* encephalitis</u> • The double-strength tablet daily dose of sulfamethoxazole-trimethoprim recommended as the preferred regimen for *Pneumocystis (carinii) jiroveci* prophylaxis is effective against *Toxoplasma* encephalitis as well and is therefore recommended. Sulfamethoxazole-

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	trimethoprim, one double-strength tablet three times weekly, is an alternative.
	• If patients cannot tolerate sulfamethoxazole-trimethoprim, the recommended alternative is dapsone-pyrimethamine plus leucovorin, which is also effective against *Pneumocystis (carinii) jiroveci* pneumonia.
	• Atovaquone with or without pyrimethamine/leucovorin can also be considered.
	• Prophylactic monotherapy with dapsone, pyrimethamine, azithromycin, or clarithromycin cannot be recommended on the basis of available data. Aerosolized pentamidine does not protect against *Toxoplasma* encephalitis and is not recommended.
	• Prophylaxis against *Toxoplasma* encephalitis should be discontinued among adult and adolescent patients who have responded to antiretroviral therapy with an increase in CD4+ counts to >200 cells/µL for >3 months. Prophylaxis for *Toxoplasma* encephalitis should be reintroduced if the CD4+ count decreases to <100–200 cells/µL.
	
	<u>Treatment of *Toxoplasma* encephalitis</u>
	• The initial therapy of choice for *Toxoplasma* encephalitis consists of the combination of pyrimethamine plus sulfadiazine plus leucovorin.
	• The preferred alternative regimen for patients with *Toxoplasma* encephalitis who are unable to tolerate or who fail to respond to first-line therapy is pyrimethamine plus clindamycin plus leucovorin.
	• Sulfamethoxazole-trimethoprim was reported in a small randomized trial to be effective and better tolerated than pyrimethamine-sulfadiazine. On the basis of less in vitro activity and less experience with sulfamethoxazole-trimethoprim, treatment with this drug may be considered an option.
	• Acute therapy for *Toxoplasma* encephalitis should be continued for at least six weeks, if there is clinical and radiologic improvement.
	
	<u>Treatment of latent tuberculosis infection</u>
	• Human immunodeficiency virus-infected persons, regardless of age, should be treated for latent tuberculosis infection if they have no evidence of active tuberculosis and:
	  o A positive diagnostic test for latent tuberculosis infection and no prior history of treatment for active or latent tuberculosis.
	  o A negative diagnostic test for latent tuberculosis infection but are close contacts of persons with infectious pulmonary tuberculosis.
	  o A history of untreated or inadequately treated healed tuberculosis (i.e., old fibrotic lesions on chest radiography) regardless of diagnostic tests for latent tuberculosis infection.
	• Treatment options for latent tuberculosis infection include isoniazid daily or twice weekly for nine months.
	• Due to an increased risk of fatal and severe hepatotoxicity, a two-month regimen of daily rifampin and pyrazinamide is not recommended for latent tuberculosis infection treatment regardless of human immunodeficiency virus status.
	• Human immunodeficiency virus-infected persons receiving isoniazid should receive pyridoxine to minimize the risk of developing peripheral neuropathy. Alternatives for individuals who cannot take isoniazid or who have been exposed to a known isoniazid-resistant

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	index case include either rifampin or rifabutin alone for four months. • For persons exposed to isoniazid- and/or rifampin-resistant tuberculosis, decisions to treat with one or two drugs other than isoniazid, rifampin, or rifabutin should be based on the relative risk of exposure to organisms broadly resistant to other antimycobacterial drugs and should be made in consultation with public health authorities. • Directly observed therapy should be used with intermittent dosing regimens when otherwise feasible to maximize regimen completion rates. • There is no evidence to suggest that latent tuberculosis infection treatment should be continued beyond the recommended duration in persons with human immunodeficiency virus infection. Therefore, latent tuberculosis infection treatment should be discontinued after completing the appropriate number of doses. <u>Treatment of active tuberculosis disease</u> • Recommendations for anti-tuberculosis treatment regimens in human immunodeficiency virus -infected adults follow the same principles as for adults without human immunodeficiency virus -infection. • Treatment of drug susceptible tuberculosis disease should include a six-month regimen with an initial phase of isoniazid, rifampin or rifabutin, pyrazinamide, and ethambutol administered for two months followed by isoniazid and rifampin (or rifabutin) for four additional months. • When drug-susceptibility testing confirms the absence of resistance to isoniazid, rifampin, and pyrazinamide, ethambutol may be discontinued before two months of treatment have been completed. • For patients with cavitary lung disease and cultures positive for *Mycobacterium tuberculosis* after completion of two months of therapy, treatment should be extended with isoniazid and rifampin for an additional three months for a total of nine months. • All human immunodeficiency virus-infected patients treated with isoniazid should receive pyridoxine supplementation. • For patients with extrapulmonary tuberculosis, a six- to nine-month regimen (two months of isoniazid, rifampin, pyrazinamide, and ethambutol followed by four to seven months of isoniazid and rifampin) is recommended. • Exceptions to the recommendation for a six- to nine-month regimen for extrapulmonary tuberculosis include central nervous system disease (tuberculoma or meningitis) and bone and joint tuberculosis, for which many experts recommend nine to 12 months. • Adjuvant corticosteroids should be added when treating central nervous system and pericardial disease. • Treatment with corticosteroids should be started intravenously as early as possible with change to oral therapy individualized according to clinical improvement. • Recommended corticosteroid regimens are dexamethasone 0.3 to 0.4 mg/kg tapered over six to eight weeks or prednisone 1 mg/kg for three weeks, then tapered for three to five weeks. <u>Treatment of varicella zoster virus disease</u> • For uncomplicated varicella, the preferred treatment options are valacyclovir (1 gram orally three times daily), or famciclovir (500 mg orally three times daily) for five to seven days. Oral acyclovir (20

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	mg/kg body weight up to a maximum dose of 800 mg five times daily) can be an alternative. • Prompt antiviral therapy should be instituted in all human immunodeficiency virus-seropositive patients whose herpes zoster is diagnosed within one week of rash onset (or any time before full crusting of lesions). The recommended treatment options for acute localized dermatomal herpes zoster in human immunodeficiency virus-infected patients are oral valacyclovir, famciclovir, or acyclovir (doses as above) for seven to 10 days, although longer durations of therapy should be considered if lesions resolve slowly. Valacyclovir or famciclovir are preferred because of their improved pharmacokinetic properties and simplified dosing schedule. • If cutaneous lesions are extensive or if visceral involvement is suspected, intravenous acyclovir should be initiated and continued until clinical improvement is evident. A switch from intravenous acyclovir to oral antiviral therapy (to complete a 10 to 14 day treatment course) is reasonable when formation of new cutaneous lesions has ceased and the signs and symptoms of visceral varicella zoster virus infection are clearly improving. • Optimal antiviral therapy for progressive outer retinal necrosis remains undefined. Specific treatment should include systemic therapy with at least one intravenous drug (selected from acyclovir, ganciclovir, foscarnet, and cidofovir) coupled with injections of at least one intravitreal drug (selected from ganciclovir and foscarnet). Treatment regimens for progressive outer retinal necrosis recommended by certain specialists include a combination of intravenous ganciclovir and/or foscarnet plus intravitreal injections of ganciclovir and/or foscarnet. The prognosis for visual preservation in involved eyes is poor, despite aggressive antiviral therapy. • Other infectious disease states mentioned within these guidelines note that the treatment guidelines for that disease state should be utilized. • The guideline specifies that detailed recommendations for the treatment of human herpesvirus-8 and associated malignancies are beyond the scope of these guidelines. • Other excluded infectious disease states offer no specific therapy or utilize medications not licensed in the United States.
Center for International Blood and Marrow Transplant Research/ National Marrow Donor Program/ European Blood and Marrow Transplant Group/ American Society of Blood and Marrow Transplantation/ Canadian Blood and Marrow Transplant Group/ Infectious Diseases Society of America/ Society for Healthcare Epidemiology of America/ Association of Medical Microbiology and Infectious Diseases Canada/ Centers for Disease Control and Prevention: **Guidelines for Preventing Infectious Complications**	<u>Cytomegalovirus (CMV) recommendations</u> • Hematopoietic cell transplantation (HCT) candidates should be tested for CMV antibodies prior to transplant to determine their risk for primary CMV infection and reactivation after HCT. • CMV-seropositive HCT recipients and CMV-seronegative recipients with CMV-seropositive donors should be placed on CMV preventative therapy from time of engraftment until at least 100 days after HCT. • A prophylaxis strategy against early CMV replication for allogeneic recipients involves administering prophylaxis to all allogeneic recipients at risk throughout the period from engraftment to 100 days after HCT. Ganciclovir, high-dose acyclovir, and valacyclovir are all effective at reducing the risk for CMV infection after HCT. • Ganciclovir is often used as a first-line drug for preemptive therapy. Although foscarnet is as effective as ganciclovir, it is currently more commonly used as a second-line drug, because of the requirement for pre-hydration and electrolyte monitoring. Preemptive therapy should be given for a minimum of two weeks. Patients who are ganciclovir-intolerant should be treated with foscarnet.

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Among Hematopoietic Stem Cell Transplantation Recipients: A Global Perspective (2009)[46]	<u>Fungal infection recommendations</u> • Fluconazole is the drug of choice for the prophylaxis of invasive candidiasis before engraftment in allogeneic hematopoietic cell transplant recipients, and may be started from the beginning or just after the end of the conditioning regimen. • The optimal duration of fluconazole prophylaxis is not defined. • Fluconazole is not effective against *Candida krusei* and *Candida glabrata* and should not be used for prophylaxis against these strains. • Micafungin is an alternative prophylactic agent. • Itraconazole oral solution has been shown to prevent invasive fungal infections, but use of this drug is limited by poor tolerability and toxicities. • Voriconazole and posaconazole may be used for prevention of candidiasis post-engraftment. • Oral amphotericin B, nystatin, and clotrimazole troches may control superficial infection and control local candidiasis but have not been shown to prevent invasive candidiasis. • Transplant patients with candidemia or candidiasis may still receive transplants if their infection is diagnosed early and treated aggressively with amphotericin B or appropriate doses of fluconazole. • Autologous recipients have a lower risk of infection compared to allogeneic recipients and may not require prophylaxis, though it is still recommended in patients who have underlying hematologic malignancies, those who will have prolonged neutropenia and mucosal damage, or have recently received fludarabine. Itraconazole oral solution has been shown to prevent mold infections. • In patients with graft-vs-host disease, posaconazole has been reported to prevent invasive mold infections. • Patients with prior invasive aspergillosis should receive secondary prophylaxis with a mold-active drug. The optimal drug has not been determined, but voriconazole has been shown to have benefit for this indication. <u>Hepatitis B virus (HBV) recommendations</u> • Limited data suggests HCT donors with detectable HBV DNA should receive antiviral therapy for four weeks or until viral load is undetectable. Expert opinion suggests entecavir for this use. • HCT recipients with active HBV posttransplant should be treated with lamivudine for at least six months in autologous HCT recipients and for six months after immunosuppressive therapy has stopped in allogenic HCT recipients. <u>Hepatitis C virus (HCV) recommendations</u> • Treatment for chronic HCV should be considered in all HCV-infected HCT recipients. • The patient must be in complete remission from the original disease, be >2 years posttransplant without evidence of either protracted GVHD, have been off immunosuppression for 6 months, and have normal blood counts and serum creatinine. • Treatment should consist of full-dose peginterferon and ribavirin and should be continued for 24 to 48 weeks, depending on response. <u>Herpes simplex virus (HSV) recommendations</u> • Acyclovir prophylaxis should be offered to all HSV-seropositive

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	allogenic recipients to prevent HSV reactivation during the early transplant period for up to 30 days. • Routine acyclovir prophylaxis is not indicated for HSV-seronegative allogenic recipients. • Use of ganciclovir for CMV prophylaxis will provide sufficient prophylaxis for HSV. • Foscarnet is the treatment of choice for acyclovir-resistant HSV. • Valacyclovir is equally effective at HSV prophylaxis when compared to acyclovir. • Foscarnet is not recommended for routine HSV prophylaxis among HCT recipients due to renal and infusion-related toxicity. Patients who receive foscarnet for other reasons (e.g., CMV prophylaxis) do not require additional acyclovir prophylaxis. • There is inadequate data to make recommendations regarding the use of famciclovir for HSV prophylaxis. • HSV prophylaxis lasting >30 days after HCT might be considered for persons with frequent recurrences of HSV infection. Acyclovir or valacyclovir can be used during phase I (pre-engraftment) for administration to HSV-seropositive autologous recipients who are likely to experience substantial mucositis from the conditioning regimen. <u>Respiratory syncytial virus (RSV) recommendations</u> • Some researchers recommend preemptive aerosolized ribavirin for patients with RSV upper respiratory infection (URI), especially those with lymphopenia (during the first three months after HCT) and preexisting obstructive lung disease (late after HCT). • Although a definitive, uniformly effective preemptive therapy for RSV infection among HCT recipients has not been identified, certain other strategies have been proposed, including systemic ribavirin, RSV antibodies (i.e., passive immunization with high-RSV-titer IVIG, RSV immunoglobulin) in combination with aerosolized ribavirin, and RSV monoclonal antibody. • No randomized trial has been completed to test the efficacy of these strategies; therefore, no specific recommendation regarding any of these strategies can be given at this time. <u>Varicella zoster virus (VZV) recommendations</u> • Long-term acyclovir prophylaxis to prevent recurrent VZV infection is recommended for the first year after HCT for VZV-seropositive allogenic and autologous HCT recipients. Acyclovir prophylaxis may be continued beyond one year in allogenic HCT recipients who have graft-vs-host disease or require systemic immunosuppression. • Valacyclovir may be used in place of acyclovir when oral medications are tolerated. • There is not enough data to recommend use of famciclovir in place of valacyclovir or acyclovir for VZV prophylaxis. • Any HCT recipient with VZV-like rash should receive preemptive intravenous acyclovir therapy until two days after the lesions have crusted • Acyclovir or valacyclovir may be used in place of VZV immunoglobulin for post-exposure therapy.
Infectious Diseases Society of America: **Clinical Practice Guideline for the Use of**	<u>Antifungal therapy in high risk patients</u> • Empirical antifungal therapy and investigation for invasive fungal infections should be considered for patients with persistent or recurrent

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Antimicrobial Agents in Neutropenic Patients with Cancer (2010)[47] **Reviewed and deemed current as of April 2013**	fever after four to seven days of antibiotics and whose overall duration of neutropenia is expected to be greater than seven days. • Data are insufficient to recommend a specific empirical antifungal agent for a patient already receiving antifungal prophylaxis, but switching to a different class of antifungals that is given intravenously should be considered. • Preemptive antifungal management is acceptable as an alternative to empirical antifungal therapy in a subset of high-risk neutropenic patients. Those who remain febrile after four to seven days of broad-spectrum antibiotics but are clinically stable, have no clinical or chest and sinus computed tomography signs of fungal infection, have negative serologic assay results for evidence of invasive fungal infection, and have no recovery of fungi from any body site may have antifungal agents withheld. Antifungal therapy should be instituted if any of these indicators of possible invasive fungal infection are identified. • Prophylaxis against *Candida* infection is recommended in patient groups in whom the risk of invasive candidal infection is substantial, such as allogeneic hematopoietic stem cell transplant recipients or those undergoing intensive remission-induction or salvage-induction chemotherapy for acute leukemia. Fluconazole, itraconazole, voriconazole, posaconazole, micafungin, and caspofungin are all acceptable alternatives. • Prophylaxis against invasive *Aspergillus* infections with posaconazole should be considered for selected patients >13 years of age who are undergoing intensive chemotherapy for acute myeloid leukemia or myelodysplastic syndrome in whom the risk of invasive aspergillosis without prophylaxis is substantial. <u>Antifungal therapy in low risk patients</u> • In low-risk patients, the risk of invasive fungal infection is low, and therefore routine use of empirical antifungal therapy is not recommended. • Antifungal prophylaxis is not recommended for patients in whom the anticipated duration of neutropenia is less than seven days. <u>Antiviral prophylaxis</u> • Herpes simplex virus–seropositive patients undergoing allogeneic hematopoietic stem cell transplantation or leukemia induction therapy should receive acyclovir antiviral prophylaxis. • Antiviral treatment for herpes simplex or varicella-zoster virus infection is only indicated if there is clinical or laboratory evidence of active viral disease.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the nucleosides and nucleotides are noted in Tables 3 and 4. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Nucleosides and Nucleotides (Drugs A-F)[1-15]

Indication	Acyclovir	Adefovir	Cidofovir	Entecavir	Famciclovir
Cytomegalovirus Infection					
Treatment of cytomegalovirus retinitis in patients with acquired immunodeficiency syndrome (AIDS)			✔		
Hepatitis B Virus Infection					
Treatment of chronic hepatitis B in patients with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease		✔		✔	
Herpes Simplex Virus Infection					
Treatment of herpes genitalis	✔				✔
Treatment of herpes labialis	✔ ^				✔
Treatment of herpes simplex encephalitis	✔ §				
Treatment of mucocutaneous herpes simplex virus infections in immunocompromised patients	✔ §				
Treatment of neonatal herpes simplex virus infections	✔ §				
Treatment of recurrent orolabial or genital herpes in HIV-infected adults					✔
Varicella-Zoster Virus Infection					
Treatment of chickenpox	✔ ‡				
Treatment of herpes zoster (shingles)	✔ ‡				✔
Treatment of herpes zoster (shingles) infection in immunocompromised patients	✔ §				

§Intravenous formulation only
‡Oral formulations only
^Buccal tablet formulation only

Table 4. FDA-Approved Indications for the Nucleosides and Nucleotides (Drugs G-V)[1-15]

Indication	Ganciclovir	Ribavirin	Telbivudine	Valacyclovir	Valganciclovir
Cytomegalovirus Infection					
Prevention of cytomegalovirus disease in transplant recipients at risk from CMV disease	✔				
Prevention of cytomegalovirus disease in pediatric kidney or heart transplant patients at high risk					✔
Prevention of cytomegalovirus disease in adult kidney, heart, or kidney-pancreas transplant patients at high risk					✔
Treatment of cytomegalovirus retinitis in immunocompromised patients, including patients with acquired immunodeficiency syndrome (AIDS)	✔				✔
Hepatitis B Virus Infection					
Treatment of chronic hepatitis B in adult patients with evidence of viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease			✔		
Hepatitis C Virus Infection					
Treatment of chronic hepatitis C in combination with interferon alfa-2b (pegylated and non-pegylated) in patients with compensated liver disease		✔ ‡			
Treatment of chronic hepatitis C in combination with peginterferon alfa-2a in patients with compensated liver disease and who have not been previously treated with interferon alpha		✔ §			
Herpes Simplex Virus Infection					
Chronic suppressive therapy of recurrent episodes of genital herpes in immunocompetent and in HIV-1-infected adults				✔	
Reduction of transmission of genital herpes in immunocompetent adults				✔	
Treatment of the initial episode of genital herpes in immunocompetent adults				✔	
Treatment of recurrent episodes of genital herpes in immunocompetent adults				✔	
Treatment of herpes labialis				✔	
Respiratory Syncytial Virus					
Treatment of hospitalized infants and young children with severe lower respiratory tract infections due to respiratory syncytial virus		✔ †			
Varicella-Zoster Virus Infection					
Treatment of chickenpox				✔	
Treatment of herpes zoster (shingles) in immunocompetent adults				✔	

‡Capsule formulation only
†Inhalation formulation only
§Tablet formulation only

IV. Pharmacokinetics

The pharmacokinetic parameters of the nucleosides and nucleotides are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Nucleosides and Nucleotides[1-15]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Acyclovir	Oral: 10 to 20	9 to 33	Not reported	Renal (62 to 91)	2.2 to 20
Adefovir	59	≤4	Intestinal, Liver	Renal (45)	7.5
Cidofovir	Not reported	≤6	Not reported	Renal (80 to 100)	2.5
Entecavir	100	13	Not reported	Renal (62 to 73)	24
Famciclovir	75 to 77	<20	Liver	Renal (73)	2 to 2.3
Ganciclovir	5	1 to 2	Not reported	Renal (91)	3.5
Ribavirin	Oral: 20-64	0	Not reported	Renal (40 to 60)	Inh: 9.5 Oral: 298
Telbivudine	Not reported	3.3	Not reported	Renal (42)	40 to 49
Valacyclovir	55	14 to 18	Liver	Renal (42)	2.5 to 3.3
Valganciclovir	60	Not reported	Not reported	Renal	4

V. Drug Interactions

Significant drug interactions with the nucleosides and nucleotides are listed in Table 6.

Table 6. Significant Drug Interactions with the Nucleosides and Nucleotides[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Ganciclovir, valganciclovir	1	Zidovudine	Coadministration of ganciclovir with zidovudine may result in life-threatening hematologic toxicity.
Ribavirin	1	Nucleoside analogues	Administration of nucleoside analogues has resulted in fatal and nonfatal lactic acidosis.
Ribavirin	1	Thiopurines	Inhibition of inosine monophosphate dehydrogenase by ribavirin may increase the concentration of methylated metabolites of thiopurines leading to myelotoxicity.
Ganciclovir, ribavirin, valganciclovir	2	Didanosine	Plasma concentrations and pharmacologic effects of didanosine may be increased by ganciclovir. Didanosine toxicity may result.
Ganciclovir, valganciclovir	2	Probenecid	Plasma concentrations of ganciclovir may be increased by probenecid. Ganciclovir toxicity may result.
Acyclovir	2	Theophyllines	Plasma theophylline concentrations may be elevated, increasing the pharmacologic and adverse effects.

Significance level 1 = major severity; significance level 2 = moderate severity

VI. Adverse Drug Events

The most common adverse drug events reported with the nucleosides and nucleotides are listed in Table 7. The boxed warnings for the nucleosides and nucleotides are listed in Tables 8 to 15.

Table 7. Adverse Drug Events (%) Reported with the Nucleosides and Nucleotides[1-15]

Adverse Events	Acyclovir	Adefovir	Cidofovir	Entecavir	Famciclovir	Ganciclovir	Ribavirin	Telbivudine	Val-acyclovir	Val-ganciclovir
Cardiovascular System										
Cardiac arrest	-	-	-	-	-	✔	-	-	-	-
Chest pain	-	-	-	-	-	-	5 to 9	-	-	-
Conduction abnormalities	-	-	-	-	-	✔	✔	-	-	-
Flushing	-	-	-	-	-	-	4	-	-	-
Hypertension	-	-	-	-	-	✔	-	-	✔	12 to 18
Hypotension	✔	-	✔	-	-	✔	-	-	-	-
Tachycardia	-	-	-	-	-	-	-	-	✔	✔
Torsades de Pointes	-	-	-	-	-	✔	-	-	-	-
Ventricular tachycardia	-	-	-	-	-	✔	-	-	-	-
Central Nervous System										
Abnormal dreams	-	-	-	-	-	✔	-	-	-	-
Abnormal thinking	-	-	-	-	-	✔	-	-	-	-
Agitation	✔	-	✔	-	-	-	10 to 33	-	✔	✔
Anxiety	-	-	✔	-	-	✔	✔	-	-	-
Ataxia	✔	-	✔	-	-	-	-	-	✔	-
Chills	-	-	22	-	-	10	-	-	-	-
Coma	✔	-	-	-	-	-	✔	-	✔	-
Confusion	✔	-	✔	-	✔	✔	10 to 21	-	✔	✔
Depression	✔	-	✔	-	-	✔	13 to 36	-	-	✔
Dizziness	✔	-	✔	<1	✔	✔	17 to 26	4	3	✔
Extrapyramidal symptoms	-	-	-	-	-	✔	-	-	-	-
Fatigue/lethargy/malaise	12	-	-	1	1-5	✔	14 to 70	13	-	✔
Fever	✔	-	14 to 58	-	-	48	32 to 61	4	-	31
Hallucinations	✔	-	✔	-	✔	✔	✔	-	-	✔
Headache	2	9	30	2	9 to 39	✔	43 to 69	10	13 to 38	6 to 22
Insomnia	✔	-	✔	<1	-	✔	26 to 41	3	-	6 to 20
Malaise	-	-	-	-	-	-	6	-	-	-
Memory impairment	-	-	-	-	-	-	6	-	-	-
Neuropathy	-	-	-	-	-	9	✔	-	-	9
Paresthesia	✔	-	✔	-	1 to 3	✔	-	-	-	8

Adverse Events	Acyclovir	Adefovir	Cidofovir	Entecavir	Famciclovir	Ganciclovir	Ribavirin	Telbivudine	Val-acyclovir	Val-ganciclovir
Psychotic reactions	✔	-	-	-	-	-	✔	-	✔	✔
Seizure	✔	-	✔	-	-	✔	-	-	✔	✔
Somnolence/drowsiness	✔	-	-	<1	✔	✔	-	-	-	-
Suicidal ideation	-	-	-	-	-	-	1 to 2	-	-	-
Tremors	-	-	22	-	-	✔	25 to 48	-	✔	12 to 28
Dermatological										
Alopecia	-	-	27	✔	-	✔	27 to 36	-	✔	-
Dry skin	-	-	-	-	-	-	10 to 25	-	-	-
Eczema	-	-	-	-	-	-	4 to 5	-	-	-
Erythema multiforme	-	-	-	-	✔	-	-	-	✔	-
Photosensitivity	-	-	-	-	-	-	12 to 21	-	✔	-
Pruritus	2	✔	✔	-	<4	5	13 to 29	2	✔	✔
Rash	2	✔	30	✔	<3	✔	17 to 28	4	✔	-
Stevens-Johnson syndrome	✔	-	-	-	✔	✔	✔	-	-	-
Toxic epidermal necrolysis	✔	-	-	-	✔	-	-	-	-	-
Urticaria	2	-	-	-	✔	-	-	-	✔	-
Gastrointestinal										
Abdominal pain/discomfort	✔	9	✔	-	<8	✔	8	6	1 to 11	15
Anorexia	✔	-	23	-	-	14	21 to 51	-	-	✔
Aphthous stomatitis	-	-	-	-	-	✔	-	-	-	-
Constipation	-	-	-	-	-	✔	5	-	-	-
Dehydration	-	-	-	-	-	-	-	-	2	✔
Diarrhea	2 to 3	3	26	<1	2 to 9	44	11	6	1 to 5	16 to 41
Dyspepsia/heartburn	-	3	-	<1	-	✔	<1 to 16	3	-	✔
Dysphagia	-	-	-	-	-	✔	-	-	-	-
Eructation	-	-	-	-	-	✔	-	-	-	-
Flatulence	-	4	-	-	<5	✔	-	-	-	-
Nausea	2 to 7	5	7 to 69	<1	2 to 13	-	25 to 47	5	5 to 15	8 to 30
Oral moniliasis	-	-	18	-	-	-	-	-	-	-
Taste perversion	-	-	-	-	-	-	4 to 9	-	-	-
Ulceration	-	-	-	-	-	✔	✔	-	-	-
Vomiting	3 to 7	✔	7 to 69	<1	1 to 5	13	9 to 42	-	6	3 to 21
Weight loss	-	-	-	-	-	-	10 to 29	-	-	-
Xerostomia	-	-	-	-	-	-	12	-	-	-
Genitourinary										
Glycosuria	-	-	-	4	-	-	-	-	-	-
Hematuria	✔	11	-	9	-	-	-	-	-	-

Adverse Events	Acyclovir	Adefovir	Cidofovir	Entecavir	Famciclovir	Ganciclovir	Ribavirin	Telbivudine	Val-acyclovir	Val-ganciclovir
Proteinuria/albuminuria	-	-	50	-	-	-	-	-	-	-
Hematological										
Anemia	✔	-	24	-	<1	5 to 26	11 to 17	-	-	7 to 16
Aplastic anemia	-	-	-	-	-	-	✔	-	✔	✔
Hematocrit decreased	-	-	-	-	-	5 to 26	11 to 35	-	<1	-
Hemoglobin decreased	-	-	-	-	-	5 to 26	11 to 35	-	<1	-
Hemolytic anemia	-	-	-	-	-	-	10 to 13	-	-	-
Leukocytosis	✔	-	-	-	-	-	-	-	-	-
Leukopenia	✔	-	-	-	1	41	6 to 45	-	-	-
Monocytes increased	-	-	-	-	-	-	-	-	-	-
Neutropenia	-	-	24 to 43	-	3	14 to 26	8 to 42	2	≤18	17 to 19
Thrombocytopenia	✔	-	-	-	✔	6	1 to 15	<1	3	6 to 22
Laboratory Test Abnormalities										
Alkaline phosphatase	-	-	-	-	-	-	-	-	4	-
Alanine/aspartate aminotransferase increased	1 to 2	8 to 20	-	2 to 12	2 to 3	✔	1 to 3	3 to 7	2 to 16	-
Bilirubin increased/decreased	✔	-	-	2 to 3	2	-	10 to 32	<1	-	-
Blood urea nitrogen increased	5 to 10	-	-	-	-	-	-	-	-	-
Creatine phosphokinase increased	-	-	-	-	-	-	-	11 to 13	-	-
Hyperglycemia	-	-	-	2 to 3	-	-	-	-	-	✔
Hyperkalemia	-	-	-	-	-	-	-	-	-	✔
Hyperuricemia	-	-	-	-	-	-	33 to 38	-	-	-
Hypokalemia	-	-	-	-	-	-	-	-	-	✔
Hyponatremia	-	-	-	-	-	✔	-	-	-	-
Hypophosphatemia	-	-	-	-	-	-	-	-	-	✔
Lactic acidosis	-	-	-	✔	-	-	-	✔	-	-
Serum bicarbonate decreased	-	-	16	-	-	-	-	-	-	-
Serum creatinine increased	5 to 10	32 to 51	12	1 to 2	<1	2 to 50	-	-	-	3 to 50
Musculoskeletal										
Arthralgia/myalgia	✔	-	-	-	-	-	-	3 to 4	1 to 6	✔
Asthenia	-	13	43	-	-	-	5 to 10	-	-	-
Rhabdomyolysis	-	-	-	-	-	✔	-	✔	-	-
Respiratory										
Cough	-	6 to 8	19	-	-	✔	7 to 23	6	-	-
Dyspnea	-	-	8 to 23	-	-	✔	5 to 26	-	✔	✔

Adverse Events	Acyclovir	Adefovir	Cidofovir	Entecavir	Famciclovir	Ganciclovir	Ribavirin	Telbivudine	Val-acyclovir	Val-ganciclovir
Nasopharyngitis	-	-	-	-	-	-	13	-	16	✔
Respiratory tract infection	-	-	9	-	-	-	-	-	9	-
Rhinitis/ rhinorrhea	-	5	-	-	-	-	8	-	2	✔
Special Senses										
Decreased intraocular pressure	-	-	24	-	-	-	-	-	-	-
Iritis	-	-	✔	-	-	-	-	-	-	-
Retinal detachment	-	-	-	-	-	-	-	-	-	15
Tinnitus	-	-	-	-	-	✔	19 to 28	-	-	-
Uveitis	-	-	✔	-	-	-	-	-	-	-
Visual disturbances	✔	-	✔	-	-	✔	5	-	✔	-
Other										
Anaphylaxis	-	-	-	✔	-	✔	✔	-	✔	✔
Dysmenorrhea	-	-	-	-	<8	-	-	-	1 to 8	-
Edema	✔	-	-	-	-	-	-	-	-	✔
Fanconi syndrome	-	✔	1	-	-	-	-	-	-	-
Flu-like symptoms	-	-	-	-	-	-	13 to 31	-	-	-
Infection	-	-	12 to 28	-	-	13	3 to 6	-	-	✔
Injection site reactions	9	-	✔	-	-	✔	5 to 23	-	-	-
Pain	✔	-	25	-	-	✔	5	4	-	✔
Sepsis	-	-	-	-	-	15	-	-	-	✔
Sweating	-	-	-	-	-	12	11	-	-	-
Weakness	-	-	-	-	-	-	9 to 10	-	-	-

✔ Percent not specified
- Event not reported

Table 8. Boxed Warning for Adefovir[1]

WARNING
Severe acute exacerbations of hepatitis have been reported in patients who have discontinued anti–hepatitis B therapy, including adefovir. Closely monitor hepatic function with both clinical and laboratory follow-up for at least several months in patients who discontinue anti–hepatitis B therapy. If appropriate, resumption of anti–hepatitis B therapy may be warranted. In patients at risk of or having underlying renal dysfunction, chronic administration of adefovir may result in nephrotoxicity. Closely monitor renal function in these patients; they may require dose adjustment. HIV resistance may emerge in chronic hepatitis B patients with unrecognized or untreated HIV infection treated with anti–hepatitis B therapies that may have activity against HIV (e.g., adefovir). Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs alone or in combination with other antiretrovirals.

Table 9. Boxed Warning for Cidofovir[1]

WARNING
Renal impairment is the major toxicity of cidofovir. Cases of acute renal failure resulting in dialysis or contributing to death have occurred with as few as 1 or 2 doses of cidofovir. To reduce possible nephrotoxicity, IV prehydration with normal saline and administration of probenecid must be used with each cidofovir infusion. Renal function (serum creatinine and urine protein) must be monitored within 48 hours prior to each dose of cidofovir and the dose of cidofovir modified for changes in renal function as appropriate (see Administration and Dosage). Cidofovir is contraindicated in patients who are receiving other nephrotoxic agents. Neutropenia has been observed in association with cidofovir treatment. Therefore, neutrophil counts should be monitored during cidofovir therapy. Cidofovir is indicated only for the treatment of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome (AIDS). In animal studies, cidofovir was carcinogenic, teratogenic and caused hypospermia (see Warnings, Carcinogenesis, Mutagenesis, and Fertility impairment).

Table 10. Boxed Warning for Entecavir[1]

WARNING
Severe acute exacerbations of hepatitis B: Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued antihepatitis B therapy, including entecavir. Closely monitor hepatic function with clinical and laboratory follow-up for at least several months in patients who discontinue antihepatitis B therapy. If appropriate, initiation of antihepatitis B therapy may be warranted. **Patients co-infected with HIV and chronic hepatitis B virus:** Limited clinical experience suggests there is a potential for the development of resistance to HIV nucleoside reverse transcriptase inhibitors (NRTIs) if entecavir is used to treat chronic hepatitis B virus (HBV) infection in patients with HIV infection that is not being treated. Therapy with entecavir is not recommended for HIV/HBV co-infected patients who are not also receiving highly active antiretroviral therapy (HAART). **Lactic acidosis and severe hepatomegaly:** Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs alone or in combination with antiretrovirals.

Table 11. Boxed Warning for Ganciclovir[1]

WARNING
The clinical toxicity of ganciclovir IV includes granulocytopenia, anemia and thrombocytopenia. In animal studies ganciclovir was carcinogenic, teratogenic and caused aspermatogenesis. Ganciclovir IV is indicated for use only in the treatment of cytomegalovirus (CMV) retinitis in immunocompromised patients and for the prevention of CMV disease in transplant patients at risk for CMV disease.

Table 12. Boxed Warning for Ribavirin (Inhalation Solution)[1]

WARNING
Use of aerosolized ribavirin in patients requiring mechanical ventilator assistance should be undertaken only by health care providers and support staff familiar with this mode of administration and the specific ventilator being used. Strict attention must be paid to procedures that have been shown to minimize the accumulation of drug precipitate, which can result in mechanical ventilator dysfunction and associated increases in pulmonary pressures. Sudden deterioration of respiratory function has been associated with the initiation of aerosolized ribavirin use in infants. Carefully monitor respiratory function during treatment. If the initiation of aerosolized ribavirin treatment appears to produce sudden deterioration of respiratory function, stop treatment and reinstitute it only with extreme caution, continuous monitoring, and consideration of coadministration of bronchodilators. Aerosolized ribavirin is not indicated for use in adults. Be aware that ribavirin has been shown to produce testicular lesions in rodents and to be teratogenic in all animal species in which adequate studies have been conducted (rodents and rabbits).

Table 13. Boxed Warning for Ribavirin (Oral)[1]

WARNING
Ribavirin monotherapy is not effective for the treatment of chronic hepatitis C virus (HCV) infection and should not be used alone for this indication. The primary clinical toxicity of ribavirin is hemolytic anemia, which may result in worsening of cardiac disease and lead to fatal and nonfatal myocardial infarctions (MIs). Do not treat patients with a history of significant or unstable cardiac disease with ribavirin. Significant teratogenic and/or embryocidal effects have been demonstrated in all animal species exposed to ribavirin. In addition, ribavirin has a multiple-dose half-life of 12 days, and it may persist in nonplasma compartments for as long as 6 months. Therefore, ribavirin therapy is contraindicated in women who are pregnant and in the male partners of women who are pregnant. Extreme care must be taken to avoid pregnancy during therapy and for 6 months after completion of treatment in both female patients and female partners of male patients who are taking ribavirin therapy. At least 2 reliable forms of effective contraception must be used during treatment and during the 6-month posttreatment follow-up period.

Table 14. Boxed Warning for Telbivudine[1]

WARNING
Lactic acidosis and severe hepatomegaly with steatosis, including fatal cases, have been reported with the use of nucleoside analogs alone or in combination with antiretrovirals. Severe acute exacerbations of hepatitis B have been reported in patients who have discontinued anti–hepatitis B therapy, including telbivudine. Closely monitor hepatic function with clinical and laboratory follow-up for at least several months in patients who discontinue anti–hepatitis B therapy. If appropriate, resumption of anti–

hepatitis B therapy may be warranted.

Table 15. Boxed Warning for Valganciclovir[1]

WARNING
The clinical toxicity of valganciclovir, which is metabolized to ganciclovir, includes granulocytopenia, anemia, and thrombocytopenia. In animal studies, ganciclovir was carcinogenic and teratogenic and caused aspermatogenesis.

VII. Dosing and Administration

The usual dosing regimens for the nucleosides and nucleotides are listed in Table 16.

Table 16. Usual Dosing Regimens for the Nucleosides and Nucleotides[1-15]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Acyclovir	Treatment of chickenpox: Oral: 800 mg four times daily for five days Treatment of herpes genitalis: Initial therapy: Injection, 5 mg/kg infused over one hour, every eight hours for five days; Oral, 200 mg every four hours, five times daily for 10 days Chronic suppressive therapy: Oral, 400 mg twice daily for up to 12 months; alternative regimens include 200 mg three to five times daily Intermittent therapy: Oral, 200 mg every four hours, five times daily for five days Treatment of herpes labialis: Buccal tablet: One 50 mg buccal tablet should be applied as a single dose to the upper gum region Treatment of herpes simplex encephalitis: Injection: 10 mg/kg infused over one hour, every eight hours for 10 days Treatment of mucocutaneous herpes simplex virus infections in immunocompromised patients: Injection: 5 mg/kg infused over one hour, every eight hours for seven days	Treatment of chickenpox: ≥2 years of age: Oral, 20 mg/kg per dose four times daily for five days >40 kg: Oral, 800 mg four times daily for five days Treatment of herpes simplex encephalitis: Birth to three months of age: Injection, 10 mg/kg infused over one hour, every eight hours for 10 days Three months to ≤12 years of age: Injection, 20 mg/kg infused over one hour, every eight hours for 10 days ≥12 years of age: Injection, 10 mg/kg infused over one hour, every eight hours for 10 days Treatment of mucocutaneous herpes simplex virus infections in immunocompromised patients: <12 years of age: Injection, 10 mg/kg infused over one hour, every eight hours for seven days Children ≥12 years of age should receive adult dose Treatment of herpes zoster (shingles) infection in immunocompromised patients: <12 years of age: Injection, 20 mg/kg infused over one hour,	Buccal tablet: 50 mg Capsule: 200 mg Injection: 50 mg/mL 500 mg 1,000 mg Suspension: 200 mg/5 mL Tablet: 400 mg 800 mg

<table>
<tr><th>Generic Name(s)</th><th>Usual Adult Dose</th><th>Usual Pediatric Dose</th><th>Availability</th></tr>
<tr><td></td><td><u>Treatment of herpes zoster (shingles):</u>
Oral: 800 mg every four hours, five times daily for seven to 10 days

<u>Treatment of herpes zoster (shingles) infection in immunocompromised patients:</u>
Injection: 10 mg/kg infused over one hour, every eight hours for seven days</td><td>every eight hours for seven days

≥12 years of age: Injection, 10 mg/kg infused over one hour, every eight hours for seven days</td><td></td></tr>
<tr><td>Adefovir</td><td><u>Treatment of chronic hepatitis B in patients with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease:</u>
Tablet: 10 mg once daily</td><td><u>Treatment of chronic hepatitis B in patients with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease:</u>
≥12 years of age: Tablet, 10 mg once daily</td><td>Tablet:
10 mg</td></tr>
<tr><td>Cidofovir</td><td><u>Treatment of cytomegalovirus retinitis in patients with acquired immunodeficiency syndrome</u>:
Injection: induction, 5 mg/kg once weekly for two weeks; maintenance, 5 mg/kg once every two weeks</td><td>Safety and efficacy in children have not been established</td><td>Injection:
75 mg/mL</td></tr>
<tr><td>Entecavir</td><td><u>Treatment of chronic hepatitis B in patients with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease (Compensated Liver Disease):</u>
Nucleoside-treatment-naïve patients: tablet, 0.5 mg once daily

Lamivudine or telbivudine resistant patients: tablet, 1 mg once daily

<u>Treatment of chronic hepatitis B in patients with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease (Decompensated Liver Disease):</u>
Tablet: 1 mg once daily</td><td><u>Treatment of chronic hepatitis B in patients with evidence of active viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease:</u>
Children ≥ 2 years of age and weighing at least 10 kg, once daily dosing of oral solution (mL):
<table>
<tr><th>Body weight (kg)</th><th>Treatment naïve patients[a]</th><th>Lamivudine experienced patients[b]</th></tr>
<tr><td>10 to 11</td><td>3</td><td>6</td></tr>
<tr><td>> 11 to 14</td><td>4</td><td>8</td></tr>
<tr><td>> 14 to 17</td><td>5</td><td>10</td></tr>
<tr><td>> 17 to 20</td><td>6</td><td>12</td></tr>
<tr><td>> 20 to 23</td><td>7</td><td>14</td></tr>
<tr><td>> 23 to 26</td><td>8</td><td>16</td></tr>
<tr><td>> 26 to 30</td><td>9</td><td>18</td></tr>
<tr><td>> 30</td><td>10</td><td>20</td></tr>
</table>
[a]Children with body weight greater than 30 kg should receive 10 mL (0.5 mg) of oral solution or one 0.5 mg tablet once daily
[b]Children with body weight greater than 30 kg should receive 20 mL (1 mg) of oral solution or one 1 mg tablet</td><td>Solution:
0.05 mg/mL

Tablet:
0.5 mg
1 mg</td></tr>
</table>

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		once daily	
Famciclovir	Treatment of herpes genitalis: Tablet: recurrent episodes, 1,000 mg twice daily for one day; suppressive therapy, 250 mg twice daily Treatment of herpes labialis: Tablet: 1,500 mg as a single dose Treatment of recurrent orolabial or genital herpes in HIV-infected adults: Tablet: 500 mg twice daily for seven days Treatment of herpes zoster (shingles): Tablet: 500 mg every eight hours for seven days	Safety and efficacy in children have not been established	Tablet: 125 mg 250 mg 500 mg
Ganciclovir	Treatment of cytomegalovirus retinitis in immunocompromised patients, including patients with acquired immunodeficiency syndrome (AIDS): Injection: induction, 5 mg/kg every 12 hours for 14 to 21 days; maintenance, 5 mg/kg once daily, seven days per week, or 6 mg/kg once daily, five days per week Prevention of cytomegalovirus disease in transplant recipients at risk from CMV disease: Injection: 5 mg/kg every 12 hours for seven to 14 days, followed by 5 mg/kg once daily, seven days per week or 6 mg/kg once daily, five days per week	Safety and efficacy in children have not been established	Injection: 500 mg
Ribavirin	Treatment of chronic hepatitis C in combination with interferon alfa-2b (pegylated and non-pegylated) in patients with compensated liver disease: Capsule, with interferon alfa-2b: >76 kg, 600 mg in the morning and 600 mg in the evening for 24 to 48 weeks; ≤ 75 kg, 400 mg in the morning and 600 mg in the evening for 24 to 48 weeks Capsule, with peginterferon alfa-2b: < 66 kg, 800 mg/day; 66 to 80 kg, 1,000 kg/day; 81 to 105	Treatment of chronic hepatitis C in combination with interferon alfa-2b (pegylated and non-pegylated) in patients with compensated liver disease: Capsule, solution, children ≥ 3 years of age, with interferon or peginterferon alfa-2b: < 47 kg, 15 mg/kg/day; 47 to 59 kg, 800 mg/day; 60 to 73 kg, 1,000 mg/day; > 73 kg, 1,200 mg/day for 48 weeks in genotype 1 and 24 weeks in genotypes 2 and 3	Capsule: 200 mg Tablet dose pack: 200-400 mg 400-400 mg 600-400 mg 600-600 mg Inhalation solution: 6 g Solution: 40 mg/ml

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	mg, 1,200 mg/day; > 150 kg, 1,400 kg/day for 24 or 48 weeks Treatment of chronic hepatitis C in combination with peginterferon alfa-2a in patients with compensated liver disease and who have not been previously treated with interferon alpha: Tablet, genotypes 1 and 4: < 75 kg, 1,000 mg/day; ≥ 75 kg, 1,200 mg/day for 48 weeks Tablet, genotypes 2 and 3: 800 mg/day for 24 weeks Tablet, HIV co-infection: 800 mg/day for 48 weeks regardless of genotype	Treatment of chronic hepatitis C in combination with peginterferon alfa-2a in patients with compensated liver disease and who have not been previously treated with interferon alpha: Tablet, children ≥ 5 years of age: 23 to 33 kg, 400 mg/day; 34 to 46 kg, 600 mg/day; 47 to 59 kg, 800 mg/day; 60 to 74 kg, 1,000 kg/day; ≥ 75 kg, 1,200 kg/day for 24 weeks in genotypes 2 and 3 and 48 weeks for other genotypes Treatment of hospitalized infants and young children with severe lower respiratory tract infections due to respiratory syncytial virus: Inhalation solution: 20 mg/mL aerosolized over 12 to 18 hours once daily for three to seven days	Tablet: 200 mg 400 mg 600 mg
Telbivudine	Treatment of chronic hepatitis B in adult patients with evidence of viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease: Tablet: 600 mg once daily	Treatment of chronic hepatitis B in adult patients with evidence of viral replication and either evidence of persistent elevations in serum aminotransferases (ALT or AST) or histologically active disease: Tablet, ≥16 years of age: 600 mg once daily	Tablet: 600 mg
Valacyclovir	Treatment of the initial episode of genital herpes in immunocompetent adults: Tablet: 1 gram twice daily for 10 days Treatment of recurrent episodes of genital herpes in immunocompetent adults: Tablet: 500 mg twice daily for three days Reduction of transmission of genital herpes in immunocompetent adults: Tablet: 500 mg once daily for the source partner Chronic suppressive therapy of recurrent episodes of genital herpes in immunocompetent and	Treatment of chickenpox: Tablet, Children two to 18 years of age: 20 mg/kg three times daily for five days, total dose should not exceed 1 gram three times daily Treatment of herpes labialis: Tablet, children ≥12 years of age: 2 grams twice daily for one day taken 12 hours apart	Tablet: 500 mg 1,000 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	in HIV-1-infected adults: Tablet, immunocompetent: 1 gram once daily Tablet, HIV-infected: 500 mg twice daily Treatment of herpes labialis: Tablet: 2 grams twice daily for one day taken 12 hours apart Treatment of herpes zoster (shingles) in immunocompetent adults: Tablet: 1 gram three times daily for seven days		
Valganciclovir	Treatment of cytomegalovirus retinitis in immunocompromised patients, including patients with acquired immunodeficiency syndrome (AIDS): Tablet: induction, 900 mg twice daily for 21 days; maintenance, 900 mg once daily Prevention of cytomegalovirus disease in adult kidney, heart, or kidney-pancreas transplant patients at high risk: Tablet, heart or kidney-pancreas transplant: 900 mg once daily starting within 10 days of transplantation until 100 days posttransplantation Tablet, kidney transplant: 900 mg once daily starting within 10 days of transplantation until 200 days posttransplantation	Prevention of cytomegalovirus disease in pediatric kidney or heart transplant patients at high risk: Solution, tablet, in children four months to 16 years of age: The dose is calculated based on body surface area and creatinine clearance and is administered once daily starting within 10 days of transplantation until 100 days posttransplantation	Solution: 50 mg/mL Tablet: 450 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the nucleosides and nucleotides are summarized in Table 17.

Table 17. Comparative Clinical Trials with the Nucleosides and Nucleotides

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Cytomegalovirus Infections				
Thomas et al.[48] (2009) Acyclovir 800 mg three times daily for 6 months All patients received triple immuno-suppressive therapy	RETRO Patients who received a lung or heart transplant who were CMV seropositive or had CMV seropositive donors	N=78 Mean 4.3 years	Primary: Risk of CMV disease and infection at one year, graft dysfunction Secondary: Not reported	Primary: The one-year risk of CMV infection was similar in R-/D+ and R+/D+ patients (76 and 75%, respectively). R+/D- patients had significantly lower risk of CMV infection compared to all D+ patients (40%; P=0.002). R-/D+ patients had a one-year risk of CMV disease of 37% compared to a 2% risk in R+ patients (P<0.0001). CMV disease developed after a mean of 90 days after transplantation. Acute rejection episodes were similar between all groups (R-/D+ 65%, R+/D+ 66%, R+/D- 65%; P=0.1). Acute rejection was not more common in patients with CMV infection (66%) vs those without CMV infection (64%; P=0.1). Acute rejection was not more common in patients with CMV disease (71%) vs those without CMV infection (65%; P=0.1). Patients with CMV infection had a higher cumulative risk of graft dysfunction at one year (P=0.012). Secondary: Not reported
Flechner et al.[49] (1998) Acyclovir 800 mg once daily, 800 mg twice daily, 800 mg three times	PRO, RCT Adult recipients of their first or second kidney-only transplants	N=101 Mean 14 months	Primary: Time to CMV infection during the first six months after trans-plantation	Primary: At the six-month observation point, CMV was isolated in 14 of 39 (35.9%) acyclovir-treated patients compared to one of 40 (2.5%) ganciclovir-treated patients (P=0.0001). Secondary: Symptomatic CMV disease occurred in nine of the 14 infected acyclovir-

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
daily, or 800 four times daily vs ganciclovir 500 mg, 1,000 mg once daily, 1,000 mg twice daily, or 1,000 mg three times daily			Secondary: Incidence symptomatic CMV disease	treated patients compared to none in the ganciclovir-treated group (P=0.01). Drug-related adverse events were not reported.
Burns et al.[50] (2002) Acyclovir 800 mg PO 5 times a day to day 100 after transplantation vs ganciclovir 5 mg/kg IV every weekday (Monday to Friday) to day 100 All patients received IV ganciclovir 5 mg/kg every 12 hours 7 days to 2 days prior to transplantation, then acyclovir IV 10 mg/kg every 8 hours from 1 day	RCT Patients undergoing allogenic stem cell transplant positive for CMV antibodies	N=91 100 days	Primary: Incidence of CMV antigenemia (≥1 positive cell/ 50,000 leukocytes examined) Secondary: Incidence of CMV disease at 1 year and survival rates	Primary: CMV antigenemia occurred in 41% of patients taking acyclovir compared to 31% of those taking ganciclovir (P=0.22). Secondary: CMV disease occurred in 17% of patients taking acyclovir compared to 13% of those taking ganciclovir (P=0.59). Survival of patients one year after transplant was similar between treatment groups (64% on ganciclovir vs 54% on acyclovir; P=0.38). There were three deaths associated with CMV disease in the acyclovir-treated group and one death in the ganciclovir-treated group (P=0.38). Drug-related adverse events were not reported.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
prior until neutrophil engraftment				
Rubin et al.[51] (2000) Acyclovir 400 mg PO three times daily vs ganciclovir 1,000 mg PO three times daily All patients received IV ganciclovir 5 mg/kg/day for 5 to 10 days after transplantation	RCT Patients ≥12 years old undergoing a first kidney, heart or liver transplant and positive for CMV antibodies	N=155 12 weeks	Primary: Incidence of CMV disease in six months post-transplant Secondary: Occurrence of allograft rejections, clinical infection rates, lympho-proliferative disease, and drug toxicities	Primary: Significantly more CMV disease occurred in patients taking acyclovir compared to those receiving ganciclovir (32 vs 50%; P<0.05). Secondary: Allograft rejections occurred in 46% of patients taking acyclovir compared to 46% of those receiving ganciclovir (P=NS). There were no differences in the overall incidence of non-CMV infection between the two treatment groups. Leukopenia developed in 12 patients treated with ganciclovir and two patients treated with acyclovir (P<0.05). Thrombocytopenia rates were comparable in both treatment groups. No patients had to discontinue their CMV prophylaxis due to these episodes.
Winston et al.[52] (2003) Acyclovir 800 mg PO every 6 hours from day 15 to day 100 after transplantation vs ganciclovir 1,000 mg PO every 8 hours from day 15 to day 100	RCT Patients undergoing liver transplant positive for CMV antibodies	N=219 100 days	Primary: Incidence of CMV disease, rates of leukopenia and thrombocytopenia, survival after one year Secondary: Not reported	Primary: CMV disease occurred in 7.3% of patients taking acyclovir compared to 0.9% of those receiving ganciclovir (P=0.019). Leukopenia occurred in 35% of patients treated with ganciclovir and 18% of patients being treated with acyclovir (P=0.009). Sixteen patients (15%) on ganciclovir had to discontinue their CMV prophylaxis due to leukopenia compared to none on acyclovir (P<0.001). Total and severe rates of thrombocytopenia were comparable in both treatment groups. Survival of patients one year after transplant was similar between treatment groups (81% on ganciclovir vs 85% on acyclovir). Only one death associated with CMV disease occurred, and that death occurred in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
All patients received IV ganciclovir 6 mg/kg/day from day 1 to day 14 after transplantation				an acyclovir-treated patient. The incidence of drug-related adverse events was not reported. Secondary: Not reported
Winston et al.[53] (1995) Acyclovir 800 mg PO four times daily to day 100 after transplantation vs ganciclovir 5 mg/kg IV every weekday (Monday to Friday) to day 100 after transplantation All patients received IV ganciclovir 6 mg/kg/day from postoperative day 1 to day 30	RCT Patients undergoing liver transplant	N=250 100 days	Primary: Incidence of CMV infection Secondary: Incidence of CMV disease	Primary: Significantly more CMV infection occurred in patients taking acyclovir compared to those receiving ganciclovir (38 vs 5%; P<0.0001). Secondary: Symptomatic CMV disease occurred at a significantly higher incidence in those patients taking acyclovir compared to those receiving ganciclovir (10 vs 0.8%; P=0.002). Drug-related adverse events reported were comparable between the two treatment groups.
Ljungman et al.[54] (2002) Acyclovir 800 mg four times daily	DB, MC, RCT Patients age ≥13 years old that received an	N=748 18 weeks	Primary: Time to CMV infection in blood or broncho-alveolar lavage	Primary: Time to CMV infection in blood or BAL or CMV disease was significantly prolonged with valacyclovir compared to acyclovir (HR, 0.59; 95% CI, 0.46 to 0.76; P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
until week 18 after transplantation vs valacyclovir PO 2,000 mg four times daily until week 18 after transplantation All patients initially received acyclovir IV 500 mg/m^2 from transplantation to day 28 or discharge	allogenic bone marrow transplant seropositive for CMV antibody		(BAL) or CMV disease and time to death Secondary: Time to CMV infection at other sites, time to development of CMV disease (definitive or presumed) and opportunistic infection	Death rates did not differ between treatment groups (24 vs 25%; HR, 0.68; 95% CI, 0.73 to 1.31; P=0.089). Secondary: Time to CMV infection in other sites was significantly prolonged with valacyclovir compared to acyclovir (HR, 0.59; 95% CI, 0.45 to 0.71; P<0.0001). Time to definitive CMV disease episodes did not differ between the treatment groups (HR, 0.71; 95% CI, 0.30 to 1.65; P=0.421). Time to presumed CMV disease episodes did not differ between the treatment groups (HR, 0.67; 95% CI, 0.33 to 1.36; P=0.269). The incidence of bacterial and/or fungal infections was comparable between treatment groups. Drug-related adverse events were comparable between treatment groups. The most commonly reported adverse events were nausea, vomiting, abdominal pain, and diarrhea.
Amir et al.[55] (2010) Ganciclovir IV 5 mg/kg every 12 hours for 6 weeks, then valganciclovir PO (weight based) every 12 hours for 6 weeks, then once daily to age 1 year	RETRO Children with congenital CMV infection	N=23 12 months	Primary: Auditory function BSER (brainstem evoked response), adverse effects Secondary: Not reported	Primary: Best ear was normal at birth in 65% of infants and was normal at ≥1 year in 85% of patients (P=0.365). In 26% of affected ears, an improvement in hearing was demonstrated. In the remaining, 72% had no change in hearing and 2% had a decrease in hearing. There was no difference in hearing outcomes in infants when compared to the short-term protocol tested by Kimberlin et al. (35 to 40% in each group had hearing defects). Of patients normal at baseline, 35% had a worsening in hearing at ≥ 1 year in the Kimberlin study compared to no change in hearing in the 25 normal ears in the current study (P=0.001). Improvement occurred in 57% of current study patients compared to 39% in the Kimberlin study (P=0.38). When number of ears was analyzed, 76% had normal hearing compared to 35% in the Kimberlin group (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The most frequent side effects were neutropenia and central line infections. Secondary: Not reported
Studies of Ocular Complications of AIDS Research Group[56] (2001) Ganciclovir surgically placed intraocular implant and ganciclovir 1,000 mg PO TID vs cidofovir IV 5 mg/kg once weekly for 2 doses, then 5 mg/kg every other week	RCT Patients with HIV with active CMV retinitis	N=61 34 months	Primary: Retinitis progression (new lesions that covered >25% of a standard disk area or movement of border a pre-described length), loss of visual acuity of >15 letters and rate of loss of visual field Secondary: Serious ocular complications and mortality rates	Primary: Retinitis progression occurred at a rate of 0.67 per person/year in the ganciclovir group compared to 0.71 per person/year with cidofovir (P=0.72). Loss of visual acuity occurred at a rate of 0.78 per person/year in the ganciclovir group compared to 0.47 per person/year with cidofovir (P=0.28). Visual field loss occurred at a rate of seven degrees per month with ganciclovir compared to two degrees with cidofovir (P=0.048). Secondary: Vitreous hemorrhage was reported at a rate of 0.13 per person/year in the ganciclovir group compared to none with cidofovir (P=0.014). Uveitis was reported at a rate of 0.09 per person/year in the ganciclovir group compared of 0.35 per person/year in cidofovir (P=0.066). Mortality rates were 0.41 per person/year in the ganciclovir group compared to 0.49 per person/year with cidofovir (P=0.59).
Winston et al.[57] (2003) Ganciclovir IV 5 mg/kg every 12 hours for 1 week, then 6 mg/kg once daily for 5 days per week until day 100 after transplantation	DB, MC, RCT Patients age ≥13 years old that received an allogenic bone marrow transplant seropositive for CMV antibody	N=168 100 days	Primary: Incidence of CMV infection, survival rates at 180 days, incidence of other herpesvirus infection, bacterial infection, fungal infection and incidence of neutropenia	Primary: CMV infection occurred in 12% of patients who received valacyclovir and 19% patients who received ganciclovir (HR, 1.42; 95% CI, 0.391 to 2.778; P=0.934). HSV infections occurred in 4% of patients treated with valacyclovir and 5% taking ganciclovir. VZV infections developed in 2% of patients treated with valacyclovir and 1% taking ganciclovir. After 180 days, 47% of patients treated with valacyclovir and 36% taking ganciclovir died as a result of complications (HR, 1.193; 95% CI, 0.739 to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs valacyclovir PO 2,000 mg QID until day 100 after transplantation All patients initially received acyclovir IV 500 mg/m^2 from transplantation to engraftment			Secondary: Not reported	1.925; P=0.470). Bacterial infections occurred in 32% of patients treated with valacyclovir and 41% taking ganciclovir. Fungal infections occurred in 10% of patients treated with valacyclovir and 18% taking ganciclovir. Significantly less patients taking valacyclovir developed neutropenia compared to ganciclovir (13 vs 32%; P=0.007). Secondary: Not reported
Pavlopoulou et al.[58] (2005) Ganciclovir 1,000 mg PO three times daily for 3 months vs valacyclovir 2,000 mg four times daily for 3 months	PRO, RCT Patients age ≥14 years who received a renal transplant	N=83 6 months	Primary: Occurrence of CMV infection or disease and drug-related adverse effects Secondary: Frequency of acute graft rejection, non-CMV infections, renal function and healthcare utilization	Primary: CMV infection occurred in 19.0% of patients on valacyclovir and 17.5% of patients taking ganciclovir. The difference was not significant. No drug-related adverse events that could be attributed to either drug were recorded during the prophylaxis treatment stage. Secondary: Acute rejection episodes occurred in 11.6% with valacyclovir and 12.5% with ganciclovir. The difference was not significant. Other herpesvirus infections occurred in 2% of patients on valacyclovir and 5% of patients taking ganciclovir. The difference was not significant. Other nonviral infections occurred at a rate of 90% in the ganciclovir group compared to 53.5% with valacyclovir (P=0.003). The difference in infection rates was due to a higher incidence of urinary tract infections observed in the ganciclovir-treated patients (20 vs 10 with valacyclovir). Renal function did not differ between treatment groups. Use of medical inpatient and outpatient resources did not differ between treatment groups.
Paya et al.[59]	RCT	N=372	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(2004) Ganciclovir 1,000 mg three times daily until day 100 after transplantation vs valganciclovir PO 900 mg once daily until day 100 after transplantation	Patients age ≥13 years old negative for CMV who received a solid organ transplant from a CMV positive donor (D+/R-)	100 days	Incidence of CMV infection after 6 months Secondary: Incidence of CMV viremia, incidence of acute graph rejection after CMV disease and graft loss	After 6 months, CMV infection occurred in 12.1% of patients who received valganciclovir and 15.2% in those taking ganciclovir (95% CI, –0.042 to 0.110). Secondary: The incidence of CMV viremia was comparable between treatment groups at 6 months (39.7% valganciclovir vs 43.2% ganciclovir) and at 12 months (48.5% valganciclovir vs 48.8% ganciclovir). The incidence of patients with ≥1 acute graft rejection episode was similar for both treatment groups at six and 12 months. Reported drug-related adverse events were comparable between treatment groups. The most commonly reported adverse events were diarrhea, tremor, graft rejection and headache.
Martin et al.[60] (2002) Ganciclovir IV 5 mg/kg twice daily for 3 weeks and then 5 mg/kg once daily for 1 week vs valganciclovir PO 900 mg twice daily for 3 weeks then 900 mg once daily for 1 week	RCT Adult HIV patients with newly diagnosed CMV retinitis	N=160 4 weeks	Primary: Progression of retinitis during the first four weeks Secondary: Proportion of patients achieving satisfactory response and time to progression to retinitis	Primary: After four weeks, 10% of patients on ganciclovir and 9.9% of patients on valganciclovir had progression of CMV retinitis (difference, 0.1%; 95% CI, –9.7 to 10.0). Secondary: Satisfactory response to therapy was achieved in 77% of patients on ganciclovir and 71.9% of patients on valganciclovir (difference, 5.2%; 95% CI, –20.4 to 10.1). Median time to progression of retinitis was 125 days with ganciclovir and 160 days with valganciclovir. Diarrhea was the most commonly reported adverse event and was reported in 19% of patients on valganciclovir compared to 10% of patients on ganciclovir (P=0.11). Neutropenia was reported with similar frequency between the two treatment groups.
Weclawiak et al.[61] (2010) Ganciclovir IV	RETRO Kidney transplant recipients who were	N=182 Mean 23 to 34	Primary: Incidence of CMV infection and disease, patient and	Primary: There was a lower rate of CMV reactivation at one year in the valganciclovir group compared to the ganciclovir preemptive group (28 vs 67.4%, respectively; P<0.001). At the end of follow-up, the respective

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
10 mg/kg/day for 3 weeks vs valganciclovir 900 mg/day for 3 months	CMV-seropositive	months	graft survival at one and two years Secondary: Not reported	incidences of CMV reactivation was 33.3% with valganciclovir and 68.9% with ganciclovir (P<0.001). Valganciclovir therapy resulted in a longer time to CMV infection than ganciclovir (211 vs 45 days, respectively; P<0.001). Valganciclovir prophylaxis resulted in a significantly lower overall incidence of CMV disease compared to ganciclovir treatment (2.68 vs 9.8%, respectively; P=0.021). The incidence of CMV disease within the first 100 days posttransplant was greater in the ganciclovir group compared to valganciclovir (8.3 vs 0%; P=0.01). There was no difference 100 days posttransplant (2.68% with ganciclovir and 1.65% with valganciclovir; P=NS). The long-term follow-up showed similar mortality rates among the treatment groups (3% with ganciclovir and 4.7% with valganciclovir). At one year, 24.2% of patients from the prophylactic group had experienced at least one episode of acute allograft rejection compared to 25.3% of patients from the preemptive group (P=0.941). At the end of follow-up, the incidence of acute allograft rejection was 27.3% in the prophylactic group and 31.1% in the pre-emptive group (P=0.492). Secondary: Not reported
Said et al.[62] (2007) Ganciclovir 5 mg/kg per day IV for 2 weeks (GAN) vs valganciclovir 900	RCT Kidney transplant recipients who were seropositive for CMV and who were receiving induction immuno-suppression	N=110 6 months	Primary: Onset of the disease, positive test for CMV, fever, leukopenia, systemic CMV manifestations, graft function, and rejection episodes Secondary:	Primary: There was no statistical difference among the three groups in the incidence of acute rejection episodes or graft loss. There were six patients in the GAN group (14.6%) with CMV disease compared to seven patients in the VAL2w group (30.4%) and four patients in VAL3m group (8.7%). The incidence of fever with a positive CMV test was significantly higher (P=0.035) in the VAL2w compared to the other two groups. In contrast, the incidence of leukopenia with negative CMV tests was significantly higher (P=0.040) in the VAL3m group compared to the GAN group and relatively similar to the VAL2w group.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg orally per day for 2 weeks (VAL2w) vs valganciclovir 900 mg orally per day for 3 months (VAL3m)			Not reported	Serum creatinine was significantly higher in the VAL2w group at three and six months (P=0.011 and P=0.020, respectively) compared to the GAN group and at one month (P=0.049) in the VAL3m group compared to the GAN group. Secondary: Not reported
Reischig et al.[63] (2008) Valacyclovir 2 g four times daily for 3 months vs valganciclovir 900 mg twice daily for at least 14 days	RCT Renal transplant recipients at risk for CMV	N=66 12 months	Primary: Incidence of CMV viremia and CMV disease, rate of acute rejection Secondary: Not reported	Primary: The 12-month incidence of CMV viremia was higher in the preemptive group than the prophylaxis group (92 vs 59%, respectively; P<0.001). The incidence of CMV disease was not significantly different in the preemptive group compared to the prophylaxis group (6 vs 9%, respectively; P=0.567). The onset of CMV viremia was delayed in the valacyclovir group compared to the valganciclovir group (37 vs 187 days, respectively; P<0.001). There was a higher rate of biopsy-proven acute rejection in the preemptive group than in the prophylaxis group (36 vs 15%, respectively; P=0.034). Secondary: Not reported
Leone et al.[64] (2010) Valacyclovir for 6 months vs valganciclovir for 6 months	RETRO Kidney transplant recipients	N=550 Variable duration	Primary: Incidence of CMV disease, acute rejection; patient and graft survival, other infections, malignancies, hypertension diabetes	Primary: The incidence of CMV disease was highest with no prophylaxis (33.2%) and lowest in the valganciclovir prophylaxis group (8.6%; P<0.001). Valganciclovir prophylaxis had lower incidence of CMV during the first six months (37.5%) compared to valacyclovir (75%; P=0.018) and no prophylaxis (90.5%; P<0.01). Time to onset of posttransplant CMV was significantly longer in valganciclovir-treated patients (228 days) compared to no prophylaxis (33

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs no prophylaxis			Secondary: Not reported	days; P=0.044) and compared to valacyclovir (93 days; P=NS). There was no difference in episodes of graft rejection between valganciclovir (74.3%), valacyclovir (73.4%), and no prophylaxis groups (72.6%). There were fewer herpes viral infections in patients treated with valganciclovir (5.3%) compared to valacyclovir (15.5%; P=0.014) and compared to no prophylaxis (14.5%; P<0.001). There was no difference in incidence of malignancy between groups. There was a significantly lower proportion of patients with hypertension in patients treated with valganciclovir (25.7%) compared to valacyclovir (45.7%; P<0.001) and no prophylaxis (48.4%; P<0.001) There was a higher incidence of diabetes in the valganciclovir group (20.8%) compared to no prophylaxis (12.6%; P=0.032). Secondary: Not reported
Asberg et al.[65] (2007) Valganciclovir 900 mg twice daily vs ganciclovir 5 mg/kg IV twice daily Both treatments were administered for an induction period of 21 days,	RCT, OL, AC, MC Adult solid organ transplant recipients with CMV disease	N=321 49 days	Primary: Treatment success (defined as the eradication of CMV viremia at Day 21) Secondary: Clinical assessment of CMV disease activity, time to viremia below the limit of detection (<200 copies/mL), viral load kinetics	Primary: In the intention-to-treat population, viral eradication (<600 copies/mL) was achieved in 45.1% of the valganciclovir-treated patients and in 48.4% of the ganciclovir-treated patients at Day 21 (95% CI, –14.0 to 8.0%). Viral eradication at Day 49 was 67.1% in valganciclovir- and 70.1% in ganciclovir-treated patients (P=NS). Secondary: Clinical resolution of CMV disease occurred at a mean of 15.1 days (95% CI, 13.0 to 17.2) and 15.1 days (95% CI, 13.0 to 17.3) for the valganciclovir and ganciclovir groups, respectively (P=0.880). At Day 21, clinical success was achieved in 127 of 164 valganciclovir-treated patients (77.4%) and 126 of 157 patients (80.3%) in the IV ganciclovir arm; by Day 49 clinical success was achieved in 140 of 164

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
followed by valganciclovir 900 mg daily until Day 49			and safety and tolerability	patients (85.4%) and 132 of 157 patients (84.1%), respectively. Resolution of fever and disappearance of active disease occurred at similar time points in both arms. Median baseline viral loads were not different between the groups. Viral clearance (<600 copies/mL) at Day 21 was achieved in 74 of 133 patients (55.6%) in the valganciclovir group and 76 of 126 patients in the ganciclovir group (60.3%; P=NS), and increased to 110 of 133 patients (82.7%) and 110 of 126 patients (87.3%), respectively, at Day 49 (P=NS). The mean time to a clinically relevant drop in viral load (≥0.3 natural log units) was 6.1 ± 4.5 days (N=120) for valganciclovir and 6.6 ± 4.7 days for ganciclovir (P=NS). Median times to viral eradication using either the 600 copies or 200 copies cutoff were similar in both arms. The median viral load half-life was 11.5 days (8.3 to 16.5 days) and 10.4 days (7.9 to 14.5 days) for valganciclovir- and ganciclovir-treated patients, respectively (P=0.932). During the first 21 days, treatment was discontinued in 11 (6.7%) valganciclovir vs seven (4.5%) ganciclovir patients, respectively (P=NS). There were no major differences in the frequencies of adverse events between the treatment groups.
Shiley et al.[66] (2009) Valganciclovir 900 mg daily vs ganciclovir 1,000 mg PO three times daily or	RETRO Orthotopic liver transplant patients at high risk for CMV	N=66 Variable duration	Primary: Development of CMV disease Secondary: Mortality, rejection episodes, other infections	Primary: The incidence of CMV was 12.1%, with the mean number of days to onset of 190. A total of 22% of valganciclovir patients developed CMV compared to 5.1% of patients receiving ganciclovir (P=0.056). Secondary: A total of 15% of patients died, but no deaths were attributable to CMV disease.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ganciclovir 6 mg/kg/day IV Prophylaxis was continued for the first 100 days after transplantation				There was a higher incidence of rejection in patients who developed CMV (50%; RR, 10; P=0.0025). The incidence of other infections was similar between the treatment groups (P=0.19). Other infections occurred more frequently in patients that developed CMV (62.5%) vs those that did not (36.7%). However, this trend did not reach statistical significance (P=0.11).
Lapidus-Krol et al.[67] (2010) Valganciclovir PO up to 900 mg/day vs ganciclovir PO 30 mg/kg/dose up to 1 gram/dose three times daily Treatment was given for 3 months in R+/D+ or R+/D- recipients and for 6 months in R-/D+.	RETRO Children who underwent kidney or liver transplant	N=92 12 months	Primary: Symptomatic or tissue invasive CMV, safety Secondary: Not reported	Primary: The overall incidence of CMV episode was 13.7% in valganciclovir-treated patients and 19.5% in ganciclovir-treated patients (P=0.573). The overall time to CMV infection was not different among the treatment groups (P=0.46). Rates of acute allograft rejection were similar in valganciclovir-treated patients compared to ganciclovir-treated patients (25 vs 34%, respectively; P=NS) and between patients with CMV infection compared to noninfected patients (40 vs 27.3%, respectively; P=NS). There was no difference in adverse events between valganciclovir and ganciclovir. Secondary: Not reported
Palmer et al.[68] (2010) Valganciclovir 900 mg once daily for 3 months vs valganciclovir 900 mg once daily for	PRO, RCT, DB, PC Adults receiving their first lung transplant who were at risk for CMV	N=136 13 months posttransplant	Primary: CMV end-organ disease Secondary: CMV disease severity, CMV infection, acute rejection, opportunistic infections,	Primary: Patients treated with short-course valganciclovir had a greater incidence of CMV disease (32%) compared to patients in the extended-course group (4%; P<0.001). Secondary: There was a significant reduction in disease severity with extended-course valganciclovir compared to short-course valganciclovir (110,000 vs 3,200 copies/mL, respectively; P=0.009). There was a significant reduction in CMV infection with extended-course

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
12 months			ganciclovir resistance and safety	valganciclovir compared to short-course valganciclovir (64 vs 10%, respectively; P<0.001) There was no difference in rates of acute rejection, opportunistic infections, adverse events, resistance or adverse events between the two groups.
Kalil et al.[69] (2011) Valganciclovir 900 mg daily (VGC) vs valganciclovir 450 mg daily (VGC) vs ganciclovir 3 grams/day, valacyclovir 3 to 8 grams/day or preemptive therapy (controls)	MA Valganciclovir use for CMV prevention in any type of solid organ transplant	N=3,074 (20 trials) Variable duration	Primary: Prevention of CMV disease Secondary: Leukopenia and neutropenia risk; risk of allograft rejection, loss and death	Primary: <u>Valganciclovir 900 mg daily vs controls</u> The risk of developing CMV disease was 1.06 with VGC 900 mg vs controls (P=0.812). There was no difference in the subgroup analysis of types of controls (ganciclovir or preemptive therapy) or type of organ transplant. The risk of leukopenia was 5.24 for VGC 900 mg vs controls a (P=0.0004). The risk for acute allograft rejection was 1.71 for VGC 900 mg vs controls (P=0.43). The risk of neutropenia was higher with 900 mg VGC compared to controls (RR, 3.72; P=0.002). The risk of allograft rejection, allograft loss and death was not significantly higher with VGC 900 mg compared to control. <u>Valganciclovir 450 mg daily vs controls</u> The risk of developing CMV disease was 0.77 with VGC 450 mg vs control (P=0.23). There was no difference in the subgroup analysis of types of controls (ganciclovir or preemptive therapy) or type of organ transplant. The risk of leukopenia was 1.58 for VGC 450 mg vs controls (P=0.07). The risk for acute allograft rejection was 0.80 for VGC 450 mg vs controls (P=0.34). The risk of neutropenia was 2.92 with VGC 450 mg vs controls (P=0.002).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The risk of allograft rejection, allograft loss and death was not significantly higher with VGC 450 mg compared to control. <u>Valganciclovir 900 mg vs valganciclovir 450 mg</u> Adjusted comparison of VGC 900 mg vs VGC 450 mg showed there was an increased risk of leukopenia in the VGC 900 mg group (OR, 3.32; P=0.0005). Risk of neutropenia between VGC 900 mg and 450 mg could not be conducted due to differing definitions in the literature. Adjusted comparison of VGC 900 mg vs VGC 450 mg showed there was an increased risk of allograft rejection in the VGC 900 mg group (OR, 2.56; P=0.0005). There was no difference in risk between treatment groups for death or allograft loss.
Hodson et al.[70] (2008) Antiviral medications (acyclovir, ganciclovir, valacyclovir, valganciclovir) vs placebo or no treatment	MA Solid organ transplant recipients who received antiviral therapy for CMV prophylaxis	N=3,737 (32 trials) Variable duration	Primary: Incidence of CMV disease and CMV infection; all-cause mortality Secondary: Not reported	Primary: <u>Overall</u> Prophylaxis with all agents significantly reduced the risk for CMV disease overall (RR, 0.42; 95% CI, 0.34 to 0.52), CMV syndrome (RR, 0.41; 95% CI, 0.29 to 0.57) and CMV invasive organ disease (RR, 0.34; 95% CI, 0.21 to 0.55) compared to placebo or no treatment. The average risk of CMV infection in the placebo/no treatment arms was 49% (range 36 to 100%). Prophylaxis significantly reduced CMV infection (RR, 0.61; 95% CI, 0.48 to 0.77). The treatment efficacy did not vary according to antiviral medication used on subgroup analysis. When analyzed separately acyclovir (RR, 0.45; 95% CI, 0.29 to 0.69), ganciclovir (RR, 0.44; 95% CI, 0.34 to 0.58) and valacyclovir (RR, 0.30; 95% CI, 0.19 to 0.49) significantly reduced the risk for CMV disease compared to placebo or no treatment. The average all-cause mortality rate reported at one year or less post-transplant in the placebo/no treatment arms of all studies was 7.1% (range

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				0 to 37%). Prophylaxis significantly reduced all cause mortality (RR, 0.63; 95% CI, 0.43 to 0.92). <u>Ganciclovir vs acyclovir</u> In head-to-head studies, ganciclovir was more effective than acyclovir in preventing CMV disease in all recipients (RR, 0.37; 95% CI, 0.23 to 0.60), in CMV positive recipients (RR, 0.27; 95% CI, 0.13 to 0.55) and in CMV negative recipients of CMV positive organs (RR, 0.64; 95% CI, 0.41 to 0.99). There were no significant differences in the risk of death due to CMV disease (RR, 0.33; 95% CI, 0.07 to 1.58) or all-cause mortality (RR, 1.13; 95% CI, 0.82 to 1.58). <u>Valganciclovir vs ganciclovir</u> Valganciclovir and ganciclovir were not significantly different in the prevention of CMV disease at six months or one year post-transplant. There were no significant differences at six months and one year in the prevention of CMV syndrome and CMV invasive organ disease. There were no significant differences at six months and one year in the prevention of CMV infection. No significant differences were detected between medications in death due to CMV disease or all-cause mortality. <u>Valacyclovir vs ganciclovir</u> The risk of CMV disease and CMV infection did not differ significantly with valacyclovir compared to ganciclovir prophylaxis. No significant differences were detected in all-cause mortality. <u>Prophylaxis with different regimens of ganciclovir</u> No significant differences were detected in CMV disease, CMV syndrome, CMV invasive tissue disease, or CMV infection when ganciclovir was administered daily vs three times weekly. No difference in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				all-cause mortality was detected. No significant differences were detected in CMV disease, CMV syndrome, CMV invasive tissue disease or CMV infection when comparing PO vs IV ganciclovir. There was no difference in all-cause mortality. Secondary: Not reported
Hepatitis B				
Vassiliadis et al.[71] (2010) Adefovir 10 mg once daily plus lamivudine 100 mg daily vs adefovir 10 mg once daily	PRO, RCT Adult patients with HBeAg (-) chronic hepatitis B receiving lamivudine with documented genotypic resistance to lamivudine	N=60 20 to 60 months	Primary: Virologic response and normalization of ALT levels Secondary: Rate of resistance	Primary: Virologic response in the combination group was not significantly different than the adefovir monotherapy group (84.4 vs 73.3%; P=0.56). Mean virologic response was eight months in both groups (P=0.18). At 48 months, the proportion of patients with undetectable HBV-DNA was higher in the combination therapy group than in the monotherapy group (88.9 vs 46.7%; P=0.009). Normalization of ALT levels was higher in the combination group compared to the monotherapy group (90.9 vs 57.1%; P=0.01). At 36 and 48 months, the proportion of patients with normalized ALT levels was higher in the combination group than in the monotherapy group (97.2 vs 53.3%; P<0.001 and 100 vs 53.3%; P<0.001, respectively). All patients treated with combination therapy had sustained undetectable HBV-DNA; four of 11 patients treated with monotherapy had breakthrough (34%; P<0.001). A total of 4.4% of patients in the combination group had emergence of adefovir resistance vs 40% of patients in the monotherapy group (P<0.001). Resistance in both groups occurred more frequently in those patients that did not achieve a virologic response. There was no difference in adverse events between the groups.
Ha et al.[72] (2012)	RCT	N=91	Primary: Antiviral efficacy,	Primary: Adefovir+entecavir combination therapy significantly suppressed HBV

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Adefovir monotherapy 10 mg/day vs lamivudine 100 mg/day and adefovir 10 mg/day vs entecavir 1 mg/day and adefovir 10 mg/day	Adult chronic hepatitis B patients with the documented presence of lamivudine-resistance mutations that developed during sequential monotherapy with lamivudine	24 months minimum	frequency of the occurrence of viral breakthrough, genotypic resistance Secondary: Not reported	DNA to a greater extent than adefovir monotherapy or adefovir add-on lamivudine therapy at three (P=0.002 and 0.009), six (P=0.003 and 0.004), 12 (P=0.008 and 0.005), and 24 (P=0.012 and 0.014) months after the initiation of rescue antiviral treatment; adefovir add-on lamivudine therapy significantly suppressed HBV DNA to a greater extent than adefovir monotherapy at three (P=0.003), six (P=0.004), 12 (P=0.002), and 24 (P=0.026) months after the initiation of rescue antiviral treatment. The rate of HBV DNA polymerase chain reaction undetectability (<60 IU/mL) at six months after the initiation of adefovir monotherapy, adefovir add-on lamivudine therapy, and adefovir+entecavir combination therapy was 27.5, 56.7, and 78.1%, respectively (P=0.024). However, at 12 and 24 months after the initiation of each rescue antiviral treatment, the rate of HBV DNA polymerase chain reaction undetectability showed no significant difference (P>0.05). Viral breakthrough and genotypic mutations were detected in eight (27.6%) and four (13.3%) patients in the adefovir monotherapy and adefovir add-on lamivudine therapy groups, respectively; whereas no case of viral breakthrough and genotypic resistance was detected in the adefovir+entecavir combination therapy group at 24 months after the initiation of each antiviral treatment (P<0.05). Secondary: Not reported
Sun et al.[73] (2011) Adefovir 10 mg daily for 72 weeks vs peginterferon alfa-2a 180 µg/week for 48 weeks	OL, RCT Adult patients with chronic hepatitis B with lamivudine resistance	N=235 6 months posttreatment	Primary: Rate of HBeAg seroconversion at week 72 Secondary: Not reported	Primary: At six months posttreatment, significantly more patients in the peginterferon group achieved HBeAg seroconversion compared to adefovir (14.6 vs 3.8%; P=0.01). Overall, the response rate for all patients with lamivudine-resistant HBV was very low at any time period during the study. Patients taking peginterferon alfa-2a experienced a serious adverse event rate of 7.8% compared to 2.4% in the adefovir-treated group. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Not reported
Pessôa et al.[74] (2008) Entecavir 1 mg/day for 24 weeks vs placebo for 24 weeks All patients continued lamivudine (300 mg four times daily)-containing HAART regimens; OL entecavir was allowed after 24 weeks	PRO, RCT, DB, PC HIV/HBV co-infected patients >16 years of age with no evidence of hepatitis C or D, currently on lamivudine containing HAART for ≥24 weeks prior to enrollment or infected with lamivudine-resistant-associated HBV	N=68 48 weeks	Primary: Mean change from baseline in HBV DNA at 24 weeks Secondary: Mean change in serum HBV DNA adjusted from baseline at 48 weeks; proportion of patients with HBV-DNA <300 copies/mL at 24 and 48 weeks; ALT normalization; proportion of patients with seroconversion; adverse events	Primary: At 24 weeks, the mean HBV-DNA for entecavir-treated patients was 5.52 log_{10} compared to 9.27 log_{10} in patients receiving placebo. The mean change from baseline in entecavir-treated patients was -3.65 log_{10} copies/mL vs +0.11 log_{10} copies/mL for placebo (95% CI, -4.49 to -3.04; P<0.0001). Secondary: At 48 weeks, the mean HBV-DNA for entecavir-treated patients was 4.97 log_{10} compared to 5.63 log_{10} in patients receiving placebo. The mean HBV-DNA change from baseline was -4.2 log_{10} in patients receiving entecavir from start of study. The mean HBV-DNA change from baseline was -3.65 log_{10} in patients randomized to placebo at the start of study who crossed over to open-label entecavir. ALT normalization occurred in 34% of entecavir-treated patients compared to 8% in placebo-treated patients (P=0.08). Loss of HBeAg occurred in one entecavir patient by week 48, but in no placebo treated patients (P=0.56). At week 24, HBeAg seroconversion occurred in one patient in the entecavir group. There were similar frequencies of adverse events in the entecavir (86%) and placebo (82%) groups. Headache and nasopharyngitis were the most common reported adverse events in both groups. There was no change to CD4 cell counts or HIV RNA levels.
Leung et al.[75] (2009) Entecavir (ETV) 0.5 mg daily for 52 weeks	RCT, OL Patients ≥16 years of age, had HBeAg-positive chronic hepatitis B infection,	N=132 52 weeks	Primary: Mean reduction in serum HBV DNA by polymerase chain reaction assay at week 12	Primary: The mean reduction in serum HBV DNA level at week 12 was significantly greater in patients randomized to ETV compared to ADV (-6.23 vs -4.42 log_{10} copies/mL; P<0.0001). Secondary: The mean decrease in serum HBV DNA levels was greater with ETV than

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs adefovir (ADV) 10 mg daily for 52 weeks	compensated liver disease with a serum ALT level between 1.3 and 10 times the upper limit of normal, and had never received treatment with nucleosides or nucleotides with activity against HBV		Secondary: Mean change in HBV DNA from baseline to weeks 24 and 48; proportion of patients with undetectable serum HBV DNA (<300 copies/mL) at weeks 12, 24, and 48; proportion of patients with normalization of serum ALT; HBe seroconversion at week 48; and safety	ADV at weeks 2, 4, 8, 24, and 48. The proportion of patients with HBV DNA of <300 copies/mL was higher in patients treated with ETV than in those treated with ADV at weeks 12, 24, and 48. At week 24, 15 ETV-treated patients (45%) and four ADV-treated patients (13%) achieved HBV DNA <300 copies/mL At week 48, 19 ETV-treated patients (58%) and six ADV-treated patients (19%) achieved HBV DNA <300 copies/mL. Normalization of serum ALT was documented in 25 (76%) ETV-treated patients and 20 (63%) ADV-treated patients at week 48. HBeAg loss and HBe seroconversion rates were similar for both ETV-treated and ADV-treated patients. For ETV-treated patients, HBeAg loss and HBe seroconversion rates were six of 33 (18%) and five of 33 (15%), respectively, vs seven of 32 (22%) and seven of 32 (22%), respectively, for ADV-treated patients (P=NS). Treatment was generally safe and well tolerated.
Zhao et al.[76] (2011) Entecavir 0.5 mg daily vs adefovir 10 mg daily	MA Nucleoside naïve, HBeAg (+), Asian patients treated with either entecavir or adefovir	N=267 (6 trials) 48 weeks	Primary: Efficacy at 48 weeks Secondary: Not reported	Primary: The rate of undetected serum HBV-DNA was significantly higher in entecavir-treated patients vs adefovir therapy (RR, 1.73; 95% CI, 1.38 to 2.17; P<0.0001). The rate of ALT normalization was significantly higher in the entecavir-treated patients vs adefovir therapy (RR, 1.25; 95% CI, 1.06 to 1.49; P<0.009). The rate of HBeAg clearance was not significantly different in entecavir-treated patients vs adefovir therapy (RR, 0.77; 95% CI, 0.40 to 1.35; P=0.36). The rate of HBeAg seroconversion was not significantly different in entecavir-treated patients vs adefovir therapy (RR, 0.74; 95% CI, 0.28 to 1.94; P=0.53). Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Not reported
Zhao et al.[77] (2012) Entecavir (ETV) 0.5 to 1.0 mg/day vs adefovir (ADV) 10 mg/day	MA Chronic hepatitis B patients treated with either entecavir or adefovir	N=1230 (13 RCTs) 24 or 48 weeks	Primary: HBeAg seroconversion rate, serum HBeAg clearance rate, serum HBV DNA clearance rate, ALT normalization rate Secondary: Safety	Primary: Higher serum HBeAg clearance rates were observed in patients treated with ETV than in patients treated with ADV at the 24th and 48th weeks of treatment (16.5 vs 12.2%; RR, 1.38; 95% CI, 0.72 to 2.64; P=0.33; 28.1 vs 20.8%; RR, 1.35; 95% CI, 1.02 to 1.79; P<0.05, respectively). The HBeAg seroconversion rates were reported in six trials. The meta-analysis results showed that the HBeAg seroconversion rates were greater for patients treated with ETV than for patients treated with ADV at the 24th and 48th weeks of treatment, but there was no statistically significant difference (13.0 vs 5.6%; RR, 2.34; 95% CI, 0.76 to 7.18; P=0.14; 19.9 vs 13.7%; RR, 1.46; 95% CI, 0.95 to 2.25; P=0.09, respectively). The combined serum HBV-DNA clearance rate in the ETV treatment group was higher than that in the ADV group at the 24th and 48th weeks of treatment (59.6 vs 31.8%; RR, 1.82; 95% CI, 1.49 to 2.23; P<0.01; 78.3 vs 50.4%; RR, 1.61; 95% CI, 1.32 to 1.96; P<0.01, respectively). The combined ALT normalization rates were significantly higher in the ETV treatment groups (68.6 vs 59.3%; RR, 1.17; 95% CI, 1.03 to 1.22; P=0.02; 86.2 vs 78.0%; RR, 1.11; 95% CI, 1.04 to 1.19; P< 0.01, respectively). Secondary: Treatment was generally safe and well tolerated. The most frequently reported adverse events included headache, upper respiratory tract infection, nasopharyngitis, pyrexia, and flulike symptoms. The differences between patients treated with ETV and ADV were not significant.
Chang et al.[78] (2006) ETV-022 Entecavir 0.5 mg/day vs	RCT, DB Adult patients with HBeAg-positive chronic hepatitis B who had not previously been treated with a	N=715 52 weeks	Primary: Histologic improvement after 48 weeks of treatment Secondary: Serum HBV-DNA	Primary: After 48 weeks, a histologic response was demonstrated in 72% of entecavir-treated patients and 62% lamivudine-treated patients (P=0.009). Secondary: Significantly more patients had undetectable serum HBV DNA while on entecavir compared to lamivudine (67 vs 36%; P<0.001). HBeAg loss occurred in 22% of entecavir-treated patients and 20% of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
lamivudine 100 mg/day	nucleoside analogue		at 48 weeks, HBeAg status, decrease in Ishak fibrosis score, and ALT	those treated with lamivudine (P=0.45). HBeAg seroconversion occurred in 21% of entecavir-treated patients and 18% of those treated with lamivudine (P=0.33). Significantly more patients had normalization of ALT while on entecavir compared to lamivudine (68 vs 60%; P=0.02). The frequency and severity of adverse drug events were comparable between treatment groups. The most commonly reported adverse events were headache, upper respiratory tract infection, nasopharyngitis, cough, pyrexia, upper abdominal pain, fatigue, and diarrhea.
Chang et al.[79] (2009) ETV-022 Entecavir 0.5 mg/day vs lamivudine 100 mg/day ETV-901 Entecavir 0.5 to 1 mg/day ± lamivudine	RCT, DB Adult patients with HBeAg-positive chronic hepatitis B who had not previously been treated with a nucleoside analogue	N=407 96 weeks	Primary: Serum HBV-DNA, HBeAg status, ALT, safety Secondary: Not reported	Primary: A total of 64% of entecavir-treated patients had HBV-DNA<300 copies/mL at week 48, which increased to 74% at the end of dosing. A total of 66% of entecavir-treated patients had ALT normalization at 48 weeks, which increased to 79% at the end of dosing in year two. A total of 40% of lamivudine-treated patients had HBV-DNA <300 copies/mL at week 48, which decreased to 37% at the end of dosing. A total of 71% of lamivudine-treated patients had ALT normalization at 48 weeks, which decreased to 68% at the end of dosing in year two. At the end of dosing, 11% of entecavir-treated patients and 12% of lamivudine-treated patients experienced HBe seroconversion. Cumulative confirmed ALT normalization was achieved in 87 and 79% of entecavir and lamivudine treated patients, respectively (P<0.0056). Cumulative confirmed HBV-DNA <300 copies/mL was achieved in 80% of entecavir-treated patients compared to 39% of lamivudine-treated patients at two years (P<0.001). The proportion of patients experiencing HBe seroconversion (31 vs 25%), HBsAg loss (5 vs 3%), and HBsAg seroconversion (2 vs 2%) did not different significantly among the treatment groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Through two years of therapy, headache (10% with entecavir and 8% with lamivudine), fatigue (6% with entecavir and 5% with lamivudine), and increased ALT levels (4% with entecavir and 7% with lamivudine) were the most common adverse events reported. Secondary: Not reported
Chang et al.[80] (2010) ETV-022 Entecavir 0.5 mg/day vs lamivudine 100 mg/day ETV-901 Entecavir 0.5 to 1 mg/day ± lamivudine	RCT, DB Adult patients with HBeAg-positive chronic hepatitis B who had not previously been treated with a nucleoside analogue	N=146 240 weeks	Primary: Serum HBV-DNA, HBeAg status, ALT, safety Secondary: Not reported	Primary: At year one, 55% of patients achieved HBV DNA <300 copies/mL, which increased to 83% at year two, and 94% at year five. A total of 65% of patients achieved ALT normalization at one year, 78% at two years, and 80% at year five. At year five, the mean ALT level for the entecavir group was 33 IU/L, a decrease from the mean level of 122 IU/L at baseline. At year two, 31% of patients achieved HBeAg seroconversion and 5% of patients achieved HBsAg loss. These patients were not enrolled into ETV-901. Of the 141 patients enrolled in ETV-901, 23% achieved HBeAg seroconversion and 1.4% achieved HBsAg loss during ETV-901. One patient developed entecavir resistance that emerged at year three. No patient discontinued therapy due to an adverse event in ETV-901. A total of 16% had a grade 3/4 adverse event; 20% had a serious adverse event; 5% experienced death. Secondary: Not reported
Lai et al.[81] (2006) Entecavir 0.5 mg once daily vs	DB, RCT Adult patients with HBeAg-negative hepatitis B not previously treated with a nucleoside analogue	N=648 52 weeks	Primary: Histologic improvement at week 48 Secondary: Reduction in HBV DNA level and	Primary: After 48 weeks, a histologic response was demonstrated in 70% of entecavir-treated patients and 61% lamivudine-treated patients (P=0.01). Secondary: Significantly more patients had undetectable serum HBV DNA while on entecavir compared to the number of those on lamivudine with undetectable serum HBV DNA (90 vs 72%; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
lamivudine 100 mg once daily			ALT normalization	Significantly more patients had normalization of ALT while on entecavir compared to lamivudine (78 vs 71%; P=0.045). The frequency and severity of adverse drug events was comparable between treatment groups. The most commonly reported adverse events were headache, upper respiratory tract infection, upper abdominal pain, influenza, nasopharyngitis, dyspepsia, fatigue, back pain, arthralgia, diarrhea, insomnia, cough, nausea, and myalgia.
Gish et al.[82] (2007) Entecavir 0.5 mg once daily vs lamivudine 100 mg once daily	RCT, DB Adult patients with HBeAg-negative hepatitis B not previously treated with a nucleoside analogue	N=407 96 weeks	Primary: Proportions of patients with HBV DNA levels <300 copies/mL by polymerase chain reaction, normalization of ALT levels, and HBeAg seroconversion at the end of dosing (up to 96 weeks) Secondary: Not reported	Primary: For all treated patients, the cumulative analysis showed that a higher proportion of entecavir-treated than lamivudine-treated patients achieved confirmed HBV DNA levels <300 copies/mL by polymerase chain reaction assay through 96 weeks of treatment (entecavir 80% and lamivudine 39%; P<0.0001). Through 96 weeks of therapy, for all treated patients, a higher cumulative proportion of entecavir- treated (87%) than lamivudine-treated (79%) patients achieved confirmed normalization of ALT levels (P<.0056). Through 96 weeks of treatment and 6 months of post-treatment follow-up, 5% of entecavir-treated and 3% of lamivudine-treated patients achieved confirmed HBsAg loss, and 2% of patients in both treatment groups achieved seroconversion to antibody to hepatitis B surface antigen. Over the course of two years of treatment, 31% of entecavir-treated patients and 26% of lamivudine-treated patients became responders. Fewer entecavir-treated (8%) than lamivudine-treated (41%) patients were nonresponders during this 96-week period. The frequency of on-treatment adverse events was comparable (entecavir, 87%; lamivudine, 84%). Serious adverse events on-treatment occurred in 8% of patients in both treatment groups. Secondary: Not reported
Sherman et al.[83]	RCT, DB, AC	N=286	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(2006) Entecavir 1 mg daily vs lamivudine 100 mg daily	HBsAg (+) patients ≥16 years of age who were receiving ongoing lamivudine therapy and were refractory to that therapy	52 weeks	Histologic improvement and composite endpoint (HBV-DNA <0.7 mEq/ml and ALT <1.25 times the upper limit of normal), virologic endpoints, serologic endpoints, biochemical endpoints Secondary: Not reported	Histologic improvement occurred in 55% of patients treated with entecavir compared to 28% of patients treated with lamivudine (P<0.0001). A total of 34% of entecavir patients and 16% of lamivudine patients had improvement in Ishak fibrosis scores (P=0.0019). A total of 55% of patients treated with entecavir reached the composite endpoint compared to 4% of lamivudine patients (P=0.001). A total of 9% of entecavir-treated patients and <1% of lamivudine-treated patients achieved combined HBV-DNA <0.7 mEq/mL and loss of HBeAg at 48 weeks (P=0.008). Mean changes from baseline in HBV-DNA was -5.11 $\log_{10}$ copies/mL in entecavir-treated patients vs -0.48 $\log_{10}$ copies in lamivudine-treated patients (P<0.001). The proportion of patients achieving HBV-DNA <300 copies/mL at 48 weeks was higher in entecavir-treated patients (19%) compared to lamivudine-treated patients (1%; P<0.001). Loss of HBeAg occurred more frequently in entecavir patients compared to lamivudine patients (10 vs 3%, respectively; P<0.0278). HBeAg seroconversion was not significantly different between entecavir patients (8%) and lamivudine patients (3%; P=0.06). More entecavir- treated patients achieved ALT normalization compared to lamivudine-treated patients (61 vs 15%, respectively; P<0.0001). Secondary: Not reported
Yim et al.[84] (2013) ACE Entecavir	MC, OL, PRO, RCT HBeAg-positive or -negative chronic	N=219 24 months	Primary: Virological response Secondary:	Primary: Degree of HBV DNA reduction was significantly greater in the adefovir–lamivudine combination group compared with the entecavir group through 24 months (P<0.001). Virological response (i.e. HBV DNA < 60 IU/mL) at month 24 was significantly higher in the adefovir–lamivudine

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
monotherapy vs adefovir–lamivudine combination	HBV patients confirmed by hepatitis B surface antigen (HBsAg) being positive more than 6 months, aged over 16 years old, having serum ALT above 1.5 times the upper limit of normal, history of treatment with lamivudine more than 6 months, proven lamivudine resistant mutations, compensated liver disease		Degrees of HBV DNA reduction, mean HBV DNA levels, ALT normalization, HBeAg seroconversion, development of resistant mutation, virological breakthrough, biochemical breakthrough, adverse events	combination group compared with entecavir group as 56.6% (51 of 90 patients who completed follow-up) vs 40.0% (36 of 90 patients who completed follow-up) respectively (P = 0.025). The cumulative virological response rates up to month 24 were significantly higher in the combination group (P = 0.046). Secondary: The rates of ALT normalization of the adefovir–lamivudine combination group were not significantly different compared with those of the entecavir monotherapy group at month 12. HBeAg loss rates were 19.7% (15/76) and 20.8% (16/77) in the adefovir–lamivudine combination group and the entecavir monotherapy group respectively (P = 0.873). HBeAg seroconversion rates were 10.5% (8/76) and 13.0% (10/77) respectively (P = 0.637).
Huang et al.[85] (2013) Entecavir monotherapy vs adefovir–lamivudine combination	MA Patients with chronic hepatitis B caused by HBV infection with lamivudine resistance	N=696 (8 studies) 48 weeks	Primary: Undetectable HBV DNA rate, virologic breakthrough rate, ALT normalization rate, HBeAg loss rate, HBeAg seroconversion, adverse reactions Secondary: Not reported	Primary: At week 48 of treatment, 54.9% of all patients in the adefovir–lamivudine combination group and 53.4% of all patients in the entecavir group reached undectable HBV DNA levels (P=NS). There were no significant differences in ALT normalization rates between groups at week 48. The rate of HBeAg loss at week 48 of treatment was similar between the two groups. The rate of HBeAg seroconversion at week 48 of treatment was 14.7% in the adefovir–lamivudine combination group and 17.2% in the entecavir group. In this analysis, 2.2% of all patients in the adefovir–lamivudine group and 11.7% of all patients in the entecavir group reached virologic breakthrough at week 48 of treatment (P=0.002).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				There was no statistically significant difference in adverse reaction rate between the two groups. Secondary: Not reported
Ceylan et al.[86] (2013) Entecavir vs tenofovir	RETRO Patients HBsAg positive for at least 6 months, HBV-DNA positive pretreatment, tenofovir or entecavir monotherapy for at least 3 months	N=117 24 months	Primary: Side effects, HBeAg positivity, serum HBV DNA levels at the 3rd, 6th, 12th, 18th and 24th months Secondary: Not reported	Primary: The cumulative probabilities of virologic responses in 3rd, 6th, 12th, 18th, and 24th months of treatment were 28.8, 54.1, 80.8, 97.6, and 100% in tenofovir and 25.5, 33.8, 60.9, 85.8, and 95.3% in entecavir group, respectively. Virological response was better in patients using tenofovir (OR, 1.796; P=0.014) and having high fibrosis score (OR, 0.182; P=0.018). Entecavir was more effective in reducing serum HBV DNA levels at the 3rd month of treatment (serum HBV DNA decline of 4.45 and 3.96 $\log_{10}$ units for entecavir and tenofovir respectively, P=0.031), but decline rates were similar at other months. There was no difference between the two treatment groups in terms of side effect rates and discontinuation of treatment due to side effects. Secondary: Not reported
Li et al.[87] (2013) Telbivudine 600 mg/day	OL Patients positive for both HBsAg and HBeAg for at least 6 months with HBV DNA >6 $\log_{10}$ copies/mL after 12 months of adefovir monotherapy and ALT levels greater than two times the upper limit of normal	N=42 18 months	Primary: Virologic response, biochemical response, serologic response, virologic breakthrough, safety Secondary: Not reported	Primary: Virologic response: HBV DNA was reduced rapidly three months after switching to telbivudine treatment with a median decrease of 1.74 (range, 1.52 to 4.50) $\log_{10}$ copies/mL compared with baseline (P<0.001), and 64.3% (27/42) of patients achieved virologic response. Biochemical response: At 18 months, the biochemical response rate reached 65.8% (25/38) with ALT levels of 0.83 (0.35 to 2.90) x upper limit of normal (P<0.001 compared with baseline). Serologic response: Twelve (30.8%) patients became HBeAg negative and seven (17.9%) seroconverted at 18 months. Virologic breakthrough: Only one patient experienced virologic breakthrough during telbivudine treatment at 12 months.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Safety: Generally, telbivudine therapy was very safe, and the majority of patients tolerated the therapy. Secondary: Not reported
Sun et al.[88] (2014) Telbivudine 600 mg daily monotherapy group (Mono) vs telbivudine-based optimized group (patients started telbivudine 600 mg daily and adefovir 10 mg daily was added to patients with suboptimal response) (Optimize)	MC, OL, RCT Patients aged 18 to 65 years were eligible if Hepatitis B surface antigen (HBsAg)-positive for at least 6 months, HBeAg-positive, and HBeAb-negative, HBV DNA >5 $\log_{10}$ copies/mL, ALT ≥2 and <10 x upper limit of normal with no previous nucleos(t)ide analog treatment	N=599 2 years	Primary: Virologic response at week 104 Secondary: HBV DNA reduction from baseline, ALT normalization, resistance, serologic response	Primary: More patients in the Optimize group achieved virological response than those in the Mono group at week 52 (65.3 vs 56.9%; P<0.033) and week 104 (76.7 vs 61.2%; P<0.001). In addition, at week 104 serum HBV DNA reduction from baseline was significantly greater in the Optimize group (6.3 $\log_{10}$) than the Mono group (6.1 $\log_{10}$; P<0.001). Secondary: 80.7% of patients in the Optimize group achieved normalization of ALT compared with 79.2% of patients in the Mono group at week 104 (P=0.649). Optimize and Mono groups achieved HBeAg loss (29.0 vs 31.1%; P=0.574) and HBeAg seroconversion (23.7 vs 22.1%; P=0.643). The rates of virological breakthrough and genotypic resistance in the Optimize group were significantly lower compared to those in the Mono group by week 52 (1.0 vs 7.7%; P<0.001 for virological breakthrough; 0.7 vs 7.0%; P<0.001 for resistance) and week 104 (6.0 vs 30.4%; P<0.001 for virological breakthrough; 2.7 vs 25.8%; P<0.001 for resistance). Among the safety population, both treatments were well tolerated. Adverse events were reported in nearly 40% of patients in both treatment arms and most adverse events were not attributed to study drug by the clinical investigators.
Chan et al.[89] (2007) Telbivudine 600 mg daily for 52 weeks (group A) vs	RCT, OL Patients 18 to 70 years of age with chronic hepatitis B and no history or signs of hepatic decompensation, positivity for serum	N=136 52 weeks	Primary: HBV DNA reduction from baseline values at week 24 Secondary: HBV DNA reduction from	Primary: At week 24, the reduction in mean serum HBV DNA level from baseline in group A differed from that in pooled groups B and C (-6.30 vs -4.97 $\log_{10}$ copies/mL; P<0.001), as did the proportion of patients whose serum HBV DNA levels were undetectable by PCR (39 vs 12%; P<0.001). Serum HBV DNA levels remained at or above 5 $\log_{10}$ copies/mL in more adefovir recipients than telbivudine recipients (42 vs 5%; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
adefovir 10 mg daily for 52 weeks (group B) vs adefovir 10 mg daily for 24 weeks followed by telbivudine 600 mg daily for the remaining 28 weeks (group C)	hepatitis B surface antigen (HBsAg), positivity for serum HBeAg, serum ALT level between 1.3 and 10 times the upper limit of normal, and serum HBV DNA levels of at least 6 log_{10} copies/mL		baseline values at week 52, comparisons of mean residual HBV DNA levels, proportions of patients with HBV DNA who were polymerase chain reaction (PCR)-negative or had HBV DNA values less than 5, 4, or 3 log_{10} copies/mL; serum ALT normalization; HBeAg loss and seroconversion; HBsAg loss and seroconversion; and primary treatment failure	Group A and pooled groups B and C differed in the proportions of patients with HBV DNA levels that remained at or above 3 log_{10} copies/mL (50 vs 78%; P<0.003) and 4 log_{10} copies/mL (32 vs 61%; P<0.003). Secondary: In patients switched from adefovir to telbivudine at week 24 (group C), mean HBV DNA levels rapidly decreased by approximately 1.4 log_{10} copies/mL after week 24; within eight weeks, they were nearly identical to levels in patients in group A. An increase in HBeAg seroconversion was seen in group C, although the differences were not statistically significant. At week 52, mean residual HBV DNA levels in groups A and C differed from those in group B (3.01 log_{10} copies/mL and 3.02 log_{10} copies/mL, respectively, vs 4.00 log_{10} copies/mL; P<0.004). Reductions of mean serum HBV DNA levels were greater in groups A and C (-6.56 and -6.44 log_{10} copies/mL, respectively) than in group B (-5.99 log_{10} copies/mL; P=0.18 and P=0.28, respectively). More patients in groups A and C than in group B were PCR-negative at week 52, although these differences did not reach statistical significance (60% and 54% vs 40%; P=0.07 and P=0.20, respectively). The rate of primary treatment failure (HBV DNA levels remaining >5 log_{10} copies/mL through week 52) in group B (29%) also differed from that in group A (2%; P<0.008) and in group C (11%; P=0.042). Loss of HBeAg was more common in group A than in pooled groups B and C at week 24, and was more common in groups A and C at week 52 (30% and 26%, respectively) than in group B (21%), although intergroup differences were not statistically significant. No patient experienced HBsAg loss or seroconversion. At week 52, ALT normalization occurred in 79% of patients in group A

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				and 85% of patients in group C, compared to 85% of those in group B (P=0.45 and P=0.98, respectively).
Zheng et al.[90] (2010) Telbivudine 600 mg daily vs entecavir 0.5 mg daily	PRO, RCT, OL, PG Adult Chinese patients with previously untreated HBeAg-positive HBV	N=131 24 weeks	Primary: Mean reduction in HBV-DNA copies at 24 weeks Secondary: Mean reduction in HBV-DNA at 12 weeks, absence of HBV-DNA; absence of HBeAg, HBeAg seroconversion, normalization of ALT, adverse events	Primary: Mean reductions in HBV-DNA from baseline at week 24 were not significantly different between the telbivudine and entecavir groups (6.00 vs 5.80 $\log_{10}$, respectively). Secondary: Mean reductions in HBV-DNA from baseline at 12weeks were not significantly different between the telbivudine and entecavir groups (4.99 vs 4.69 $\log_{10}$, respectively). There was no significant difference in undetectable HBV-DNA at 12 weeks between the telbivudine and entecavir groups (43.1 vs 34.8%, respectively; P=0.334). There was no significant difference in undetectable HBV-DNA at 24 weeks between the telbivudine and entecavir groups (67.7 vs 57.6%, respectively; P=0.232). At 12 weeks, there were higher rates of HBeAg absence (20 vs 3%; P=0.002) and seroconversion (13.8 vs 3%; P=0.03) in the telbivudine group compared to entecavir group, respectively. At 24 weeks, there was no significant difference in rates of HBeAg absence (36.9 vs 28.8%) or seroconversion (24.6 vs 13.6%) in the telbivudine group compared to entecavir group, respectively. There was no difference in normalization of ALT levels at 24 weeks in the telbivudine and entecavir groups (78.5 vs 74.2%; respectively). Adverse events were similar between each group with the most common being upper respiratory tract infection, fatigue, diarrhea, and coughing.
Tsai et al.[91] (2014) Telbivudine 600 mg daily	RETRO Treatment-naïve chronic hepatitis B patients	N=230 ≥2 years	Primary: ALT normalization, HBeAg seroconversion,	Primary: There are no significant differences between telbivudine and entecavir groups in HBeAg seroconversion at year two after treatment (46.4 vs 42.9%). The proportions of ALT normalization and undetectable HBV DNA are significantly greater in the entecavir group than the telbivudine

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs entecavir 0.5 mg daily			undetectable serum HBV DNA (<60 copies/mL), and virological resistance, safety Secondary: Not reported	group at year two after treatment (85.2 vs 78.4%; P=0.048; 96.5 vs 74.8%; P<0.001). The cumulative rates of resistance were 7.8, 21.7, and 24.9% in the telbivudine group at years one, two, and three, respectively, which was significantly greater than in the entecavir group (0, 0.9, and 0.9% at years one, two, and three, respectively, P<0.001). The entecavir group showed significantly greater DNA undetectability and lower resistance both in HBeAg-positive and HBeAg-negative patients after two years of treatment. Secondary: Not reported
Liu et al.[92] (2014) Telbivudine 600 mg/day vs entecavir 0.5 mg/day	MA Nucleos(t)ide-naive Asian patients with HBeAg-positive chronic hepatitis B	N=867 (7 RCTs) ≥12 weeks	Primary: Rate of the viral response (the number of patients with undetectable levels of serum HBV DNA by polymerase chain reaction), the rate of the biochemical response (the number of patients with serum ALT normalization), and the rates of HBeAg loss and seroconversion Secondary: Not reported	Primary: The rates of undetectable serum HBV DNA were similar between the entecavir group and the telbivudine group at weeks 12 and 48, with no significant differences observed (at 12 weeks, 148/340 vs 152/347, RR, 1.00; P=0.98; 95% CI, 0.84 to 1.18; at 48 weeks, 255/303 vs 258/309, RR, 1.01; P=0.81; 95% CI, 0.94 to 1.08). However, the rate of undetectable serum HBV DNA in the telbivudine group was significantly higher than that in the entecavir group at 24 weeks (209/319 vs 238/324, RR, 0.89; P=0.03; 95% CI, 0.80 to 0.99). There were no significant differences between the entecavir group and the telbivudine group in serum ALT normalization at 12, 24, and 48 weeks after the start of treatment. At 12, 24 and 48 weeks of treatment, the rates of HBeAg loss were significantly greater in the telbivudine group than in the entecavir group (12 weeks, P<0.00001; 24 weeks, P=0.01; 48 weeks, P=0.01). HBeAg seroconversion rates were significantly higher in the telbivudine group than in the entecavir group (12 weeks, P<0.0001; 24 weeks, P=0.004; 48 weeks, P=0.0002).
Lai et al.[93] (2007) Telbivudine 600	RCT, DB, MC Adults aged 16 to 70 years with	N=1,370 52 weeks	Primary: Therapeutic response (defined as reduction of	Primary: Reduction in serum HBV DNA levels at week 52 was significantly greater in the telbivudine group than in the lamivudine group. The difference was evident by week 12 in HBeAg-positive patients (reductions of 5.71 $\log_{10}$

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg once daily vs lamivudine 100 mg once daily	HBeAg-positive or HBeAg-negative chronic hepatitis B and compensated liver disease		serum HBV DNA levels to <5 log_{10} copies/mL and normalization of ALT level or loss of serum HBeAg) Secondary: Proportion of patients with HBV DNA non-detectable (<300 copies/mL), HBeAg loss, normalization of serum ALT level	copies per milliliter for telbivudine and 5.42 log_{10} copies per milliliter for lamivudine, P=0.01) and by week eight in HBeAg-negative patients (reductions of 4.36 log_{10} copies per milliliter for telbivudine and 4.08 log_{10} copies per milliliter for lamivudine, P=0.02), and it persisted through week 52. Secondary: At week 52, the proportion of patients in whom serum HBV DNA levels were undetectable by polymerase chain reaction assay was significantly greater in the telbivudine group than in the lamivudine group among HBeAg-positive patients (60.0 vs 40.4%, P<0.001) and HBeAg-negative patients (88.3 vs 71.4%, P<0.001). The mean time required for serum HBV DNA to become undetectable by polymerase chain reaction assay was significantly shorter in the telbivudine group than in the lamivudine group among HBeAg-positive patients (34 weeks vs 39 weeks, P<0.001) and HBeAg-negative patients (20 weeks vs 26 weeks, P<0.001). Primary treatment failure was less frequent with telbivudine than with lamivudine among both HBeAg-positive and HBeAg-negative patients, but the difference was significant only for HBeAg-positive patients. Among HBeAg-positive patients, 25.7% of those in the telbivudine group and 23.3% of those in the lamivudine group had HBeAg loss (P=0.40) and 22.5% of those in the telbivudine group and 21.5% of those in the lamivudine group had HBeAg seroconversion (P=0.73). The rates of normalization of serum alanine aminotransferase at week 52 were high (levels more than 70%) in both treatment groups, with results meeting non-inferiority criteria in the HBeAg-positive and in the HBeAg-negative subgroups. The frequencies of adverse events through week 52 were similar for patients who received telbivudine and for those who received lamivudine. Serious adverse events were reported for 18 patients in the telbivudine group (2.6%) and 33 in the lamivudine group (4.8%).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Hou et al.[94] (2008) Telbivudine 600 mg once daily vs lamivudine 100 mg once daily	RCT, DB, MC Chinese adults aged 16 to 70 years with HBeAg-positive or HBeAg-negative chronic hepatitis B and compensated liver disease	N=332 52 weeks	Primary: Therapeutic response (defined as reduction of serum HBV DNA levels to <5 $\log_{10}$ copies/mL and normalization of ALT level or loss of serum HBeAg) Secondary: Serum HBV DNA changes from baseline, proportion of patients with HBV DNA non-detectable (<300 copies/mL), HBeAg loss and seroconversion, normalization of serum ALT level	Primary: <u>HBeAg-Positive Patients</u> Telbivudine resulted in a greater reduction in serum HBV DNA levels, compared to lamivudine. This difference in HBV DNA suppression was significant by week eight and continued through week 52. <u>HBeAg-Negative Patients</u> Telbivudine produced a greater mean reduction of serum HBV DNA (5.5 $\log_{10}$ for telbivudine vs 4.8 $\log_{10}$ for lamivudine). However, these efficacy differences were not analyzed statistically because of the limited power for statistical comparisons within the small HBeAg-negative patient population. Secondary: <u>HBeAg-Positive Patients</u> At week 52, serum HBV DNA reduction from baseline was significantly greater for telbivudine (6.3 $\log_{10}$) than lamivudine (5.5 $\log_{10}$; P<0.001). Serum HBV DNA became PCR-negative (<300 copies/mL) more rapidly in telbivudine-treated patients and PCR negativity at week 52 was significantly more frequent with telbivudine treatment compared to lamivudine (67 vs 38%, P<0.001). The proportion of patients with primary treatment failure (serum HBV DNA remained above 5 $\log_{10}$ copies/mL throughout the 52 weeks of treatment) was significantly lower with telbivudine compared to lamivudine (4 vs 18%, P<0.001). Therapeutic response was significantly more common in the telbivudine group (85%) compared to lamivudine (62%; P<0.001), and serum ALT levels were normalized in 87% of telbivudine recipients vs 75% of lamivudine recipients (P<0.007). HBeAg loss was significantly more frequent in the telbivudine group compared to lamivudine (31 vs 20%; P<0.047). HBeAg seroconversion was more frequent with telbivudine (25%)

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				compared to lamivudine (18%), but this difference was not statistically significant (P=0.14). No patient experienced HBsAg loss or seroconversion. <u>HBeAg-Negative Patients</u> Telbivudine as compared to lamivudine produced higher rates of therapeutic response (100 vs 82%), ALT normalization (100 vs 78%), and PCR-negative HBV DNA (85 vs 77%), and less primary treatment failure (0% for telbivudine vs 5% for lamivudine). However, these efficacy differences were not analyzed statistically because of the limited power for statistical comparisons within the small HBeAg-negative patient population. No patient experienced HBsAg loss or seroconversion. Both study drugs were generally well tolerated. Adverse events were reported in about half of the patients in both treatment arms; most adverse events were not attributed to the study drug by the clinical investigators.
Liaw et al.[95] (2009) Telbivudine 600 mg once daily vs lamivudine 100 mg once daily	RCT, DB, MC Adults aged 16 to 70 years with HBeAg-positive or HBeAg-negative chronic hepatitis B and compensated liver disease	N=1,370 2 years	Primary: Therapeutic response (defined as reduction of serum HBV DNA levels to <5 $\log_{10}$ copies/mL and normalization of ALT level or loss of serum HBeAg) Secondary: Serum HBV DNA changes from baseline, proportion of patients with HBV DNA non-detectable (<300 copies/mL), HBeAg loss and	Primary: In HBeAg-positive and HBeAg-negative patients at week 104, therapeutic response was achieved by significantly more recipients of telbivudine (63.3 and 77.5%, respectively) than lamivudine (48.2 and 66.1%, respectively; P<0.001 and P<0.007). Secondary: Reductions in serum HBV DNA level from baseline to week 104 were significantly greater with telbivudine compared to lamivudine in HBeAg-positive and HBeAg-negative patients. At week 104, serum HBV DNA was non-detectable in significantly more patients treated with telbivudine vs lamivudine in HBeAg-positive patients and HBeAg-negative patients. The mean time required to achieve non-detectable HBV DNA was significantly shorter with telbivudine vs lamivudine in HBeAg-positive patients (34 vs 39 weeks; P<0.001) and also in HBeAg-negative patients (20 vs 26 weeks; P<0.001). The rates of serum ALT normalization at week 104 were 70 and 62%

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			seroconversion, normalization of serum ALT level	among HBeAg-positive patients treated with telbivudine and lamivudine, respectively (P <0.05). In HBeAg-negative patients, normalization of ALT level by week 104 was achieved by 78 and 70% of telbivudine and lamivudine recipients, respectively (P=0.073). In all HBeAg-positive patients, a larger proportion of telbivudine recipients experienced HBeAg loss compared to lamivudine (P=0.056). The rates of HBeAg loss and seroconversion were proportionally greater in telbivudine compared to lamivudine recipients at all study visits from week 12 to week 104 and the difference increased over time. The proportion of patients reporting at least one adverse event through week 104 was similar for telbivudine and lamivudine (81 vs 77%, respectively).
Chan et al.[96] (2012) Telbivudine 600 mg once daily vs lamivudine 100 mg once daily	DB, MC, PRO, RCT Adults (18 to 70) with decompensated chronic hepatitis B	N=228 Primary and secondary analyses were performed at weeks 52 and 104	Primary: Composite endpoint of "clinical response", defined as the achievement of the following criteria: serum HBV DNA <10,000 copies/mL, normal serum ALT Level, improvement in/stabilization of Child-Turcotte-Pugh (CTP) score Secondary: individual components of the protocol-defined efficacy endpoint, safety	Primary: Clinical response (newly defined as HBV DNA <300 copies/mL and serum ALT normalization) was always higher in telbivudine-treated compared to lamivudine-treated patients from 24 to 104 weeks. Using a multivariate analysis, the following predictive factors of achieving this new combined endpoint at week 104 were identified: treatment with telbivudine (OR, 2.09; 95% CI, 1.05 to 4.18; P=0.037) and week 24 HBV DNA <300 copies/mL (OR, 3.48; 95% CI, 1.42 to 8.53; P=0.0064). The original primary efficacy endpoint for "clinical response" was achieved at week 52 in the intent-to-treat population for 56.2% of patients in the telbivudine group vs 54.0% in the lamivudine group. At week 104, 39.1% of patients in the telbivudine group had a clinical response compared with 36.4% in the lamivudine group. Consequently, demonstration of noninferiority was not achieved at 52 weeks (primary endpoint), but was achieved at 104 weeks (confirmatory endpoint). Secondary: Rates of 2-year cumulative virologic breakthrough were 28% for telbivudine-treated patients and 39% for lamivudine-treated patients. No significant difference in survival at week 104 was observed between patients with or without virologic breakthrough both in telbivudine-treated patients (P=0.23) and in lamivudine-treated patients (P=0.22).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Rates of cumulative genotypic resistance were 11% (n=13) in telbivudine-treated patients and 14% (n=16) in lamivudine-treated patients during year one. There were no significant differences between the treatment groups for adverse events that led to study drug discontinuation.
Jiang et al.[97] (2013) Telbivudine 600 mg once daily vs lamivudine 100 mg once daily	MA Adults with chronic hepatitis B	8 RCTs 12 to 24 months	Primary: Biochemical response, HBeAg seroconversion, virological response, virologic breakthrough, therapeutic response, adverse effects Secondary: Not reported	Primary: The biochemical response rate in the telbivudine group was higher than the lamivudine group at two years (P<0.00001). The rate of seroconversion was statistically significant in favor of the the telbivudine group at 24 months, but did not reach significance at 12 months. At 12 months, the response rate in the telbivudine group was higher than the lamivudine group (RR, 1.43; 95% CI, 1.12 to 1.84; P=0.005). When a low quality study was removed, the response rate between the two groups was not statistically significant by use of a random effects model (P=0.06). Three trials demonstrated the virological response rate at 24 months. The response rate in the telbivudine group was higher than the lamivudine group (RR, 1.46; 95% CI, 1.35 to 1.58; P<0.00001). When a low quality study was removed, the difference between the two groups was still statistically significant (P<0.00001). The rate of virologic breakthrough in the lamivudine group was higher than the telbivudine group. The difference was statistically significant for both time periods. The response rate was similar at 12 months and a statistically significant difference in favor of telbivudine was shown at 24 months. Adverse effects were similar between groups. Secondary: Not reported
Woo et al.[98]	MA	20 trials	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(2010) Lamivudine, adefovir, entecavir, peginterferon, telbivudine, tenofovir	Adults with HBeAg-positive and/or HBeAg-negative HBV	12 months	HBV-DNA levels <1000 copies/mL normalization of ALT levels HBeAg loss with seroconversion decreased HBsAg titer improved liver histology, adverse events Secondary: Not reported	Adefovir (four trials) HBeAg (+) Patients and HBeAg (-) Patients: Adefovir was not significantly better than lamivudine for outcomes. Adefovir did not rank in the top four for any outcome. Entecavir (three trials) HBeAg (+) Patients: Entecavir demonstrated greater efficacy compared to lamivudine in liver histology improvement (OR, 1.56; 95% CI, 1.12 to 2.19). Entecavir ranked first in predicted probability of improving liver histology (PP, 0.56; 95% CI, 0.12 to 0.94). Entecavir ranked in the top five therapies for all other outcomes. HBeAg (-) Patients: In direct comparisons, entecavir was not more efficacious than lamivudine. In indirect comparisons, entecavir was more efficacious than lamivudine for all outcomes and ranked in the top four for all outcomes. Lamivudine (10 trials) HBeAg (+) Patients: In direct comparisons, placebo was significantly less effective than lamivudine at ALT normalization (OR, 0.11; 95% CI, 0.03 to 0.38) and improving liver histology (OR, 0.27; 95% CI, 0.09 to 0.84). In indirect comparisons, lamivudine was superior to placebo in all outcomes except HBsAg loss. HBeAg (-) Patients: Lamivudine was more effective than placebo in indirect comparisons at achieving undetectable HBV-DNA. Lamivudine was ranked in the bottom two therapies for all other

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				outcomes. <u>Peginterferon (two trials)</u> HBeAg (+) Patients: In direct comparisons, PEG-INF was more effective than lamivudine monotherapy for HBeAg loss and HBsAg loss. PEG-INF was within the top four therapies for HBeAg seroconversion, HBeAg loss, HBsAb loss, and histologic improvement of the liver. HBeAg (-) Patients: PEG-INF was less effective than lamivudine in achieving undetectable HBV-DNA or ALT normalization. <u>Telbivudine (four studies)</u> HBeAg (+) Patients: In direct comparisons, telbivudine was more effective at achieving undetectable HBV-DNA compared to lamivudine (OR, 2.34; 95% CI, 1.31 to 5.36) and liver histology improvement (OR, 1.41; 95% CI, 1.09 to 1.84). Telbivudine ranked second for HBeAg loss and ranked last for HBsAg loss. HBeAg (-) Patients: In direct comparisons, telbivudine was not more efficacious than lamivudine. <u>Tenofovir (one study)</u> HBeAg (+) Patients: In indirect comparisons, tenofovir showed greater efficacy compared to lamivudine at achieving undetectable HBV-DNA (OR, 23.34; 95% CI, 6.19 to 76.39). Tenofovir ranked in the top three for all outcomes except HBeAg loss (no data). Tenofovir ranked first for achieving undetectable HBV-DNA (PP, 0.88; 95% CI, 069 to 0.97); normalization of ALT levels (PP, 0.66; 95%

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				CI, 0.41 to 0.91); HBeAg seroconversion (PP, 0.2; 95% CI, 0.07 to 0.43); HBsAg loss (PP, 0.05; 95% CI, 0.00 to 0.54). HBeAg (-) Patients: In direct comparisons, tenofovir was not more efficacious than lamivudine. In indirect comparisons, tenofovir ranked first for HBV-DNA suppression, histologic improvement and second for ALT normalization. <u>Lamivudine + Peginterferon</u> HBeAg (+) Patients: In direct comparisons, combination therapy was more effective than lamivudine monotherapy at inducing undetectable HBV-DNA (OR, 3.08; 95% CI, 1.88 to 4.91). The combination was ranked first in inducing HBeAg loss (PP, 0.39; 95% CI, 0.18 to 0.63); ranked third for HBeAg seroconversion; ranked second for HBsAg loss. HBeAg (-) Patients: Combination therapy was more effective than lamivudine at inducing undetectable HBV-DNA levels (OR, 2.40; 95% CI, 1.41 to 4.19). Combination therapy was less effective than lamivudine at inducing normalization of ALT levels (OR, 0.35; 95% CI, 0.23 to 0.55). <u>Lamivudine + Telbivudine</u> HBeAg (+) Patients: There was no benefit with combination therapy over lamivudine monotherapy. <u>Lamivudine + Adefovir</u> HBeAg (+) Patients: There was no benefit with combination therapy over lamivudine monotherapy.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Hepatitis C				
Brok et al.[99] (2005) Interferon monotherapy vs interferon in combination with ribavirin	MA Patients with hepatitis C patients without HIV who received interferon monotherapy or a combination of ribavirin and interferon	N=9,991 (72 trials) Variable duration	Primary: Failure of SVR ≥6 months and liver-related morbidity plus all-cause mortality Secondary: Failure of end-of-treatment virologic response, failure of histological response, quality of life (QOL) and adverse events	Primary: Compared to monotherapy, combination therapy with ribavirin significantly reduced the number with failure of SVR (RR, 0.73; 95% CI, 0.71 to 0.75). For the combined total of all patients studied, combination therapy significantly reduced morbidity and mortality (OR, 0.46; 95% CI, 0.22 to 0.96); however, morbidity and mortality were not significantly reduced compared to patients classified as naïve alone, nonresponders alone, or relapsers alone. Secondary: Combination therapy significantly reduced the number of patients with failure of virologic response at end-of-treatment (RR, 0.70; 95% CI, 0.67 to 0.72). Failure of histological response was significantly reduced with combination therapy, significantly reducing the number of patients with failure with grading (RR, 0.84; 95% CI, 0.80 to 0.87) and staging (RR, 0.95; 95% CI, 0.92 to 0.97). Where measured, combination therapy was found to significantly increase QOL, including measures of general health, social functioning and mental health. Anemia was reported in 22% of patients on combination therapy compared to 0.8% on monotherapy therapy (RR, 18.22; 95% CI, 12.92 to 25.70). Rates of leukopenia were significantly higher in patients treated with combination therapy (RR, 4.32; 95% CI, 1.56 to 11.90). Rates of dermatological and gastrointestinal adverse events also occurred significantly more often with combination therapy.
Swain et al.[100] (2010)	9 RCTs (Pooled analysis)	N=3,460 Variable	Primary: Percentage of patients with	Primary: A total of 1.2% of patients reported a major clinical event during the follow-up period. The most common reported events were ascites,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Peginterferon alfa-2a 90 to 270 µg/week plus ribavirin 800 to 1,600 mg/day	Patients with chronic hepatitis C	duration	significant clinical events (death, liver transplant, decompensated liver disease, encephalopathy or ascites, hepatic malignancy); undetectable HCV RNA (<50 IU/mL) at last assessment in the primary trial Secondary: Not reported	encephalopathy, and hepatic malignancy. A total of 89.1% of patients had undetectable HCV RNA at the last visit of their primary study and at least one HCV RNA assessment in the long-term follow-up period of the study. Of these patients, 98.7% continued to have an undetectable HCV RNA at a mean of four years after the end of their primary study. The main findings of this study showed that patients treated with peginterferon alfa-2a plus ribavirin do not require frequent follow-up laboratory assessment of their HCV RNA status. Secondary: Not reported
McHutchison et al.[101] (1998) Interferon alfa-2b 3 MIU three times a week for 24 to 48 weeks vs interferon alfa-2b 3 MIU three times a week plus ribavirin 1,000 to 1,200 mg once daily for 24 or 48 weeks	DB, PC, RCT Adult patients with hepatitis C	N=912 24 to 48 weeks	Primary: SVR 24 weeks after treatment Secondary: ALT and histologic improvement	Primary: SVR was significantly higher for all those on combination therapy (31 to 38%) compared to those receiving interferon alone (6 to 13%; P<0.001). Secondary: ALT levels normalized at the end of treatment in 58 to 65% of patients on combination therapy compared to 24 to 28% on monotherapy. Histologic improvement was significantly higher in patients on combination therapy (57 to 61%) compared to those on monotherapy (41 to 44%). Anemia necessitating a reduction in ribavirin dose occurred in 8% of patients on combination therapy. Dyspnea, pharyngitis, pruritus, rash, nausea, insomnia, and anorexia were more common with combination therapy than monotherapy. Dose reductions due to an adverse event occurred in 13 to 17% of patients on combination therapy compared to 9 to 12% in monotherapy.
Enriquez et al.[102] (2000)	RCT Adult patients with	N=120 24 to 48 weeks	Primary: Virologic response at end of treatment	Primary: Virologic response at the end of therapy was 44.8% in those treated for 24 weeks and 46.8% in those treated for 48 weeks (P=0.85).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Interferon alfa-2b 3 MIU three times a week plus ribavirin 1,000 to 1,200 mg once daily for 24 weeks vs interferon alfa-2b 3 MIU three times a week plus ribavirin 1,000 to 1,200 mg once daily for 48 weeks	hepatitis C who had previously received one or more courses of interferon alfa without achieving a sustained response		and SVR at six months after treatment Secondary: Not reported	SVR at six months was significantly higher in those treated for 48 weeks (37.1 vs 15.5%; P=0.013). Dose adjustments due to decreased hemoglobin levels occurred in 5% of patients treated for 48 weeks and 3% in those treated for 24 weeks. Influenza-like symptoms were reported in most patients for both treatment groups during the first two to four weeks. Secondary: Not reported
Poynard et al.[103] (1998) Interferon alfa-2b 3 MIU three times a week plus ribavirin 1,000 to 1,200 mg once daily for 24 weeks vs interferon alfa-2b 3 MIU three times a week plus ribavirin 1,000 to 1,200 mg once daily for 48 weeks vs	MC, PC, RCT, Adult patients with compensated hepatitis C not previously treated	N=832 48 weeks	Primary: SV) at week 24 after treatment Secondary: ALT and histological improvement	Primary: SVR was significantly higher for both combination regimens compared to monotherapy (P<0.001). SVR was observed in 43% of combination therapy patients treated for 48 weeks and in 35% of those treated for 24 weeks compared to 19% with SVR among those treated with monotherapy. Secondary: ALT normalization was significantly higher with combination therapy patients treated for 48 weeks (50%) compared to those treated for 24 weeks (39%; P=0.02) and those on monotherapy (24%; P<0.001). Inflammation improvement was significantly higher in patients on 48 weeks of combination therapy (63%) compared to those on 24 weeks therapy (52%; P=0.05) and monotherapy (39%; P<0.001). Those on 24 weeks of combination therapy had significantly greater improvement in inflammation compared to monotherapy (52 vs 39%; P=0.007). Significantly more patients treated for 48 weeks (monotherapy and combination therapy) discontinued therapy due to an adverse reaction, compared to those treated for 24 weeks.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
interferon alfa-2b 3 MIU three times a week plus placebo for 48 weeks				
Manns et al.[104] (2001) Interferon alfa-2b 3 MIU three times a week plus ribavirin 1,000 to 1,200 mg daily vs peginterferon alfa-2a 1.5 µg/kg/week plus ribavirin 800 mg daily vs peginterferon alfa-2a 1.5 µg/kg/week for 4 weeks, then 0.5 µg/kg/week plus ribavirin 1,000 to 1,200 mg daily	RCT Adult patients with a confirmed diagnosis of hepatitis C not previously treated	N=1,530 48 weeks	Primary: SVR Secondary: SVR for genotype 1, 2, and 3	Primary: SVR rates were significantly higher for the high-dose peginterferon regimen (54%) compared to low-dose peginterferon (47%; P=0.01) and interferon (47%; P=0.01). Secondary: The SVR rate for genotype 1 was 42% for the high-dose peginterferon regimen compared to 34% for low-dose peginterferon and 33% for interferon (P=0.02 vs high-dose peginterferon). The SVR rates for genotype 2 and 3 were approximately 80% for all treatment groups. The side-effect profiles were comparable among treatment groups.
Fried et al.[105] (2002) Interferon alfa-2b 3 MIU three times	RCT Adult patients with a confirmed diagnosis of	N=1,121 48 weeks	Primary: SVR at 24 weeks after therapy Secondary:	Primary: SVR rates 24 weeks after therapy were significantly higher for the peginterferon combination regimen (56%) compared to the interferon combination regimen (44%; P<0.001) and peginterferon monotherapy regimen (29%; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
a week plus ribavirin 1,000 to 1,200 mg daily vs peginterferon alfa-2a 180 µg/week vs peginterferon alfa-2a 180 µg/week plus ribavirin 1,000 to 1,200 mg/day	hepatitis C not previously treated with interferon alfa		Virologic response at end of therapy and virologic response for genotype 1, 2, and 3	Secondary: Virologic response rates at end of therapy were significantly higher for the peginterferon combination regimen (69%) compared to interferon (52%; P<0.001) and peginterferon monotherapy (59%; P=0.01). SVR rates for genotype 1 were significantly higher for the peginterferon combination regimen (46%) compared to interferon (36%; P=0.01) and peginterferon monotherapy (21%; P<0.001). SVR rates for genotype 2 or 3 were significantly higher for the peginterferon combination regimen (76%) compared to interferon (61%; P=0.005) and peginterferon monotherapy (45%). Withdrawals due to adverse events were comparable between treatment groups. The most common reason for discontinuation was a psychiatric disorder. Both peginterferon regimens had a lower incidence of influenza-like symptoms and depression compared to interferon (P<0.05).
Lam et al.[106] (2010) Peginterferon alfa-2a 180 µg/week plus ribavirin 800 to 1,200 mg daily for 24 weeks vs peginterferon alfa-2a 180 µg/week plus ribavirin 800 to 1,200 mg daily for 48 weeks	OL, MC, RCT Treatment-naïve adults with chronic hepatitis C genotype 6	N=60 24 to 48 weeks	Primary: SVR at the end of treatment period Secondary: Rapid virologic response (RVR), complete early virologic response (EVR), end of treatment response(ETR), biochemical response, and treatment adherence	Primary: At the end of the treatment period, there was no significant difference between the patients randomized to either 24 or 48 weeks of peginterferon for sustained virologic response (70% for 24 weeks vs 79% for 48 weeks; P=0.48). Secondary: Of the subgroup of patients who had HCV RNA polymerase chain reaction testing at week 4 of therapy, 85% in the 24 week group and 63% in the 48 week group achieved RVR (P=0.12). RVR was a significant predictor of SVR in the 48-week group and trending towards significance in the 24-week group: 82 and 83% of those with RVR achieved SVR compared to 33 and 29% for the 24-week and 48-week groups, respectively (P=0.07 and P=0.02). A similar percentage of patients in both the 24-week and 48-week groups achieved complete EVR (96 vs 97%, P=0.90) and ETR (89 vs 94%,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				P=0.48). Normalization of serum ALT levels 6 months after therapy was lower in the 24-week group compared to the 48-week group (78 vs 91%; P=0.16). Treatment adherence was 63% in the 24-week group compared to 79% for the 48-week group (P=0.18). There were no differences between the two treatment groups for rates of adverse events.
Ferenci et al.[107] (2010) Peginterferon alfa-2a 180 µg/week plus ribavirin 1,000 to 1,200 mg/day for 48 weeks (group A) vs peginterferon alfa-2a 180 µg/week plus ribavirin 1,000 to 1,200 mg/day for 72 weeks (group B)	RCT, MC Adult patients with chronic hepatitis C genotype 1/4 who had early virologic response (undetectable HCV RNA at 24 weeks)	N=517 24 weeks posttreatment	Primary: Relapse and SVR (defined as an undetectable HCV RNA at the end of the 24 week follow-up) Secondary: Not reported	Primary: The relapse rate was 33.6% in group A and 18.5% in group B (P=0.0115). The SVR rate was 51.1% in group A and 58.6% in group B (P>0.1). The overall SVR rate was 50.4%, including 115 of 150 patients with an RVR treated for 24 weeks and four of 78 patients without an EVR. There was no significant difference for rates of adverse events between the two treatment groups. Overall, there was a 17.3% adverse event rate in the 48 week group and 22.7% adverse event rate in the 72 week group. Secondary: Not reported
Van Vlierberghe et al.[108] (2010) Peginterferon alfa-2b 1.5 µg/kg/week plus	OL, OBS Treatment-naïve adult patients with chronic hepatitis C	N=219 48 weeks	Primary: SVR defined by undetectable HCV RNA six months after treatment completion	Primary: A total of 49.3% of patients had an undetectable HCV RNA at the end of 48 weeks of therapy. However, there was a fairly significant dropout rate and loss to follow-up (98 patients; 44.7%). A total of 41 patients discontinued therapy at various time points due to adverse events (n=23) or serious adverse events (n=18). The most

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
ribavirin 800 to 1,200 mg/day for 48 weeks			Secondary: Not reported	common serious adverse events were anemia, fatigue/asthenia/malaise, and fever. Secondary: Not reported
Buti et al.[109] (2010) Peginterferon alfa-2b 1.5 µg/kg/week plus ribavirin 800 to 1,400 mg/day for 48 weeks (group A) vs peginterferon alfa-2b 1.5 µg/kg/week plus ribavirin 800 to 1,400 mg/day for 72 weeks (group B)	OL, MC, RCT Adult patients with chronic hepatitis C genotype 1	N=1,428 48 to 72 weeks	Primary: SVR at the end of the treatment period Secondary: End-of-treatment virologic response, relapse rates, adverse events	Primary: At the end of the treatment period, there was no difference in the rates of SVR between the two treatment groups (43 vs 48%; P=0.644). Secondary: End-of-treatment response was 83 and 70% in groups A and B, respectively. Relapse rates were similar in slow responders treated for 48 or 72 weeks (47 vs 33%; P=0.169). There was no significant difference between the two groups when comparing adverse events; however the raw rates of adverse events in the group receiving 72 weeks of treatment were higher and may represent a clinical significance (3.5 vs 8.2%).
Katz et al.[110] (2012) Peginterferon (alfa-2a or alfa-2b) and ribavirin for 72 weeks vs peginterferon	MA Genotype 1 hepatitis C patients who are slow virological responders to peginterferon and ribavirin treatment (two definitions of slow responders: 1) patients with ≥2 log	N=1369 (7 trials)	Primary: Mortality, liver-related morbidity Secondary: SVR24, relapse, adherence, adverse events	Primary: Overall mortality, HCV-related mortality, and liver-related morbidity were not reported by any of the included trials. Secondary: When pooling the results of the five trials which defined slow responders according to the first definition, a small but significant increase in the SVR proportion was seen after extending treatment to 72 weeks (RR, 1.43; 95% CI, 1.07 to 1.92; P=0.02, I2=8%). In a meta-analysis of the three trials which defined the slow responders as patients without rapid virologic response, a statistically significant difference between the two groups (RR, 1.27; 95% CI, 1.07 to 1.50; P=0.006, I2=38%) was also

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(alfa-2a or alfa-2b) and ribavirin for 48 weeks	viral reduction but still detectable HCV RNA after 12 weeks of treatment and undetectable HCV RNA after 24 weeks of treatment; 2) patients with detectable HCV RNA after four weeks of treatment)			found. The end of treatment response was not significantly different between slow responders who were treated for 48 weeks and those treated for 72 weeks. This lack of difference was identified with both definitions of slow responders. The length of treatment did not affect the adherence proportion (RR, 0.95; 95% CI, 0.84 to 1.07; P=0.42, I2=69%, 3 trials).
Brady et al.[111] (2010) Peginterferon alfa-2b 3.0 µg/kg/week for 12 weeks, then 1.5 µg/kg/week for 36 weeks, plus ribavirin 11 to 15 mg/kg/day for 48 weeks (induction group) vs peginterferon alfa-2b 1.5 µg/kg/week plus ribavirin 11 to 15 mg/kg/day for 48 weeks (SOC)	RCT, OL Treatment-naïve adult patients with chronic hepatitis C genotype 1 or 4	N=610 6 months	Primary: SVR defined as persistent loss of HCV RNA at 6 months of follow-up evaluation after completion of 48 weeks of treatment Secondary: Early virologic response (virus-negative at week 12); subgroup analysis of SVR response in African American and Hispanic populations	Primary: Complete early virologic response was 62.6 vs 57.7% in induction vs SOC (P=NS). Overall SVR was 32% in the induction group vs 29% in SOC group (P=0.434). Secondary: A total of 48.8% of patients from the induction group and 42.8% of patients from the SOC group discontinued therapy before 48 weeks (P=0.2). Overall SVR in African Americans was similar in the patients receiving induction therapy (35%) vs SOC (32%; P=0.9). Overall SVR for Hispanic patients was similar in patients receiving induction therapy (36.1%) vs SOC (22.5%; P=0.292). As shown in other studies with peginterferon alfa-2b combined with ribavirin, there was a large portion of patients experience adverse events. There were no significant life-threatening adverse events reported in any study group. There were also no significant differences between the two study groups for rates of adverse events.
McHutchison et al.[112] (2009)	RCT, DB, MC Patients ≥18 years	N=3,070 24 weeks	Primary: SVR (defined as undetectable	Primary: The rates of SVR did not differ significantly among the three treatment groups, with a rate of 39.8% (95% CI, 36.8 to 42.8) for standard-dose

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Peginterferon alfa-2b 1.5 µg/kg/week plus ribavirin 800 to 1,400 mg/day for 48 weeks (standard-dose arm) vs peginterferon alfa-2b 1.0 µg/kg/week plus ribavirin 800 to 1,400 mg/day for 48 weeks (low-dose arm) vs peginterferon alfa-2a 180 µg/week plus ribavirin 1,000 to 1,200 mg/day for 48 weeks	of age with compensated liver disease due to chronic HCV genotype 1 infection and a detectable plasma HCV RNA level who had not been previously treated for hepatitis C infection	posttreatment	HCV RNA levels 24 weeks after the completion of therapy) Secondary: Rates of virologic response during the treatment phase and relapse (defined as an undetectable HCV RNA level at the end of the treatment phase, with a detectable HCV RNA level during the follow-up period)	peginterferon alfa-2b, 38.0% (95% CI, 35.0 to 41.0) for low-dose peginterferon alfa-2b, and 40.9% (95% CI, 37.9 to 43.9) for peginterferon alfa-2a, (P=0.20 for standard-dose vs low-dose peginterferon alfa-2b; P=0.57 for standard-dose peginterferon alfa-2b vs peginterferon alfa-2a). Secondary: Response rates at the end of the treatment phase were higher with peginterferon alfa-2a than with either peginterferon alfa-2b regimen, however the virologic relapse rate was also higher. HCV RNA suppression at treatment weeks four and 12 was strongly associated with achievement of sustained virologic response in all three treatment groups. Fewer than 5% of patients who had a reduction from the baseline HCV RNA level of less than 1 $\log_{10}$ IU/ml at week four also had a sustained virologic response. A prolonged time (>12 weeks of therapy) to undetectable HCV RNA level was associated with a higher likelihood of relapse after treatment. Rates of sustained virologic response were similar among the three treatment groups, within the subgroups of patients receiving the same dose of ribavirin. Relapse rates were 23.5% for standard-dose peginterferon alfa-2b, 20.0% for low-dose peginterferon alfa-2b, and 31.5% for peginterferon alfa-2a (95% CI, –13.2 to –2.8 for the standard dose regimens; 95% CI, –1.6 to 8.6% for standard-dose peginterferon alfa-2b vs low-dose peginterferon alfa-2b). The types and frequencies of adverse events were similar among the three groups. The most common adverse events included influenza-like symptoms, depression, and the hematologic events of anemia and neutropenia. The proportion of patients with neutropenia was 21.1% in patients receiving peginterferon alfa-2a, 19.4% in patients receiving standard-dose peginterferon alfa-2b, and 12.5% in patients receiving low-dose peginterferon alfa-2b. Most psychiatric adverse events were mild or moderate and were not treatment-limiting.
McHutchison et	DB, MC, PC, RCT	N=263	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
al.[113] (2009) PROVE1 Peginterferon alfa-2a 180 µg/week, ribavirin 1,000 to 1,200 mg/day and telaprevir 1,250 mg as a single dose, then 750 mg 3 times daily for 12 weeks, followed by peginterferon alfa-2a and ribavirin for 12 weeks (T12PR24) vs peginterferon alfa-2a 180 µg/week, ribavirin 1,000 to 1,200 mg/day and telaprevir 1,250 mg as a single dose, then 750 mg 3 times daily for 12 weeks, followed by peginterferon alfa-2a and ribavirin for 36 weeks (T12PR48) vs	Patients 18 to 65 years of age with chronic genotype 1 HCV infection who were treatment-naïve	72 weeks	SVR, rapid virologic response rates, relapse rates, viral breakthrough, safety Secondary: Not reported	The SVR rate was 61% in the T12PR24 group compared to 41% in the PR48 group (P=0.02).The SVR rates were 67% in the T12PR48 group (P=0.002 and P=0.51 for the comparison with the PR48 group and the T12PR24 group, respectively) and 35% in the T12PR12 group. In a subgroup of black patients, rates of SVR were 11% in the PR48 group and 44% in the telaprevir-based groups. Rates of rapid virologic response were higher with telaprevir- based therapy than without it (P<0.001 for each comparison). At the end of treatment, 75% of patients in the PR48 group and 76% of those in the telaprevir-based groups had normal ALT values. Only 2% of patients in the T12PR24 group had a relapse compared to 6% of patients in the T12PR48 group and 33% of patients in the T12PR12 group. In the PR48 group, 23% of patients had a relapse. Among the telaprevir-treated patients, 7% of patients had viral breakthrough. The most common adverse events were rash, pruritus, nausea, and diarrhea with telaprevir. The proportion of patients who discontinued treatment because of an adverse event was higher in the three telaprevir-based treatment groups (21%) than in the PR48 group (11%). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
peginterferon alfa-2a 180 µg/week, ribavirin 1,000 to 1,200 mg/day and telaprevir 1,250 mg as a single dose, then 750 mg 3 times daily for 12 weeks (T12PR12) vs peginterferon alfa-2a 180 µg/week and ribavirin 1,000 to 1,200 mg/day for 48 weeks (PR48)				
McHutchison et al.[114] (2010) PROVE3 Peginterferon alfa-2a 180 µg/week, ribavirin 1,000 to 1,200 mg/day and telaprevir 1,125 mg as a single dose, then 750 mg 3 times daily for 12 weeks, followed by peginterferon alfa-2a and ribavirin for	RCT Patients 18 to 70 years of age with chronic hepatitis C virus infection genotype 1 who had previously been treated for HCV infection with peginterferon alfa and ribavirin but did not have a sustained virologic response	N=465 72 weeks	Primary: SVR, early response, virologic breakthrough, relapse rate Secondary: Not reported	Primary: SVR rates were significantly higher in the telaprevir-treated groups (T12PR24, 51%; T24PR48, 53%; and T24P24, 24%) compared to the PR48 group (14%; P<0.001, P<0.001, P=0.02, respectively). The response rates at the end of treatment period, at week four and at week 12 were all higher in the telaprevir groups compared to the control group. Relapse rates were 30, 13, and 53% in the T12PR24, T24PR48 and T24P24 groups, respectively compared to 53% in the PR48 group. Virologic breakthrough at week 24 was 13, 12, and 32% in the T12PR24, T24PR48 and T24P24 groups, respectively compared to 3% in the PR48 group. In the telaprevir groups, those with breakthrough were mostly non-responders. In patients with a previous nonresponse, SVR rates were 39, 38, and 11%

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
12 weeks (T12PR24) vs peginterferon alfa-2a 180 µg/week, ribavirin 1,000 to 1,200 mg/day and telaprevir 1,125 mg as a single dose, then 750 mg 3 times daily for 24 weeks, followed by peginterferon alfa-2a and ribavirin for 24 weeks (T24PR48) vs peginterferon alfa-2a 180 µg/week and telaprevir 1,125 mg as a single dose, then 750 mg 3 times daily for 24 weeks (T24P24) vs peginterferon alfa-2a 180 µg/week and ribavirin 1,000 to 1,200 mg/day				in the T12PR24, T24PR48, and T24P24 groups, respectively compared to 9% in the PR48 group. In patients with a previous relapse, SVR rates were 69, 76, and 42% in the T12PR24, T24PR48 and T24P24 groups, respectively compared to 20% in the PR48 group. SVR was significantly associated with T12PR24 and T24PR48 groups, an undetectable HCV RNA level during previous PR therapy, and low baseline viral load (<800,000 IU/ml). Rash and pruritus were more common in the telaprevir groups than PR48 group. The incidence was 50% in T12PR24 and 60% in T24PR48 groups compared to 20% in PR48. Severe grade 3 rash occurred in 5% of T12PR24, 4% of T245PR48 and 3% of T24P24 compared to 0% in PR48. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
for 48 weeks (PR48)				
Kwo et al.[115] (2010) SPRINT-1 Peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 800 to 1,400 mg/day for 48 weeks (PR48) vs peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 800 to 1,400 mg/day for 4 weeks, followed by peginterferon alfa-2b, ribavirin, and boceprevir 800 mg 3 times a day for 24 weeks (PRB24) vs peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 800 to 1,400 mg/day for 4 weeks, followed by peginterferon	MC, OL, RCT Patients 18 to 60 years of age with hepatitis C genotype 1 who were treatment-naïve	N=595 72 weeks	Primary: SVR and viral breakthrough Secondary: Not reported	Primary: All four boceprevir groups had significantly better SVR than the PR48 control group. In the 28-week treatment groups, the SVR was 56% in the PR4/PRB24 group (P=0.005 vs control) and 54% in the PRB28 group (P=0.013 vs control). In the 48-week treatment groups, the SVR was 75% in the PR4/PRB44 group (P<0.0001 vs control) compared to 67% in the PRB48 group (P<0.0001 vs control). There were significantly lower relapse rates in the 48-week treatment groups compared to PR48 control (PRB48, P=0.0079; PR4/PRB44, P=0.0002). Low-dose ribavirin was associated with a high rate of viral breakthrough (27%), and a rate of relapse (22%) similar to control (24%). The rate of breakthrough in the boceprevir lead-in groups was 4% compared to 9% in the boceprevir groups with no lead in (P=0.057). In the 28-week treatment groups, 82% of patients in the PR4/PRB24 group and 74% in the PRB28 group who had rapid virological response achieved SVR. In the 48-week treatment groups, 94% of patients assigned to PR4/PRB44 and 84% assigned to PRB48 who achieved undetectable hepatitis C virus RNA by week four of boceprevir achieved SVR. The most common side effects in the boceprevir group were fatigue, anemia, nausea and headache, which was similar to PR48 control. The rate of dysgeusia and anemia was higher in boceprevir groups than other groups. Treatment discontinuation was nine to 19% in boceprevir studies compared to 8% in the PR48 control group. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
alfa-2b, ribavirin, and boceprevir 800 mg 3 times a day for 44 weeks (PRB44) vs peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 800 to 1,400 mg/day plus boceprevir 800 mg 3 times a day for 28 weeks (PRB28) vs peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 800 to 1,400 mg/day plus boceprevir 800 mg 3 times a day for 48 weeks (PRB48) vs peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 400 to 1,000 mg/day for 4 weeks, followed by peginterferon				

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
alfa-2b, ribavirin, and boceprevir 800 mg 3 times a day for 48 weeks (PRB48)				
Kowdley et al.[116] (2013) ATOMIC Cohort A: sofosbuvir 400 mg orally once daily, peginterferon 180 µg subcutaneously once a week, and ribavirin orally as a divided weight-based daily dose (<75 kg received 1000 mg and those ≥75 kg received 1200 mg) for 12 weeks vs Cohort B received the same drugs at the same doses for 24 weeks vs Cohort C received the same regimen as individuals in cohort A followed	MC, OL, R Patients with chronic HCV infection (genotypes 1, 4, 5, or 6), aged 18 years or older, and had not previously received treatment for HCV infection	N=316 12 to 24 weeks (plus 24 weeks of follow up)	Primary: SVR24 Secondary: Safety	Primary: Cohort A: 46 of 52 (89%; 95% CI, 77 to 96%) Cohort B: 97 of 109 (89%; 95% CI, 82 to 94%) Cohort C: 135 of 155 (87%; 95% CI, 81 to 92%) No difference was found in the proportions of patients achieving SVR24 between cohorts A and B (P=0.94) or between cohorts A and C (P=0.78), suggesting no additional benefit of treatment durations longer than 12 weeks. Secondary: Most patients (97 to 99%) had at least one adverse event during the study. The most common adverse events were those consistent with the known safety profile for peginterferon and ribavirin: fatigue, headache, and nausea.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
by an additional 12 weeks of sofosbuvir monotherapy for half the patients, or sofosbuvir plus ribavirin for the other half (with patients randomly allocated to these subcohorts)				
Lawitz et al.[117] (2013) NEUTRINO and FISSION NEUTRINO: Sofosbuvir 400 mg once daily for 12 weeks, peginterferon alfa-2a 180 µg once weekly for 12 weeks, and ribavirin 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) for 12 weeks FISSION: Sofosbuvir 400 mg once daily for 12 weeks and ribavirin 1,000 mg/day (weight	NEUTRINO: MC, OL, SG Patients ≥18 years of age with confirmed diagnosis of chronic HCV infection (genotypes 1, 4, 5, or 6), serum HCV RNA levels of ≥10,000 IU/mL during screening, and who had never received treatment for HCV infection FISSION: AC, MC, OL, R Patients ≥18 years of age with confirmed diagnosis of chronic HCV infection (genotypes 2 or 3), serum HCV RNA levels of	NEUTRINO: N=327 12 weeks FISSION: N=499 24 weeks	NEUTRINO: Primary: SVR12 Secondary: Not reported FISSION: Primary: SVR12 Secondary: Not reported	NEUTRINO: Primary: Treatment with sofosbuvir added to peginterferon alfa-2a and ribavirin achieved a SVR12 in 90% of patients (95% CI, 87 to 93). In addition, this regimen was found to be more effective in achieving a SVR12 compared to an adjusted historical response rate of 60% (P<0.001) observed in studies of telaprevir and boceprevir. The rate of SVR12 was 92% (95% CI, 89 to 95) among patients without cirrhosis and 80% (95% CI, 67 to 89) among those with cirrhosis. A SVR12 occurred in 98% of patients with the CC genotype of IL28B, as compared to 87% of patients with the non–CC IL28B genotype. Rates of SVR12 were similar among various HCV genotypes: 89% for patients with genotype 1 (92% for genotype 1a and 82% for genotype 1b) and 96% for those with genotype 4. The single patients with genotype 5 and all six patients with genotype 6 achieved SVR12. Secondary: Not reported FISSION: Primary: A SVR12 was achieved in 67% of patients in both sofosbuvir plus ribavirin group and peginterferon alfa-2a plus ribavirin group.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<75 kg) or 1,200 mg/day (weight ≥75 kg) for 12 weeks vs peginterferon alfa-2a 180 µg once weekly for 24 weeks and ribavirin 800 mg/day in two divided doses for 24 weeks	≥10,000 IU/mL during screening, and who had never received treatment for HCV infection			Response rates in patients receiving sofosbuvir plus ribavirin were lower among patients with genotype 3 infection than among those with genotype 2 infection (56 vs 97%). Among patients with cirrhosis at baseline, 47% of patients receiving sofosbuvir plus ribavirin had a SVR12 compared to 38% of those receiving peginterferon alfa-2a plus ribavirin. Secondary: Not reported
Lawitz et al.[118] (2013) Cohort A (HCV genotype 1 patients): sofosbuvir 200 mg, sofosbuvir 400 mg, or placebo (randomized 2:2:1) for 12 weeks in combination with peginterferon (180 µg per week) and ribavirin (1000 to 1200 mg daily), followed by peginterferon and ribavirin for an additional 12 weeks or 36 weeks (depending on	DB, RCT Treatment-naive patients aged 18 to 70 with HCV genotypes 1, 2, and 3 and no cirrhosis	N=122 (Cohort A) N=25 (Cohort B)	Primary: Safety and tolerability Secondary: SVR12, SVR24	Primary: The most common adverse events during sofosbuvir dosing (up to week 12) were fatigue, headache, nausea, chills, pain, and insomnia. Most adverse events were mild or moderate in severity. Eight patients in cohort A discontinued treatment because of an adverse event, six within the first 12 weeks of treatment (three in the placebo group and three in the 400 mg sofosbuvir group). Secondary: In cohort A, compared with the placebo group, SVR12 and SVR24 were more common in the 200 mg sofosbuvir group (differences of 30%; 95% CI, 12 to 49; P=0.001, and 28%, nine to 46; P=0.0017, respectively) and in the 400 mg sofosbuvir group (differences of 32%; 13 to 51; P=0.0005, and 30%, 11 to 49; P=0.0006, respectively). Of the 25 patients in cohort B, most achieved both SVR12 and SVR24 (23 patients (92%) for both SVR12 and 24; 95% CI, 74 to 99).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
viral response) Cohort B (genotypes 2 or 3): open-label sofosbuvir 400 mg plus peginterferon and ribavirin for 12 weeks				
Gane et al.[119] (2013) Group 1: Sofosbuvir 400 mg and ribavirin 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) for 12 weeks Group 2: Group 1 treatment plus 4 weeks of concomitant peginterferon alfa-2a 180 µg once weekly Group 3: Group 1 treatment plus 8 weeks of concomitant peginterferon alfa-2a 180 µg once weekly	OL Patients19 years of age or older, who had chronic HCV infection without cirrhosis	N=95	Primary: Serum HCV RNA levels, safety Secondary: Not reported	Primary: Viral suppression was rapid in all patients, regardless of genotype, status with respect to previous treatment, baseline viral load, race or ethnic group, IL28B status, and presence or absence of interferon in the regimen. All 95 patients had an undetectable level of HCV RNA by week four, with viral suppression sustained through the end of treatment. All 40 patients with HCV genotype 2 or 3 infection who received sofosbuvir and ribavirin for 12 weeks had an undetectable level of serum HCV RNA at two, four, eight, 12, 24, and 48 weeks after treatment. The presence or absence of peginterferon alfa-2a appeared to have no effect on viral kinetics or rate of sustained virologic response. Six of the 10 patients in the sofosbuvir monotherapy group had a sustained virologic response at 12 and 24 weeks after treatment. All 95 patients completed treatment. The most common adverse events were headache, fatigue, insomnia, nausea, rash, and anemia. Hematologic abnormalities were more common among patients who received interferon than among those who did not. Neutropenia and thrombocytopenia were not observed in the groups that did not receive interferon. However, sofosbuvir monotherapy was associated with a modest decrease in the hemoglobin level. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Group 4: Group 1 treatment plus 8 weeks of concomitant peginterferon alfa-2a 180 µg once weekly (additional groups amended): Group 5: Sofosbuvir 400 mg daily monotherapy for 12 weeks Group 6: Sofosbuvir plus peginterferon and ribavirin for 8 weeks				
Zeuzem et al.[120] (2014) VALENCE Sofosbuvir 400 mg once daily for 12 weeks and ribavirin 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) for 12 weeks vs	DB, MC, PC, R Patients ≥18 years of age with confirmed diagnosis of chronic HCV infection (genotypes 2 or 3) and serum HCV RNA levels of ≥10,000 IU/mL during screening	N=419 12 weeks (genotype 2) or 24 weeks (genotype 3)	Primary: SVR12 Secondary: Not reported	Primary: Treatment with sofosbuvir plus ribavirin achieved a SVR12 in 93% (95% CI, 85 to 98) of patients with HCV genotype 2 receiving 12 weeks of therapy and 85% (95% CI, 80 to 89) of patients with HCV genotype 3 receiving 24 weeks of therapy. Among patients with genotype 2 infection receiving sofosbuvir plus ribavirin, high SVR12 rates were observed in treatment-naïve non-cirrhotics (96.7%; 95% CI, 82.8 to 99.9), treatment-naïve cirrhotics (100%; 95% CI, 15.8 to 100), and treatment-experienced non-cirrhotics (93.8%; 95% CI, 79.2 to 99.2), whereas lower SVR12 rate was observed in treatment-experienced cirrhotics with genotype 2 infection (77.8%; 40.0 to 97.2). Similarly, among patients with genotype 3 infection receiving sofosbuvir plus ribavirin, high SVR12 rates were observed in treatment-naïve non-

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo After study initiation, on the basis of emerging data from phase 3 trials, the study was unblinded, treatment for all patients with genotype 3 infection was extended to 24 weeks, the placebo group was terminated, and the goals of the study were redefined to be descriptive and not include hypothesis testing.				cirrhotics (94.6%; 95% CI, 86.3 to 97.6), treatment-naïve cirrhotics (92.3%; 95% CI, 64.0 to 99.8), and treatment-experienced non-cirrhotics (86.7%; 95% CI, 78.4 to 92.7), whereas lower SVR12 rate was observed in treatment-experienced cirrhotics with genotype 3 infection (61.7%; 46.4 to 75.5). Secondary: Not reported
Lawitz et al.[121] (2014) COSMOS Group 1: simeprevir and sofosbuvir with ribavirin for 24 weeks vs Group 2: simeprevir and sofosbuvir without ribavirin for 24	OL, RCT Patients ≥18 years of age with chronic HCV genotype 1 infections who had previously not responded to pegylated interferon and ribavirin or were treatment naïve	N=167 12 or 24 weeks	Primary: SVR12 Secondary: SVR4, SVR24, on-treatment failure, viral relapse	Primary: 154 (92%) of 167 of patients achieved SVR12, 90% (95% CI, 81 to 96) in cohort 1 and 94% (87 to 98) in cohort 2. SVR12 was seen in 98 (91%) of 108 patients who received ribavirin vs 56 (95%) of 59 of those who did not. Rates were similar by treatment status (38 [95%] of 40 treatment-naive patients vs 116 [91%] of 127 previous non-responders) or treatment duration (77 [94%] of 82 after 12 weeks of treatment vs 77 [91%] of 85 after 24 weeks). Secondary: All patients who achieved SVR12 also achieved SVR4. More than 91% of patients overall achieved SVR4. Rapid virological response was achieved in 81% of patients overall, but SVR12 was still achieved in all but one who had detectable HCV RNA titers four weeks after the start of treatment.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
weeks vs Group 3: simeprevir and sofosbuvir with o ribavirin for 12 weeks vs Group 4: simeprevir and sofosbuvir without ribavirin for 12 weeks [Cohort 1: previous non-responders to peginterferon and ribavirin with moderate liver fibrosis (METAVIR score F0–F2); Cohort 2: previous non-responders to peginterferon and ribavirin or treatment naïve with severe liver fibrosis (METAVIR score F3–F4)]				No patients experienced on-treatment virological failure, including viral breakthrough. Six patients had viral relapse after the end of treatment. At the time of relapse, five of the six had developed resistance-associated mutations to simeprevir, but none to sofosbuvir.
Herpes Simplex Virus Infections				

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Chosidow et al.[122] (2001) Acyclovir 200 mg five times daily for 5 days vs famciclovir 125 mg twice daily for 5 days	DB, PG, RCT Adult patients with genital herpes who had ≥3 occurrences within the past 12 months	N=204 10 days	Primary: Lesion healing time, defined as re-epithelialization of the lesions Secondary: Proportion of healed lesions at the different days of clinical evaluation and duration of symptoms	Primary: Mean healing times were 5.13 days with famciclovir and 5.38 days with acyclovir (difference, 0.25 days; 95% CI, –0.32 to 0.82). Famciclovir was considered statistically equivalent to acyclovir. Secondary: There were no significant differences between the two treatment groups in the proportion of patients having complete healing at the different days of evaluation. Duration of symptoms was comparable between treatment groups. Drug-related adverse events did not differ between treatment groups in severity or frequency. The most commonly reported adverse events included headache, nausea, gastrointestinal disorder and sore throat.
Romanowski et al.[123] (2000) Acyclovir 400 mg five times daily for 7 days vs famciclovir 500 mg twice daily for 7 days	DB, PG, RCT Adult patients with HIV clinically diagnosed with mucocutaneous HSV infection (orolabial or genital) and prior history of lesions	N=293 7 days	Primary: Proportion of patients developing new lesions during treatment Secondary: Time to complete healing, time to cessation of viral shedding, duration of lesion-associated symptoms and number of withdrawals due to treatment failure	Primary: The percentage of patients developing new lesions occurred in 16.7% of the famciclovir-treated patients and 13.3% of the acyclovir-treated patients (95% CI, –4.8 to 11.5). Secondary: Median time to complete healing was calculated as 7 days in both treatment groups (HR, 1.01; 95% CI, 0.79 to 1.29; P=0.95). Median time to cessation of viral shedding was 2 days for both treatment groups (HR, 0.93; 95% CI, 0.68 to 1.27; P=0.64). Median time to loss of lesion-associated symptoms was 4 days in both treatment groups (HR, 0.99; 95% CI, 0.75 to 1.30; P=0.93). Two patients treated with acyclovir and one patient treated with famciclovir withdrew due to treatment failure. The occurrence of drug-related adverse events was comparable between treatment groups. The most commonly reported adverse events were headache, nausea, and diarrhea.
Warkentin et al.[124]	RCT, SB	N=151	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(2002) Acyclovir 400 mg three times daily vs valacyclovir 500 mg twice daily vs valacyclovir 250 mg twice daily	Patients ≥16 years old with a hematologic malignancy receiving chemotherapy or undergoing stem cell transplant positive for HSV antibody	Median 35 days	Incidence of HSV infection Secondary: Evidence of CMV infection or disease, VZV infection, and genital or disseminated HSV	The incidence of HSV infection was similar between all treatment groups (P=0.08). Secondary: None of the patients developed CMV infection or disease, VZV infection, or genital or disseminated HSV infection during the study. Overall rates of adverse events were comparable between the 3 treatment groups (P=0.53). Gastrointestinal adverse events were most commonly reported (48%) followed by nephrotoxicity (30%).
Wald et al.[125] (2006) Famciclovir 250 mg twice daily vs valacyclovir 500 mg once daily	DB, RCT (2 trials) Two randomized trials of adult patients with recurrent genital herpes with ≥6 recurrences in the past year	N=390 10 to 16 weeks	Primary: Time to recurrence, proportion of days with HSV detected by polymerase chain reaction (PCR) Secondary: Time to first virologic-confirmed recurrence and proportion of days with subclinical shedding	Primary: Time to recurrence was comparable between the two treatment groups (HR, 1.17; 95% CI, 0.78 to 1.76; P=0.45). HSV was detected by PCR on 3.2% of days with famciclovir compared to 1.3% of the days with valacyclovir (HR, 2.33; 95% CI, 1.18 to 4.89; P=0.014). Secondary: Time to virologic-confirmed recurrence was significantly shorter with famciclovir compared to valacyclovir (HR, 2.15; 95% CI, 1.00 to 4.60; P=0.049). HSV shedding was detected on 32.4% of days with famciclovir compared to 1.1% of the days with valacyclovir (HR, 2.05; 95% CI, 1.07 to 4.11; P=0.031). Drug-related adverse events were mild and comparable between treatment groups. The most commonly reported adverse event was headache.
Abudalu et al.[126] (2008) Famciclovir 1 g	DB, MC, RCT Immunocompetent adults aged ≥18	N=1,179 14 days	Primary: Time to healing (defined as loss of crust plus re-	Primary: In the modified ITT population, the time to healing of non-aborted lesions was similar for patients who received single-day famciclovir (4.25 days) and patients who received 3-day valacyclovir (4.08 days; P=0.48).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
twice daily as a single dose vs valacyclovir 500 mg twice daily for 3 days	years with genital herpes, laboratory evidence of HSV infection, and experienced ≥4 recurrences of genital herpes in the preceding 12 months		epithelialization of all non-aborted lesions) Secondary: Proportion of patients with aborted lesions and patient-reported time to resolution of genital herpes-associated symptoms	In the per protocol population, the time to healing of non-aborted lesions was similar for patients who received single-day famciclovir (4.45 days) and patients who received 3-day valacyclovir (4.14 days; P=0.44). Secondary: A similar proportion of patients in both treatment groups comprising the ITT population experienced aborted lesions, including 32.7% (121 of 370 patients) in the famciclovir group and 33.6% (128 of 381) in the valacyclovir group. In the ITT population, patients receiving single-day famciclovir had similar median times to resolution of all symptoms associated with recurrent genital herpes, as well as similar median time to resolution of each individual symptom (i.e., pain, itching, tingling, burning, and tenderness), compared to the 3-day valacyclovir group.
Bodsworth et al.[127] (2009) Famciclovir 1 gram twice daily as a single dose vs valacyclovir 500 mg twice daily for 3 days	DB, MC, RCT Immunocompetent adults aged ≥18 years with genital herpes, laboratory evidence of HSV infection, and experienced ≥4 recurrences of genital herpes in the preceding 12 months	N=751 6 months	Primary: Time to next recurrence, antiviral resistance Secondary: Not reported	Primary: The frequency of patients with next recurrence and the time to next recurrence was similar between those assigned the single-day famciclovir and 3-day valacyclovir regimen. The median time to next recurrence from treatment initiation was 33.5 days in the famciclovir group and 38.0 days in the valacyclovir group. Susceptibility to penciclovir was evaluated in 573 viral isolates obtained before and during treatment of the initial outbreak, or before treatment of the subsequent outbreak. None exhibited resistance to penciclovir. Secondary: Not reported
Lebrun-Vignes et al.[128] (2007) Acyclovir (ACV), famciclovir (FVC), valacyclovir (VACV)	MA Immunocompetent individuals with genital herpes	N=6,158 (14 trials) Variable duration	Primary: Recurrence of genital herpes Secondary: Not reported	Primary: The global RR of developing at least one recurrence during the trial was reduced by 47% (95% CI, 45 to 49). The number of patients needed to treat was 2.15 (95% CI, 2.06 to 2.25). The analysis according to the drug showed the efficacy of each antiviral agent tested (all doses and regimens pooled), with RR reductions of 53% (95% CI, 51 to 57) for ACV, 43% (95% CI, 41 to 47) for VACV, and 42%

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs placebo				(95% CI, 35 to 50) for FCV. Analysis according to the total daily dose of each drug showed that all the studied ACV doses were effective. The best evaluated daily dose was 800 mg. For VACV, all the doses studied were effective with the best evaluated daily dose being 500 mg. The results of this analysis suggested a dose-dependent response with 250 mg/day being less effective than 500 mg/day, and a maximum efficacy above 500 mg/day. For FCV, 125 mg/day was not effective, but higher doses achieved significant efficacy, with a clear dose-effect response between 250 and 750 mg/day. For ACV 800 mg/day, all regimens (once, twice, or four times daily) had significant efficacy, with the best evaluated regimen being the twice-daily (400 mg) schedule (total 800 mg). No difference in efficacy was found between the two (once or twice daily) regimens for VACV at 500 mg/day. Only the FCV (250 mg) twice-daily schedule (total 500 mg/day) was effective, with the once-daily administration failing to reach significance. Secondary: Not reported
Herpes Zoster Virus Infections				
Tyring et al.[129] (2001) Acyclovir 800 mg five times daily for 10 days vs	DB, MC, RCT Patients 12 years and older with immunosuppression with clinical evidence of herpes zoster	N=148 10 days	Primary: Proportion of patients with new lesions while on medication, time to complete healing of lesions, and time to resolution of acute phase pain	Primary: New lesion formation was reported in 77% of patients treated with famciclovir and 73% of patients taking acyclovir (95% CI, –9.2 to 18.6%). Median time to complete healing was 20 days with famciclovir and 21 days with acyclovir (HR, 0.98; 95% CI, 0.67 to 1.42). Median time to loss of acute phase pain was 14 days with famciclovir and 17 days with acyclovir (HR, 1.11; 95% CI, 0.71 to 1.75).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
famciclovir 500 mg three times daily for 10 days			Secondary: Not reported	Drug-related adverse events reported were comparable between the two treatment groups. The most commonly reported adverse events were nausea, headache and vomiting. Secondary: Not reported
Shafran et al.[130] (2004) Acyclovir 800 mg five times a day vs famciclovir 750 mg once daily vs famciclovir 500 mg twice daily vs famciclovir 250 mg three times daily	DB, MC, RCT Adult patients with herpes zoster lesions for <72 hours	N=559 7 days	Primary: Healing rates Secondary: Not reported	Primary: There were no significant differences between any of the treatment groups in respect to healing rates. The frequency of drug-related adverse reactions was comparable between all treatment groups. Secondary: Not reported
Tyring et al.[131] (2001) Acyclovir 800 mg five times daily for 7 days vs	DB, MC, RCT (2 trials) Adult patients with herpes zoster infection involving primarily the ophthalmic branch of the trigeminal	N=454 6 months	Primary: Patients that experienced a severe ocular manifestation (e.g., glaucoma, anterior uveitis, iridocyclitis) and nonsevere	Primary: After six months, one or more ocular manifestations occurred in 58.0% of famciclovir-treated patients compared to 58.2% of acyclovir-treated patients. There was no significant difference between treatment groups. Secondary: The percentage of patients who experienced one or more severe ocular manifestations was 41.2% in famciclovir-treated patients and 39.8% in acyclovir-treated patients (95% CI, 0.72 to 1.56). There were no

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
famciclovir 500 mg three times daily for 7 days	nerve		manifestations (conjunctivitis, punctate epithelial keratopathy, episcleritis) Secondary: Proportion of severe and non-severe ocular manifestations and loss of visual acuity	significant differences between the treatment groups. The percentage of patients who experienced one or more non-severe ocular manifestation was 44.9% in famciclovir-treated patients and 43.4% in acyclovir-treated patients (95% CI, 0.73 to 1.55). There were no significant differences between the treatment groups. The percentage of patients who experienced visual acuity loss was 2.6% in famciclovir-treated patients and 6.3% in acyclovir-treated patients (OR, 0.4; 95% CI, 0.15 to 1.08). There were no significant differences between the treatment groups. Drug-related adverse events were comparable between treatment groups. The most commonly reported adverse events were nausea (10%), headache (5%) and vomiting (5%).
Beutner et al.[132] (1995) Acyclovir 800 mg five times daily for 7 days vs valacyclovir 1,000 mg three times daily for 7 days vs valacyclovir 1,000 mg three times daily for 14 days	RCT Adult immunocompetent patients ≥50 years old with herpes zoster	N=1,141 6 months	Primary: Time to resolution of zoster-associated pain, time to cessation of new lesion formation and/or lesion area increase and time to ≥50% healed rash Secondary: Time to resolution of zoster-associated abnormal sensations and pain intensity	Primary: Median time to resolution of zoster-associated pain was 38 days with valacyclovir 7-day treatment (P=0.001 vs acyclovir) and 44 days with valacyclovir 14-day treatment (P=0.03 vs acyclovir) compared to 51 days with acyclovir. Time to cessation of new lesion and time to ≥50% healed rash was 5 days in all treatment groups. Secondary: Median time to resolution of zoster-associated abnormal sensations was 45 days with valacyclovir 7-day treatment (HR, 1.18; 95% CI, 0.99 to 1.41 vs acyclovir) and 38 days with valacyclovir 14-day treatment (HR, 1.27; 95% CI, 1.07 to 1.52 vs acyclovir) compared to days with acyclovir. Rates of rash healing were comparable between treatment groups (HR, 1.01; 95% CI, 0.93 to 1.30; P=0.26). Pain intensity did not differ among the treatment groups. Drug-related adverse events were comparable among treatment groups and mild in severity. The most commonly reported adverse events were

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				headache, nausea, vomiting, diarrhea and constipation.
Tyring et al.[133] (2000) Famciclovir 500 mg three times daily for 7 days vs valacyclovir 1,000 mg three times daily for 7 days	DB, MC, RCT Immunocompetent patients ≥50 years old with herpes zoster	N=597 24 weeks	Primary: Time to resolution of zoster-associated pain Secondary: Time to resolution of zoster-associated abnormal sensations, rash healing and lesion dissemination	Primary: Median time to resolution of zoster-associated pain was 42 days with valacyclovir and 49 days with famciclovir (HR, 1.02; 95% CI, 0.84 to 1.23; P=0.84). Secondary: Median time to resolution of zoster-associated abnormal sensation was 42 days with valacyclovir and 35 days with famciclovir (HR, 1.00; 95% CI, 0.82 to 1.21; P=0.98). Rates of rash healing were comparable between treatment groups (HR, 1.01; 95% CI, 0.93 to 1.30; P=0.26). No cases of lesion dissemination were reported. Drug-related adverse events were reported in 34% of patients taking valacyclovir and 38% of patients taking famciclovir. The most commonly reported adverse events were headache, nausea and constipation.
Klein et al.[134] (2011) Valacyclovir 1,000 mg twice daily (VAC) vs placebo	DB, PC, RCT VZV-seropositive patients undergoing autologous or allogeneic hematopoietic stem cell transplantation	N=53 24 months	Primary: Incidence of herpes zoster Secondary: Not reported	Primary: In the ITT analysis, the incidence of VZV was 11% in the VAC group compared to 23% in the placebo arm (P=0.21). In the MITT analysis, the incidence of VZV was 0% in the VAC group compared to 23% in the placebo arm (P=0.025). A total of 17.4% of patients in both VAC and placebo groups had dose reductions due to myelosuppression; 8.7 and 15.4% in the VAC and placebo arm, respectively had dose reductions due to gastrointestinal toxicity; 4.3 and 7.7% in the VAC and placebo arm, respectively had dose reductions due to musculoskeletal adverse events. There were more discontinuations in the placebo group compared to the VAC group due to gastrointestinal toxicity (7.7 vs 4.3%, respectively). There were more discontinuations in the VAC group due to leucopenia

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				compared to placebo (8.7 vs 0%, respectively). Secondary: Not reported

Drug regimen abbreviations: IV=intravenous, PO=oral, PRN=as needed
Study abbreviations: AC=active control, CI=confidence interval, DB=double-blind, HR=hazard ratio, MA=meta-analysis, MC=multicenter, NS=not significant, OBS=observational study, OL=open label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PP=predicted probability PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=rate ratio, SB=single-blind
Miscellaneous abbreviations: AIDS= acquired immunodeficiency syndrome, ALT=alanine aminotransferase, CMV=cytomegalovirus, DNA= deoxyribonucleic acid, HAART= highly active antiretroviral therapy, HBV=hepatitis B virus, HIV=human immunodeficiency virus, HSV=herpes simplex virus, MIU=million international units, NS=not significant, RNA=ribonucleic acid, SVR= sustained virologic response, VZV=varicella-zoster virus

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 18. Relative Cost of the Nucleosides and Nucleotides

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Acyclovir	buccal tablet, capsule, injection, suspension, tablet	Zovirax®*, Sitavig®	$$$-$$$$	$
Adefovir	tablet	Hepsera®*	$$$$$	$$$$$
Cidofovir	injection	Vistide®*	$$$$$	N/A
Entecavir	solution, tablet	Baraclude®*	$$$$$	N/A
Famciclovir	tablet	Famvir®*	$$$$$	$$
Ganciclovir	injection	Cytovene®*	$$$$$	$$$$$
Ribavirin	capsule, inhalation solution, solution, tablet	Copegus®*, Rebetol®*, Virazole®	$$$$$	$$$$
Telbivudine	tablet	Tyzeka®	$$$$$	N/A
Valacyclovir	tablet	Valtrex®*	$$$$-$$$$$	$
Valganciclovir	solution, tablet	Valcyte®	$$$$$	N/A

*Generic is available in at least one dosage form or strength.
N/A=Not available

X. Conclusions

The nucleosides and nucleotides are approved for the treatment of infections caused by herpes simplex virus (HSV), varicella-zoster virus (VZV) and cytomegalovirus (CMV), as well as for the treatment of chronic hepatitis B, chronic hepatitis C, and respiratory syncytial virus.[1-15] The majority of products in this review are available in a generic formulation..

Cidofovir, ganciclovir, and valganciclovir are approved for the treatment of CMV retinitis in patients with acquired immunodeficiency syndrome (AIDS). Studies have demonstrated similar efficacy in terms of protecting vision and guidelines do not give preference to one antiviral agent over another.[45,56,60] Ganciclovir and valganciclovir are also approved for the prevention of CMV disease in transplant patients, and studies have demonstrated similar efficacy with these agents.[58-59,62,65,67,69-70]

Adefovir, entecavir, and telbivudine are approved for the treatment of chronic hepatitis B. Other FDA-approved agents include interferon alfa, peginterferon alfa, lamivudine, and tenofovir. Although any of the agents can be used, guidelines recommend peginterferon alfa, tenofovir, or entecavir for the initial treatment of patients with HBeAg-positive and HBeAg-negative chronic hepatitis B.[31] Several clinical trials have demonstrated greater efficacy with entecavir and telbivudine than lamivudine.[78,81-83,93-95,98] Serum HBV DNA levels were also reduced to a greater extent with telbivudine (24 weeks) and entecavir (12 weeks) compared to adefovir.[75-77,89] In one study, telbivudine and entecavir decreased HBV-DNA levels to a similar extent after 24 weeks of therapy.[90] However, telbivudine is associated with a high rate of resistance; therefore, telbivudine monotherapy has a limited role in the treatment of hepatitis B.[31] Among the approved therapies for chronic hepatitis B, lamivudine is associated with the highest rate of resistance, and entecavir and tenofovir are associated with the lowest rates of resistance in drug-naïve patients. Judicious use of these agents is the most effective way to reduce the development of resistance.[31] Patients with minimal disease and those who are unlikely to achieve a sustained response should not be treated with the nucleoside/nucleotide analogues, especially if they are <30 years of age.[31]

Until recently, triple therapy with hepatitis C protease inhibitor, peginterferon alfa, and ribavirin has been the standard of care in the treatment of HCV genotype 1 infection.[27,32-33] The 2014 consensus recommendations from the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America prefer sofosbuvir-based combination therapy for most patients with chronic HCV genotype 1 infection.[32] All-oral sofosbuvir plus simeprevir (with or without ribavirin) off-label regimen is recommended in patients who are either peginterferon alfa ineligible, prior null or partial responders to peginterferon alfa and ribavirin dual therapy, or liver transplant recipients.[32] The FDA-approved simeprevir, peginterferon alfa, and ribavirin triple therapy regimen is generally recommended as an alternative, rather than a preferred regimen, by the consensus recommendations. Ribavirin inhalation solution is approved for the treatment of hospitalized infants and young children with severe lower respiratory tract infection due to respiratory syncytial virus. The American Academy of Pediatrics does not recommended the routine use of ribavirin inhalation solution; however, it may be considered for use in select patients with potentially life-threatening RSV infections.[44]

Acyclovir, famciclovir, and valacyclovir are approved for the treatment of herpes simplex virus infections and varicella-zoster virus infections. Guidelines recommend the use of systemic antiviral therapy for the treatment genital herpes and herpes zoster and do not give preference to one agent over another.[18,39-42,45] There are no published guidelines on the management of labial herpes. Several comparative trials have demonstrated similar efficacy with acyclovir, famciclovir, and valacyclovir for the treatment of labial and genital herpes, as well as herpes zoster.[122-131,133]

Therefore, all brand nucleosides and nucleotides within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand nucleoside or nucleotide is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of HCV Antivirals
AHFS Class 081840
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I. Overview

The hepatitis C virus (HCV) is an enveloped ribonucleic acid (RNA) virus that is transmitted through exposure with infected blood. HCV infection is one of the main causes of chronic liver disease worldwide, and the long-term impact of infection is highly variable, from minimal changes to extensive fibrosis and cirrhosis with or without hepatocellular carcinoma.[1] There are seven genotypes of HCV (genotypes 1 to 7), with genotype 1 being the most common in the United States, followed by genotypes 2 and 3.[1-2] The goal of hepatitis C treatment is HCV eradication in order to prevent complications and death. Genotyping is helpful in the clinical management of patients with hepatitis C for determining the choice of therapy. Assessment of liver disease severity is also recommended for predicting prognosis and determining the timing of therapy.[3-4] Due to the slow evolution of chronic infection, it is difficult to demonstrate if treatment prevents complications of liver disease; therefore, response to treatment is defined by surrogate virological parameters. Sustained virologic response (SVR), defined as the absence of HCV RNA 24 weeks following discontinuation of treatment, has historically been the most important primary endpoint in clinical trials. Recently, SVR 12 (undetectable HCV RNA 12 weeks after the end of therapy) has also been accepted as a primary endpoint for regulatory approval in the United States due to concordance with SVR 24.[3]

The newly approved direct-acting antiviral agents include the nonstructural protein 3 protease inhibitors, boceprevir, telaprevir, and simeprevir as well as the nonstructural protein 5B polymerase inhibitor, sofosbuvir.[5-11] Boceprevir, simeprevir, and telaprevir are direct-acting antivirals which inhibit the replication of HCV host cells by binding to the NS3/4A protease of HCV genotype 1a and 1b.[5-10] Sofosbuvir is a nucleotide analog inhibitor of HCV nonstructural protein 5B RNA polymerase, which is essential for viral replication the hepatitis C.[5-7,11] Prior to the availability of direct-acting antiviral agents, combination of peginterferon alfa and ribavirin has been the standard of care for the treatment of chronic hepatitis C.[1-4,12-17] The consensus recommendations from the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America give preference to sofosbuvir-based combination therapy for most patients with chronic HCV genotype 1, whereas telaprevir- and boceprevir-containing regimens are considered to be markedly inferior due to higher rates of serious adverse events, longer treatment duration, high pill burden, numerous drug-drug interactions, frequency of dosing, intensity of monitoring for continuation and stopping of therapy, and dietary requirements.[4]

The HCV antivirals that are included in this review are listed in Table 1. Telaprevir (Incivek®) is scheduled to be discontinued in the United States by October 2014. This review encompasses all dosage forms and strengths. There are no generic products available. This class was last reviewed in May 2012.

Table 1. HCV Antivirals Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Boceprevir	capsule	Victrelis®	none
Simeprevir	capsule	Olysio®	none
Sofosbuvir	tablet	Sovaldi®	none
Telaprevir	tablet	Incivek®	none

PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the HCV antivirals are summarized in Table 2.

Table 2. Treatment Guidelines Using the HCV Antivirals

Clinical Guideline	Recommendation(s)
American Association for the	• It may be advisable to delay treatment for some patients with

Clinical Guideline	Recommendation(s)
Study of Liver Diseases, Infectious Diseases Society of America, and International Antiviral Society-USA: **Recommendations for testing, managing, and treating hepatitis C (2014)**[4]	documented early fibrosis stage (F0 to 2), because waiting for future highly effective, pangenotypic, direct-acting antiviral combinations in interferon-free regimens may be prudent. Potential advantages of waiting to begin treatment will be provided in a future consensus guideline update. • A regimen is classified as either "recommended" when it is favored for most patients or "alternative" when optimal in a particular subset of patients in that category. When a treatment is clearly inferior or is deemed harmful, it is classified as "not recommended." • Recommendations for peginterferon alfa and ribavirin relapsers are the same as for treatment-naïve persons as described below. • Interferon ineligible criteria: o Intolerance to interferon alfa. o Autoimmune hepatitis and other autoimmune disorders. o Hypersensitivity to peginterferon alfa or any of its components. o Decompensated hepatic disease. o Major uncontrolled depressive illness. o A baseline neutrophil count below 1,500/µL, a baseline platelet count below 90,000/µL, or baseline hemoglobin below 10 g/dL. o A history of preexisting cardiac disease. <u>When and in whom to initiate HCV therapy</u> • Treatment is recommended for patients with chronic HCV infection. • Liver-related complications in which HCV treatment is most likely to provide the most immediate and impactful benefits are assigned "highest" and "high" priorities. • Highest priority due to highest risk for severe complications: o Advanced fibrosis (F3) or compensated cirrhosis (F4) o Organ transplant recipients o Severe extrahepatic hepatitis C (type 2 or 3 essential mixed cryoglobulinemia with end-organ manifestations e.g., vasculitis) o Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis • High priority due to high risk for complications: o Fibrosis (F2) o Human immunodeficiency virus (HIV) or hepatitis B virus (HBV)-coinfection o Other coexistent liver disease (e.g., non-alcoholic steatohepatitis) o Debilitating fatigue o Type 2 Diabetes mellitus (insulin resistant) o Porphyria cutanea tarda • Persons whose risk of HCV transmission is high and in whom HCV treatment may yield transmission reduction benefits: o Men who have sex with men with high-risk sexual practices o Active injection drug users o Incarcerated persons o Persons on long-term hemodialysis • Factors associated with accelerated fibrosis progression: o Fibrosis stage o Inflammation grade o Older age at time of infection o Male sex

Clinical Guideline	Recommendation(s)
	o Organ transplant o Alcohol consumption o Nonalcoholic fatty liver disease o Obesity o Insulin resistance o Genotype 3 o HIV or HBV-coinfection Treatment of HCV genotype 1 in treatment-naïve patients and relapsers with prior peginterferon alfa and ribavirin • Recommended treatments: o Interferon eligible: sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. o Interferon ineligible: sofosbuvir plus simeprevir with or without ribavirin for 12 weeks. • Alternative treatments: o Interferon eligible: simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks (for genotype 1a, baseline resistance testing for Q80K should be performed and alternative treatments considered if this mutation is present). o Interferon ineligible: sofosbuvir plus ribavirin for 24 weeks. • Treatments that are not recommended: o Boceprevir or telaprevir plus peginterferon alfa and ribavirin for 24 or 48 weeks. o Peginterferon alfa and ribavirin for 48 weeks. o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. Treatment of HCV genotype 2 in treatment-naïve patients and relapsers with prior peginterferon alfa and ribavirin • Recommended treatments: o Sofosbuvir plus ribavirin for 12 weeks. • Alternative treatments: o None. • Treatments that are not recommended: o Peginterferon alfa and ribavirin for 24 weeks. o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. o Any regimen with boceprevir, telaprevir, or simeprevir. Treatment of HCV genotype 3 in treatment-naïve patients and relapsers with prior peginterferon alfa and ribavirin • Recommended treatments: o Sofosbuvir plus ribavirin for 24 weeks. • Alternative treatments: o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Treatments that are not recommended: o Peginterferon alfa and ribavirin for 24 to 48 weeks. o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. o Any regimen with boceprevir, telaprevir, or simeprevir. Treatment of HCV genotype 4 in treatment-naïve patients and relapsers with prior peginterferon alfa and ribavirin • Recommended treatments: o Interferon eligible: sofosbuvir plus peginterferon alfa and

Clinical Guideline	Recommendation(s)
	ribavirin for 12 weeks. o Interferon ineligible: sofosbuvir plus ribavirin for 24 weeks. • Alternative treatments: o Simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 to 48 weeks. • Treatments that are not recommended: o Peginterferon alfa and ribavirin for 48 weeks. o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. o Any regimen with boceprevir or telaprevir. <u>Treatment of HCV genotype 5 or 6 in treatment-naïve patients and relapsers with prior peginterferon alfa and ribavirin</u> • Recommended treatments: o Interferon eligible: sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Alternative treatments: o Peginterferon alfa and ribavirin for 48 weeks. • Treatments that are not recommended: o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. o Any regimen with boceprevir or telaprevir. <u>Recommendations for patients with HCV genotype 1 with prior null or partial response to peginterferon alfa and ribavirin</u> • Recommended treatments: o Sofosbuvir plus simeprevir with or without ribavirin for 12 weeks. • Alternative treatments: o Sofosbuvir for 12 weeks plus peginterferon alfa and ribavirin for 12 to 24 weeks. o Sofosbuvir plus ribavirin for 24 weeks. o Simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks (for genotype 1a, baseline resistance testing for Q80K should be performed and alternative treatments considered if this mutation is present). • Treatments that are not recommended: o Boceprevir or telaprevir plus peginterferon alfa and ribavirin. o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. <u>Recommendations for patients with HCV genotype 1 with prior null or partial response to peginterferon alfa and ribavirin plus either boceprevir or telaprevir</u> • Recommended treatments: o Sofosbuvir for 12 weeks plus peginterferon alfa and ribavirin for 12 to 24 weeks. • Alternative treatments: o Interferon eligible: Sofosbuvir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks. o Interferon ineligible: Sofosbuvir plus ribavirin for 24 weeks. • Treatments that are not recommended: o Boceprevir, simeprevir, or telaprevir plus peginterferon alfa and ribavirin. o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral.

Clinical Guideline	Recommendation(s)
	o A recommendation for simeprevir use for patients with previous telaprevir or boceprevir exposure has not been provided due to potential risk of preexistent resistance to protease inhibitor treatment. <u>Recommendations for patients with HCV genotype 2 with prior null or partial response to peginterferon alfa and ribavirin</u> • Recommended treatments: o Sofosbuvir plus ribavirin for 12 weeks; ▪ In treatment-experienced cirrhotics only, the decision to extend therapy to 16 weeks should be made on a case-by-case basis. • Alternative treatments: o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks (cirrhotics only) • Treatments that are not recommended: o Boceprevir or telaprevir plus peginterferon alfa and ribavirin. o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. <u>Recommendations for patients with HCV genotype 3 with prior null or partial response to peginterferon alfa and ribavirin</u> • Recommended treatments: o Sofosbuvir plus ribavirin for 24 weeks. • Alternative treatments: o Sofosbuvir plus ribavirin for 16 weeks (cirrhotics only). o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Treatments that are not recommended: o Peginterferon alfa and ribavirin with or without protease inhibitor. o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. <u>Recommendations for patients with HCV genotype 4 with prior null or partial response to peginterferon alfa and ribavirin</u> • Recommended treatments: o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Alternative treatments: o Sofosbuvir plus ribavirin for 24 weeks. • Treatments that are not recommended: o Peginterferon alfa and ribavirin with or without protease inhibitor o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. <u>Recommendations for patients with HCV genotype 5 or 6 with prior null or partial response to peginterferon alfa and ribavirin</u> • Recommended treatments: o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Alternative treatments: o None. • Treatments that are not recommended: o Peginterferon alfa and ribavirin with or without protease inhibitor. o Monotherapy with peginterferon alfa, ribavirin, or a direct-

Clinical Guideline	Recommendation(s)
	acting antiviral. Initial treatment of human immunodeficiency virus (HIV)/HCV co-infected patients with HCV genotype 1 who are treatment-naïve or prior peginterferon alfa and ribavirin relapsers • Recommended treatments: o Interferon eligible: sofosbuvir plus peginterferon and ribavirin for 12 weeks. o Interferon ineligible: ▪ Sofosbuvir plus ribavirin for 24 weeks. ▪ Sofosbuvir plus simeprevir with or without ribavirin for 12 weeks. • Alternative treatments: o Interferon eligible: simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks (for genotype 1a, baseline resistance testing for Q80K should be performed and alternative treatments considered if this mutation is present). o Interferon ineligible: none. • Treatments that are not recommended: o Boceprevir or telaprevir plus peginterferon alfa and ribavirin for 24 or 48 weeks. o Peginterferon alfa and ribavirin for 48 weeks. o Simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 48 weeks. • Allowable antiretroviral therapy: o For sofosbuvir use: all except didanosine, zidovudine, or tipranavir. o For simeprevir use: limited to raltegravir, rilpivirine, maraviroc, enfuvirtide, tenofovir, emtricitabine, lamivudine, abacavir. Recommendations for HIV/HCV co-infected patients with HCV genotype 1 with prior null or partial response to peginterferon alfa and ribavirin • Recommended treatments: o Sofosbuvir plus simeprevir with or without ribavirin for 12 weeks. • Alternative treatments: o Interferon eligible: sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. o Interferon ineligible: sofosbuvir plus ribavirin for 24 weeks. • Treatments that are not recommended: same as for treatment-naïve or prior peginterferon alfa and ribavirin relapsers above. • Allowable antiretroviral therapy: same as for treatment-naïve or prior peginterferon alfa and ribavirin relapsers above. Treatment of HIV/HCV co-infected patients with HCV genotype 2 • Recommended treatments (regardless of treatment history): o Sofosbuvir plus ribavirin for 12 weeks. • Alternative treatments: o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks (only in prior nonresponders to peginterferon alfa and ribavirin eligible for peginterferon alfa). • Treatments that are not recommended: o Peginterferon alfa and ribavirin for 24 to 48 weeks. o Any regimen with boceprevir, telaprevir, or simeprevir. o Allowable antiretroviral therapy: same as above.

Clinical Guideline	Recommendation(s)

	Treatment of HIV/HCV co-infected patients with HCV genotype 3
	• Recommended treatments (regardless of treatment history):
	  o Sofosbuvir plus ribavirin for 24 weeks.
	• Alternative treatments:
	  o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks (only in prior nonresponders to peginterferon alfa and ribavirin eligible for peginterferon alfa).
	• Treatments that are not recommended:
	  o Peginterferon alfa and ribavirin for 24 to 48 weeks.
	  o Any regimen with boceprevir, telaprevir, or simeprevir.
	  o Allowable antiretroviral therapy: same as above.
	
	Treatment of HIV/HCV co-infected patients with HCV genotype 4
	• Recommended treatments (regardless of treatment history):
	  o Interferon eligible: sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks.
	  o Interferon ineligible: sofosbuvir plus ribavirin for 24 weeks.
	• Alternative treatments:
	  o None.
	• Treatments that are not recommended:
	  o Peginterferon alfa and ribavirin for 48 weeks.
	  o Any regimen with boceprevir, telaprevir, or simeprevir.
	  o Allowable antiretroviral therapy: same as above.
	
	Treatment of HIV/HCV co-infected patients with HCV genotype 5 or 6
	• Recommended treatments (regardless of treatment history):
	  o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks.
	• Alternative treatments:
	  o None.
	• Treatments that are not recommended:
	  o Peginterferon alfa and ribavirin for 48 weeks.
	  o Any regimen with boceprevir, telaprevir, or simeprevir.
	  o Allowable antiretroviral therapy: same as above.
	
	Treatment of patients with cirrhosis
	• Treatment-naive patients with compensated cirrhosis, including those with hepatocellular carcinoma, should receive the same treatment as recommended for patients without cirrhosis.
	• Patients with decompensated cirrhosis (moderate or severe hepatic impairment; Child Turcotte Pugh class B or C) should be referred to a medical practitioner with expertise in that condition (ideally in a liver transplant center).
	• Recommended regimen for patients with any HCV genotype who have decompensated cirrhosis (moderate or severe hepatic impairment; Child Turcotte Pugh class B or C) who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma.
	  o Sofosbuvir plus weight-based ribavirin (with consideration of the patient's creatinine clearance and hemoglobin level) for up to 48 weeks.
	  o This regimen should be used only by highly experienced HCV provider.
	• The following regimens are not recommended for patients with decompensated cirrhosis (moderate or severe hepatic impairment; Child Turcotte Pugh class B or C):

Clinical Guideline	Recommendation(s)
	o Any interferon-based therapy. o Monotherapy with peginterferon alfa, ribavirin, or a direct-acting antiviral. o Telaprevir, boceprevir, or simeprevir-based regimens. <u>Treatment of patients who develop recurrent HCV infection post-liver transplant</u> • Recommended regimen for treatment-naive patients with HCV genotype 1 in the allograft liver, including those with compensated cirrhosis. o Sofosbuvir plus simeprevir with or without dose-adjusted ribavirin for 12 to 24 weeks. • Alternate regimen for treatment-naive patients with genotype 1 HCV in the allograft liver, including those with compensated cirrhosis. o Sofosbuvir and dose-adjusted ribavirin (with consideration of the patient's creatinine clearance and hemoglobin level), with or without peginterferon alfa, for 24 weeks. • Recommended regimen for treatment-naive patients with HCV genotype 2 or 3 in the allograft liver, including those with compensated cirrhosis. o Sofosbuvir plus dose-adjusted ribavirin (with consideration for creatinine clearance and hemoglobin level) for 24 weeks. • Treatment-naive patients with decompensated allograft HCV infection should receive the same treatment as recommended for patients with decompensated cirrhosis (moderate or severe hepatic impairment; Child Turcotte Pugh class B or C).
Department of Veterans Affairs National Hepatitis C Resource Center Program and the Office of Public Health: **HCV Infection: Treatment Considerations (2014)**[13]	<u>Treatment considerations</u> • The urgency of treating HCV should be based on the risk of developing decompensated cirrhosis or dying from liver or liver-related disease, and prolonging graft survival in liver transplant recipients. • Urgent treatment should be considered in patients with advanced cirrhosis, selected patients with hepatocellular carcinoma awaiting liver transplant, post-transplant recipients with cirrhosis, and patients with serious extra-hepatic manifestations of HCV. • Patients with mild liver disease (F0 to F2) may consider waiting until newer therapies are available that may improve the chance of treatment success and reduce treatment-related adverse effects; approval is anticipated over the next 12 to 24 months. • Factors that may complicate adherence, such as active substance abuse, neurocognitive disorders, and lack of social support, should be addressed before initiating medications. • Sofosbuvir or simeprevir should not be used as monotherapy or in reduced dosages; neither drug should be restarted if discontinued. • Interferon ineligible or intolerant criteria: o Platelet count <75,000/mm^3. o Decompensated liver cirrhosis (Child Turcotte Pugh class B or C). o Severe mental health conditions that may be exacerbated by interferon or may respond poorly to medical therapy. o Autoimmune diseases that may be exacerbated by interferon-mediated immune modulation. o Inability to complete a prior treatment course due to documented interferon-related adverse effects. • Treatment of patients with HCV/HIV co-infection is similar to that of

Clinical Guideline	Recommendation(s)
	HCV mono-infected patients. Drug-drug interactions must be carefully considered. Treatment of HCV genotype 1 in treatment-naïve, non-cirrhotic or cirrhotic interferon eligible patients • Preferred regimen: o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Alternative regimen: o Simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks (do not use in genotype 1a with Q80K polymorphism). Treatment of HCV genotype 1 in treatment-naïve, non-cirrhotic interferon ineligible patients • Preferred regimens: o Sofosbuvir plus ribavirin for 24 weeks. o Sofosbuvir plus simeprevir with or without ribavirin for 12 weeks. • Alternative regimen: o None. Treatment of HCV genotype 1 in treatment-naïve, cirrhotic interferon ineligible patients • Preferred regimen: o Sofosbuvir plus simeprevir with or without ribavirin for 12 weeks. • Alternative regimen: o None. Treatment of HCV genotype 1 in treatment-experienced, non-cirrhotic interferon eligible patients • Preferred regimen: o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Alternative regimen: o Simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks (relapsers) or 48 weeks (prior partial or null responders); do not use in genotype 1a with Q80K polymorphism or previous failure of boceprevir- or telaprevir-based therapy. Treatment of HCV genotype 1 in treatment-experienced, cirrhotic interferon eligible patients • Preferred regimen: o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Alternative regimen (peginterferon alfa and ribavirin null responders only): o Sofosbuvir plus simeprevir with or without ribavirin for 12 weeks. Treatment of HCV genotype 1 in treatment-experienced, non-cirrhotic or cirrhotic interferon ineligible patients • Preferred regimen: o Sofosbuvir plus simeprevir with or without ribavirin for 12 weeks. • Alternative regimen:

Clinical Guideline	Recommendation(s)
	o None. Treatment of HCV genotype 2 in treatment-naïve patients • Preferred regimen: o Sofosbuvir plus ribavirin for 12 weeks. • Alternative regimen: o None. Treatment of HCV genotype 2 in treatment-experienced patients • Preferred regimens: o Sofosbuvir plus ribavirin for 12 to 16 weeks. o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks (interferon eligible only). • Alternative regimen: o None. Treatment of HCV genotype 3 in treatment-naïve patients • Preferred regimens: o Sofosbuvir plus ribavirin for 24 weeks. • Alternative regimen: o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks (interferon eligible only). Treatment of HCV genotype 3 in treatment-experienced cirrhotic patients • Preferred regimens: o Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks (interferon eligible only). • Alternative regimen: o Sofosbuvir plus ribavirin for 24 weeks (interferon ineligible only). Treatment of HCV genotype 1, 2, 3, or 4 in patients with hepatocellular carcinoma • Preferred regimens: o Sofosbuvir plus ribavirin for 24 to 48 weeks or until liver transplant, whichever occurs first. • Alternative regimen: o None. Treatment of patients with HCV genotype 1, 2, 3, or 4 infection post-liver transplant • Sofosbuvir plus ribavirin with or without peginterferon for 24 weeks Treatment of patients with HCV genotype 1, 2, 3, or 4 infection post-other solid organ transplant (kidney, heart, or lung) • Discuss with transplant center. Do not use peginterferon-containing regimens. Sofosbuvir has not been studied in non-liver transplant recipients. Discontinuing HCV treatment based on lack of virologic response • Patients receiving sofosbuvir-based regimen should have HCV ribonucleic acid (RNA) assessed at week 4 of treatment; if the HCV RNA is detectable at week 4 or at any time point thereafter, reassess HCV RNA in 2 weeks. If the repeated HCV RNA increased (i.e., >1 $\log_{10}$ IU/mL from nadir) or if the HCV RNA is ≥25 IU/mL at week 8

Clinical Guideline	Recommendation(s)
	of therapy, discontinuation of all treatment should be strongly considered. • Patients receiving simeprevir plus peginterferon and ribavirin regimen should have HCV RNA levels assessed at week 4, 12, and 24; if the HCV RNA is ≥25 IU/mL at any of these time points, all treatment should be discontinued. Use in renal insufficiency • Sofosbuvir use is not recommended if creatinine clearance <30 mL/min or end-stage renal disease due to insufficient safety and efficacy data. • No simeprevir dose adjustment is needed if creatinine clearance <30 mL/min. • Peginterferon alfa-2a dosage should be reduced to 135 µg/week once weekly for creatinine clearance <30 mL/min, including hemodialysis. • Peginterferon alfa-2b dosage should be reduced by 25% for creatinine clearance 30 to 50 mL/min and by 50% for creatinine clearance <30 mL/min, including hemodialysis. • Ribavirin should be dosed at 200 mg daily alternating with 400 mg daily for creatinine clearance 30 to 50 mL/min and 200 mg daily for creatinine clearance <30 mL/min, including hemodialysis. Use in hepatic impairment • No simeprevir dosage recommendation can be provided in moderate to severe hepatic impairment (Turcotte Pugh Class B or C) due to higher simeprevir exposures. • No sofosbuvir dosage adjustment in required for patients with any degree of renal impairment. • Peginterferon alfa use is not recommended in patients with moderate or severe hepatic impairment (Turcotte Pugh Class B or C). Mental health and substance-use disorders • Patients with severe mental health conditions (e.g., psychotic disorders, bipolar disorder, major depression, posttraumatic stress disorder) who are engaged in mental health treatment should be considered for therapy on a case-by-case basis; interferon use may worsen these conditions. Substance or alcohol use • The presence of current heavy alcohol use (>14 drinks per week for men or >7 drinks per week for women), binge alcohol use (>4 drinks per occasion at least once per month), or active injection drug use warrants referral to an addiction specialist before treatment initiation. • There are no published data supporting minimal length of abstinence as an inclusion criterion for HCV antiviral treatment. • Patients with active substance- or alcohol-use disorders should be considered for therapy on a case-by-case basis and care should be coordinated with substance-use treatment specialist.
Department of Veterans Affairs Hepatitis C Resource Center Program and the National Hepatitis C Program Office: **Update on the management and treatment of hepatitis C virus infection (2012)**[14]	Recommendations in patients being considered for HCV therapy • All patients with chronic HCV infection should be evaluated for HCV antiviral treatment. • Patients should be counseled on their likelihood of achieving SVR, based upon individual factors such as body mass index, genotype, race, stage of fibrosis, and viral load before initiating therapy. • IL28B genotype testing can be performed before peginterferon-

Clinical Guideline	Recommendation(s)
	ribavirin therapy with or without a protease inhibitor, if the results would alter treatment decisions. Recommendations for treatment-naïve patients with genotype 1 infection • Peginterferon alfa and ribavirin, in combination with boceprevir (800 mg three times daily with food) or telaprevir (750 mg three times daily with 20 grams of fat), is the standard of care for most treatment-naïve genotype 1-infected patients. • If a telaprevir-containing regimen is used in treatment-naïve noncirrhotic patients who achieve an extended rapid virologic response (eRVR), telaprevir should be discontinued at week 12 and peginterferon-ribavirin should be continued for an additional 12 weeks. If HCV RNA is detectable at week four, but <1,000 IU/mL and remains <1,000 IU/mL or becomes undetectable at week 12, telaprevir should be discontinued at week 12, and peginterferon-ribavirin can be continued for another 36 weeks. • If a telaprevir-containing regimen is used in treatment-naïve cirrhotics who achieve an HCV RNA that is undetectable or <1,000 IU/mL at treatment weeks four and 12, telaprevir should be discontinued at week 12, and peginterferon-ribavirin can be continued for 36 more weeks. • If a boceprevir-containing regimen is used in treatment-naïve noncirrhotics, if HCV RNA declines by ≥1 $\log_{10}$ during the four-week lead-in, and HCV RNA is undetectable at weeks eight to 24, treatment with boceprevir-peginterferon-ribavirin for 24 weeks is sufficient. If HCV RNA is detectable at week eight, but <100 IU/mL at week 12, and negative at week 24, boceprevir-peginterferon-ribavirin should be continued until week 36, followed by peginterferon-ribavirin alone for 12 more weeks. If HCV RNA declines by <1 $\log_{10}$ during the lead-in, boceprevir-peginterferon-ribavirin can be continued for 44 weeks. • If a boceprevir-containing regimen is used in treatment-naïve cirrhotics, 44 weeks of boceprevir-peginterferon-ribavirin is required after the four-week lead-in. Recommendations for treatment of nonresponders and relapsers with genotype 1 infection • For patients who previously failed peginterferon-ribavirin, retreatment with boceprevir or ribavirin and peginterferon-ribavirin may be considered, particularly in patients who were relapsers. • If a boceprevir-containing regimen is used for retreatment of noncirrhotic prior partial responders or relapsers, the treatment duration is 36 weeks if HCV RNA is undetectable from weeks eight to 24. If HCV RNA is detectable at week 12, but <100 IU / mL and is undetectable from weeks 24 to 36, boceprevir can be discontinued at week 36 and peginterferon-ribavirin can be continued for an additional 12 weeks. • If a boceprevir-containing regimen is used for re-treatment in cirrhotics, the treatment duration is 48 weeks if HCV RNA is detectable at week 12, but <100 IU/mL, and becomes undetectable from weeks 24 to 36. • If a boceprevir-containing regimen is used for retreatment of prior null responders, the treatment duration is 48 weeks if HCV RNA is detectable at week 12, but <100 IU/mL, and becomes undetectable from weeks 24 to 36. • If a telaprevir-containing regimen is used for retreatment of prior relapsers, and HCV RNA is undetectable from weeks four and 12, telaprevir should be discontinued at week 12 and peginterferon-

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	ribavirin should be continued for an additional 12 weeks. If HCV RNA is detectable, but <1,000 IU/mL at week four and/or 12, telaprevir can be discontinued at week 12, and peginterferon-ribavirin can be continued for an additional 36 weeks.
	• If a telaprevir-containing regimen is used for re-treatment of prior partial responders or null responders, and HCV RNA is <1,000 IU/mL at weeks four and 12, telaprevir should be discontinued at week 12 and peginterferon-ribavirin should be continued for an additional 36 weeks.
	
	<u>Recommendations for dose modification</u>
	• Peginterferon alfa and ribavirin doses should be reduced in response to decreases in white blood cells, neutrophils, hemoglobin or platelets.
	• If ribavirin is stopped for seven or more days in patients concomitantly receiving boceprevir or telaprevir, then the protease inhibitor should also be permanently discontinued. The protease inhibitors should be either continued at full dose or discontinued.
	• A ribavirin dose reduction should be used as initial management of HCV treatment-related anemia in a symptomatic patient with a hemoglobin <10 g/dL. Erythropoietin may be administered in patients with symptomatic anemia related to peginterferon-ribavirin therapy with or without protease inhibitors to limit anemia-related ribavirin dose reductions or dose discontinuations.
	• A peginterferon dose reduction should be used as initial management of HCV treatment-related neutropenia (an absolute neutrophil count of <750, or as clinically indicated). Granulocyte colony-stimulating factor should not be given as primary therapy to prevent peginterferon alfa dose reductions.
	
	<u>Recommendations for treatment monitoring</u>
	• Patients should be monitored for treatment-related adverse effects at least every two weeks early in the course of therapy, and every one to two months during treatment as clinically indicated.
	• Assessment of treatment adherence and screening for depression, suicidal ideation, alcohol, and illicit drug use should be performed at every visit.
	• Patients should be counseled about avoiding pregnancy through the use of two forms of contraception during treatment and for six months posttreatment. If a patient is receiving a boceprevir- or telaprevir-containing regimen, two alternative effective methods of contraception, such as intrauterine devices and barrier methods, should be used in at-risk patients and partners during and for at least six months after treatment.
	• In patients receiving telaprevir-peginterferon-ribavirin, all treatment should be stopped if any of the following occur:
	  o HCV RNA level >1,000 IU/mL at week four or 12.
	  o Detectable HCV RNA levels at week 24 or at any time point thereafter.
	  o HCV RNA rebounds at any time point (≥1 $\log_{10}$ increase from the nadir HCV RNA).
	• In patients receiving boceprevir-peginterferon-ribavirin, all treatment should be stopped if any of the following occur:
	  o HCV RNA level ≥100 IU/mL at week 12 with a boceprevir-containing regimen.
	  o Detectable HCV RNA levels at week 24 or at any time point thereafter.
	  o HCV RNA rebounds at any time point (≥1 $\log_{10}$ increase from

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	the nadir HCV RNA). • Do not switch to the other protease inhibitor if virologic failure occurs with one protease inhibitor. Recommendations for groups with special considerations for therapy • Peginterferon alfa monotherapy may be used to treat patients with contraindications to ribavirin. • For patients who achieve RVR and have a low baseline viral load (HCV RNA <400,000 IU/mL), 24-weeks of treatment with peginterferon-ribavirin may be sufficient. • Treatment can be deferred in patients with minimal inflammation and/or minimal portal fibrosis on liver biopsy. • HCV genotype 1-infected patients with compensated cirrhosis (Child-Pugh Class <7), adequate neutrophils (>1.5 k/mm^3), and adequate platelet counts (>75 k/mm^3) should be considered for treatment with boceprevir (for 44 weeks) or telaprevir (for 12 weeks) combined with peginterferon-ribavirin at standard doses for 48 weeks. • Patients with cirrhosis continue to be at risk for hepatocellular carcinoma and should undergo routine screening regardless of viral clearance status. Recommendations for treatment-naïve and -experienced patients with genotype 2 or 3 infection • Treatment-naïve patients should be treated with peginterferon-ribavirin for 24 weeks. • For patients with low viral load (HCV RNA <600,000 IU/mL) and mild fibrosis who achieve a RVR, 12 to 18 weeks of treatment may be sufficient. • For patients with genotype 3 infection and a high HCV RNA (>600,000 IU/mL), steatosis or advanced fibrosis, treatment beyond 24 weeks may improve response. • Retreatment duration is 48 weeks. Recommendations in patients with genotype 4 infection • Appropriate candidates with HCV genotype 4 infections should be treated with peginterferon alfa-2a 180 µg per week or peginterferon alfa-2b 1.5 µg/kg per week, plus ribavirin up to 1,400 mg per day for 48 weeks. Recommendations in patients with decompensated cirrhosis • Liver transplantation is the treatment of choice in patients with decompensated cirrhosis. • Antiviral therapy is contraindicated in most patients with decompensated cirrhosis. • Interferon-based therapy in combination with ribavirin can be considered for patients awaiting liver transplantation if they have a Child-Pugh score <7 and a Model for End-Stage Liver Disease score ≤18. • If beginning antiviral therapy, the interferon dose should be reduced and growth factors may be used to for treatment-associated cytopenias. Recommendations in patients following solid organ transplantation • Interferon-based antiviral therapy is contraindicated in patients who have received a heart, lung or kidney transplant. • In patients with biopsy-proven chronic HCV disease following liver

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	transplantation, peginterferon-ribavirin for 48 weeks may be considered. • Monitor antiviral therapy in post-liver transplant patients on antiviral therapy and discontinue if rejection is documented. Pre-emptive antiviral therapy early post-transplantation in patients without histological recurrence should be avoided. Recommendations in patients with renal disease • Considered modified doses of antiviral therapy with interferon (standard or pegylated). • Antiviral therapy for HCV treatment is not recommended in patients following renal transplant; however, it may be considered if patients develop fibrosing cholestatic hepatitis. Recommendations in patients with comorbid conditions • Antiviral therapy is not recommended in patients with a limited life expectancy. In addition, peginterferon-ribavirin, treatment should be avoided in comorbid conditions that may be exacerbated by treatment. Recommendations for patients on methadone • Antiviral therapy should be offered to patients enrolled in a methadone maintenance program who meet criteria for therapy. Coordinated HCV treatment between providers and substance abuse specialists should occur. Recommendations in patients with ongoing alcohol use • Encourage patients to decrease alcohol consumption or to abstain, and refer for behavioral intervention to reduce alcohol use. Antiviral therapy may be used in patients who are otherwise appropriate candidates, regardless of prior alcohol use. Alcohol reduces adherence and treatment response. Recommendations in obese patients and those with hepatic steatosis • Patients with a body mass index >30 should be considered for antiviral treatment. Control comorbid conditions prior to initiation of antiviral therapy. Recommendations in patients with human immunodeficiency virus (HIV)/HCV coinfection • Patients with controlled HIV infection and evidence of liver disease on biopsy should be considered for HCV antiviral therapy. Treatment should consist of peginterferon-ribavirin at doses similar to those with HCV for a duration of 48 weeks. Recommendations in patients with acute HCV infection • Observe patients for eight to 20 weeks from time of initial exposure to monitor for spontaneous resolution of infection. • In patients who fail to resolve infection spontaneously, treatment with peginterferon alfa, with or without ribavirin for 24 to 48 weeks should be used, based on genotype and HCV RNA response during therapy.
European Association for the Study of the Liver: **Treatment of Hepatitis (2014)**[3]	Goals and endpoints of HCV therapy • The goal of therapy is to eradicate HCV infection, to prevent hepatic cirrhosis, decompensation of cirrhosis, hepatocellular carcinoma, and death. • The endpoint of therapy is SVR, defined by undetectable HCV RNA

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	12 and 24 weeks after the end of treatment; SVR usually equates to cure of infection in more than 99% of patients.
	• Both SVR 12 and SVR 24 have been accepted in the US and Europe, given that their concordance is 99%.
	
	<u>Indications for treatment</u>
	• All treatment-naïve and -experienced patients with compensated disease due to HCV should be considered for therapy.
	• Treatment should be prioritized for patients with significant fibrosis (F3 to F4).
	• Treatment is justified in patients with moderate fibrosis (F2).
	• In patients with no or mild disease (F0 to F1), the indication for and timing of therapy can be individualized.
	• Patients with decompensated cirrhosis who are on the transplant list should be considered for interferon-free, ideally ribavirin-free therapy.
	
	<u>Treatment considerations for HIV/HCV-coinfection</u>
	• Indications for HCV treatment and treatment regimens in HCV/HIV co-infected persons are identical to those in patients with HCV mono-infection.
	• The use of cobicistat-based regimens, efavirenz, delavirdine, etravirine, nevirapine, ritonavir, and any HIV protease inhibitor, boosted or not by ritonavir, is not recommended in HIV-infected patients receiving simeprevir.
	• Daclatasvir dose should be adjusted to 30 mg daily in HIV-infected patients receiving atazanavir/ritonavir and to 90 mg daily in those receiving efavirenz.
	• No drug-drug interaction has been reported between sofosbuvir and antiretroviral drugs.
	
	<u>Treatment options for HCV genotype 1 infection</u>
	• Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks.
	  o The most efficacious and the easiest to use interferon alfa-containing option, without the risk of selecting resistant viruses in case of treatment failure.
	• Simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks (in treatment-naïve and prior relapsers, including cirrhotics) or 48 weeks (in prior partial and null responders, including cirrhotics).
	  o Not recommended for HCV genotype 1a with Q80K polymorphism.
	  o HCV RNA levels should be monitored on treatment. Treatment should be stopped if HCV RNA level is ≥25 IU/mL at week four, 12, or 24.
	• Daclatasvir plus peginterferon alfa and ribavirin for 24 weeks (HCV genotype 1b only).
	  o Not recommended for HCV genotype 1a given the preliminary data available, pending results of on-going large-scale studies.
	  o Daclatasvir should be given for 12 weeks in combination with peginterferon alfa and ribavirin. Daclatasvir, in combination with peginterferon alfa and ribavirin, should be continued for an additional 12 weeks (24 weeks total) in patients who do not achieve an HCV RNA level <25 IU/mL at week 4 and undetectable at week 10. Peginterferon alfa and ribavirin should be continued alone between week 12 and 24 (24 weeks

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	total) in patients who achieve an HCV RNA level <25 IU/mL at week 4 and undetectable at week 10.
	• Sofosbuvir plus ribavirin for 24 weeks.
	  o Due to suboptimal SVR rates, reserve for interferon alfa ineligible patients when no other interferon-free option is available.
	• Sofosbuvir plus simeprevir for 12 weeks.
	  o The addition of ribavirin should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis.
	• Sofosbuvir plus daclatasvir for 12 weeks (treatment-naïve) or 24 weeks (treatment-experienced, including prior telaprevir or boceprevir failures).
	  o The addition of ribavirin should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis.
	
	<u>Treatment options for HCV genotype 2 infection</u>
	• Sofosbuvir plus ribavirin for 12 weeks (or 16 to 20 weeks in cirrhotics, especially treatment-experienced).
	• Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks is an option for cirrhotic and/or treatment-experienced patients.
	
	<u>Treatment options for HCV genotype 3 infection</u>
	• Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks
	• Sofosbuvir plus ribavirin for 24 weeks
	  o Suboptimal in treatment-experienced cirrhotics, who should be proposed an alternative treatment option.
	• Sofosbuvir plus daclatasvir for 12 weeks (treatment-naïve) or 24 weeks (treatment-experienced, pending data with 12 weeks of therapy).
	  o The addition of ribavirin should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis.
	
	<u>Treatment options for HCV genotype 4 infection</u>
	• Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks.
	• Simeprevir for 12 weeks plus peginterferon alfa and ribavirin for 24 weeks (in treatment-naïve and prior relapsers, including cirrhotics) or 48 weeks (in prior partial and null responders, including cirrhotics).
	  o HCV RNA levels should be monitored on treatment. Treatment should be stopped if HCV RNA level is ≥25 IU/mL at week four, 12, or 24.
	• Daclatasvir plus peginterferon alfa and ribavirin for 24 weeks.
	  o Daclatasvir should be given for 12 weeks in combination with peginterferon alfa and ribavirin. Daclatasvir, in combination with peginterferon alfa and ribavirin, should be continued for an additional 12 weeks (24 weeks total) in patients who do not achieve an HCV RNA level <25 IU/mL at week four and undetectable at week 10. Peginterferon alfa and ribavirin should be continued alone between week 12 and 24 (24 weeks total) in patients who achieve an HCV RNA level <25 IU/mL at week four and undetectable at week 10.
	• Sofosbuvir plus ribavirin for 24 weeks.
	  o Should be reserved for interferon alfa intolerant or -ineligible patients.

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	• Sofosbuvir plus simeprevir for 12 weeks.
	  o The addition of ribavirin should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis.
	• Sofosbuvir plus daclatasvir for 12 weeks (treatment-naïve) or 24 weeks (treatment-experienced).
	  o The addition of ribavirin should be considered in patients with predictors of poor response to anti-HCV therapy, especially prior non-responders and/or patients with cirrhosis.
	
	Treatment options for HCV genotype 5 or 6 infection
	• Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks.
	• Sofosbuvir plus ribavirin for 24 weeks.
	  o Should be reserved for interferon alfa intolerant or ineligible patients.
	
	Treatment monitoring
	• A real-time polymerase chain reaction-based assay with a lower limit of detection of <15 IU/mL should be used to monitor HCV RNA levels during and after therapy.
	• In patients treated with sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks, HCV RNA should be measured at baseline and at weeks 4, 12, and 12 or 24 weeks after the end of therapy.
	• In patients treated with simeprevir for 12 weeks plus peginterferon alfa and ribavirin for an additional 24 or 48 weeks, HCV RNA should be measured at baseline, week four, 12, 24 (end of treatment in treatment-naïve and prior relapsers), week 48 (end of treatment in prior partial and null responders), and 12 or 24 weeks after the end of therapy.
	• In patients treated with daclatasvir for 12 to 24 weeks plus peginterferon alfa and ribavirin for 24 weeks, HCV RNA should be measured at baseline, week four, 10, and 24 (end of treatment), and 12 or 24 weeks after the end of therapy.
	• In patients treated with sofosbuvir plus simeprevir with or without ribavirin for 12 weeks; sofosbuvir plus daclatasvir with or without ribavirin for 12 or 24 weeks; and sofosbuvir plus ribavirin 12 or 24 weeks, HCV RNA should be measured at baseline, week 2 (assessment of adherence), week four, week 12 or 24 (end of treatment), and 12 or 24 weeks after the end of therapy.
	
	Stopping (futility) rules
	• Treatment with simeprevir plus peginterferon alfa and ribavirin should be stopped if HCV RNA level is ≥25 IU/mL at treatment week four, 12 or 24.
	• No futility rules have been defined for other treatment regimens.
	
	Virological response-guided triple therapy
	• With the triple combination of daclatasvir plus peginterferon alfa and ribavirin, patients who do not achieve an HCV RNA level <25 IU/mL at week 4 and undetectable at week 10 should receive the three drugs for 24 weeks.
	• Patients who achieve an HCV RNA level <25 IU/mL at week four and undetectable at week 10 should stop daclatasvir at week 12 and continue with peginterferon alfa and ribavirin dual therapy until week 24.
	• No response-guided therapy is used in other treatment regimens.

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	Measures to improve treatment adherence • HCV treatment should be delivered within a multidisciplinary team setting, with experience in HCV assessment and therapy. • Counseling on the importance of adherence is recommended. • In persons who actively inject drugs, access to harm reduction programs is mandatory. • Patients should be counseled to abstain from alcohol during antiviral therapy; patients with on-going alcohol consumption during treatment should receive additional support during antiviral therapy. • HCV treatment can be considered also for patients actively using drugs if they wish to receive treatment and are able and willing to maintain regular appointments. Retreatment of non-sustained virological responders • Patients who failed on a regimen containing sofosbuvir as the only direct-acting antiviral can be retreated with a combination of sofosbuvir and simeprevir (HCV genotypes 1 or 4 only), or a combination of sofosbuvir and daclatasvir (all genotypes). • Patients who failed on a regimen containing simeprevir, telaprevir or boceprevir as the only direct-acting antiviral can be retreated with a combination of sofosbuvir and daclatasvir. • Patients who failed on a regimen containing daclatasvir as the only direct-acting antiviral can be retreated with a combination of sofosbuvir and simeprevir (HCV genotypes 1 or 4 only). • Patients who failed on a regimen containing sofosbuvir and simeprevir can be retreated with a combination of sofosbuvir and daclatasvir. • Patients who failed on a regimen containing sofosbuvir and daclatasvir can be retreated with a combination of sofosbuvir and simeprevir (HCV genotypes 1 or 4 only). • Alternatively, patients who failed on any of the new treatment regimens including sofosbuvir, simeprevir and/or daclatasvir can wait until new treatment combinations are available if they do not need urgent therapy. • The utility of HCV resistance testing prior to retreatment in patients who failed on any of the new treatment regimens including sofosbuvir, simeprevir and/or daclatasvir is unknown. Treatment of patients with severe liver disease • Patients with compensated cirrhosis should be treated, in the absence of contraindications, in order to prevent short- to mid-term complications; interferon-free regimens are preferred. • If a 12 to 24 week interferon-based direct-acting antiviral regimen is considered tolerable in patients with compensated cirrhosis and good liver function and without cytopenia, these patients can be treated as recommended above across genotypes. • Patients with cirrhosis should undergo regular surveillance for hepatocellular carcinoma, irrespective of SVR. Patients with an indication for liver transplantation • In patients awaiting liver transplantation, antiviral therapy is indicated, because it prevents graft infection if HCV RNA has been undetectable at least 30 days prior to transplantation. • Patients with conserved liver function (Child Pugh class A) in whom the indication for transplantation is hepatocellular carcinoma should be

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	treated with sofosbuvir plus ribavirin until liver transplantation. • Patients with conserved liver function (Child Pugh class A) in whom the indication for transplantation is hepatocellular carcinoma can also be treated with sofosbuvir, peginterferon alfa and ribavirin for 12 weeks. • In patients with conserved liver function (Child Pugh class A) in whom the indication for transplantation is hepatocellular carcinoma, the addition of another direct acting antiviral drug is likely to improve the prevention of HCV recurrence post-transplant; therefore, patients awaiting liver transplantation with genotype 1 to 4 infection can be treated with sofosbuvir, daclatasvir and ribavirin for 12 weeks prior to transplantation. • Patients with decompensated cirrhosis awaiting liver transplantation (Child Pugh class B and C) can be treated with sofosbuvir plus ribavirin until liver transplantation in experienced centers under close monitoring. Interferon alfa is contraindicated in these patients. • The addition of another direct-acting antiviral drug is likely to improve the prevention of HCV recurrence post-transplant; therefore, patients with decompensated cirrhosis awaiting liver transplantation (Child Pugh class B and C) with genotype 1 to 4 infection should be treated with sofosbuvir, daclatasvir and ribavirin until liver transplantation in experienced centers under close monitoring. • Patients with decompensated cirrhosis not on transplant waiting list should only be offered an interferon-free regimen within a clinical trial, an expanded access program or within experienced centers, because the efficacy, safety and outcomes have not yet been established for this group. <u>Post-liver transplantation recurrence</u> • Patients with post-transplant recurrence of HCV infection should be considered for therapy. • Patients with HCV genotype 2 infection must sofosbuvir plus ribavirin for 12 to 24 weeks, pending more data in this population. • Patients with HCV genotype 1, 3, 4, 5 or 6 infection can be treated with sofosbuvir plus daclatasvir for 12 to 24 weeks, with or without ribavirin, pending more data in this population. • Patients with HCV genotype 1 or 4 infection can be treated with sofosbuvir plus simeprevir for 12 to 24 weeks, with or without ribavirin, pending more data in this population. • No dose adjustment is required for tacrolimus or cyclosporine with any of the above combinations. Careful monitoring is important in the absence of safety data in this population. <u>Hepatitis B virus (HBV) co-infection</u> • Patients should be treated with the same regimens, following the same rules as HCV mono-infected patients. • If HBV replicates at significant levels before, during or after HCV clearance, concurrent HBV nucleoside/nucleotide analogue therapy is indicated. <u>Hemodialysis patients</u> • Hemodialysis patients, particularly those who are suitable candidates for renal transplantation, should be considered for antiviral therapy. • Hemodialysis patients should receive an interferon alfa-free and ribavirin-free regimen.

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	• Due to the lack of safety and efficacy data, the need for dose adjustments for sofosbuvir, simeprevir and daclatasvir is unknown. • Given the lack of data, extreme caution is recommended and sofosbuvir should not be administered to patients with an estimated glomerular filtration rate <30 mL/min/1.73 m^2 or with end-stage renal disease. <u>Non-hepatic solid organ transplant recipients</u> • HCV treatment before kidney transplantation may avoid liver-related mortality in the post-transplant patient, and may prevent HCV-specific causes of renal graft dysfunction. • Where possible, interferon-free and ribavirin-free antiviral regimen should be given to potential transplant recipients before listing for renal transplantation; however, no safety and efficacy data is available in this population. • Given the lack of data, extreme caution is recommended and sofosbuvir should not be administered to patients with an estimated glomerular filtration rate <30 mL/min/1.73 m^2 or with end-stage renal disease. • In non-hepatic solid organ transplant recipients, patients with an indication for anti-HCV therapy should receive an interferon-free regimen. • Patients with HCV genotype 2 infection must be treated with sofosbuvir plus ribavirin for 12 to 24 weeks, pending more data in this population. • Patients with HCV genotype 1, 3, 4, 5 or 6 infection can be treated with sofosbuvir plus daclatasvir for 12 to 24 weeks, with or without ribavirin, pending more safety data in this population. • Patients with HCV genotype 1 or 4 infection can be treated with sofosbuvir plus simeprevir for 12 to 24 weeks, with or without ribavirin, pending more data in this population. • No dose adjustment is required for tacrolimus or cyclosporine with any of these combinations. Careful monitoring is important in the absence of safety data in this population. <u>Active drug addicts and patients on stable maintenance substitution</u> • HCV treatment for people who inject drugs (PWIDs) should be considered on an individualized basis and delivered within a multidisciplinary team setting. • Sofosbuvir and simeprevir can be used in PWIDs on opioid substitution therapy. They do not require specific methadone and buprenorphine dose adjustment, but monitoring for signs of opioid toxicity or withdrawal should be undertaken. More data is needed with daclatasvir. • Consideration of interferon-containing or interferon-free therapy in PWIDs should be undertaken on an individualized basis, but those with early liver disease can be advised to await further data and/or potential development of improved therapies. • The regimens that can be used in PWIDs are the same as in non-PWIDs. • Awareness should be raised that liver transplantation is a therapeutic option in those with a history of injection drug use. • Opioid substitution therapy is not a contraindication for liver transplantation and individuals on opioid substitution should not be advised to reduce or stop therapy.

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	Treatment of acute hepatitis C • Peginterferon alfa monotherapy for 24 weeks can be used in patients with acute hepatitis C, who will achieve SVR in as many as 90% of cases. • Peginterferon alfa plus ribavirin for 24 weeks is recommended in patients with acute hepatitis C who are HIV-coinfection. • Although no data is available yet, interferon-free regimens can theoretically be used in patients with acute hepatitis C and are expected to achieve high SVR rates. • Note: Daclatasvir is not currently Food and Drug Administration-approved in the United States.
European Association for the Study of the Liver: **Management of Hepatitis C Virus Infection (2013)**[1]	Goals and endpoints of HCV therapy • The goal of therapy is to eradicate HCV infection. • The endpoint of therapy is SVR, defined by undetectable HCV RNA 24 weeks after the end of therapy; SVR usually equates to cure of infection in more than 99% of patients. • Undetectable HCV RNA at 12 weeks after the end of therapy (SVR 12) has been accepted in the US and Europe given concordance with SVR 24 is 99%; however, this concordance needs to be further validated in ongoing clinical trials. Indications for treatment • All treatment-naïve patients with compensated disease due to HCV should be considered for therapy. • Treatment should be scheduled, not deferred, for patients with significant fibrosis (F3 to F4). • In patients with less severe disease, indication for and timing of therapy can be individualized. First line treatment of chronic hepatitis C genotype 1 • Triple therapy with boceprevir or telaprevir added to peginterferon alfa and ribavirin is the approved standard of care for chronic hepatitis C genotype 1. There is no head-to-head comparison to allow recommendation of boceprevir or telaprevir as preferred therapy. • Patients with cirrhosis should never receive abbreviated treatment with boceprevir or telaprevir regimens. • Selected patients with high likelihood of SVR to peginterferon alfa and ribavirin or with contraindications to boceprevir or telaprevir can be treated with dual therapy. • When lead-in is used to identify patients with peginterferon alfa sensitive infection, the possibility of continuation of dual therapy should have been discussed with the patient prior to initiation of treatment. • Both peginterferon alfa-2a (180 µg/week) and peginterferon alfa-2b (1.5 µg/kg/week) can be used in dual or triple therapy. • Ribavirin should be dosed following the peginterferon alfa label for triple therapy. • Ribavirin should be administered at a weight-based dose of 15 mg/kg/day in dual therapy First line treatment of chronic hepatitis C genotypes 2, 3, 4, 5, and 6 • The combination of peginterferon alfa and ribavirin is the approved standard of care for chronic hepatitis C genotypes 2, 3, 4, 5, and 6.

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	• Ribavirin should be administered at a weight-based dose of 15 mg/kg/day for genotypes 4, 5 and 6, and at a flat dose of 800 mg/day for genotypes 2 and 3. • Patients with genotypes 2 and 3 with baseline factors suggesting low responsiveness should receive weight-based ribavirin at a dose of 15 mg/kg/day. Treatment monitoring • A real-time polymerase chain reaction-based assay with a lower limit of detection of <15 IU/mL should be used to monitor triple therapy. • During triple therapy in HCV genotype 1 patients, HCV RNA measurements should be performed at weeks four, eight, 12, 24, and end of treatment when administering boceprevir, and at weeks four, 12, 24, and end of treatment when administering telaprevir. • During dual therapy in any HCV genotype, HCV RNA levels should be assessed at baseline, weeks four, 12, 24 and end of treatment. • The end-of-treatment virological response and the SVR at 12 or 24 weeks after the end of treatment must be assessed. • Whether the baseline HCV RNA level is low or high may be a useful criterion to guide treatment decisions during dual therapy. The safest threshold level for discriminating low and high baseline HCV RNA is 400,000 IU/mL. • Dual therapy for all HCV genotypes should be stopped at week 12 if the HCV RNA decrease is <2 $\log_{10}$ IU/mL and at week 24 if HCV RNA is still detectable. • Triple therapy with boceprevir should be stopped if HCV RNA is >100 IU/mL at treatment week 12 or if HCV RNA is detectable at treatment week 24. • Triple therapy with telaprevir should be stopped if HCV RNA is >1,000 IU/mL at weeks four or 12 of therapy. • Dual therapy duration should be tailored to the on-treatment virological response at weeks four and 12. The likelihood of SVR is directly proportional to the rapidity of HCV RNA disappearance. • For patients receiving dual therapy who achieve an RVR and who have low baseline viral titre (<400,000 IU/mL), treatment for 24 weeks (genotype 1) or 16 weeks (genotype 2 or 3) can be considered. If negative predictors of response (i.e., advanced fibrosis/cirrhosis, metabolic syndrome, insulin resistance, hepatic steatosis) are present, published evidence for equal efficacy of shortened treatment is lacking. • Patients receiving dual therapy with genotypes 2 or 3, and with any adverse predictor of SVR, and who achieve an early virological response or a delayed virological response without an RVR, can be treated for 48 weeks. • Genotype 1 patients receiving dual therapy who demonstrate a delayed virological response can be treated for 72 weeks, provided that their HCV RNA is undetectable at week 24. Treatment dose reductions and stopping rules • The peginterferon alfa dose should be reduced if the absolute neutrophil count falls below 750/mm^3, or the platelet count falls below 50,000/mm^3. Peginterferon alfa should be stopped if the neutrophil count falls below 500/mm^3 or the platelet count falls below 25,000/mm^3 or if severe unmanageable depression develops. • If neutrophil or platelet counts rise, treatment can be restarted, but at a reduced peginterferon alfa dose.

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	• If hemoglobin <10 g/dL occurs, the dose of ribavirin should be adjusted downward by 200 mg at a time, and ribavirin should be stopped if hemoglobin falls below 8.5 g/dL. • Treatment should be stopped in case of a severe hepatitis flare or severe sepsis. • Boceprevir or telaprevir doses should not be reduced during therapy due to the risk of the development of antiviral resistance. If boceprevir or telaprevir have been stopped, they should never be reintroduced in the same course of treatment. Measures to improve treatment success rates • Full adherence to all antiviral drugs should be the aim in order to optimize SVR rates and to reduce the risk of emergence of specific drug resistance. • Body weight adversely influences the response to peginterferon alfa and ribavirin; therefore, a reduction of body weight in overweight patients prior to therapy may increase the likelihood of SVR. • Insulin resistance is associated with treatment failure for dual therapy; however, insulin sensitizers have no proven efficacy in improving SVR rates in these patients. • Counseling on abstaining from alcohol during antiviral therapy should be provided. • In dual therapy, recombinant erythropoietin can be administered when the hemoglobin level falls <10 g/dL in order to reduce the need for ribavirin dose reduction. • In patients receiving boceprevir or telaprevir-based triple therapy, ribavirin dose reduction should be the initial response to significant anemia. • There is no evidence that neutropenia during peginterferon alfa and ribavirin therapy is associated with more frequent infection episodes, or that the use of granulocyte colony stimulating factor reduces the rate of infections and/or improves SVR rates. • Patients with a history and/or signs of depression should be seen by a psychiatrist before therapy. Patients who develop depression during therapy should be treated with antidepressants. Preventative antidepressant therapy in selected patients may reduce the incidence of this condition during treatment, without any impact on SVR. Post treatment follow up of patients who achieve an SVR • Noncirrhotic patients with SVR should be retested for alanine transaminase and HCV RNA at 48 weeks post-treatment, and then discharged if alanine transaminase is normal and HCV RNA is negative. • Cirrhotic patients with SVR should undergo surveillance for hepatocellular carcinoma every six months by means of ultrasound. • If present, portal hypertension and esophageal varices should be managed, though index variceal bleed is seldom observed in low-risk patients after the achievement of SVR. • Patients with ongoing drug use should not be excluded from HCV treatment on the basis of perceived risk of reinfection. • Following SVR, monitoring for HCV reinfection through annual HCV RNA assessment should be undertaken on people who inject drugs with ongoing risk behavior. Retreatment of nonsustained virological responders to peginterferon alfa

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	and ribavirin • Patients infected with HCV genotype 1 who failed to eradicate HCV in prior therapy with peginterferon alfa and ribavirin should be considered for retreatment with the triple combination of peginterferon alfa, ribavirin and a protease inhibitor. • The previous response to interferon-based therapy is an important predictor of success of triple therapy. If the pattern of prior response to dual therapy is not clearly documented, the patient should not be treated with abbreviated response-guided therapy. • Patients with cirrhosis and prior null responders have a lower chance of cure and should not be treated with response-guided therapy with either boceprevir or telaprevir. • Patients infected with HCV genotypes other than 1 and who failed on prior therapy with non-pegylated interferon alfa, with or without ribavirin, can be re-treated with pegylated interferon alfa and ribavirin. Treatment of patients with severe liver disease • Patients with compensated cirrhosis should be treated, in the absence of contraindications, in order to prevent short to midterm complications. • Monitoring and management of side effects, especially those linked to portal hypertension, low platelet count, and low serum albumin should be done particularly carefully. Growth factors may be useful in this group. • Patients with cirrhosis should undergo regular surveillance for hepatocellular carcinoma, irrespective of SVR. • In patients awaiting liver transplantation, antiviral therapy, when feasible, prevents graft reinfection if an SVR is achieved. • Antiviral therapy may be started while awaiting liver transplantation, with the goal of achieving SVR or HCV RNA negativity before transplantation. • In patients with Child-Pugh B cirrhosis, antiviral therapy is offered on an individual basis in experienced centers, preferentially in patients with predictors of good response. • Patients with Child-Pugh C cirrhosis should not be treated with the current interferon alfa-based antiviral regimens due to a high risk of life-threatening complications. • Treatment can be started at low doses of peginterferon alfa and ribavirin, following a low accelerated dose regimen or at full doses. In the latter case, dose reductions and treatment interruptions are required in >50% of cases. • Patients with post-transplant recurrence of HCV infection should initiate therapy once chronic hepatitis is established and histologically proven. Significant fibrosis or portal hypertension one year after transplantation predicts rapid disease progression and graft loss and indicates urgent antiviral treatment. • For patients with HCV genotype 1, protease inhibitor-based therapy can be used, but frequent monitoring and dose adjustment of tacrolimus and cyclosporine are required. • Graft rejection is rare but may occur during peginterferon alfa treatment. A liver biopsy should be performed whenever liver tests worsen on antiviral therapy. Treatment of special groups • Indications for HCV treatment in patients with HIV coinfection are

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	identical to those in patients with HCV monoinfection. The same peginterferon alfa regimen should be used in HIV coinfected patients. Longer treatment duration may be considered for patients with genotype 2 and 3 who exhibit slow early viral kinetics. • Patients coinfected with HIV and HCV genotype 1 should be considered for telaprevir or boceprevir triple therapy regimen, but special care should be taken to minimize or avoid potential drug-drug interactions. • HIV patients with a diagnosis of acute HCV infection should be treated with peginterferon and ribavirin, with duration dependent on viral kinetics independent of HCV genotype. • Patients coinfected with hepatitis B should be treated with telaprevir or boceprevir triple therapy regimen, following the same rules as monoinfected patients. • If hepatitis B virus replicates at significant levels before, during or after HCV clearance, concurrent hepatitis B virus nucleoside/nucleotide analogue therapy is indicated. • Patients on hemodialysis, particularly those who are suitable candidates for renal transplantation, should be considered for antiviral therapy. • Antiviral treatment should comprise peginterferon alfa at an appropriately reduced dose. • Ribavirin can be used at very low doses, but with caution. • Boceprevir or telaprevir can be used with caution in patients with impaired creatinine clearance, and dose adjustment is probably unnecessary. • Patients with HCV and end stage renal disease scheduled for kidney transplantation should undergo antiviral therapy prior to transplantation due to the increased risk of acute transplant rejection. • Interferon alfa-based antiviral treatment is associated with a significant risk of renal graft rejection, and it should be avoided unless there is a powerful indication for antiviral treatment (e.g., aggressive cholestatic hepatitis). • Regular alcohol consumption should be strongly discouraged. • Treatment of patients with active illicit drug abuse has to be individualized. • Patients with hemoglobinopathies can be treated with combination therapy but need careful monitoring. <u>Follow up of untreated patients and of patients with treatment failure</u> • Untreated patients with chronic hepatitis C and those who failed prior treatment should be followed regularly. • Non-invasive methods for staging fibrosis are best suited for follow-up assessment at intervals. • Hepatocellular carcinoma screening must be continued indefinitely in patients with cirrhosis. <u>Treatment of acute hepatitis C</u> • Peginterferon alfa monotherapy for 24 weeks is recommended in patients with acute hepatitis C and achieves SVR in >90% of patients. • Patients failing to respond to monotherapy should be retreated according to the standard of care for chronic hepatitis C.
World Health Organization: **Guidelines for the Screening, Care and Treatment of**	<u>Recommendations for treatment of HCV infection</u> • All adults and children with chronic HCV infection, including people who inject drugs, should be assessed for antiviral treatment.

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Persons with Hepatitis C Infection (2014)[15]	• Peginterferon alfa in combination with ribavirin is recommended for the treatment of chronic HCV infection rather than standard non-peginterferon alfa with ribavirin.
	• Where access to treatment for HCV infection is limited, priority for treatment should be given to patients with advanced liver disease (F3 and F4).
	• Treatment with the direct-acting antivirals telaprevir or boceprevir, given in combination with peginterferon alfa and ribavirin, is suggested for genotype 1 chronic HCV infection rather than peginterferon alfa and ribavirin alone.
	• In high-income settings, HCV treatment with peginterferon alfa and ribavirin and with boceprevir or telaprevir plus peginterferon alfa and ribavirin has been evaluated as being cost–effective.
	• Sofosbuvir, given in combination with ribavirin with or without peginterferon alfa (depending on the HCV genotype), is recommended in genotypes 1, 2, 3 and 4 HCV infection rather than peginterferon alfa and ribavirin alone (or no treatment for persons who cannot tolerate peginterferon alfa); recommendation made without taking resource use into consideration.
	• Simeprevir, given in combination with peginterferon alfa and ribavirin, is recommended for persons with genotype 1b HCV infection and for persons with genotype 1a HCV infection without the Q80K polymorphism rather than peginterferon alfa and ribavirin alone; recommendation made without taking resource use into consideration.
	• Absolute contraindications to peginterferon alfa:
	  o Uncontrolled depression, psychosis, or epilepsy.
	  o Uncontrolled autoimmune disease.
	  o Decompensated cirrhosis (Child–Pugh ≥B7 or B6 in HCV/HIV coinfection).
	  o Pregnancy or unwillingness to use contraception.
	  o Breastfeeding women.
	  o Severe concurrent medical disease including severe infections.
	  o Poorly controlled hypertension, cardiac failure, or diabetes.
	  o Solid organ transplant (except liver transplant recipients).
	  o Chronic obstructive pulmonary disease.
	  o Age <2 years old.
	• Relative contraindications to peginterferon alfa:
	  o Abnormal hematological indices:
	  ▪ Hemoglobin <13 g/dL in men or <12 g/dL in women.
	  ▪ Neutrophil count <1.5x10^9/L.
	  ▪ Platelet count <90x10^9/L.
	  o Serum creatinine >1.5 mg/dL.
	  o Hemoglobinopathies (sickle cell disease or thalassemia).
	  o Significant coronary artery disease.
	  o Untreated thyroid disease.
	• Treatment for HCV infection is both efficacious and cost-effective in people who inject drugs and is therefore recommended.
	• Specialist care needs to address the additional needs of special populations of patients, including people who inject drugs, persons coinfected with (or at risk for infection with) HIV, children and adolescents, and those with cirrhosis.
	• The decision to initiate treatment for HCV/HIV-coinfection is more complex than in those with HCV monoinfection, as response rates are lower, risk of potential toxicities is higher and treatment is complicated

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	by a high pill burden, overlapping toxicities, and interactions between drugs used for treating HCV and HIV.

American Association for the Study of Liver Diseases: **An Update on Treatment of Genotype 1 Chronic Hepatitis C Virus Infection (2011)**[12]	• The optimal therapy for HCV genotype 1 is the use of boceprevir or telaprevir in combination with peginterferon alfa and ribavirin.
	• Boceprevir and telaprevir should not be used without peginterferon alfa and weight-based ribavirin.
	
	<u>Treatment-naïve patients</u>
	• The recommended dose of boceprevir is 800 mg three times daily (every seven to nine hours) with food plus peginterferon alfa and weight-based ribavirin for 24 to 44 weeks, preceded by four weeks of lead in peginterferon alfa plus ribavirin alone.
	  o Patients without cirrhosis treated with boceprevir, peginterferon alfa and ribavirin, whose HCV ribonucleic acid (RNA) levels at weeks eight and 24 is undetectable, may be considered for a shortened duration of treatment of 28 weeks in total (four weeks lead in of peginterferon alfa and ribavirin, followed by 24 weeks of triple therapy).
	  o Triple therapy should be stopped if the HCV RNA level is >100 IU/mL at treatment week 12 or detectable at treatment week 24.
	• The recommended dose of telaprevir is 750 mg three times daily (every seven to nine hours) with food (not low fat) plus peginterferon alfa and weight-based ribavirin for 12 weeks followed by an additional 12 to 36 weeks of peginterferon alfa plus ribavirin (without telaprevir).
	  o Patients without cirrhosis treated with telaprevir, peginterferon alfa and ribavirin, whose HCV RNA level at weeks four and 12 is undetectable should be considered for a shortened duration of therapy of 24 weeks.
	  o Triple therapy should be stopped if the HCV RNA levels is >1,000 IU/mL at treatment weeks four or 12 and/or detectable at treatment week 24.
	• Patients with cirrhosis treated with either boceprevir or telaprevir in combination with peginterferon alfa and ribavirin should receive therapy for a duration of 48 weeks.
	
	<u>Treatment-experienced patients</u>
	• Re-treatment with boceprevir or telaprevir, in combination with peginterferon alfa and weight-based ribavirin, can be recommended for patients who had virological relapse or were partial responders after a prior course of treatment with standard interferon alfa or peginterferon alfa and/or ribavirin.
	• Retreatment with telaprevir, in combination with peginterferon alfa and weight-based ribavirin, may be considered for prior null responders to a course of standard interferon alfa or peginterferon alfa and/or weight-based ribavirin.
	• Response-guided therapy of treatment-experienced patients using either a boceprevir- or telaprevir-based regimen can be considered for relapsers, may be considered for partial responders, but cannot be recommended for null responders.
	• Patients re-treated with boceprevir plus peginterferon alfa and ribavirin who continue to have detectable HCV RNA >100 IU at week 12 should be withdrawn from all therapy because of the high likelihood of developing antiviral resistance.
	• Patients re-treated with telaprevir plus peginterferon alfa and ribavirin who continue to have detectable HCV RNA >1,000 IU at weeks four

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	or 12 should be withdrawn from all therapy because of the high likelihood of developing antiviral resistance. Adverse events • Patients who develop anemia on protease inhibitor-based therapy for chronic hepatitis C should be managed by reducing the ribavirin dose. • Patients on protease inhibitor-based therapy should undergo close monitoring of HCV RNA levels and the protease inhibitors should be discontinued if virological breakthrough (greater than one log increase in serum HCV RNA above nadir) is observed. • Patients who fail to have a virological response, who experience virological breakthrough, or who relapse on one protease inhibitor should not be re-treated with other protease inhibitors. Use and Interpretation of HCV RNA results during triple therapy • An HCV assay with a lower limit of quantification of equal to or less than 25 IU/mL and a limit of HCV RNA detection of approximately 10 to 15 IU/mL should be used for monitoring response to therapy and decision making during triple therapy. • Response-guided therapy should only be considered when no virus is detected by a sensitive assay four weeks after initiation of the HCV protease inhibitor. IL28B testing • IL28B genotype is a robust pretreatment predictor of sustained virologic response (SVR) to peginterferon alfa and ribavirin as well as to protease inhibitor triple therapy in patients with chronic HCV genotype 1. Testing may be considered when the patient or provider wish additional information on the probability of treatment response or on the probable treatment needed.
National Institutes of Health, the Centers for Disease Control and Prevention, and the Human Immunodeficiency Virus Medicine Association of the Infectious Diseases Society of America: **Guidelines for Prevention and Treatment of Opportunistic Infections in Human Immunodeficiency Virus - Infected Adults and Adolescents (2013)**[18]	Aspergillosis • Voriconazole is the drug of choice but should be used cautiously with human immunodeficiency virus protease inhibitors and efavirenz. Amphotericin B deoxycholate at 1 mg/kg daily or lipid-formulation amphotericin B at 5 mg/kg daily are alternatives, as is caspofungin at 50 mg daily and posaconazole. • Other echinocandins, such as micafungin and anidulafungin, are reasonable alternatives. • For treatment failure (if voriconazole was used initially) substitution with amphotericin B, posaconazole, or echinocandins might be considered; the amphotericin B or echinocandins would be rational for those who began therapy with voriconazole or posaconazole. Candidiasis (mucocutaneous) • Oral fluconazole is as effective as topical therapy for oropharyngeal candidiasis and is considered the drug of choice. Initial episodes of oropharyngeal candidiasis can be adequately treated with topical therapy, including clotrimazole troches, nystatin suspension or pastilles, or miconazole mucoadhesive tablets. Itraconazole oral solution for seven to 14 days is as effective as oral fluconazole but less well tolerated. Posaconazole oral solution is also as effective as fluconazole and is generally better tolerated than itraconazole. Intravenous amphotericin B is usually effective and can be used among patients with refractory disease. Both conventional amphotericin B and lipid complex and liposomal amphotericin B have been used.

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	• Systemic antifungals are required for effective treatment of esophageal candidiasis. A 14 to 21-day course of either fluconazole (oral or intravenous) or oral itraconazole solution is highly effective. Oral ketoconazole or itraconazole capsules are less effective than fluconazole because of variable absorption. Although intravenous caspofungin or intravenous voriconazole are effective in treating esophageal candidiasis among human immunodeficiency virus -infected patients, oral or intravenous fluconazole remain the preferred therapies. Azole-refractory esophageal candidiasis can be treated with posaconazole, amphotericin B, anidulafungin, caspofungin, micafungin, or voriconazole. • Vulvovaginal candidiasis in human immunodeficiency virus -infected women is usually uncomplicated (90%) and responds readily to short-course oral or topical treatment with any of several therapies, including oral fluconazole, topical azoles, and itraconazole oral solution. Severe or recurrent episodes of vaginitis require oral fluconazole or topical antifungal therapy for ≥7 days. <u>Coccidioidomycosis</u> • For patients with clinically mild infection, such as focal pneumonia or a positive coccidioidal serologic test alone, initial therapy with a triazole antifungal is appropriate. • For patients with either diffuse pulmonary involvement or severely ill patients with extrathoracic disseminated disease, amphotericin B is the preferred initial therapy. Therapy with amphotericin B should continue until clinical improvement is observed. Some specialists would use a triazole antifungal concurrently with amphotericin B and continue the triazole once amphotericin B is stopped. <u>Cryptococcosis</u> • The recommended initial standard treatment is amphotericin B combined with flucytosine for ≥2 weeks for those with normal renal function. • The combination of amphotericin B with fluconazole is less effective than amphotericin B combined with flucytosine in terms of clearing *Cryptococcus* from the cerebrospinal fluid but is better than amphotericin B alone. • Fluconazole combined with flucytosine is an alternative to amphotericin B plus flucytosine, but is less effective than amphotericin B and is recommended only for persons unable to tolerate or unresponsive to standard treatment. • After at least a two-week period of successful induction therapy, amphotericin B and flucytosine may be discontinued and follow-up therapy initiated with fluconazole. This should continue for eight weeks. Itraconazole is an acceptable though less effective alternative. • The optimal therapy for those with treatment failure is not established. For those initially treated with fluconazole, therapy should be changed to amphotericin B, with or without flucytosine, and continued until a clinical response occurs. Liposomal amphotericin B may have improved efficacy over the deoxycholate formulation and should be considered in treatment failures. Higher doses of fluconazole in combination with flucytosine might also be useful. <u>Cryptosporidiosis</u> • In the setting of severe immunosuppression, antiretroviral therapy with immune restoration to a CD4+ count >100 cells/μL leads to resolution

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	of clinical cryptosporidiosis and is the mainstay of treatment. • All patients with cryptosporidiosis should be offered antiretroviral therapy as part of the initial management of their infection. • Management should include symptomatic treatment of diarrhea. Rehydration and repletion of electrolyte losses by either the oral or intravenous route are important. Severe diarrhea can exceed >10 L/day among patients with acquired immunodeficiency syndrome, often requiring intensive support. Aggressive efforts at oral rehydration should be made with oral rehydration solutions. <u>Prevention of Cytomegalovirus</u> • Cytomegalovirus end-organ disease is best prevented by using antiretroviral therapy to maintain the CD4+ count >100 cells/µL. • Although oral valganciclovir would likely prevent the occurrence of cytomegalovirus retinitis in patients with CD4+ counts <50 cells/µL, such therapy is not generally recommended because of the potential to induce cytomegalovirus resistance, the utility of treating disease when it occurs, and the lack of demonstrated survival advantage. <u>Treatment of Cytomegalovirus disease</u> • Oral valganciclovir, intravenous ganciclovir, intravenous ganciclovir followed by oral valganciclovir, intravenous foscarnet, and intravenous cidofovir are all effective treatments for cytomegalovirus retinitis. • The ganciclovir implant, a surgically-implanted reservoir of ganciclovir, which lasts approximately six months, also is very effective but it no longer is being manufactured. In its absence, some clinicians will use intravitreal injections of ganciclovir or foscarnet in conjunction with oral valganciclovir, at least initially, to provide immediate high intraocular levels of drug and presumably faster control of the retinitis. • Systemic therapy has been shown to reduce morbidity in the contralateral eye. This should be considered when choosing between the oral, intravenous, and local options. • The choice of initial therapy for cytomegalovirus retinitis should be individualized based on the location and severity of the lesion(s), the level of underlying immune suppression, and other factors such as concomitant medications and ability to adhere to treatment. • No one regimen has been proven in a clinical trial to have greater efficacy in terms of protecting vision, and thus clinical judgment must be used when choosing a regimen. • In studies conducted in the pre-antiretroviral therapy era, ganciclovir intraocular implant plus oral ganciclovir was superior to once-daily intravenous ganciclovir for treatment of cytomegalovirus retinitis; however, the implant is no longer manufactured. Assuming that this observation can be extended to other combinations of systemically and locally administered drugs, human immunodeficiency virus-specialists often recommend intravitreal ganciclovir or foscarnet injections plus oral valganciclovir as the preferred initial therapy for patients with immediate sight-threatening lesions. Intravitreal injections deliver high concentrations of the drug to the target organ immediately while steady-state concentrations in the eye are achieved with systemically delivered medications. For patients with small peripheral lesions, oral valganciclovir alone often is adequate. • After induction therapy, secondary prophylaxis (i.e., chronic maintenance therapy) should be continued until immune reconstitution occurs as a result of antiretroviral therapy. Regimens demonstrated to

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	be effective for chronic suppression in randomized, controlled clinical trials include parenteral ganciclovir, oral valganciclovir, parenteral foscarnet, combined parenteral ganciclovir and foscarnet, and parenteral cidofovir. Management of Cytomegalovirus retinitis treatment failures • When patients relapse while receiving maintenance therapy, induction with the same drug followed by reinstitution of maintenance therapy can control the retinitis, although for progressively shorter periods of time with each relapse. • Ganciclovir and foscarnet in combination appear to be superior in efficacy to either agent alone and should be considered for patients whose disease does not respond to single-drug therapy, and for patients with multiple relapses of retinitis. This drug combination, however, is associated with substantial toxicity. Treatment of Hepatitis B Virus coinfection in patients not receiving antiretroviral therapy • For patients with CD4+ counts >350 cells/µL who are not receiving antiretroviral therapy but meet criteria for hepatitis B virus treatment, adefovir or peginterferon alfa-2a monotherapy for 48 weeks might be considered, with close monitoring of hepatitis B virus deoxyribonucleic acid levels and follow-up to evaluate for hepatitis B e antigen seroconversion. However, early initiation of antiretroviral therapy should also be considered for human immunodeficiency virus/hepatitis B virus -coinfected persons with CD4+ counts >350 cells/µL. Treatment of Hepatitis B Virus coinfection in patients who require antiretroviral therapy • For human immunodeficiency virus-infected persons, some experts recommend combination therapy with two agents active against hepatitis B virus to reduce the risk of hepatitis B virus drug resistance; although, there are no results from controlled trials as yet to support this strategy. • Among patients infected with hepatitis B virus, hepatitis C virus, and human immunodeficiency virus, consideration of the need for antiretroviral therapy should be the first priority. If antiretroviral therapy is not required, interferon-based therapy, which suppresses both hepatitis C virus and hepatitis B virus, should be considered. If interferon-based therapy for hepatitis C virus has failed, treatment of chronic hepatitis B with nucleoside or nucleotide analogs is recommended. Treatment of Hepatitis C coinfection • Antiviral treatment for hepatitis C virus infection should be considered for all human immunodeficiency virus-infected persons with acute or chronic hepatitis C virus infection. • The combination of peginterferon alfa (PegIFN) plus ribavirin is the recommended backbone of therapy for HIV/HCV-co-infected patients regardless of HCV genotype. • Antiviral treatment with PegIFN is not recommended in patients with decompensated liver disease. • For HCV-genotype-1-infected patients who are not co-infected with HIV, a HCV NS3/4A protease inhibitor (PI), either boceprevir or telaprevir, in combination with PegIFN/ribavirin is recommended on

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	the basis of large clinical trials demonstrating significantly higher SVR rates with an acceptable safety/tolerability profile compared to PegIFN/ribavirin alone.
	• For HIV/HCV co-infected patients, preliminary data from small, ongoing clinical trials of boceprevir or telaprevir plus PegIFN/ribavirin for the treatment of HCV genotype 1 infection in HIV/HCV co-infected patients demonstrate greater efficacy than PegIFN/ribavirin alone, with a safety and tolerability profile similar to that observed in HCV monoinfected patients treated with boceprevir or telaprevir plus PegIFN/ribavirin. Preliminary recommendations are as follows:
	  o PegIFN is recommended for use for all HCV genotypes
	  o Ribavirin is recommended for use with PegIFN for all HCV genotypes.
	  o Boceprevir is approved for use in combination with PegIFN/ribavirin in HCV-genotype-1-monoinfected-patients. For HIV/HCV-co-infected patients, the regimen being evaluated is PegIFN/ribavirin administered for four weeks (lead-in phase) followed by boceprevir 800 mg orally every 7 to 9 hours (with a light snack) added to PegIFN/ribavirin for an additional 44 weeks.
	  o Telaprevir is approved for use in combination with PegIFN/ribavirin in HCV-genotype-1-monoinfected-patients. Dosing regimens lasting 48 weeks are being evaluated.
	• Patients with contraindications to the use of ribavirin can be treated with peginterferon alfa (2a or 2b) monotherapy. However, substantially lower sustained viral response rates are expected in persons not receiving ribavirin. HCV PIs should not be administered without ribavirin because of the high likelihood of virologic failure.
	
	<u>Treatment of herpes simplex virus disease</u>
	• Orolabial lesions can be treated with oral valacyclovir, famciclovir, or acyclovir for five to 10 days.
	• Severe mucocutaneous herpes simplex virus lesions are best treated initially with intravenous acyclovir. Patients may be switched to oral therapy after the lesions have begun to regress. Therapy should be continued until the lesions have completely healed.
	• Genital herpes simplex virus infection should be treated with oral valacyclovir, famciclovir, or acyclovir for five to 14 days. Short-course therapy (one, two, or three days) should not be used in patients with human immunodeficiency virus infection.
	• Most recurrences of genital herpes can be prevented by use of daily anti- herpes simplex virus therapy, and this is recommended for persons who have frequent or severe recurrences.
	• Suppressive therapy with oral acyclovir, valacyclovir, or famciclovir is effective in preventing recurrences. Suppressive therapy with valacyclovir should be 500 mg twice daily in human immunodeficiency virus -infected persons or twice-daily regimens with acyclovir or famciclovir should be used.
	
	<u>Management of herpes simplex virus treatment failure</u>
	• The treatment of choice for acyclovir-resistant herpes simplex virus is intravenous foscarnet. Topical trifluridine, cidofovir, and imiquimod also have been used successfully for lesions on external surfaces, although prolonged application for 21 to 28 days or longer might be required.

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	Histoplasmosis • Patients with moderately severe to severe disseminated histoplasmosis should be treated with an intravenous lipid formulation of amphotericin B for ≥2 weeks or until they clinically improve followed by oral itraconazole (200 mg three times daily for three days and then 200 mg twice daily for a total of ≥12 months). • In patients with less severe disseminated histoplasmosis, oral itraconazole at 200 mg three times daily for three days followed by 200 mg twice daily is appropriate initial therapy. Treatment of Isosporiasis (also known as Cystoisosporiasis) • Sulfamethoxazole-trimethoprim is the antimicrobial agent of choice for treatment of isosporiasis. It is the only agent whose use is supported by substantial published data and clinical experience. Therefore, potential alternative therapies should be reserved for patients with documented sulfa intolerance or in whom treatment fails. The traditional treatment regimen has been a 10-day course of Sulfamethoxazole-trimethoprim (800-160 mg) administered orally four times daily. • Intravenous administration of Sulfamethoxazole-trimethoprim should be considered for patients with potential or documented malabsorption. • Single-agent therapy with pyrimethamine has been used, with anecdotal success for treatment and prevention of isosporiasis. Pyrimethamine (50 to 75 mg/day) plus leucovorin (10 to 25 mg/day) to prevent myelosuppression may be an effective treatment alternative; it is the option for sulfa-intolerant patients. Leishmaniasis • Due to similar efficacy and a better toxicity profile, clinicians consider liposomal amphotericin B as the drug of choice for visceral leishmaniasis in human immunodeficiency virus-coinfected patients. The optimal amphotericin B dosage has not been determined. • Regimens with efficacy include conventional amphotericin B 0.5 to 1.0 mg/kg body weight/day intravenous to achieve a total dose of 1.5 to 2.0 g, or liposomal or lipid complex preparations of two to four mg/kg body weight administered on consecutive days or in an interrupted schedule (e.g., 4 mg/kg on Days 1 to 5, 10, 17, 24, 31, and 38) to achieve a total cumulative dose of 20 to 60 mg/kg body weight. A higher daily dosage is recommended for liposomal or lipid complex preparations than for conventional amphotericin B. Preventing disseminated *Mycobacterium avium* complex disease • Human immunodeficiency virus-infected adults and adolescents should receive chemoprophylaxis against disseminated *Mycobacterium avium* complex disease if they have a CD4+ count <50 cells/µL. • Azithromycin or clarithromycin are the preferred prophylactic agents. • The combination of clarithromycin and rifabutin is no more effective than clarithromycin alone for chemoprophylaxis, is associated with a higher rate of adverse effects than either drug alone, and should not be used. • The combination of azithromycin with rifabutin is more effective than azithromycin alone; however, the additional cost, increased occurrence of adverse effects, potential for drug interactions, and absence of a survival difference compared to azithromycin alone do not warrant a routine recommendation for this regimen.

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	• Azithromycin and clarithromycin also each confer protection against respiratory bacterial infections.
	• If azithromycin or clarithromycin cannot be tolerated, rifabutin is an alternative prophylactic agent for *Mycobacterium avium* complex disease, although drug interactions may make this agent difficult to use.
	• Primary *Mycobacterium avium* complex disease prophylaxis should be discontinued among adult and adolescent patients who have responded to antiretroviral therapy with an increase in CD4+ counts to >100 cells/µL for ≥3 months. Primary prophylaxis should be reintroduced if the CD4+ count decreases to <50 cells/µL.
	
	<u>Treatment of disseminated *Mycobacterium avium* Complex Disease</u>
	• Initial treatment of *Mycobacterium avium* complex disease should consist of two or more antimycobacterial drugs to prevent or delay the emergence of resistance.
	• Clarithromycin is the preferred first agent; however, azithromycin can be substituted for clarithromycin when drug interactions or clarithromycin intolerance preclude the use of clarithromycin.
	• Testing of *Mycobacterium avium* complex disease isolates for susceptibility to clarithromycin or azithromycin is recommended for all patients.
	
	<u>Treatment of Penicilliosis marneffei</u>
	  • Penicilliosis is caused by the dimorphic fungus *Penicillium marneffei*, which is known to be endemic in Southeast Asia (especially Northern Thailand and Vietnam) and southern China.
	  • The recommended treatment is liposomal amphotericin B, three to five mg/kg body weight/day intravenously for two weeks, followed by oral itraconazole, 400 mg/day for a subsequent duration of 10 weeks, followed by secondary prophylaxis.
	  • Patients with mild disease can be initially treated with oral itraconazole 400 mg/day for eight weeks, followed by 200 mg/day for prevention of recurrence.
	  • The alternative drug for primary treatment in the hospital is intravenous voriconazole, 6 mg/kg every 12 hours on day one and then 4 mg/kg every 12 hours for at least three days, followed by oral voriconazole, 200 mg twice daily for a maximum of 12 weeks.
	  • Patients with mild disease can be initially treated with oral voriconazole 400 mg twice a day on day one, and then 200 mg twice daily for 12 weeks. The optimal dose of voriconazole for secondary prophylaxis after 12 weeks has not been studied.
	
	<u>Primary prophylaxis of *Pneumocystis (carinii) jiroveci* pneumonia</u>
	• Sulfamethoxazole-trimethoprim is the recommended prophylactic agent. One double-strength tablet daily is the preferred regimen. However, one single-strength tablet daily is also effective and might be better tolerated than one double-strength tablet daily. One double-strength tablet three times weekly is also effective. Sulfamethoxazole-trimethoprim at a dose of one double-strength tablet daily confers cross-protection against toxoplasmosis and selected common respiratory bacterial infections. Lower doses of sulfamethoxazole-trimethoprim likely also confer such protection.
	• For patients who have an adverse reaction that is not life threatening,

Clinical Guideline	Recommendation(s)
	chemoprophylaxis with sulfamethoxazole-trimethoprim should be continued if clinically feasible; for those who have discontinued such therapy because of an adverse reaction, reinstituting sulfamethoxazole-trimethoprim should be strongly considered after the adverse event has resolved. Patients who have experienced adverse events, including fever and rash, might better tolerate reintroduction of the drug with a gradual increase in dose (i.e., desensitization), according to published regimens or reintroduction of sulfamethoxazole-trimethoprim at a reduced dose or frequency; as many as 70% of patients can tolerate such reinstitution of therapy. • If sulfamethoxazole-trimethoprim cannot be tolerated, alternative prophylactic regimens include dapsone, dapsone/pyrimethamine plus leucovorin, aerosolized pentamidine and atovaquone. • Primary *Pneumocystis (carinii) jiroveci* pneumonia prophylaxis should be discontinued for adult and adolescent patients who have responded to antiretroviral therapy with an increase in CD4+ counts to >200 cells/µL for >3 months. Prophylaxis should be reintroduced if the CD4+ count decreases to <200 cells/µL. <u>Treatment of *Pneumocystis (carinii) jiroveci* pneumonia</u> • Sulfamethoxazole-trimethoprim is the treatment of choice. The dose must be adjusted for abnormal renal function. Multiple randomized clinical trials indicate that sulfamethoxazole-trimethoprim is as effective as parenteral pentamidine and more effective than other regimens. Adding leucovorin to prevent myelosuppression during acute treatment is not recommended because of questionable efficacy and some evidence for a higher failure rate. Oral outpatient therapy of sulfamethoxazole-trimethoprim is highly effective among patients with mild-to-moderate disease. • Patients who have *Pneumocystis (carinii) jiroveci* despite sulfamethoxazole-trimethoprim prophylaxis are usually effectively treated with standard doses of sulfamethoxazole-trimethoprim. • Patients with documented or suspected *Pneumocystis (carinii) jiroveci* and moderate-to-severe disease, as defined by room air pO_2 <70 mm Hg or arterial-alveolar O_2 gradient >35 mm Hg, should receive adjunctive corticosteroids as early as possible, and certainly within 72 hours after starting specific *Pneumocystis (carinii) jiroveci* therapy. • The recommended duration of therapy for *Pneumocystis (carinii) jiroveci* is 21 days. • Patients who have a history of *Pneumocystis (carinii) jiroveci* should be administered chemoprophylaxis for life (i.e., secondary prophylaxis or chronic maintenance therapy) with sulfamethoxazole-trimethoprim unless immune reconstitution occurs as a result of antiretroviral therapy. • Secondary prophylaxis should be discontinued for adult and adolescent patients whose CD4+ count has increased from <200 cells/µL to >200 cells/µL for >3 months as a result of antiretroviral therapy. Prophylaxis should be reintroduced if the CD4+ count decreases to <200 cells/µL. If *Pneumocystis (carinii) jiroveci* recurs at a CD4+ count of ≥200 cells/µL, lifelong prophylaxis should be administered. <u>Primary prophylaxis of *Toxoplasma* encephalitis</u> • The double-strength tablet daily dose of sulfamethoxazole-trimethoprim recommended as the preferred regimen for *Pneumocystis (carinii) jiroveci* prophylaxis is effective against *Toxoplasma* encephalitis as well and is therefore recommended. Sulfamethoxazole-

Clinical Guideline	Recommendation(s)

	trimethoprim, one double-strength tablet three times weekly, is an alternative.
	• If patients cannot tolerate sulfamethoxazole-trimethoprim, the recommended alternative is dapsone-pyrimethamine plus leucovorin, which is also effective against *Pneumocystis (carinii) jiroveci* pneumonia.
	• Atovaquone with or without pyrimethamine/leucovorin can also be considered.
	• Prophylactic monotherapy with dapsone, pyrimethamine, azithromycin, or clarithromycin cannot be recommended on the basis of available data. Aerosolized pentamidine does not protect against *Toxoplasma* encephalitis and is not recommended.
	• Prophylaxis against *Toxoplasma* encephalitis should be discontinued among adult and adolescent patients who have responded to antiretroviral therapy with an increase in CD4+ counts to >200 cells/µL for >3 months. Prophylaxis for *Toxoplasma* encephalitis should be reintroduced if the CD4+ count decreases to <100 to 200 cells/µL.
	
	<u>Treatment of *Toxoplasma* encephalitis</u>
	• The initial therapy of choice for *Toxoplasma* encephalitis consists of the combination of pyrimethamine plus sulfadiazine plus leucovorin.
	• The preferred alternative regimen for patients with *Toxoplasma* encephalitis who are unable to tolerate or who fail to respond to first-line therapy is pyrimethamine plus clindamycin plus leucovorin.
	• Sulfamethoxazole-trimethoprim was reported in a small randomized trial to be effective and better tolerated than pyrimethamine-sulfadiazine. On the basis of less in vitro activity and less experience with sulfamethoxazole-trimethoprim, treatment with this drug may be considered an option.
	• Acute therapy for *Toxoplasma* encephalitis should be continued for at least six weeks, if there is clinical and radiologic improvement.
	
	<u>Treatment of latent tuberculosis infection</u>
	• Human immunodeficiency virus-infected persons, regardless of age, should be treated for latent tuberculosis infection if they have no evidence of active tuberculosis and:
	  o A positive diagnostic test for latent tuberculosis infection and no prior history of treatment for active or latent tuberculosis.
	  o A negative diagnostic test for latent tuberculosis infection but are close contacts of persons with infectious pulmonary tuberculosis.
	  o A history of untreated or inadequately treated healed tuberculosis (i.e., old fibrotic lesions on chest radiography) regardless of diagnostic tests for latent tuberculosis infection.
	• Treatment options for latent tuberculosis infection include isoniazid daily or twice weekly for nine months.
	• Due to an increased risk of fatal and severe hepatotoxicity, a two-month regimen of daily rifampin and pyrazinamide is not recommended for latent tuberculosis infection treatment regardless of human immunodeficiency virus status.
	• Human immunodeficiency virus-infected persons receiving isoniazid should receive pyridoxine to minimize the risk of developing peripheral neuropathy. Alternatives for individuals who cannot take isoniazid or who have been exposed to a known isoniazid-resistant

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	index case include either rifampin or rifabutin alone for four months. • For persons exposed to isoniazid- and/or rifampin-resistant tuberculosis, decisions to treat with one or two drugs other than isoniazid, rifampin, or rifabutin should be based on the relative risk of exposure to organisms broadly resistant to other antimycobacterial drugs and should be made in consultation with public health authorities. • Directly observed therapy should be used with intermittent dosing regimens when otherwise feasible to maximize regimen completion rates. • There is no evidence to suggest that latent tuberculosis infection treatment should be continued beyond the recommended duration in persons with human immunodeficiency virus infection. Therefore, latent tuberculosis infection treatment should be discontinued after completing the appropriate number of doses. <u>Treatment of active tuberculosis disease</u> • Recommendations for anti-tuberculosis treatment regimens in human immunodeficiency virus -infected adults follow the same principles as for adults without human immunodeficiency virus -infection. • Treatment of drug susceptible tuberculosis disease should include a six-month regimen with an initial phase of isoniazid, rifampin or rifabutin, pyrazinamide, and ethambutol administered for two months followed by isoniazid and rifampin (or rifabutin) for four additional months. • When drug-susceptibility testing confirms the absence of resistance to isoniazid, rifampin, and pyrazinamide, ethambutol may be discontinued before two months of treatment have been completed. • For patients with cavitary lung disease and cultures positive for *Mycobacterium tuberculosis* after completion of two months of therapy, treatment should be extended with isoniazid and rifampin for an additional three months for a total of nine months. • All human immunodeficiency virus-infected patients treated with isoniazid should receive pyridoxine supplementation. • For patients with extrapulmonary tuberculosis, a six- to nine-month regimen (two months of isoniazid, rifampin, pyrazinamide, and ethambutol followed by four to seven months of isoniazid and rifampin) is recommended. • Exceptions to the recommendation for a six- to nine-month regimen for extrapulmonary tuberculosis include central nervous system disease (tuberculoma or meningitis) and bone and joint tuberculosis, for which many experts recommend nine to 12 months. • Adjuvant corticosteroids should be added when treating central nervous system and pericardial disease. • Treatment with corticosteroids should be started intravenously as early as possible with change to oral therapy individualized according to clinical improvement. • Recommended corticosteroid regimens are dexamethasone 0.3 to 0.4 mg/kg tapered over six to eight weeks or prednisone 1 mg/kg for three weeks, then tapered for three to five weeks. <u>Treatment of varicella zoster virus disease</u> • For uncomplicated varicella, the preferred treatment options are valacyclovir (1 gram orally three times daily), or famciclovir (500 mg orally three times daily) for five to seven days. Oral acyclovir (20

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	mg/kg body weight up to a maximum dose of 800 mg five times daily) can be an alternative. • Prompt antiviral therapy should be instituted in all human immunodeficiency virus-seropositive patients whose herpes zoster is diagnosed within one week of rash onset (or any time before full crusting of lesions). The recommended treatment options for acute localized dermatomal herpes zoster in human immunodeficiency virus-infected patients are oral valacyclovir, famciclovir, or acyclovir (doses as above) for seven to 10 days, although longer durations of therapy should be considered if lesions resolve slowly. Valacyclovir or famciclovir are preferred because of their improved pharmacokinetic properties and simplified dosing schedule. • If cutaneous lesions are extensive or if visceral involvement is suspected, intravenous acyclovir should be initiated and continued until clinical improvement is evident. A switch from intravenous acyclovir to oral antiviral therapy (to complete a 10 to 14 day treatment course) is reasonable when formation of new cutaneous lesions has ceased and the signs and symptoms of visceral varicella zoster virus infection are clearly improving. • Optimal antiviral therapy for progressive outer retinal necrosis remains undefined. Specific treatment should include systemic therapy with at least one intravenous drug (selected from acyclovir, ganciclovir, foscarnet, and cidofovir) coupled with injections of at least one intravitreal drug (selected from ganciclovir and foscarnet). Treatment regimens for progressive outer retinal necrosis recommended by certain specialists include a combination of intravenous ganciclovir and/or foscarnet plus intravitreal injections of ganciclovir and/or foscarnet. The prognosis for visual preservation in involved eyes is poor, despite aggressive antiviral therapy. • Other infectious disease states mentioned within these guidelines note that the treatment guidelines for that disease state should be utilized. • The guideline specifies that detailed recommendations for the treatment of human herpesvirus-8 and associated malignancies are beyond the scope of these guidelines. • Other excluded infectious disease states offer no specific therapy or utilize medications not licensed in the United States.
American Gastroenterological Association: **Medical Position Statement on the Management of Hepatitis C (2006)**[17]	• Therapy is indicated for previously untreated patients with chronic hepatitis C, circulating HCV RNA, elevated aminotransferase levels, evidence on liver biopsy of moderate to severe hepatitis grade and stage, and compensated liver disease. • Patients with normal ALT activity are candidates for antiviral therapy or for monitoring without intervention, as determined on an individual basis and as influenced by patient factors such as motivation, genotype, histologic activity, and fibrosis. • Patients with compensated cirrhosis who can tolerate therapy are candidates for treatment. • The treatment of choice is pegylated interferon alfa plus ribavirin. • Patients with genotypes 1 and 4 require 48 weeks of therapy with pegylated interferon and high daily doses of ribavirin (1,000 to 1,200 mg, depending on weight). • Patients with genotypes 2 and 3 can be treated for only 24 weeks with pegylated interferon and with 800 mg of ribavirin daily, with the following exceptions:

Clinical Guideline	Recommendation(s)
	o A longer duration of therapy may be considered on an individual patient basis taking into account factors such as elevated viral level, cirrhosis, or delayed response to therapy. o 12 weeks of therapy suffices in patients in whom HCV RNA levels are undetectable at week 4. o Patients with genotype 3, with high levels of HCV RNA or advanced fibrosis on liver biopsy, may require treatment for 48 weeks. • Therapy with peginterferon alfa and ribavirin should be strongly considered for patients who experienced a relapse after a course of standard interferon alfa/ribavirin combination therapy, while a longer duration of therapy in patients who experienced a relapse after 12 months of treatment with peginterferon alfa plus ribavirin is of unproven efficacy. • For children, the general principles of management are the same as those for adults, except that treatment is not recommended for children younger than 3 years. • For HIV-infected individuals, the optimal therapy consists of peginterferon alfa plus ribavirin for 48 weeks, regardless of genotype. Because of potential drug-drug interactions in patients on HIV treatment regimens that include didanosine, HIV regimens should be altered in those starting combination therapy for HCV infection. If didanosine is critical to the HIV regimen, ribavirin should be avoided.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the HCV antivirals are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the HCV Antivirals[5-11]

Indication	Boceprevir	Simeprevir	Sofosbuvir	Telaprevir
Hepatitis C				
Treatment of chronic hepatitis C genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adult patients with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous interferon and ribavirin therapy including prior null responders, partial responders, and relapsers	✔ *			✔ *
Treatment of chronic hepatitis C infection as a component of a combination antiviral treatment regimen		✔ ^	✔ †	

*Boceprevir and telaprevir efficacy have not been studied in patients who have previously failed therapy with a treatment regimen that includes this or another HCV NS3/4A protease inhibitor.
^Simeprevir efficacy has been established in combination with peginterferon alfa and ribavirin in HCV genotype 1 infected subjects with compensated liver disease (including cirrhosis). Screening patients with HCV genotype 1a infection for the presence of virus with the NS3 Q80K polymorphism at baseline is strongly recommended. Alternative therapy should be considered for patients infected with HCV genotype 1a containing the Q80K polymorphism.
†Sofosbuvir efficacy has been established in subjects with HCV genotype 1, 2, 3 or 4 infection, including those with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) and those with HCV/HIV-1 co-infection.

IV. Pharmacokinetics

The pharmacokinetic parameters of the HCV antivirals are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the HCV Antivirals[5-11]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Boceprevir	Not reported	75	Liver	Renal (9) Feces (79)	3.4
Simeprevir	Not reported	>99	Liver	Renal (<1) Feces (91)	41
Sofosbuvir	Not reported	61 to 65	Liver	Renal (80)	0.4
Telaprevir	Not reported	59 to 76	Liver	Renal (1) Feces (82)	9 to 11

V. Drug Interactions

Significant drug interactions with the HCV antivirals are listed in Table 5.

Table 5. Significant Drug Interactions with the HCV Antivirals[5,7]

Generic Name(s)	Significance Level	Interaction	Mechanism
Protease inhibitors (boceprevir, simeprevir telaprevir)	1	Barbiturates	Protease inhibitor plasma concentrations may be reduced, leading to loss of virologic response. Barbiturate concentrations may be increased or decreased.
Protease inhibitors (boceprevir, simeprevir telaprevir)	1	Benzodiazepines	Potentially serious central nervous system and respiratory depression is possible when benzodiazepines and protease inhibitors are coadministered.
Protease inhibitors (boceprevir, simeprevir telaprevir)	1	Strong CYP3A4 inducers	Plasma concentrations and pharmacologic effects of protease inhibitors may be decreased by strong CYP3A4 inducers.
Protease inhibitors (boceprevir, simeprevir telaprevir)	1	HIV protease inhibitors	Plasma concentrations and pharmacologic effects of HIV protease inhibitors may be decreased by telaprevir. Additionally, plasma concentrations and pharmacologic effects of telaprevir may be reduced by HIV protease inhibitors.
Protease inhibitors (boceprevir, simeprevir telaprevir)	1	HMG-CoA Reductase Inhibitors	Plasma concentrations and toxic effects of statins may be increased by protease inhibitors. The risk of myopathy and rhabdomyolysis may be increased.
Protease inhibitors (boceprevir, simeprevir telaprevir)	1	Immunosuppressive agents	Plasma concentration and pharmacologic effects of immunosuppressive agents may be increased by protease inhibitors.

Generic Name(s)	Significance Level	Interaction	Mechanism
Protease inhibitors (boceprevir, simeprevir telaprevir)	1	Phosphodiesterase type 5 inhibitors	Pharmacologic effects of phosphodiesterase type 5 inhibitors may be increased by protease inhibitors. Elevated plasma concentrations with toxicity characterized by hypotension, visual disturbances, and priapism may occur.
Protease inhibitors (boceprevir, simeprevir telaprevir)	1	Vasopressin receptor antagonists	Plasma concentrations and pharmacologic effects of vasopressin receptor antagonists may be increased by protease inhibitors.
Protease inhibitors (boceprevir, simeprevir telaprevir)	1	Cisapride	Cardiac, hematologic, neurologic (seizures), or other potentially serious toxicities are listed in the manufacturer's package labeling when cisapride and protease inhibitors are coadministered.
Protease inhibitors (boceprevir, simeprevir telaprevir)	1	Digoxin	Plasma concentrations and pharmacologic effects of digoxin may be increased by telaprevir. Signs and symptoms of classic toxicity to digoxin may occur.
Protease inhibitors (boceprevir, simeprevir telaprevir)	1	Nilotinib	Plasma concentrations and pharmacologic effects of nilotinib may be increased by protease inhibitors.
Protease inhibitors (boceprevir, simeprevir telaprevir)	1	Ranolazine	Plasma concentrations and pharmacologic effects of ranolazine may be increased by co-administration of protease inhibitors.
Protease inhibitors (boceprevir, telaprevir)	1	Systemic hormonal contraceptives	Concentrations of certain progestins may be elevated, increasing the risk of hyperkalemia. Estrogen concentrations may be reduced, increasing the risk of unintended pregnancy.
Protease inhibitors (boceprevir, telaprevir)	1	Direct factor Xa inhibitors	Plasma concentration and pharmacologic effects of direct factor Xa inhibitors may be increased by protease inhibitors.
Protease inhibitors (boceprevir, telaprevir)	1	Ergot alkaloids	Pharmacologic effects of ergot alkaloids may be increased by protease inhibitors. Elevated plasma concentrations with toxicity characterized by ergotism may occur.
Protease inhibitors (boceprevir, telaprevir)	1	Fentanyl and related products	Pharmacologic effects and plasma concentrations of fentanyl and related products may be increased by protease inhibitors. Severe respiratory depression may occur.

Generic Name(s)	Significance Level	Interaction	Mechanism
Protease inhibitors (boceprevir, telaprevir)	1	Colchicine	Plasma concentrations of colchicine may be increased by protease inhibitors. Life-threatening and fatal colchicine toxicity may occur.
Protease inhibitors (boceprevir, telaprevir)	1	Crizotinib	Plasma concentrations and toxic effects of crizotinib may be increased by protease inhibitors.
Protease inhibitors (boceprevir, telaprevir)	1	Docetaxel	Plasma concentrations and pharmacologic effects of docetaxel may be increased by protease inhibitors. Use of boceprevir with docetaxel may increase the risk and/or severity of docetaxel-related toxicity.
Protease inhibitors (boceprevir, telaprevir)	1	Dronedarone	Plasma concentrations and pharmacologic effects of dronedarone may be increased by protease inhibitors.
Protease inhibitors (boceprevir, telaprevir)	1	Lomitapide	Lomitapide plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions, including hepatotoxicity.
Protease inhibitors (boceprevir, telaprevir)	1	Lurasidone	Plasma concentrations and pharmacologic effects of lurasidone may be increased by protease inhibitors.
Protease inhibitors (boceprevir, telaprevir)	1	Pimozide	Pharmacologic effects of pimozide may be increased by protease inhibitors. Elevated plasma concentrations with cardiovascular toxicity may occur.
Protease inhibitors (boceprevir, telaprevir)	1	Salmeterol	Pharmacologic effects of salmeterol may be increased by protease inhibitors. Elevated salmeterol plasma concentrations with cardiovascular toxicity, such as QT prolongation, palpitations, and tachycardia may occur.
Protease inhibitors (boceprevir, telaprevir)	1	Ticagrelor	Plasma concentrations and pharmacologic effects of ticagrelor may be increased by protease inhibitors.
Protease inhibitors (boceprevir, telaprevir)	1	Toremifene	Plasma concentrations and pharmacologic effects of toremifene may be increased by protease inhibitors. Toxicity, including QT prolongation may occur.
Simeprevir	1	Antiarrhythmic agents	Concurrent use of simeprevir and antiarrhythmic agents may result in increased exposure to the antiarrhythmic agent.

Generic Name(s)	Significance Level	Interaction	Mechanism
Simeprevir	1	Erythromycin	Concurrent use of erythromycin and simeprevir may result in increased exposure of erythromycin and simeprevir.
Sofosbuvir	1	Carbamazepine	Concurrent use of carbamazepine and sofosbuvir may result in decreased exposure to and loss of efficacy of sofosbuvir.
Sofosbuvir	1	Oxcarbazepine	Concurrent use of oxcarbazepine and sofosbuvir may result in decreased exposure to and loss of efficacy of sofosbuvir.
Sofosbuvir	1	Phenobarbital	Concurrent use of phenobarbital and sofosbuvir may result in decreased exposure to and loss of efficacy of sofosbuvir.
Sofosbuvir	1	Phenytoin	Concurrent use of phenytoin and sofosbuvir may result in decreased exposure to and loss of efficacy of sofosbuvir.
Sofosbuvir	1	Primidone	Concurrent use of primidone and sofosbuvir may result in decreased exposure to and loss of efficacy of sofosbuvir.
Sofosbuvir	1	Rifabutin	Concurrent use of rifabutin and sofosbuvir may result in decreased exposure to and loss of efficacy of sofosbuvir.
Sofosbuvir	1	Rifampin	Concurrent use of rifampin and sofosbuvir may result in decreased exposure to and loss of efficacy of sofosbuvir.
Sofosbuvir	1	Rifapentine	Concurrent use of rifapentine and sofosbuvir may result in decreased exposure to and loss of efficacy of sofosbuvir.
Sofosbuvir	1	St John's Wort	Concurrent use of sofosbuvir and st john's wort may result in decreased exposure to and loss of efficacy of sofosbuvir.
Sofosbuvir	1	Tipranavir	Concurrent use of sofosbuvir and tipranavir may result in decreased exposure to and loss of efficacy of sofosbuvir.
Protease inhibitors (boceprevir, simeprevir telaprevir)	2	Azole Antifungals	Protease inhibitor and azole antifungal agent plasma concentrations may be elevated, increasing the pharmacologic effect and risk of adverse reactions

Generic Name(s)	Significance Level	Interaction	Mechanism
Protease inhibitors (boceprevir, telaprevir)	2	Alpha-1 adrenergic blockers	Alpha-1 adrenergic blocker plasma concentrations may be elevated, increasing the pharmacologic effects and risk of adverse reactions (e.g., hypotension, cardiac arrhythmias).
Protease inhibitors (boceprevir, simeprevir telaprevir)	2	Dihydropyridine calcium channel blockers	Pharmacologic effects of dihydropyridine calcium channel blockers may be increased by telaprevir.
Protease inhibitors (boceprevir, telaprevir)	2	Histone deacetylase inhibitors	Plasma concentrations and pharmacologic effects of histone deacetylase inhibitors may be increased by protease inhibitors. The potential for histone deacetylase inhibitors-related adverse effects, including QT prolongation, should be considered.
Protease inhibitors (boceprevir, telaprevir)	2	Imidazoles	Plasma concentrations and pharmacologic effects of protease inhibitors may be increased by imidazoles. In addition, plasma concentrations and pharmacologic effects of imidazoles may be increased by protease inhibitors.
Protease inhibitors (boceprevir, telaprevir)	2	Muscarinic receptor antagonists	Plasma concentrations and pharmacologic effects of muscarinic receptor antagonists may be increased by protease inhibitors.
Protease inhibitors (boceprevir, telaprevir)	2	Quinazolines	Plasma concentrations and pharmacologic or toxic effects of quinazolines may be increased by protease inhibitors.
Protease inhibitors (boceprevir, telaprevir)	2	Tyrosine kinase receptor inhibitors	Plasma concentrations and pharmacologic effects of tyrosine kinase receptor inhibitors may be increased by protease inhibitors.
Protease inhibitors (boceprevir, telaprevir)	2	Brentuximab	Plasma concentrations and pharmacologic effects of brentuximab may be increased by protease inhibitors.
Protease inhibitors (boceprevir, telaprevir)	2	Cabazitaxel	Plasma concentrations and pharmacologic effects cabazitaxel may be increased by protease inhibitors.
Protease inhibitors (boceprevir, telaprevir)	2	Cilostazol	Plasma concentration and pharmacologic effects of cilostazol may be increased by protease inhibitors.
Protease inhibitors (boceprevir, telaprevir)	2	Ruxolitinib	Plasma concentrations and pharmacologic effects of ruxolitinib may be increased by protease inhibitors.

Generic Name(s)	Significance Level	Interaction	Mechanism
Protease inhibitors (boceprevir, telaprevir)	2	Saxagliptin	Plasma concentrations and pharmacologic effects of saxagliptin may be increased by protease inhibitors.
Protease inhibitors (boceprevir, telaprevir)	2	Vilazodone	Plasma concentrations and pharmacologic effects of vilazodone may be increased by protease inhibitors.

Significance level 1 = major severity; significance level 2 = moderate severity

VI. Adverse Drug Events

The most common adverse drug events reported with the HCV antivirals are listed in Table 6. The boxed warning for telaprevir is listed in Table 7.

Table 6. Adverse Drug Events (%) Reported with the HCV Antivirals[5-11]

Adverse Events	Boceprevir	Simeprevir	Sofosbuvir	Telaprevir
Central Nervous System				
Asthenia	15 to 21	-	-	-
Chills	33 to 34	-	2 to 17	-
Dizziness	16 to 19	-	-	-
Fatigue	55 to 58	-	30 to 59	56
Headache	>10	-	24 to 36	-
Insomnia	30 to 34	-	-	-
Irritability	21 to 22	-	10 to 13	-
Dermatologic				
Alopecia	22 to 27	-	-	-
Angioedema	✔	-	-	-
Dry skin	18 to 22	-	-	-
Photosensitivity	-	5	-	-
Pruritus	-	22	11 to 27	47
Rash	16 to 17	28	8 to 18	56
Urticaria	✔	-	-	-
Gastrointestinal				
Abnormal taste	35 to 44	-	-	10
Anal pruritus	-	-	-	6
Anorectal discomfort	-	-	-	11
Appetite decreased	25 to 26	-	18	-
Diarrhea	24 to 25	-	9 to 12	26
Hemorrhoids	-	-	-	12
Increased serum lipase	-	-	≤2	-
Mouth ulceration	✔	-	-	-
Nausea	43 to 46	22	22 to 34	39
Stomatitis	✔	-	-	-
Vomiting	15 to 20	-	-	13
Xerostomia	11 to 15	-	-	-
Hematologic				
Anemia	45 to 50	-	6 to 21	36
Decreased hemoglobin	-	-	2 to 23	-
Lymphopenia	-	-	-	15
Neutropenia	14 to 31	-	1 to 17	-
Thrombocytopenia	1 to 10	-	≤1	3
Musculoskeletal				

Adverse Events	Boceprevir	Simeprevir	Sofosbuvir	Telaprevir
Arthralgia	19 to 23	-	-	-
Myalgia	-	16	6 to 14	-
Weakness	15 to 21	-	5 to 21	-
Other				
Dyspnea	8 to 11	12	-	-
Fever	-	-	4 to 18	-
Flu-like symptoms	-	-	6 to 16	-
Hyperbilirubinemia	-	<50	3	4 to 37
Hyperuricemia	-	-	-	7 to 66
Increased creatine phosphokinase	-	-	1 to 2	-
Increased serum alkaline phosphatase	-	<4	-	-
Thromboembolic events	<1	-	-	-

✓ Percent not specified
- Event not reported

Table 7. Boxed Warning for Telaprevir[9]

WARNING
Fatal and non-fatal serious skin reactions, including Stevens Johnson Syndrome (SJS), Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS), and Toxic Epidermal Necrolysis (TEN), have been reported in patients treated with telaprevir combination treatment. Fatal cases have been reported in patients with progressive rash and systemic symptoms who continued to receive telaprevir combination treatment after a serious skin reaction was identified. For serious skin reactions, including rash with systemic symptoms or a progressive severe rash, telaprevir, peginterferon alfa, and ribavirin must be discontinued immediately. Discontinuing other medications known to be associated with serious skin reactions should be considered. Patients should be promptly referred for urgent medical care.

VII. Dosing and Administration

The usual dosing regimens for the HCV antivirals are listed in Table 8.

Table 8. Usual Dosing Regimens for the HCV Antivirals[5-11]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Boceprevir	Treatment of chronic hepatitis C genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adult patients with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous interferon and ribavirin therapy including prior null responders, partial responders, and relapsers: Capsule: 800 mg administered orally three times daily (every 7 to 9 hours) with food (a meal or light snack) in combination with peginterferon alfa and ribavirin; initiate therapy with peginterferon alfa and ribavirin for four weeks, then add boceprevir to peginterferon alfa and ribavirin regimen; the duration of treatment is based on viral response, prior response status and presence of cirrhosis	Safety and efficacy in children have not been established	Capsule: 200 mg
Simeprevir	Treatment of chronic hepatitis C infection as a component of a combination antiviral treatment regimen: Capsule: 150 mg once daily with food in combination with both peginterferon alfa and ribavirin; the recommended treatment duration with peginterferon alfa and ribavirin is 12 weeks, followed by either 12 or 36 additional weeks of peginterferon alfa and ribavirin depending on prior response status	Safety and efficacy in children have not been established	Capsule: 150 mg
Sofosbuvir	Treatment of chronic hepatitis C infection as a component of a combination antiviral treatment regimen: Tablet: 400 mg once daily taken with or without food in combination with ribavirin or in combination with pegylated interferon and ribavirin; patients with genotype 1 infection who are interferon ineligible can consider sofosbuvir and ribavirin	Safety and efficacy in children have not been established	Tablet: 400 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	for 24 weeks; patients with hepatocellular carcinoma awaiting liver transplantation should use sofosbuvir and ribavirin for up to 48 weeks or until liver transplantation, whichever occurs first		
Telaprevir	Treatment of chronic hepatitis C genotype 1 infection, in combination with peginterferon alfa and ribavirin, in adult patients with compensated liver disease, including cirrhosis, who are previously untreated or who have failed previous interferon and ribavirin therapy including prior null responders, partial responders, and relapsers: Tablet: 1125 mg taken twice daily (10 to 14 hours apart) with food (not low fat) with both peginterferon alfa and ribavirin for all patients for 12 weeks, followed by a response-guided regimen of either 12 or 36 additional weeks of peginterferon alfa and ribavirin depending on viral response and prior response status	Safety and efficacy in children have not been established	Tablet: 375 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the HCV antivirals are summarized in Table 9.

Table 9. Comparative Clinical Trials with the HCV Antivirals

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Treatment of Chronic Hepatitis: Treatment-Naïve Patients				
Kwo et al.[19] (2010) SPRINT-1 Peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 800 to 1,400 mg/day for 48 weeks (PR48) vs peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 800 to 1,400 mg/day for 4 weeks, followed by peginterferon alfa-2b, ribavirin, and boceprevir 800 mg 3 times a day for 24 weeks (PRB24) vs peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 800 to 1,400 mg/day for 4 weeks, followed by peginterferon alfa-2b, ribavirin, and boceprevir 800 mg 3 times a day for 44 weeks (PRB44) vs	MC, OL, RCT Patients 18 to 60 years of age with hepatitis C genotype 1 who were treatment-naïve	N=595 72 weeks	Primary: SVR and viral breakthrough Secondary: Not reported	Primary: All four boceprevir groups had significantly better SVR than the PR48 control group. In the 28-week treatment groups, the SVR was 56% in the PR4/PRB24 group (P=0.005 vs control) and 54% in the PRB28 group (P=0.013 vs control). In the 48-week treatment groups, the SVR was 75% in the PR4/PRB44 group (P<0.0001 vs control) compared to 67% in the PRB48 group (P<0.0001 vs control). There were significantly lower relapse rates in the 48-week treatment groups compared to PR48 control (PRB48, P=0.0079; PR4/PRB44, P=0.0002). Low-dose ribavirin was associated with a high rate of viral breakthrough (27%), and a rate of relapse (22%) similar to control (24%). The rate of breakthrough in the boceprevir lead-in groups was 4% compared to 9% in the boceprevir groups with no lead in (P=0.057). In the 28-week treatment groups, 82% of patients in the PR4/PRB24 group and 74% in the PRB28 group who had rapid virological response achieved SVR. In the 48-week treatment groups, 94% of patients assigned to PR4/PRB44 and 84% assigned to PRB48 who achieved undetectable hepatitis C virus RNA by week four of boceprevir achieved SVR. The most common side effects in the boceprevir group were fatigue, anemia, nausea and headache, which was similar to PR48 control. The rate of dysgeusia and anemia was higher in boceprevir groups than

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 800 to 1,400 mg/day plus boceprevir 800 mg 3 times a day for 28 weeks (PRB28) vs peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 800 to 1,400 mg/day plus boceprevir 800 mg 3 times a day for 48 weeks (PRB48) vs peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 400 to 1,000 mg/day for 4 weeks, followed by peginterferon alfa-2b, ribavirin, and boceprevir 800 mg 3 times a day for 48 weeks (PRB48)				other groups. Treatment discontinuation was nine to 19% in boceprevir studies compared to 8% in the PR48 control group. Secondary: Not reported
Poordad et al.[20] (2011) SPRINT-2 Group 1 (control): Peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 44 weeks vs Group 2 (response-guided therapy): boceprevir 800 mg three times a day plus peginterferon	MC, PC, PG, RCT Patients ≥18 years of age with a history of no previous treatment for HCV infection, weight 40 to 125 kg, chronic infection with HCV genotype 1 and plasma	N=1,097 (N=938 [nonblack], N=159 [black]) 48 weeks (plus 24 weeks of follow up)	Primary: SVR and safety Secondary: Not reported	Primary: Among nonblack patients, the rate of SVR was 40, 67, and 68% in Groups 1, 2 and 3 (P<0.001 vs Group 1 for both Group 2 and 3). The corresponding numbers in black patients were 23, 42 (P=0.04 vs Group 1), and 53% (P=0.004 vs Group 1). Subgroup analyses revealed that at four weeks, 23 and 38% of nonblack and black patients had a decrease of <1 $\log_{10}$ IU/mL in HCV RNA level from baseline, which was associated with lower rates of SVR and higher rates of boceprevir-resistance-associated variants compared to those achieving a decrease of ≥1 $\log_{10}$ IU/mL from baseline. However, regardless of the degree of reduction achieved at week four, patients receiving boceprevir achieved consistently higher rates of SVR compared to patients who received control overall.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 24 weeks, followed by an additional 20 weeks of peginterferon alfa-2b plus ribavirin in detectable HCV RNA levels at any visit from week 8 to 24 vs Group 3 (fixed duration therapy): boceprevir 800 mg three times a day plus peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 44 weeks All patients entered a 4 week lead in period in which peginterferon alfa-2b and ribavirin were administered. The trial consisted of two cohorts enrolling nonblacks and blacks separately. Treatment was considered complete in Group 2 if the HCV RNA level was undetectable from week 8 through week 24 (total duration, 28 weeks). In all 3 treatment groups, treatment was discontinued for all patients with a detectable HCV RNA level at week 24 based on futility rules; these patients then	HCV RNA level ≥10,000 IU/mL			Response rates at the end of therapy (undetectable HCV RNA level at the time that the study therapy was discontinued) were significantly higher with boceprevir-containing regimens compared to the control regimen. Among nonblack patients, viral breakthrough (undetectable HCV RNA level and subsequent occurrence of an HCV RNA level >1,000 IU/mL) occurred in one to two percent of all patients, regardless of treatment regimen. In addition, relapse rates (undetectable HCV RNA level at the end of treatment but a detectable HCV RNA level at some point during the follow up period) were lower with boceprevir compared to control. The numbers of events among black patients were too few to permit comparison between the treatment groups. Adverse events occurred in more than 98% of all patients, with serious adverse events in 9, 11 and 12% of patients in Groups 1, 2 and 3, respectively. There were six deaths during the trial; four deaths in Group 1 and two deaths from boceprevir-containing regimens. Two suicides (one in Group 1 and one in Group 2) were determined to have possibly been related to treatment with peginterferon. Fatigue, headache, and nausea were the most commonly reported adverse events. The incidence of dysgeusia was higher with boceprevir treatment. Anemia was reported in 29 and 49% of patients receiving control and boceprevir, respectively. Overall, 13 and 21% of control- and boceprevir-treated patients required dose reductions because of anemia and erythropoietin was administered in 24 and 43% of patients. Neutropenia and thrombocytopenia also occurred more frequently with boceprevir treatment. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
entered the follow up period.				
Jacobson et al.[21] (2014) QUEST-1 Simeprevir 150 mg once daily plus peginterferon alfa-2a plus ribavirin for 12 weeks, followed by peginterferon alfa-2a plus ribavirin (simeprevir group) vs placebo plus peginterferon alfa-2a plus ribavirin for 12 weeks, followed by peginterferon alfa-2a plus ribavirin (placebo group)	DB, MC, PC, RCT Patients (aged ≥18 years) with chronic HCV genotype 1 infection and no history of HCV treatment	N=394 72 weeks	Primary: SVR12 Secondary: SVR24, rapid virological response (RVR), adverse effects	Primary: SVR12 was achieved in a higher percentage of patients in the simeprevir group than in the placebo group (80 vs 50%), and the difference stratified by HCV genotype 1 subtype and IL28B genotype was significant (29.3%; 95% CI, 20.1 to 38.6; P<0.0001). Secondary: RVR was higher in the simeprevir group than in the placebo group (80 vs 12%). In the simeprevir group, 181 (90%) of 202 patients with RVR achieved SVR12. A higher proportion of patients in the simeprevir group had SVR24 than in the placebo group (83 vs 60%; weighted difference 18.1%; 95% CI, –0.4 to 36.6; P=0.0253). Overall frequencies of adverse events were similar in the two groups during the first 12 weeks of treatment and for the entire treatment. The adverse events resulted in less than 1% of patients permanently discontinuing simeprevir or placebo in the first 12 weeks and during the entire treatment period. In the first 12 weeks, 3% of patients in the simeprevir group discontinued all study drugs compared with 2% in the placebo group.
Manns et al.[22] (2014) QUEST-2 Simeprevir 150 mg once daily plus peginterferon alfa-2a or 2b plus ribavirin for 12 weeks, followed by peginterferon alfa-2a or 2b plus ribavirin (simeprevir group) vs placebo plus peginterferon alfa-2a	DB, MC, PC, PG, RCT Patients (aged ≥18 years) with chronic HCV genotype 1 infection and no history of HCV treatment	N=391 72 weeks	Primary: SVR12 Secondary: Rapid virological response (RVR), activity, safety, and tolerability of simeprevir in the two subpopulati-	Primary: Significantly more patients achieved SVR12 in the simeprevir group than in the placebo group (209 [81%] of 257 vs 67 [50%] of 134). The adjusted difference weighted by HCV subtype, IL28B genotype, and peginterferon type as stratification factors was 32.2% (95% CI, 23.3 to 41.2; P<0.0001). Secondary: A significantly higher percentage of patients achieved SVR12 in the simeprevir group than in the placebo group, irrespective of the type of peginterferon they were given: 68 (88%) of 77 patients in the simeprevir group randomly assigned to peginterferon alfa-2a achieved SVR12 compared with 28 (62%) of 45 in the placebo group difference 33.9%; 95% CI, 21.0 to 46.8; P<0.0001). Of the patients randomly

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
or 2b plus ribavirin for 12 weeks, followed by peginterferon alfa-2a or 2b plus ribavirin (placebo group)			ons of patients who were given peginterferon alfa 2a or 2b, adverse events	assigned to peginterferon alfa-2b, 62 (78%) of 80 patients in the simeprevir group versus 18 (42%) of 43 in the placebo group achieved SVR12 (46.1%; 33.9 to 58.3; P<0.0001). Overall, the proportions of patients who had adverse events in the first 12 weeks of treatment were similar in the simeprevir and placebo groups, and the proportions were similar in the two groups for the entire treatment.
Fried et al.[23] (2013) PILLAR Simeprevir at doses of either 75 or 150 mg administered orally once daily for 12 or 24 weeks in combination with pegylated interferon (Peg-IFN) alpha-2a 180 µg/week and ribavirin (RBV) 1,000 to 1,200 mg/day vs Placebo in combination with Peg-IFN alpha-2a 180 µg/week and RBV 1,000 to 1,200 mg/day Participants who were randomized to 12 weeks of simeprevir therapy received an additional 12 weeks of placebo plus Peg-IFN and RBV.	DB, PC, RCT Adult patients with chronic hepatitis C with plasma HCV RNA >100,000 IU/mL, infection with HCV genotype 1, never received Peg-IFN, RBV, or other approved or investigational agents for chronic HCV infection	N=386 48 weeks (plus 24 weeks of follow up)	Primary: proportion of patients with HCV RNA <25 IU/mL undetectable at week 72 Secondary: SVR12, SVR24, adverse events	Primary: SVR at week 72 ranged between 70.7 and 84.8% for simeprevir regimens, compared with 64.9% of those treated with Peg-IFN and RBV alone. The differences between simeprevir 150 mg groups and placebo control were statistically significant (P<0.05). Secondary: SVR24 was achieved in 74.7 to 86.1% of those treated with simeprevir regimens, compared to 64.9% of those treated with placebo. All SVR24 comparisons between simeprevir treatment groups and placebo controls were statistically significant (P<0.05 or 0.005), except for simeprevir 75 mg for 24 weeks. The most frequent adverse events (fatigue, influenza-like illness, pruritus, headache, and nausea) were those typically associated with Peg-IFN and RBV therapy and were similar across simeprevir and placebo treatment groups.
Kowdley et al.[24] (2013) ATOMIC Cohort A: sofosbuvir 400 mg orally once daily, peginterferon	MC, OL, R Patients with chronic HCV infection (genotypes 1, 4,	N=316 12 to 24 weeks (plus 24 weeks of	Primary: SVR24 Secondary: Safety	Primary: Cohort A: 46 of 52 (89%; 95% CI, 77 to 96%) Cohort B: 97 of 109 (89%; 95% CI, 82 to 94%) Cohort C: 135 of 155 (87%; 95% CI, 81 to 92%) No difference was found in the proportions of patients achieving SVR24 between cohorts A and B (P=0.94) or between cohorts A and C

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
180 µg subcutaneously once a week, and ribavirin orally as a divided weight-based daily dose (<75 kg received 1000 mg and those ≥75 kg received 1200 mg) for 12 weeks vs Cohort B received the same drugs at the same doses for 24 weeks vs Cohort C received the same regimen as individuals in cohort A followed by an additional 12 weeks of sofosbuvir monotherapy for half the patients, or sofosbuvir plus ribavirin for the other half (with patients randomly allocated to these subcohorts)	5, or 6), aged 18 years or older, and had not previously received treatment for HCV infection	follow up)		(P=0.78), suggesting no additional benefit of treatment durations longer than 12 weeks. Secondary: Most patients (97 to 99%) had at least one adverse event during the study. The most common adverse events were those consistent with the known safety profile for peginterferon and ribavirin: fatigue, headache, and nausea.
Lawitz et al[25] (2013) NEUTRINO and FISSION NEUTRINO: Sofosbuvir 400 mg once daily for 12 weeks, peginterferon alfa-2a 180 µg once weekly for 12 weeks, and ribavirin 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) for 12 weeks FISSION: Sofosbuvir 400 mg once daily for	NEUTRINO: MC, OL, SG Patients ≥18 years of age with confirmed diagnosis of chronic HCV infection (genotypes 1, 4, 5, or 6), serum HCV RNA levels of ≥10,000 IU/mL during	NEUTRINO: N=327 12 weeks FISSION: N=499 24 weeks	NEUTRINO: Primary: SVR12 Secondary: Not reported FISSION: Primary: SVR12 Secondary: Not reported	NEUTRINO: Primary: Treatment with sofosbuvir added to peginterferon alfa-2a and ribavirin achieved a SVR12 in 90% of patients (95% CI, 87 to 93). In addition, this regimen was found to be more effective in achieving a SVR12 compared to an adjusted historical response rate of 60% (P<0.001) observed in studies of telaprevir and boceprevir. The rate of SVR12 was 92% (95% CI, 89 to 95) among patients without cirrhosis and 80% (95% CI, 67 to 89) among those with cirrhosis. A SVR12 occurred in 98% of patients with the CC genotype of IL28B, as compared to 87% of patients with the non–CC IL28B genotype. Rates of SVR12 were similar among various HCV genotypes: 89% for

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
12 weeks and ribavirin 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) for 12 weeks vs peginterferon alfa-2a 180 µg once weekly for 24 weeks and ribavirin 800 mg/day in two divided doses for 24 weeks	screening, and who had never received treatment for HCV infection FISSION: AC, MC, OL, R Patients ≥18 years of age with confirmed diagnosis of chronic HCV infection (genotypes 2 or 3), serum HCV RNA levels of ≥10,000 IU/mL during screening, and who had never received treatment for HCV infection			patients with genotype 1 (92% for genotype 1a and 82% for genotype 1b) and 96% for those with genotype 4. The single patients with genotype 5 and all six patients with genotype 6 achieved SVR12. Secondary: Not reported FISSION: Primary: A SVR12 was achieved in 67% of patients in both sofosbuvir plus ribavirin group and peginterferon alfa-2a plus ribavirin group. Response rates in patients receiving sofosbuvir plus ribavirin were lower among patients with genotype 3 infection than among those with genotype 2 infection (56 vs 97%). Among patients with cirrhosis at baseline, 47% of patients receiving sofosbuvir plus ribavirin had a SVR12 compared to 38% of those receiving peginterferon alfa-2a plus ribavirin. Secondary: Not reported
Lawitz et al.[26] (2013) Cohort A (HCV genotype 1 patients): sofosbuvir 200 mg, sofosbuvir 400 mg, or placebo (randomized 2:2:1) for 12 weeks in combination with peginterferon (180 µg per week) and ribavirin (1000 to 1200 mg daily), followed by peginterferon and	DB, RCT Treatment-naive patients aged 18 to 70 with HCV genotypes 1, 2, and 3 and no cirrhosis	N=122 (Cohort A) N=25 (Cohort B)	Primary: Safety and tolerability Secondary: SVR12, SVR24	Primary: The most common adverse events during sofosbuvir dosing (up to week 12) were fatigue, headache, nausea, chills, pain, and insomnia. Most adverse events were mild or moderate in severity. Eight patients in cohort A discontinued treatment because of an adverse event, six within the first 12 weeks of treatment (three in the placebo group and three in the 400 mg sofosbuvir group). Secondary: In cohort A, compared with the placebo group, SVR12 and SVR24 were more common in the 200 mg sofosbuvir group (differences of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ribavirin for an additional 12 weeks or 36 weeks (depending on viral response) Cohort B (genotypes 2 or 3): open-label sofosbuvir 400 mg plus peginterferon and ribavirin for 12 weeks				30%; 95% CI, 12 to 49; P=0.001, and 28%, nine to 46; P=0.0017, respectively) and in the 400 mg sofosbuvir group (differences of 32%; 13 to 51; P=0.0005, and 30%, 11 to 49; P=0.0006, respectively). Of the 25 patients in cohort B, most achieved both SVR12 and SVR24 (23 patients (92%) for both SVR12 and 24; 95% CI, 74 to 99).
Jacobson et al.[27] (2011) ADVANCE Telaprevir 750 mg three times a day plus peginterferon alfa-2a 180 µg weekly and ribavirin 1,000 or 1,200 mg/day for 12 weeks, followed by an additional 12 or 36 weeks of peginterferon alfa-2a plus ribavirin based on HCV RNA levels weeks 4 and 12 (T12PR) vs telaprevir 750 mg three times a day plus peginterferon alfa-2a 180 µg weekly and ribavirin 1,000 or 1,200 mg/day for 8 weeks, followed by an additional 16 or 40 weeks of peginterferon alfa-2a plus ribavirin based on HCV RNA levels weeks 4 and 12 (T8PR) vs peginterferon alfa-2a 180 µg	DB, MC, PC, PG, RCT Patients 18 to 70 years of age with hepatitis C virus genotype 1 infection with evidence of chronic hepatitis who were treatment-naïve	N=1,088 48 weeks (plus 24 weeks of follow up)	Primary: SVR Secondary: Proportion of patients with undetectable HCV RNA at week 72, four, 12 or both four and 12, at the end of treatment and 12 weeks after the last planned dose of treatment; safety	Primary: SVR rates were significantly higher with telaprevir-containing regimens compared to control (75, 69, and 44% with T12PR, T8PR, and control (P<0.001 for T12PR and T8PR vs control). Secondary: Seventy three, 67, and 44% of patients receiving T12PR, T8PR, and control had undetectable HCV RNA 72 weeks after starting treatment (P<0.001 for T12PR and T8PR vs control). Sixty eight, 66, and nine percent of patients, respectively, had undetectable HCV RNA at week four (rapid virologic response), and 58, 57, and eight percent of patients, respectively, had undetectable HCV RNA at weeks four and 12 (extended rapid virologic response) (P values not reported). Among patients with an extended rapid virologic response assigned to receive a total of 24 weeks of therapy, SVR rates were 89 and 83% with T12PR and T8PR (P value not reported). Among patients who had undetectable HCV RNA levels after the last dose of treatment, relapse rates were nine, nine, and 28% with T12PR, T8PR, and control (P values not reported). Subgroup analyses demonstrated that SVR rates were higher with telaprevir-containing regimens. Subgroup analyses included HCV genotype subtype (1a and 1b), African Americans, baseline HCV RNA levels (≥800,000 IU) and bridging fibrosis or cirrhosis.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
weekly plus ribavirin 1,000 or 1,200 mg/day for 48 weeks (control) Patients in the T12PR and T8PR groups who met criteria for an extended rapid virologic response (undetectable HCV RNA at weeks 4 and 12) received 12 additional weeks of treatment with peginterferon alfa-2a plus ribavirin (24 total weeks of treatment). Patients who had detectable HCV RNA either at week 4 or 12 received an additional 36 weeks of peginterferon alfa-2a plus ribavirin (48 total week of treatment).				The incidence of gastrointestinal disorders, pruritus, rash and anemia was ≥10 percentage points higher with telaprevir-containing regimens. A total of 10, 10, and seven percent of patients receiving T12PR, T8PR, and control discontinued all treatment at some time during the trial owing to adverse events (P values not reported); with seven, eight, and four percent of these patients discontinuing during the telaprevir (or placebo) phase. Anemia and rash were the most frequently reported adverse events that lead to discontinuation. One case of Stevens-Johnson syndrome occurred approximately 11 weeks after the last dose of telaprevir had been administered.
Sherman et al.[28] (2011) ILLUMINATE Peginterferon alfa-2a 180 µg weekly plus ribavirin 1,000 to 1,200 mg/day plus telaprevir 750 mg three times a day for 12 weeks (T12PR12), followed by peginterferon alfa-2a plus ribavirin for 12 or 36 weeks. Patients who achieved an extended rapid virologic response (undetectable HCV RNA levels at weeks 4 and 12) after 20 weeks were randomized to continue	MC, NI, OL, RCT Patients 18 to 70 years of age with chronic HCV genotype 1 infection for ≥6 months, no previous treatment and with no hepatitis B or HIV	N=540 24 or 48 weeks (plus 24 weeks of follow up)	Primary: SVR Secondary: Not reported	Primary: The absolute difference in SVR rate between T12PR24 vs T12PR48 was four percentage points (92 vs 88%; 95% CI, -2 to 11). The lower limit of this 95% CI (-2%) excludes the NI margin -10.5%. The SVR rate in patients who did not achieve an extended rapid virologic response therefore received a total of 48 weeks of treatment was 64% (76/118). Overall, 72% of patients had a rapid virologic response at week four and 65% of patients had an extended rapid virologic response. The overall rate of SVR was 72%. A total of 99% of patients in the 24-week group completed the treatment compared to 74% in the 48-week group (P<0.001). The relapse rates were 6% with T12PR24 and 3% with T12PR48, with an overall relapse rate of 8%.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
peginterferon alfa-2a plus ribavirin for an additional 4 (24 weeks total treatment; T12PR24) or 28 weeks (48 total weeks of treatment; T12PR48). Patients who did not achieve an extended rapid virologic response after 20 weeks received peginterferon alfa-2a plus ribavirin for an additional 28 weeks (48 total weeks of treatment).				Virologic failure during the treatment phase was uncommon (8% of the overall population, 2% of patients in the T12PR24 group, and 3% of the patients in the T12PR48 group; P=0.22). A total of 9% of patients had serious adverse events. Anemia was reported in 2% of patients. Fatigue was the most common adverse event (68%), followed by pruritus (51%), nausea (47%), anemia (39%), headache (38%), rash (37%), insomnia (34%), diarrhea (30%), and influenzalike illness (26%). During the telaprevir treatment phase, 7% of all patients discontinued treatment; 1% was attributable to rash events and 1% to anemia events.
Kumada et al.[29] (2012) (Group A) Telaprevir 750 mg three times a day plus peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,000 mg/day (based on body weight) for 12 weeks, followed by an additional 12 weeks of peginterferon alfa-2a plus ribavirin vs (Group B) Peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,000 mg/day (based on body weight) for 48 weeks	AC, DB, MC, RCT Patients 20 to 65 years of age with chronic HCV genotype 1 infection who had not received prior treatment and had a current HCV RNA ≥5.0 $\log_{10}$ IU/mL, no hematologic abnormalities and a weight of 40 to 120 kg	N=189 24 or 48 weeks (plus 24 weeks of follow up)	Primary: SVR, nonresponder rate, proportion of patients with a rapid virologic response at week four, safety, and adverse events Secondary: Not reported	Primary: Treatment with telaprevir (Group A) was associated with a statistically significant increase in SVR rate (73.0 vs 49.2%; P=0.0020) compared to standard of care (Group B). The nonresponder rate was significantly lower in Group A (triple therapy) compared to Group B (0.8 vs 20.6%; P<0.0001). A higher proportion of women achieved an SVR in Group A compared to Group B (70.0 vs 43.3%; P=0.0214). In addition, patients ≥50 years of age achieved a significantly higher SVR in Group A compared to Group B (67.1 vs 42.9%; P=0.0125). Furthermore, more patients with a high HCV RNA viral load at baseline (≥7 $\log_{10}$ IU/ml) achieved a SVR in Group A compared to Group (69.2 vs 27.8%; P=0.0132). A significantly greater proportion of patients achieved a rapid virologic response at four weeks in Group A compared to Group B (84.0 vs 4.8%; P<0.0001). The most commonly reported adverse events were anemia, pyrexia, leukocytopenia, thrombocytopenia and malaise. Drugs were discontinued due to adverse events in a similar number of patients in Groups A and B (16.7 vs 22.2%, respectively; P value not reported). Telaprevir was discontinued in 19.0% of patients in Group A.

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				Anemia occurred in 91.3 and 73.0% of patients in Groups A and B, respectively. Combined, Grade 1 and 2 anemia was more common in Group A compared to Group B (38.1 vs 17.5%; P=0.0045). Grade 3 anemia occurred in 11.1% in Group A only. During the follow-up, hemoglobin increased both in Groups A and B, and returned to pretreatment levels 12 weeks after the completion of therapy. Skin disorders occurred in a similar proportion of patients in Groups A and B (89.7 vs 84.1%, respectively; P value not reported). Most skin disorders were mild and categorized as Grade 1. Combined, skin disorders of Grades 2 to 4 occurred more frequently in Group A than Group B (46.8 vs 23.8%; P=0.0026). Serious skin disorders developed in three patients in Group A, but zero patients in Group B. Stevens-Johnson syndrome occurred in one patient after 35 days of treatment and led to the discontinuation of treatment. Secondary: Not reported
Buti et al.[30] (2014) OPTIMIZE Telaprevir 1,125 mg twice daily plus peginterferon alfa-2a 180 µg weekly and ribavirin 1,000 or 1,200 mg/day for 12 weeks, followed by an additional 12 or 36 weeks of peginterferon alfa-2a plus ribavirin based on HCV RNA levels weeks 4 and 12 (T12PR) vs Telaprevir 750 mg three times a day plus peginterferon alfa-2a	MC, NI, OL, RCT Patients 18 to 70 years of age with chronic HCV genotype 1 infection for ≥6 months who had not received prior treatment and had a current HCV RNA >1,000 IU/mL	N=740 24 or 48 weeks (plus 24 weeks of follow up)	Primary: SVR12 Secondary: Effect of IL28B genotype and liver fibrosis stage on SVR rate, tolerability and safety, and pharmacokin etics and pharmacodyn -amics of active	Primary: Of the patients treated with telaprevir twice daily, 74.3% achieved SVR12 compared to 72.8% of patients who were treated with telaprevir three times daily (difference, 1.5%; 95% CI, -4.9 to 12.0%), establishing noninferiority. Secondary: The SVR12 rate by IL28B genotype showed that the efficacy of telaprevir twice daily vs every eight hours was similar regardless of IL28B genotype (CC genotype: 92 vs 87%; CT genotype: 67 vs 68%; TT genotype: 66 vs 65%; P values not reported). The SVR12 rate by fibrosis stage showed that the efficacy of telaprevir twice daily vs every eight hours was similar regardless of fibrosis stage (no or minimal fibrosis: 80 vs 79%; portal fibrosis 79 vs 80%; bridging fibrosis: 67 vs 64%; cirrhosis: 54 vs 49%; P values not reported). The frequency of the most commonly reported adverse events was

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180 µg weekly and ribavirin 1,000 or 1,200 mg/day for 12 weeks, followed by an additional 12 or 36 weeks of peginterferon alfa-2a plus ribavirin based on HCV RNA levels weeks 4 and 12 (T12PR)			treatments	similar between telaprevir twice daily and three times daily dosing groups, including fatigue (47 vs 48%), pruritus (43 vs 42%), anemia (43 vs 41%), nausea (35 vs 38%), rash (35 vs 36%), and headache (24 vs 29%); P values not reported. Comparing the pharmacokinetic-pharmacodynamic relationships, there were no relevant differences in virological responses between telaprevir twice daily vs three times daily groups (P values not reported).
Treatment of chronic hepatitis: Treatment-experienced patients				
Bacon et al.[31] (2011) RESPOND-2 Group 1 (control): Peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 44 weeks vs Group 2 (response-guided therapy): boceprevir 800 mg three times a day plus peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 32 weeks, followed by an additional 12 weeks of peginterferon alfa-2b plus ribavirin in detectable HCV RNA levels at week 8 but undetectable at week 12 vs Group 3 (fixed duration therapy): boceprevir 800 mg three times a	DB, MC, PC, RCT Previously treated adults with HCV genotype 1 infection with responsiveness to interferon therapy for a minimum of 12 weeks	N=403 48 weeks (plus 24 weeks of follow up)	Primary: SVR, safety Secondary: Proportion of patients with an early response in whom a SVR was achieved, proportion of patients with a relapse	Primary: Rates of SVR were significantly higher with boceprevir-containing regimens compared to control, with overall rates of SVR of 21, 59, and 66% in Groups 1, 2, and 3, respectively (P<0.001). The increase observed with Groups 2 and 3 was largely due to end of treatment rates of response being higher (70 and 77 vs 31%) and relapse rates being lower (15 and 12 vs 32%) compared to Group 1. The absolute difference between Groups 2 and 1 was 34.7 percentage points (95% CI, 25.7 to 49.1), and between Groups 3 and 1 it was 45.2 percentage points (95% CI, 33.7 to 56.8). There was no difference in SVR rates between Groups 2 and 3 (OR, 1.4; 95% CI, 0.9 to 2.2). Overall, the most common adverse events were flulike symptoms, while dysgeusia, rash and dry skin were more commonly reported with boceprevir-containing regimens. A greater proportion of patients receiving boceprevir reported serious adverse events, and there were more discontinuations and dose modifications due to adverse events with boceprevir. Anemia occurred more frequently with boceprevir (43 to 46 vs 20%), and erythropoietin was administered more frequently to patients receiving boceprevir. Secondary: The proportion of patients with an undetectable HCV RNA level at week eight in Groups 2 and 3 (46 and 52%) was approximately six times the proportion in Group 1 (9%). Early response was associated with a high rate of SVR in all three treatment groups (100, 86, and 88% in Groups 1, 2, and 3; P values not reported).

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day plus peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,400 mg/day for 44 weeks All patients entered a 4 week lead in period in which peginterferon alfa-2b and ribavirin were administered. Treatment was considered complete in Group 2 if the HCV RNA level was undetectable at weeks 8 and 12 (total duration, 36 weeks). In addition, in all 3 treatment groups, treatment was discontinued for all patients with a detectable HCV RNA level at week 12 based on futility rules; these patients then entered the follow up period.				The rates of SVR among patients with prior relapse (undetectable HCV RNA level at the end of prior therapy, without subsequent attainment of a SVR) were 29, 69, and 75% in Groups 1, 2, and 3; respectively (P values not reported). And the patients with prior nonresponse (a decrease in the HCV RNA level of ≥2 log10 IU/mL by week 12 of prior therapy but a detectable HCV RNA level throughout the course of prior therapy, without subsequent attainment of a SVR), the corresponding rates were 7, 40, and 52% (P values not reported). Virologic breakthrough (achievement of an undetectable HCV RNA level and subsequent occurrence of an HCV RNA level >1,000 IU/mL) and incomplete virologic response (an increase of 1 log10 IU/mL in the HCV RNA level from the nadir, with an HCV RNA level >1,000 IU/mL) were infrequent during the treatment period. Multivariable stepwise logistic-regression analysis served to identify five baseline factor that were significantly associated with achievement of a SVR: assignment to boceprevir (OR for Groups 2 and 3 vs Group 1, 7.3 and 10.7, respectively; P<0.001 for both), previous relapse (OR vs previous nonresponse, 3.1; P<0.001), low viral load at baseline (OR vs high load, 2.5; P=0.02) and absence of cirrhosis (OR vs presence, 2.1; P=0.04).
Flamm et al[32] (2013) Peginterferon alfa-2a 180 µg weekly plus ribavirin 1,000 or 1,200 mg/day plus placebo for 48 weeks total vs boceprevir 800 mg three times a day plus peginterferon alfa-2a 180 µg weekly plus ribavirin 1,000 or 1,200 mg/day for 44	PC, PG, RCT Patients with chronic HCV genotype 1 infection who were relapsers or nonresponders to a previous course of peginterferon alfa and ribavirin	N=201 48 weeks (plus 24 weeks of follow up)	Primary: SVR Secondary: Proportion of patients whom a SVR was achieved by prior response (relapse and nonresponse), safety	Primary: Rates of SVR were significantly higher with boceprevir-containing regimens compared to placebo, with overall rates of SVR of 21% in the peginterferon/ribavirin only treatment group compared to and SVR rate of 64% with boceprevir (P<0.001). Secondary: The rates of SVR among patients with prior relapse (undetectable HCV RNA level at the end of prior therapy, without subsequent attainment of a SVR) were 28% in the peginterferon/ribavirin only treatment group compared to and SVR rate of 70% with boceprevir (P values not reported). The rates of SVR among patients with prior nonresponse (a decrease in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
weeks (total treatment duration of 48 weeks) All patients entered a 4 week lead in period in which peginterferon alfa-2a and ribavirin were administered. In addition, in all treatment groups, treatment was discontinued for all patients with a detectable HCV RNA level at week 12 based on futility rules; these patients then entered the follow up period.				the HCV RNA level of ≥2 $\log_{10}$ IU/mL by week 12 of prior therapy but a detectable HCV RNA level throughout the course of prior therapy, without subsequent attainment of a SVR), were 5% in the peginterferon/ribavirin only treatment group compared to and SVR rate of 47% with boceprevir (P values not reported). Overall, the most common adverse events were flulike symptoms, while dysgeusia, diarrhea, rash, myalgia, leukopenia and vomiting were more commonly reported with boceprevir-containing regimens. A greater proportion of patients receiving boceprevir reported serious adverse events (13 vs 10%), and there were more discontinuations (17 vs 3%) and dose modifications (43 vs 22%) due to adverse events with boceprevir. Anemia occurred more frequently with boceprevir (50 vs 57%). Anemia was managed with dose reduction in 8% of control group and 0% in the boceprevir group. Erythropoietin was administered more frequently to patients receiving boceprevir (28 vs 29%) and a combination of both interventions in 56% of the placebo group and 57% of the boceprevir group). Neutropenia occurred more frequently with boceprevir (31 vs 18%), and granulocyte colony-stimulating factor administered more frequently with boceprevir (14 vs 12%). Secondary: Not reported
Forns et al.[33] (2014) Simeprevir 150 mg once daily plus peginterferon alfa-2a 180 µg weekly plus ribavirin 1,000 or 1,200 mg/day depending on body weight, respectively (PR) for 12 weeks followed by response-guided treatment with PR alone for 12 or 36 weeks	DB, MC, PC, PG, RCT Adults >18 years with confirmed genotype 1 HCV infection and screening plasma HCV-RNA levels	N=393 24 or 48 weeks (plus 72 weeks of follow up)	Primary: SVR12 rates Secondary: SVR24, rapid virologic response (RVR) rate, viral breakthrough, on-treatment	Primary: In the simeprevir/PR arm, an SVR12 rate of 79.2% (206 of 260) was observed compared with 36.1% (48 of 133) with placebo/PR. The difference between the two groups (controlling for HCV 1 subtype and IL28B genotype as stratification factors) was statistically significant at 43.8% (95% CI, 34.6 to 53.0; P<0.001). Secondary: The RVR rate was 77.2% (200 of 259) in the simeprevir/PR group compared with 3.1% (four of 129) treated with placebo/PR. Among simeprevir-treated patients who achieved RVR, 86.5% (173 of 200)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo with PR for 12 weeks followed by PR alone for 36 weeks	>10,000 IU/mL, who had relapsed after 24 weeks or more of interferon-based therapy (undetectable HCV-RNA at end of treatment [EOT] or within 2 months after EOT, with documented relapse within 1 year after therapy).		failure, viral relapse, adverse events	subsequently achieved SVR12. The rate of on-treatment failure was 3.1% (eight of 260) for simeprevir/PR and 27.1% (36 of 133) for placebo/PR. During the first 12 weeks of treatment, the most frequent adverse events in the simeprevir/PR group (>25% of patients) were headache, fatigue, and influenza-like illness. Rash, pruritus, neutropenia, and anemia were comparable between the simeprevir and placebo groups. No patient discontinued simeprevir or placebo alone owing to adverse events.
Zeuzem et al.[34] (2014) ASPIRE Group 1: 12 weeks of simeprevir 100 mg plus peginterferon alfa-2a (PegIFN)/ ribavirin (RBV), followed by 36 weeks of PegIFN/RBV group 2: 12 weeks of simeprevir 150 mg plus PegIFN/RBV, followed by 36 weeks of PegIFN/RBV group 3: 24 weeks of simeprevir 100 mg plus PegIFN/RBV, followed by 24 weeks of PegIFN/RBV	DB, MC, PC, RCT Adults aged 18 to 70 years, chronically infected with HCV genotype 1 and with plasma HCV RNA >10,000 IU/mL at screening were included in the study. All patients must have received at least one prior course of	N=462 48 weeks (plus 72 weeks of follow up)	Primary: SVR24 Secondary: Rapid virologic Response, SVR12, adverse effects	Primary: In the overall population, SVR24 was achieved in 60.6 to 80.0% of simeprevir arms and 22.7% of the placebo arm (P<0.001). When pooling dosage dosages, SVR24 was achieved by 129 of 197 patients (65.5%; range, 60.6 to 69.7%) of the simeprevir 100 mg group and 145 of 199 patients (72.9%; range, 66.7 to 80.0%) of the simeprevir 150 mg group, compared with 15 of 66 patients (22.7%) on placebo (P<0.001 for both comparisons). Pooling treatment duration, SVR24 was achieved by 90 of 132 patients (68.2%; range, 66.7 to 69.7%) on simeprevir for 12 weeks, 92 of 133 (69.2%; range, 66.2 to 72.1%) of those on simeprevir for 24 weeks, and in 92 of 131 (70.2%; range, 0.6 to 80.0%) of those on simeprevir for 48 weeks. Secondary: The proportions of patients achieving SVR12 (60.6 to 80.0% of simeprevir- and 23% of placebo-treated patients) were very similar to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
group 4: 24 weeks of simeprevir 150 mg plus PegIFN/RBV, followed by 24 weeks of PegIFN/RBV group 5: 48 weeks of simeprevir 100 mg plus PegIFN/RBV group 6: 48 weeks of simeprevir 150 mg plus PegIFN/RBV group 7 (placebo control group): 48 weeks of simeprevir-matched placebo plus PegIFN/RBV In all simeprevir treatment arms, when patients were not receiving simeprevir, they received a matched placebo	PegIFN/RBV for >12 consecutive weeks and not discontinued therapy due to tolerability			the proportions achieving SVR24. The most frequently reported adverse events (>25% of patients) with simeprevir plus PegIFN/RBV were fatigue, headache, pruritus, influenza-like illness, and neutropenia. No major difference was reported with respect to the incidence of serious adverse events, occurring in 7.8% (N=31) and 6.1% (N=4) of patients treated with simeprevir and placebo, respectively.
McHutchison et al.[35] (2009) PROVE1 Peginterferon alfa-2a 180 µg/week, ribavirin 1,000 to 1,200 mg/day and telaprevir 1,250 mg as a single dose, then 750 mg 3 times daily for 12 weeks, followed by peginterferon alfa-2a and ribavirin for 12 weeks (T12PR24) vs peginterferon alfa-2a 180 µg/week, ribavirin 1,000 to 1,200	DB, MC, PC, RCT Patients 18 to 65 years of age with chronic genotype 1 HCV infection who were treatment-naïve	N=263 72 weeks	Primary: SVR, rapid virologic response rates, relapse rates, viral breakthrough, safety Secondary: Not reported	Primary: The SVR rate was 61% in the T12PR24 group compared to 41% in the PR48 group (P=0.02).The SVR rates were 67% in the T12PR48 group (P=0.002 and P=0.51 for the comparison with the PR48 group and the T12PR24 group, respectively) and 35% in the T12PR12 group. In a subgroup of black patients, rates of SVR were 11% in the PR48 group and 44% in the telaprevir-based groups. Rates of rapid virologic response were higher with telaprevir- based therapy than without it (P<0.001 for each comparison). At the end of treatment, 75% of patients in the PR48 group and 76% of those in the telaprevir-based groups had normal ALT values. Only 2% of patients in the T12PR24 group had a relapse compared to 6% of patients in the T12PR48 group and 33% of patients in the

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mg/day and telaprevir 1,250 mg as a single dose, then 750 mg 3 times daily for 12 weeks, followed by peginterferon alfa-2a and ribavirin for 36 weeks (T12PR48) vs peginterferon alfa-2a 180 µg/week, ribavirin 1,000 to 1,200 mg/day and telaprevir 1,250 mg as a single dose, then 750 mg 3 times daily for 12 weeks (T12PR12) vs peginterferon alfa-2a 180 µg/week and ribavirin 1,000 to 1,200 mg/day for 48 weeks (PR48)				T12PR12 group. In the PR48 group, 23% of patients had a relapse. Among the telaprevir-treated patients, 7% of patients had viral breakthrough. The most common adverse events were rash, pruritus, nausea, and diarrhea with telaprevir. The proportion of patients who discontinued treatment because of an adverse event was higher in the three telaprevir-based treatment groups (21%) than in the PR48 group (11%). Secondary: Not reported
Hézode et al.[36] (2009) PROVE2 Peginterferon alfa-2a 180 µg/week, ribavirin 1,000 to 1,200 mg/day and telaprevir 1,250 mg as a single dose, then 750 mg 3 times daily for 12 weeks, followed by peginterferon alfa-2a and ribavirin for 12 weeks (T12PR24) vs	DB, MC, PC, RCT Patients 18 to 65 years of age with chronic genotype 1 HCV infection who were treatment-naïve	N=388 72 weeks	Primary: Median time to undetectable HCV RNA level, SVR, rapid virologic response rates, relapse rates, viral breakthrough, safety Secondary:	Primary: The median time to an undetectable HCV RNA level was 113 days in the PR48 group, 28 days in the T12PR24 group, 22 days in the T12PR12 group, and 29 days in the T12P12 group. At week 4, HCV RNA levels were undetectable in 69% of patients in the T12PR24 group, 80% in the T12PR12 group, and 50% in the T12P12 group (vs 13% in the PR48 group, P<0.001 for each comparison). At week 12, HCV RNA levels were undetectable in 73% of patients in the T12PR24 group (vs 43% in the PR48 group, P<0.001), 80% in the T12PR12 group (P<0.001), and 62% in the T12P12 group (P=0.02). At the end of treatment, HCV RNA levels were higher in both groups receiving all three study drugs (70% in the T12PR24 group and 80% in

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peginterferon alfa-2a 180 µg/week, ribavirin 1,000 to 1,200 mg/day and telaprevir 1,250 mg as a single dose, then 750 mg 3 times daily for 12 weeks (T12PR12) vs peginterferon alfa-2a 180 µg/week and telaprevir 1,250 mg as a single dose, then 750 mg 3 times daily for 12 weeks (T12P12) vs peginterferon alfa-2a 180 µg/week and ribavirin 1,000 to 1,200 mg/day for 48 weeks (PR48)			Not reported	the T12PR12 group) and in the T12P12 group (62%) than in the PR48 group (55%). The rate of SVR for the PR48 group was 46%. The rate of SVR for the combined T12P12 and T12PR12 groups was 48% (P=0.89 for the comparison with the PR48 group). In the T12PR24 group, SVR was achieved in 69% of patients (P=0.004 vs PR48). The rate of SVR was not significantly higher in the T12PR12 group or the T12P12 group than in the PR48 group. In the T12PR12 group, there was a SVR in 60% of patients (P=0.12 vs PR48). In the T12P12 group, a SVR was achieved in 36% of patients (P=0.20 vs PR48). The difference between the rates in the T12PR12 group and the T12P12 group was significant (P=0.003). By week 12, viral breakthrough occurred in 1% of patients in the PR48 group, 24% of patients in the T12P12 group, 1% of patients in the T12PR12 group, and 5% of patients in the T12PR24 group. Relapse occurred in 14% of patients in the T12PR24 group, 30% of patients in the T12PR12 group, 48% of patients in the T12P12 group, and 22% of patients in the PR48 group. In the T12PR24 group, the relapse rate among those who had undetectable HCV RNA at weeks 4 and 12 was 7%. Pruritus and rash were more frequent in the telaprevir groups than in the control group. Telaprevir administration also affected hemoglobin levels during the treatment period. Twenty-eight patients (12%) in the telaprevir-based groups discontinued the study treatment because of adverse events compared to 7% in the control group. Secondary: Not reported
Marcellin et al.[37] (2011) Peginterferon alfa-2a 180 µg/week, ribavirin 1,000 to 1,200	MC, OL, RCT Patients 18 to 65 years of age with chronic	N=161 72 weeks	Primary: SVR, viral breakthrough, relapse	Primary: Rapid virologic response (RVR) was 80.0, 69.0, 82.5, and 66.7% in the q8h alfa-2a, q8h alfa-2b, q12h alfa-2a, and q12h alfa-2b groups, respectively.

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mg/day, and telaprevir 750 mg 3 times daily (q8h alfa-2a) vs peginterferon alfa-2b 1.5 µg/kg/week, ribavirin 800 to 1,200 mg/day and telaprevir 750 mg 3 times daily (q8h alfa-2b) vs peginterferon alfa-2a 180 µg/week, ribavirin 1,000 to 1,200 mg/day and telaprevir 1,125 mg every 12 hours (q12h alfa-2a) vs peginterferon alfa-2b 1.5 µg/kg/week, ribavirin 800 to 1,200 mg/day and telaprevir 1,125 mg every 12 hours (q12h alfa-2b) Patients received 12 weeks of treatment with telaprevir and peginterferon alfa/ribavirin, followed by peginterferon alfa/ribavirin alone for 12 or 36 weeks, based on on-treatment virologic response criteria. Patients with undetectable plasma HCV RNA at week 4 through week 20 were scheduled to receive a total of 24 weeks of therapy. Patients not meeting this	HCV genotype 1 infection who were treatment-naïve		Secondary: Not reported	RVR in the pooled q8h group was similar to that in the pooled q12h group (74.4 vs 74.7%). RVR rate in the pooled peginterferon alfa-2a group was higher than in the pooled peginterferon alfa-2b group (81.3 vs 67.9%). At week 12, the percentage of patients with undetectable HCV RNA increased to 92.5, 92.9, 82.5, and 84.6%, in the q8h alfa-2a, q8h alfa-2b, q12h alfa-2a, and q12h alfa-2b groups, respectively. SVR was similar in all four treatment groups: 85.0, 81.0, 82.5, and 82.1% in the q8h alfa-2a, q8h alfa-2b, q12h alfa-2a, and q12h alfa-2b groups, respectively. SVR rate was 82.9% in the pooled telaprevir q8h group and 82.3% in the pooled telaprevir q12h group. SVR rate was 83.8% in the pooled peginterferon alfa-2a group and 81.5% in the pooled peginterferon alfa-2b group. Relapse was observed in nine patients: three, two, three, and one in the q8h alfa-2a, q8h alfa-2b, q12h alfa-2a, and q12h alfa-2b groups, respectively. A total of 8.7% of viral breakthroughs were observed in one, six, three, and four patients in the q8h alfa-2a, q8h alfa-2b, q12h alfa-2a, and q12h alfa-2b groups, respectively. There were no significant adverse events or deaths during the study. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
criterion were assigned to receive a total of 48 weeks of treatment.				
McHutchison et al.[38] (2010) PROVE3 Peginterferon alfa-2a 180 µg/week, ribavirin 1,000 to 1,200 mg/day and telaprevir 1,125 mg as a single dose, then 750 mg 3 times daily for 12 weeks, followed by peginterferon alfa-2a and ribavirin for 12 weeks (T12PR24) vs peginterferon alfa-2a 180 µg/week, ribavirin 1,000 to 1,200 mg/day and telaprevir 1,125 mg as a single dose, then 750 mg 3 times daily for 24 weeks, followed by peginterferon alfa-2a and ribavirin for 24 weeks (T24PR48) vs peginterferon alfa-2a 180 µg/week and telaprevir 1,125 mg as a single dose, then 750 mg 3 times daily for 24 weeks (T24P24) vs peginterferon alfa-2a 180	RCT Patients 18 to 70 years of age with chronic hepatitis C virus infection genotype 1 who had previously been treated for HCV infection with peginterferon alfa and ribavirin but did not have a sustained virologic response	N=465 72 weeks	Primary: SVR, early response, virologic breakthrough, relapse rate Secondary: Not reported	Primary: SVR rates were significantly higher in the telaprevir-treated groups (T12PR24, 51%; T24PR48, 53%; and T24P24, 24%) compared to the PR48 group (14%; P<0.001, P<0.001, P=0.02, respectively). The response rates at the end of treatment period, at week four and at week 12 were all higher in the telaprevir groups compared to the control group. Relapse rates were 30, 13, and 53% in the T12PR24, T24PR48 and T24P24 groups, respectively compared to 53% in the PR48 group. Virologic breakthrough at week 24 was 13, 12, and 32% in the T12PR24, T24PR48 and T24P24 groups, respectively compared to 3% in the PR48 group. In the telaprevir groups, those with breakthrough were mostly non-responders. In patients with a previous nonresponse, SVR rates were 39, 38, and 11% in the T12PR24, T24PR48, and T24P24 groups, respectively compared to 9% in the PR48 group. In patients with a previous relapse, SVR rates were 69, 76, and 42% in the T12PR24, T24PR48 and T24P24 groups, respectively compared to 20% in the PR48 group. SVR was significantly associated with T12PR24 and T24PR48 groups, an undetectable HCV RNA level during previous PR therapy, and low baseline viral load (<800,000 IU/ml). Rash and pruritus were more common in the telaprevir groups than PR48 group. The incidence was 50% in T12PR24 and 60% in T24PR48 groups compared to 20% in PR48. Severe grade 3 rash occurred in 5% of T12PR24, 4% of T245PR48 and 3% of T24P24 compared to 0% in PR48.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
µg/week and ribavirin 1,000 to 1,200 mg/day for 48 weeks (PR48)				Secondary: Not reported
Zeuzem et al.[39] (2011) REALIZE Telaprevir 750 mg three times a day plus peginterferon alfa-2a 180 µg weekly plus ribavirin 1,000 to 1,200 mg/day for 12 weeks, followed by an additional 36 weeks of peginterferon alfa-2a plus ribavirin (T12PR48) vs peginterferon alfa-2a 180 µg weekly plus ribavirin 1,000 or 1,200 mg/day for 4 weeks, followed by telaprevir 750 mg three times a day plus peginterferon alfa-2a 180 µg weekly and ribavirin 1,000 to 1,200 mg/day for 12 weeks, followed by an additional 32 weeks of peginterferon alfa-2a plus ribavirin (Lead-in T12PR48) vs peginterferon alfa-2a 180 µg weekly and ribavirin 1,000 to 1,200 mg/day for 48 weeks (control) Patients could have 1 of 3	DB, MC, PC, RCT Patients 18 to 70 years of age with chronic HCV genotype 1 infection, no SVR to one previous course of peginterferon alfa and ribavirin despite receiving at least 80% of the intended dose	N=662 48 weeks (plus 24 weeks of follow up)	Primary: SVR Secondary: Effect of lead-in treatment with peginterferon alfa-2a plus ribavirin on SVR, proportion of patients who had undetectable HCV RNA at four and eight weeks, relapse, change from baseline in log_{10} HCV RNA, safety	Primary: Compared to control, SVR rates were significantly higher with telaprevir-containing regimens in patients who had a previous relapse (83, 88, and 24% with T12PR48, Lead-in T12PR48, and control), for those who did not have a previous virologic response (41, 41, and 9%), including those who had a partial response (59, 54, and 15%) and those who had no response (29, 33, and 5%) (P<0.001 for all comparisons). SVR rates were similar with T12PR48 and Lead-in T12PR48 among patients who had a relapse or no response or a partial response to previous therapy (P values not reported). Secondary: Overall, SVR rates were 64, 66, and 17% with T12PR48, Lead-in T12PR48, and control. Differences was 47 percentage points between T12PR48 and control (95% CI, 37 to 57; P<0.001) and 50 percentage points between Lead-in T12PR48 and control (95% CI, 40 to 60; P<0.001). In patients with a previous relapse, the proportion of patients with an undetectable HCV RNA were 70 and 93, three and 89, and three and 10% with T12PR48, Lead-in T12PR48, and control (P values not reported). In patients with a previous partial response, the corresponding proportions were 65 and 82, zero and 65, and zero and zero percent (P values not reported). Relapse rates were lower with telaprevir-containing regimens among patients who had a previous relapse or no response or a partial response to previous therapy. Changes in log10 HCV RNA levels are provided in graphic form only. The most frequently reported adverse events (>25% of patients) with telaprevir were fatigue, pruritus, rash, nausea, influenza-like illness,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
previous responses to peginterferon alfa plus ribavirin therapy; no response (reduction <2 log10 in HCV RNA after 12 weeks of therapy), partial response (reduction ≥2 log10 in HCV RNA after 12 weeks of therapy but with detectable HCV RNA) or relapse (undetectable HCV RNA at the end of a previous course of therapy with HCV RNA positivity thereafter).				anemia and diarrhea. Serious adverse events (12 vs 5%) and those leading to treatment discontinuation (13 vs 3%) were more frequent with telaprevir.
Muir et al.[40] (2011) Peginterferon alfa-2a 180 µg/week, ribavirin 1,000 to 1,200 mg/day and telaprevir 750 mg 3 times daily for 12 weeks, followed by peginterferon alfa-2a and ribavirin for 12 or 36 weeks If patients achieved extended rapid virologic response (eRVR) with triple therapy, they would complete a 24-week course with 12 more weeks of peginterferon alpha-2a and ribavirin alone. If patients did not achieve eRVR with triple therapy, they would complete a 48-week course with 36 more weeks of peginterferon alpha-2a and ribavirin.	MC, OL Patients with chronic genotype 1 HCV infection with a prior response to peginterferon alpha-2a and ribavirin	N=117 96 weeks	Primary: SVR Secondary: Not reported	Primary: The overall rate of SVR was 59%. The SVR rate was highest among patients who previously relapsed (97%), prior viral breakthrough patients (75%), and prior partial response patients (55%). Among prior null responders, the overall SVR rate was 37% with 56% of patients in the 48-week treatment group and 17% of patients in the 24-week treatment group. The overall relapse rate was 16%. Discontinuations due to the week four stopping rule were more frequent in patients assigned to the 24- week regimen (10%) than in those assigned to the 48-week regimen (3%). Eleven cases of viral breakthrough occurred in patients with previous null response, and seven of the 15 occurred during the first 12 weeks of retreatment that included telaprevir. Rash occurred in 27% of patients during the first 12 weeks of treatment. Pruritus occurred in 35% of patients during the telaprevir treatment phase. Decreases in hemoglobin levels, increases in uric acid levels, and increases in total bilirubin levels were more common

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				during the telaprevir treatment phase. Adverse events led to discontinuation of all study drugs in 9% of patients and 7% of patients during the telaprevir treatment phase. Secondary: Not reported
Hayashi et al[41] (2012) Telaprevir 750 mg three times a day plus peginterferon alfa-2b 1.5 µg/kg weekly plus ribavirin 600 to 1,000 mg/day (based on body weight) for 12 weeks, followed by an additional 12 weeks of peginterferon alfa-2a plus ribavirin	MC, OL Patients 20 to 65 years of age with chronic HCV genotype 1 infection who were relapsers or nonresponders to a previous course of peginterferon alfa and ribavirin with a current HCV RNA ≥5.0 $\log_{10}$ IU/mL, no hematologic abnormalities and a weight of 40 to 120 kg	N=141 (109 relapsers and 32 non-responders) 24 weeks (plus 24 weeks of follow up)	Primary; SVR, relapse, breakthrough, nonresponse, and safety Secondary: Not reported	Primary: The SVR rate was 88.1% (96/109) in patients who were prior relapsers to treatment and 34.4% in patients who were previous nonresponders to treatment 34.4% (11/32). The rapid viral response and end of treatment response rates in prior relapsers were 87.2% (95/109) and 94.5% (103/109), respectively (P values not reported). In prior nonresponders, the rapid viral response and end of treatment response rates were 71.9% (23/32) and 59.4% (19/32), respectively. In prior relapsers, the SVR rate in the patients who achieved undetectable HCV RNA at week four was significantly higher compared to patients achieving undetectable HCV RNA after week four of treatment (91.8 vs 66.7%; P=0.0487). In the prior nonresponder group, undetectable HCV RNA at week four did not appear to have an effect on SVR rates (39.1 vs 28.6%; P=1.0). The SVR rate in previous relapsers was significantly higher in males compared to females (93.9 vs 79.1%; P=0.0316), while there was no difference in SVR rate between genders in patients who were previous nonresponders to therapy. The rates of nonresponse, breakthrough and relapse were 0.9% (1/109), 0.9% (1/109) and 7.3% (8/109), respectively, in patients who were prior relapsers. The incidence of nonresponse, breakthrough and relapse in prior nonresponders was 6.3% (2/32), 18.8% (6/32) and 40.6% (13/32), respectively. The incidence of adverse events was similar between the prior relapsers and prior nonresponders. Serious adverse events were

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				reported in 11.9% (13/109) of prior relapsers and 9.4% (3/32) of prior nonresponders. Overall, the most frequently reported adverse events in prior relapsers and prior nonresponders were anemia (88.1 vs 100%, respectively), pyrexia (82.6 vs 93.8%, respectively), decreased white blood cell count (76.1 vs 69.8%, respectively), blood uric acid increase (66.1 vs 78.1%, respectively) and platelet count decrease (67.0 vs 68.6%, respectively). Overall, 17.4% of prior relapsers discontinued treatment due to adverse events compared to 12.5% of prior nonresponders. Anemia was the most frequently reported adverse event leading to discontinuation in both treatment groups. Adverse events related to skin disorders were observed in 82.3% (116/141) of patients. Skin disorders reported in over 10% of the patients were rash 39.0% (55/141), drug eruption in 24.1% (34/141), injection site reaction in 12.8% (18/141) and injection site erythema in 12.8% (18/141) of the patients. Despite ribavirin dose modification, the median hemoglobin levels in prior relapsers and prior nonresponders decreased to 10.6 and 10.4 g/dL at week 12, respectively. No patient discontinued all the study drugs because of a neutrophil decrease. Secondary: Not reported
Treatment of chronic hepatitis: Treatment-naïve and experienced patients				
Sitole et al.[42] (2013) Triple therapy with boceprevir or placebo, pegylated interferon, and ribavirin vs triple therapy with	MA Treatment-naive and treatment-experienced patients with chronic HCV genotype 1 infection	N=4144 (8 studies) 24 to 48 weeks after completion of treatment	Primary: SVR Secondary: Rate of rapid (at four weeks with telaprevir or eight weeks with	Primary: In the treatment-naive patients, SVR at 24 weeks was greater in the telaprevir treated group compared with the control group (OR, 3.31; 95% CI, 2.27 to 4.82; P <0.0001). In the treatment-experienced patients, the SVR rates at 24 weeks were similar between the active and control groups (OR, 4.21; 95% CI, 1.83 to 9.72; P<0.001). In the treatment-naive patients, SVR at 48 weeks was greater in the telaprevir treated group compared with the control group (OR, 1.98; 95% CI, 1.42 to 2.76; P<0.0001). In the treatment-experienced patients, 48-week SVR rates were similar between the triple-therapy and control

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
telaprevir or placebo, pegylated interferon, and ribavirin			boceprevir) viral response, adverse events	groups (OR, 8.46; 95% CI, 5.72 to 12.50; P<0.0001). In treatment-naive patients, 24-week SVR was improved in the group that received boceprevir compared with controls (OR, 3.55; 95% CI, 2.66 to 4.56; P<0.0001); this finding was also true in the treatment-experienced subgroup. In the treatment-naive subgroup, 48-week SVR was improved in the group that received boceprevir compared with the control group (OR, 1.98; 95% CI, 1.42 to 2.76); this finding was also true in the treatment-experienced subgroup. An indirect treatment comparison between telaprevir and boceprevir favored telaprevir for inducing 24-week SVR in treatment-naive patients (OR, 1.78; 95% CI, 1.39 to 2.28; P<0.0001); however, the rates of 48-week SVR in treatment-naive patients were similar between telaprevir and boceprevir (OR, 0.82; 95% CI, 0.60 to 1.11; P=0.2). Secondary: Treatment with telaprevir-based triple therapy did not result in more discontinuations due to adverse drug reactions compared with controls (OR, 1.43; 95% CI, 0.42 to 4.92; P=0.57). Telaprevir was associated with an increase in treatment-associated adverse events compared with placebo. Boceprevir was associated with increased prevalences of anemia and dysgeusia. Telaprevir and boceprevir were also similar regarding discontinuation from adverse drug reactions (OR, 1.23; 95% CI, 0.95 to 1.60; P=0.11).
Gane et al.[43] (2013) Group 1: Sofosbuvir 400 mg and ribavirin 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) for 12 weeks Group 2: Group 1 treatment plus 4 weeks of concomitant	OL Patients19 years of age or older, who had chronic HCV infection without cirrhosis	N=95	Primary: Serum HCV RNA levels, safety Secondary: Not reported	Primary: Viral suppression was rapid in all patients, regardless of genotype, status with respect to previous treatment, baseline viral load, race or ethnic group, IL28B status, and presence or absence of interferon in the regimen. All 95 patients had an undetectable level of HCV RNA by week four, with viral suppression sustained through the end of treatment. All 40 patients with HCV genotype 2 or 3 infection who received sofosbuvir and ribavirin for 12 weeks had an undetectable level of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
peginterferon alfa-2a 180 µg once weekly Group 3: Group 1 treatment plus 8 weeks of concomitant peginterferon alfa-2a 180 µg once weekly Group 4: Group 1 treatment plus 8 weeks of concomitant peginterferon alfa-2a 180 µg once weekly (additional groups amended): Group 5: Sofosbuvir 400 mg daily monotherapy for 12 weeks Group 6: Sofosbuvir plus peginterferon and ribavirin for 8 weeks				serum HCV RNA at two, four, eight, 12, 24, and 48 weeks after treatment. The presence or absence of peginterferon alfa-2a appeared to have no effect on viral kinetics or rate of sustained virologic response. Six of the 10 patients in the sofosbuvir monotherapy group had a sustained virologic response at 12 and 24 weeks after treatment. All 95 patients completed treatment. The most common adverse events were headache, fatigue, insomnia, nausea, rash, and anemia. Hematologic abnormalities were more common among patients who received interferon than among those who did not. Neutropenia and thrombocytopenia were not observed in the groups that did not receive interferon. However, sofosbuvir monotherapy was associated with a modest decrease in the hemoglobin level. Secondary: Not reported
Jacobson et al[44] (2013) POSITRON and FUSION POSITRON: Sofosbuvir 400 mg once daily for 12 weeks and ribavirin 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) for 12 weeks vs placebo FUSION:	POSITRON: DB, MC, PC, R Patients ≥18 years of age with confirmed diagnosis of chronic HCV infection (genotypes 2 or 3), serum HCV RNA levels of ≥10,000 IU/mL during screening, and who are not	POSITRON: N=278 12 weeks FUSION: N=201 12 to 16 weeks	POSITRON: Primary: SVR12 Secondary: Not reported FUSION: Primary: SVR12 Secondary: Not reported	POSITRON: Primary: Treatment with sofosbuvir plus ribavirin achieved a SVR12 in 78% of patients (95% CI, 72 to 83) compared to 0% among those receiving placebo (P<0.001). Response rates in patients receiving sofosbuvir plus ribavirin were lower among patients with genotype 3 infection than among those with genotype 2 infection (61 vs 93%). Among patients with genotype 3 infection receiving sofosbuvir plus ribavirin, 21% of patients with cirrhosis achieved a SVR12 compared to 68% without cirrhosis. Among patients with genotype 2 infection receiving sofosbuvir plus ribavirin, 94% of patients with cirrhosis achieved a SVR12 compared

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Sofosbuvir 400 mg once daily for 12 weeks and ribavirin 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight of ≥75 kg) for 12 weeks vs sofosbuvir 400 mg once daily for 16 weeks and ribavirin 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight of ≥75 kg) for 16 weeks	candidates for interferon therapy FUSION: AC, DB, MC, R Patients ≥18 years of age with confirmed diagnosis of chronic HCV infection (genotypes 2 or 3), serum HCV RNA levels of ≥10,000 IU/mL during screening, and who have previously not responded to treatment with an interferon containing regimen			to 92% without cirrhosis. Secondary: Not reported FUSION: Primary: Treatment with sofosbuvir plus ribavirin resulted in higher rates of SVR12 in the 12-week group (50%; 95% CI, 40 to 60) and 16-week group (73%; 95% CI, 63 to 81) compared to historical control rate of 25%. Patients receiving 16 weeks of treatment had a significantly higher rate of SVR than patients receiving 12 weeks of treatment (difference, -23%; 95% CI, -35 to -11; P<0.001). Response rates in patients with genotype 2 infection who received 12 weeks of treatment were lower than among those who received 16 weeks of treatment (86 vs 94%; difference of -8%; 95% CI, -24 to 9); however, the difference was not statistically significant. Response rates in patients with genotype 3 infection who received 12 weeks of treatment were significantly lower than among those who received 16 weeks of treatment (difference, -32%; 95% CI, -48 to -15). Among patients with cirrhosis who received 12 weeks of treatment, the rate of response was 31% (60% with HCV genotype 2 infection and 19% with HCV genotype 3 infection), as compared to 61% among patients without cirrhosis (96% with HCV genotype 2 infection and 37% with HCV genotype 3 infection). Among patients with cirrhosis who received 16 weeks of treatment, the rate of response was 66% (78% with HCV genotype 2 infection and 61% with HCV genotype 3 infection) as compared to 76% among patients without cirrhosis (100% with HCV genotype 2 infection and 63% with HCV genotype 3 infection).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Zeuzem et al[45] (2014) VALENCE Sofosbuvir 400 mg once daily for 12 weeks and ribavirin 1,000 mg/day (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) for 12 weeks vs placebo After study initiation, on the basis of emerging data from phase 3 trials, the study was unblinded, treatment for all patients with genotype 3 infection was extended to 24 weeks, the placebo group was terminated, and the goals of the study were redefined to be descriptive and not include hypothesis testing.	DB, MC, PC, R Patients ≥18 years of age with confirmed diagnosis of chronic HCV infection (genotypes 2 or 3) and serum HCV RNA levels of ≥10,000 IU/mL during screening	N=419 12 weeks (genotype 2) or 24 weeks (genotype 3)	Primary: SVR12 Secondary: Not reported	Primary: Treatment with sofosbuvir plus ribavirin achieved a SVR12 in 93% (95% CI, 85 to 98) of patients with HCV genotype 2 receiving 12 weeks of therapy and 85% (95% CI, 80 to 89) of patients with HCV genotype 3 receiving 24 weeks of therapy. Among patients with genotype 2 infection receiving sofosbuvir plus ribavirin, high SVR12 rates were observed in treatment-naïve non-cirrhotics (96.7%; 95% CI, 82.8 to 99.9), treatment-naïve cirrhotics (100%; 95% CI, 15.8 to 100), and treatment-experienced non-cirrhotics (93.8%; 95% CI, 79.2 to 99.2), whereas lower SVR12 rate was observed in treatment-experienced cirrhotics with genotype 2 infection (77.8%; 40.0 to 97.2). Similarly, among patients with genotype 3 infection receiving sofosbuvir plus ribavirin, high SVR12 rates were observed in treatment-naïve non-cirrhotics (94.6%; 95% CI, 86.3 to 97.6), treatment-naïve cirrhotics (92.3%; 95% CI, 64.0 to 99.8), and treatment-experienced non-cirrhotics (86.7%; 95% CI, 78.4 to 92.7), whereas lower SVR12 rate was observed in treatment-experienced cirrhotics with genotype 3 infection (61.7%; 46.4 to 75.5). Secondary: Not reported
Lawitz et al.[46] (2014) COSMOS Group 1: simeprevir and sofosbuvir with ribavirin for 24 weeks vs	OL, RCT Patients ≥18 years of age with chronic HCV genotype 1 infections who had previously not responded to	N=167 12 or 24 weeks	Primary: SVR12 Secondary: SVR4, SVR24, on-treatment failure, viral relapse	Primary: 154 (92%) of 167 of patients achieved SVR12, 90% (95% CI, 81 to 96) in cohort 1 and 94% (87 to 98) in cohort 2. SVR12 was seen in 98 (91%) of 108 patients who received ribavirin vs 56 (95%) of 59 of those who did not. Rates were similar by treatment status (38 [95%] of 40 treatment-naive patients vs 116 [91%] of 127 previous non-responders) or treatment duration (77 [94%] of 82 after 12 weeks of treatment vs 77 [91%] of 85 after 24 weeks).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Group 2: simeprevir and sofosbuvir without ribavirin for 24 weeks vs Group 3: simeprevir and sofosbuvir with o ribavirin for 12 weeks vs Group 4: simeprevir and sofosbuvir without ribavirin for 12 weeks [Cohort 1: previous non-responders to peginterferon and ribavirin with moderate liver fibrosis (METAVIR score F0–F2); Cohort 2: previous non-responders to peginterferon and ribavirin or treatment naïve with severe liver fibrosis (METAVIR score F3–F4)]	pegylated interferon and ribavirin or were treatment naïve			Secondary: All patients who achieved SVR12 also achieved SVR4. More than 91% of patients overall achieved SVR4. Rapid virological response was achieved in 81% of patients overall, but SVR12 was still achieved in all but one who had detectable HCV RNA titers four weeks after the start of treatment. No patients experienced on-treatment virological failure, including viral breakthrough. Six patients had viral relapse after the end of treatment. At the time of relapse, five of the six had developed resistance-associated mutations to simeprevir, but none to sofosbuvir.

Study abbreviations: AC=active control, CI=confidence interval, DB=double-blind, MA=meta-analysis, MC=multicenter, NI=non-inferiority, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, R=randomized, RCT=randomized controlled trial, RR=relative risk, SG=single group
Other abbreviations: ALT=alanine aminotransferase, HCV=hepatitis C virus, HIV=human immunodeficiency virus, IU=international units, RNA=ribonucleic acid, SVR=sustained virologic response

Additional Evidence

Dose Simplification
Kowdley et al compared SVR24 between 12- and 24-week treatment courses with sofosbuvir, finding no difference in the proportion of patients achieving SVR24 between cohorts A (12 weeks) and B (24 weeks) (P=0.94) or between cohorts A (12 weeks) and C (24 weeks) (P=0.78), suggesting no additional benefit of treatment durations longer than 12 weeks.[24] Buti et al compared telaprevir 1,125 mg twice daily to telaprevir 750 mg three times daily, establishing noninferiority in SVR12 between the groups (difference, 1.5%; 95% CI, -4.9 to 12.0%). Additionally, no differences were found regardless of IL28B genotype or fibrosis stage.[30] Comparing the pharmacokinetic-pharmacodynamic relationships, there were no relevant differences in virological responses between telaprevir twice daily vs three times daily groups, and subsequently the Food and Drug Administration-approved dosing scheduled was changed to twice daily.[5-7,9,30]

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 10. Relative Cost of the HCV Antivirals

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Boceprevir	capsule	Victrelis®	$$$$$	N/A
Simeprevir	capsule	Olysio®	$$$$$	N/A
Sofosbuvir	tablet	Sovaldi®	$$$$$	N/A
Telaprevir	tablet	Incivek®	$$$$$	N/A

N/A=Not available

X. Conclusions

The HCV antiviral agents include the nonstructural protein 3 protease inhibitors, boceprevir, telaprevir, and simeprevir as well as the nonstructural protein 5B polymerase inhibitor, sofosbuvir.[5-11] There are no generic products available. This class was last reviewed in May 2012.

Boceprevir, simeprevir, and telaprevir are Food and Drug Administration (FDA)-approved for the treatment of adults with chronic hepatitis C genotype 1 infection with compensated liver disease (including cirrhosis). Hepatitis C protease inhibitors inhibit the replication of hepatitis C virus (HCV) host cells by binding to the nonstructural 3/4A protease of HCV genotype 1a and 1b. All three agents are FDA-approved for use in treatment-naïve patients as well as those who have been previously treated with interferon-based treatment, including prior null responders, partial responders, and relapsers. Protease inhibitors must be administered in combination with peginterferon alfa and ribavirin. Because of this, warnings and precautions that are associated with these agents are applicable to protease inhibitor combination treatment.[5-10] Sofosbuvir is a novel once-daily nucleotide analog inhibitor of HCV nonstructural protein 5B ribonucleic acid (RNA) polymerase, which is essential for viral replication of HCV. The efficacy of sofosbuvir has been established in patients with HCV genotype 1, 2, 3 or 4 infection, including those with hepatocellular carcinoma meeting Milan criteria (awaiting liver transplantation) and those with HCV/human immunodeficiency virus-1 co-infection.[5-7,11] The approval has changed the way in which hepatitis C is treated.

Until recently, triple therapy with hepatitis C protease inhibitor, peginterferon alfa, and ribavirin has been the standard of care in the treatment of HCV genotype 1 infection.[1,4,13] The 2014 consensus recommendations from the American Association for the Study of Liver Diseases and the Infectious Diseases Society of America prefer sofosbuvir-based combination therapy for most patients with chronic HCV genotype 1 infection.[4] All-oral sofosbuvir plus simeprevir (with or without ribavirin) off-label regimen is recommended in patients who are either peginterferon alfa ineligible, prior null or partial responders to peginterferon alfa and ribavirin dual therapy, or liver transplant recipients.[4] The FDA-approved simeprevir, peginterferon alfa, and ribavirin triple therapy regimen is generally recommended as an alternative, rather than a preferred regimen, by the consensus recommendations. Telaprevir- and boceprevir-containing regimens are either no longer recommended in the treatment of HCV genotype 1 infection or are reserved for patients who are not candidates for the preferred and alternative regimens.[3-4] To date, no head-to-head trials between the commercially available hepatitis C protease inhibitors have been published to directly compare their efficacy. Treatment guidelines do not give preference to one specific peginterferon alfa or ribavirin product over another.[1-4,12-17] Treatment guideline recommendations for the use of hepatitis C protease inhibitors are in line with FDA-approved indications and dosing.[1,8-12,14]

The pivotal clinical trials demonstrate that treatment with sofosbuvir, in combination with ribavirin or peginterferon alfa and ribavirin, results in significantly higher sustained virologic response rates among adult patients with chronic hepatitis C genotype 1, 2, 3 and 4 infection compared to standard therapy alone.[11,25,26,44,45] Compared to combination therapy with HCV protease inhibitors for the treatment of HCV genotype 1 infection, sofosbuvir combination therapy offers potential for improved efficacy, shorter duration of treatment that is not response-guided, no viral resistance, favorable safety profile, reduced pill burden, and fewer drug-drug interactions (no CYP450 hepatic metabolism).[5-11]

Therefore, of the agents included in this review, sofosbuvir (Sovaldi®) used only in combination therapy offers significant clinical advantages over the other brand and generic products in the same class (if applicable). The drugs in this AHFS class are used in a specific patient population. Because these agents have narrow indications with limited usage, and very specific criteria must be met prior to initiating therapy, these agents should be managed through the medical justification portion of the prior authorization process.

XI. Recommendations

No brand HCV antiviral is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Antivirals, Miscellaneous
AHFS Class 081892
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I. Overview

Foscarnet is approved for the treatment of cytomegalovirus (CMV) retinitis in patients with acquired immunodeficiency syndrome (AIDS).[1-3] It is also approved for the treatment of acyclovir-resistant mucocutaneous herpes simplex virus infections in immunocompromised patients.

Foscarnet exerts its antiviral activity by a selective inhibition at the pyrophosphate binding site on virus-specific deoxyribonucleic acid (DNA) polymerases, which halts DNA chain elongation.[1-3] It is virostatic and is not structurally related to any other antiviral agent currently on the market. Foscarnet has poor oral bioavailability and must be administered intravenously. Following administration, serum levels can vary considerably.[1-4] Patients receiving foscarnet need to be carefully monitored since adverse events occur frequently and may be potentially serious.[4] Major toxicities associated with foscarnet include renal impairment, electrolyte disturbances and seizures.

The miscellaneous antivirals that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Foscarnet is available in a generic formulation. This class was last reviewed in May 2012.

Table 1. Antivirals, Miscellaneous Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Foscarnet	injection	N/A	foscarnet

N/A=Not available; PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the miscellaneous antivirals are summarized in Table 2.

Table 2. Treatment Guidelines Using the Antivirals, Miscellaneous

Clinical Guideline	Recommendation(s)
British Association for Sexual Health and Human Immunodeficiency Virus: **National Guideline for the Management of Genital Herpes (2007)**[5]	<u>Genital herpes</u> • Oral antiviral drugs are indicated within five days of the start of the episode and while new lesions are still forming. • Antiviral therapy does not alter the natural history of the disease. • Topical agents are less effective than oral agents. • Combined oral and topical treatment is of no benefit. • Intravenous therapy is indicated only when the patient cannot swallow or tolerate oral medication because of vomiting. <u>Genital herpes with human immunodeficiency virus Infection</u> • Standard systemic antiviral drugs, as used to treat genital herpes in human immunodeficiency virus-uninfected patients, have been shown to successfully treat genital herpes in patients with human immunodeficiency virus. • Resistance to antiherpes drugs is more common in those with human immunodeficiency virus co-infection and is associated with treatment failure of genital herpes. • Oral acyclovir, valacyclovir, and famciclovir are recommended for initial and suppressive treatment of genital herpes. • In severe cases, initiating therapy with acyclovir five to 10 mg/kg body

Clinical Guideline	Recommendation(s)
	weight intravenous every eight hours may necessary. • Systemic therapy with either foscarnet or cidofovir is generally preferred to treat drug resistant herpes in those with human immunodeficiency virus.
National Institutes of Health, the Centers for Disease Control and Prevention, and the Human Immunodeficiency Virus Medicine Association of the Infectious Diseases Society of America: **Guidelines for Prevention and Treatment of Opportunistic Infections in Human Immunodeficiency Virus -Infected Adults and Adolescents (2013)**[6]	Aspergillosis • Voriconazole is the drug of choice but should be used cautiously with human immunodeficiency virus protease inhibitors and efavirenz. Amphotericin B deoxycholate at 1 mg/kg daily or lipid-formulation amphotericin B at 5 mg/kg daily are alternatives, as is caspofungin at 50 mg daily and posaconazole. • Other echinocandins, such as micafungin and anidulafungin, are reasonable alternatives. • For treatment failure (if voriconazole was used initially) substitution with amphotericin B, posaconazole, or echinocandins might be considered; the amphotericin B or echinocandins would be rational for those who began therapy with voriconazole or posaconazole. Candidiasis (mucocutaneous) • Oral fluconazole is as effective as topical therapy for oropharyngeal candidiasis and is considered the drug of choice. Initial episodes of oropharyngeal candidiasis can be adequately treated with topical therapy, including clotrimazole troches, nystatin suspension or pastilles, or miconazole mucoadhesive tablets. Itraconazole oral solution for seven to 14 days is as effective as oral fluconazole but less well tolerated. Posaconazole oral solution is also as effective as fluconazole and is generally better tolerated than itraconazole. Intravenous amphotericin B is usually effective and can be used among patients with refractory disease. Both conventional amphotericin B and lipid complex and liposomal amphotericin B have been used. • Systemic antifungals are required for effective treatment of esophageal candidiasis. A 14 to 21-day course of either fluconazole (oral or intravenous) or oral itraconazole solution is highly effective. Oral ketoconazole or itraconazole capsules are less effective than fluconazole because of variable absorption. Although intravenous caspofungin or intravenous voriconazole are effective in treating esophageal candidiasis among human immunodeficiency virus -infected patients, oral or intravenous fluconazole remain the preferred therapies. Azole-refractory esophageal candidiasis can be treated with posaconazole, amphotericin B, anidulafungin, caspofungin, micafungin, or voriconazole. • Vulvovaginal candidiasis in human immunodeficiency virus -infected women is usually uncomplicated (90%) and responds readily to short-course oral or topical treatment with any of several therapies, including oral fluconazole, topical azoles, and itraconazole oral solution. Severe or recurrent episodes of vaginitis require oral fluconazole or topical antifungal therapy for ≥7 days. Coccidioidomycosis • For patients with clinically mild infection, such as focal pneumonia or a positive coccidioidal serologic test alone, initial therapy with a triazole antifungal is appropriate. • For patients with either diffuse pulmonary involvement or severely ill patients with extrathoracic disseminated disease, amphotericin B is the preferred initial therapy. Therapy with amphotericin B should continue until clinical improvement is observed. Some specialists would use a triazole antifungal concurrently with amphotericin B and continue the triazole once amphotericin B is stopped. Cryptococcosis • The recommended initial standard treatment is amphotericin B combined with flucytosine for ≥2 weeks for those with normal renal function.

Clinical Guideline	Recommendation(s)
	• The combination of amphotericin B with fluconazole is less effective than amphotericin B combined with flucytosine in terms of clearing *Cryptococcus* from the cerebrospinal fluid but is better than amphotericin B alone. • Fluconazole combined with flucytosine is an alternative to amphotericin B plus flucytosine, but is less effective than amphotericin B and is recommended only for persons unable to tolerate or unresponsive to standard treatment. • After at least a two-week period of successful induction therapy, amphotericin B and flucytosine may be discontinued and follow-up therapy initiated with fluconazole. This should continue for eight weeks. Itraconazole is an acceptable though less effective alternative. • The optimal therapy for those with treatment failure is not established. For those initially treated with fluconazole, therapy should be changed to amphotericin B, with or without flucytosine, and continued until a clinical response occurs. Liposomal amphotericin B may have improved efficacy over the deoxycholate formulation and should be considered in treatment failures. Higher doses of fluconazole in combination with flucytosine might also be useful. <u>Cryptosporidiosis</u> • In the setting of severe immunosuppression, antiretroviral therapy with immune restoration to a CD4+ count >100 cells/µL leads to resolution of clinical cryptosporidiosis and is the mainstay of treatment. • All patients with cryptosporidiosis should be offered antiretroviral therapy as part of the initial management of their infection. • Management should include symptomatic treatment of diarrhea. Rehydration and repletion of electrolyte losses by either the oral or intravenous route are important. Severe diarrhea can exceed >10 L/day among patients with acquired immunodeficiency syndrome, often requiring intensive support. Aggressive efforts at oral rehydration should be made with oral rehydration solutions. <u>Prevention of Cytomegalovirus</u> • Cytomegalovirus end-organ disease is best prevented by using antiretroviral therapy to maintain the CD4+ count >100 cells/µL. • Although oral valganciclovir would likely prevent the occurrence of cytomegalovirus retinitis in patients with CD4+ counts <50 cells/µL, such therapy is not generally recommended because of the potential to induce cytomegalovirus resistance, the utility of treating disease when it occurs, and the lack of demonstrated survival advantage. <u>Treatment of Cytomegalovirus disease</u> • Oral valganciclovir, intravenous ganciclovir, intravenous ganciclovir followed by oral valganciclovir, intravenous foscarnet, and intravenous cidofovir are all effective treatments for cytomegalovirus retinitis. • The ganciclovir implant, a surgically-implanted reservoir of ganciclovir, which lasts approximately six months, also is very effective but it no longer is being manufactured. In its absence, some clinicians will use intravitreal injections of ganciclovir or foscarnet in conjunction with oral valganciclovir, at least initially, to provide immediate high intraocular levels of drug and presumably faster control of the retinitis. • Systemic therapy has been shown to reduce morbidity in the contralateral eye. This should be considered when choosing between the oral, intravenous, and local options. • The choice of initial therapy for cytomegalovirus retinitis should be

Clinical Guideline	Recommendation(s)
	individualized based on the location and severity of the lesion(s), the level of underlying immune suppression, and other factors such as concomitant medications and ability to adhere to treatment. • No one regimen has been proven in a clinical trial to have greater efficacy in terms of protecting vision, and thus clinical judgment must be used when choosing a regimen. • In studies conducted in the pre-antiretroviral therapy era, ganciclovir intraocular implant plus oral ganciclovir was superior to once-daily intravenous ganciclovir for treatment of cytomegalovirus retinitis; however, the implant is no longer manufactured. Assuming that this observation can be extended to other combinations of systemically and locally administered drugs, human immunodeficiency virus-specialists often recommend intravitreal ganciclovir or foscarnet injections plus oral valganciclovir as the preferred initial therapy for patients with immediate sight-threatening lesions. Intravitreal injections deliver high concentrations of the drug to the target organ immediately while steady-state concentrations in the eye are achieved with systemically delivered medications. For patients with small peripheral lesions, oral valganciclovir alone often is adequate. • After induction therapy, secondary prophylaxis (i.e., chronic maintenance therapy) should be continued until immune reconstitution occurs as a result of antiretroviral therapy. Regimens demonstrated to be effective for chronic suppression in randomized, controlled clinical trials include parenteral ganciclovir, oral valganciclovir, parenteral foscarnet, combined parenteral ganciclovir and foscarnet, and parenteral cidofovir. <u>Management of Cytomegalovirus retinitis treatment failures</u> • When patients relapse while receiving maintenance therapy, induction with the same drug followed by reinstitution of maintenance therapy can control the retinitis, although for progressively shorter periods of time with each relapse. • Ganciclovir and foscarnet in combination appear to be superior in efficacy to either agent alone and should be considered for patients whose disease does not respond to single-drug therapy, and for patients with multiple relapses of retinitis. This drug combination, however, is associated with substantial toxicity. <u>Treatment of Hepatitis B Virus coinfection in patients not receiving antiretroviral therapy</u> • For patients with CD4+ counts >350 cells/µL who are not receiving antiretroviral therapy but meet criteria for hepatitis B virus treatment, adefovir or peginterferon alfa-2a monotherapy for 48 weeks might be considered, with close monitoring of hepatitis B virus deoxyribonucleic acid levels and follow-up to evaluate for hepatitis B e antigen seroconversion. However, early initiation of antiretroviral therapy should also be considered for human immunodeficiency virus/hepatitis B virus -coinfected persons with CD4+ counts >350 cells/µL. <u>Treatment of Hepatitis B Virus coinfection in patients who require antiretroviral therapy</u> • For human immunodeficiency virus-infected persons, some experts recommend combination therapy with two agents active against hepatitis B virus to reduce the risk of hepatitis B virus drug resistance; although, there are no results from controlled trials as yet to support this strategy. • Among patients infected with hepatitis B virus, hepatitis C virus, and human immunodeficiency virus, consideration of the need for antiretroviral therapy should be the first priority. If antiretroviral therapy is not required, interferon-

Clinical Guideline	Recommendation(s)

	based therapy, which suppresses both hepatitis C virus and hepatitis B virus, should be considered. If interferon-based therapy for hepatitis C virus has failed, treatment of chronic hepatitis B with nucleoside or nucleotide analogs is recommended.
	
	Treatment of Hepatitis C coinfection
	• Antiviral treatment for hepatitis C virus infection should be considered for all human immunodeficiency virus-infected persons with acute or chronic hepatitis C virus infection.
	• The combination of peginterferon alfa (PegIFN) plus ribavirin is the recommended backbone of therapy for HIV/HCV-co-infected patients regardless of HCV genotype.
	• Antiviral treatment with PegIFN is not recommended in patients with decompensated liver disease.
	• For HCV-genotype-1-infected patients who are not co-infected with HIV, a HCV NS3/4A protease inhibitor (PI), either boceprevir or telaprevir, in combination with PegIFN/ribavirin is recommended on the basis of large clinical trials demonstrating significantly higher SVR rates with an acceptable safety/tolerability profile compared to PegIFN/ribavirin alone.
	• For HIV/HCV co-infected patients, preliminary data from small, ongoing clinical trials of boceprevir or telaprevir plus PegIFN/ribavirin for the treatment of HCV genotype 1 infection in HIV/HCV co-infected patients demonstrate greater efficacy than PegIFN/ribavirin alone, with a safety and tolerability profile similar to that observed in HCV monoinfected patients treated with boceprevir or telaprevir plus PegIFN/ribavirin. Preliminary recommendations are as follows:
	  o PegIFN is recommended for use for all HCV genotypes
	  o Ribavirin is recommended for use with PegIFN for all HCV genotypes.
	  o Boceprevir is approved for use in combination with PegIFN/ribavirin in HCV-genotype-1-monoinfected-patients. For HIV/HCV-co-infected patients, the regimen being evaluated is PegIFN/ribavirin administered for four weeks (lead-in phase) followed by boceprevir 800 mg orally every 7 to 9 hours (with a light snack) added to PegIFN/ribavirin for an additional 44 weeks.
	  o Telaprevir is approved for use in combination with PegIFN/ribavirin in HCV-genotype-1-monoinfected-patients. Dosing regimens lasting 48 weeks are being evaluated.
	• Patients with contraindications to the use of ribavirin can be treated with peginterferon alfa (2a or 2b) monotherapy. However, substantially lower sustained viral response rates are expected in persons not receiving ribavirin. HCV PIs should not be administered without ribavirin because of the high likelihood of virologic failure.
	
	Treatment of herpes simplex virus disease
	• Orolabial lesions can be treated with oral valacyclovir, famciclovir, or acyclovir for five to 10 days.
	• Severe mucocutaneous herpes simplex virus lesions are best treated initially with intravenous acyclovir. Patients may be switched to oral therapy after the lesions have begun to regress. Therapy should be continued until the lesions have completely healed.
	• Genital herpes simplex virus infection should be treated with oral valacyclovir, famciclovir, or acyclovir for five to 14 days. Short-course therapy (one, two, or three days) should not be used in patients with human immunodeficiency virus infection.
	• Most recurrences of genital herpes can be prevented by use of daily anti-

Clinical Guideline	Recommendation(s)
	herpes simplex virus therapy, and this is recommended for persons who have frequent or severe recurrences. • Suppressive therapy with oral acyclovir, valacyclovir, or famciclovir is effective in preventing recurrences. Suppressive therapy with valacyclovir should be 500 mg twice daily in human immunodeficiency virus -infected persons or twice-daily regimens with acyclovir or famciclovir should be used. Management of herpes simplex virus treatment failure • The treatment of choice for acyclovir-resistant herpes simplex virus is intravenous foscarnet. Topical trifluridine, cidofovir, and imiquimod also have been used successfully for lesions on external surfaces, although prolonged application for 21 to 28 days or longer might be required. Histoplasmosis • Patients with moderately severe to severe disseminated histoplasmosis should be treated with an intravenous lipid formulation of amphotericin B for ≥2 weeks or until they clinically improve followed by oral itraconazole (200 mg three times daily for three days and then 200 mg twice daily for a total of ≥12 months). • In patients with less severe disseminated histoplasmosis, oral itraconazole at 200 mg three times daily for three days followed by 200 mg twice daily is appropriate initial therapy. Treatment of Isosporiasis (also known as Cystoisosporiasis) • Sulfamethoxazole-trimethoprim is the antimicrobial agent of choice for treatment of isosporiasis. It is the only agent whose use is supported by substantial published data and clinical experience. Therefore, potential alternative therapies should be reserved for patients with documented sulfa intolerance or in whom treatment fails. The traditional treatment regimen has been a 10-day course of Sulfamethoxazole-trimethoprim (800-160 mg) administered orally four times daily. • Intravenous administration of Sulfamethoxazole-trimethoprim should be considered for patients with potential or documented malabsorption. • Single-agent therapy with pyrimethamine has been used, with anecdotal success for treatment and prevention of isosporiasis. Pyrimethamine (50 to 75 mg/day) plus leucovorin (10 to 25 mg/day) to prevent myelosuppression may be an effective treatment alternative; it is the option for sulfa-intolerant patients. Leishmaniasis • Due to similar efficacy and a better toxicity profile, clinicians consider liposomal amphotericin B as the drug of choice for visceral leishmaniasis in human immunodeficiency virus-coinfected patients. The optimal amphotericin B dosage has not been determined. • Regimens with efficacy include conventional amphotericin B 0.5 to 1.0 mg/kg body weight/day intravenous to achieve a total dose of 1.5 to 2.0 g, or liposomal or lipid complex preparations of two to four mg/kg body weight administered on consecutive days or in an interrupted schedule (e.g., 4 mg/kg on Days 1 to 5, 10, 17, 24, 31, and 38) to achieve a total cumulative dose of 20 to 60 mg/kg body weight. A higher daily dosage is recommended for liposomal or lipid complex preparations than for conventional amphotericin B. Preventing disseminated *Mycobacterium avium* complex disease • Human immunodeficiency virus-infected adults and adolescents should receive chemoprophylaxis against disseminated *Mycobacterium avium*

Clinical Guideline	Recommendation(s)
	complex disease if they have a CD4+ count <50 cells/µL. • Azithromycin or clarithromycin are the preferred prophylactic agents. • The combination of clarithromycin and rifabutin is no more effective than clarithromycin alone for chemoprophylaxis, is associated with a higher rate of adverse effects than either drug alone, and should not be used. • The combination of azithromycin with rifabutin is more effective than azithromycin alone; however, the additional cost, increased occurrence of adverse effects, potential for drug interactions, and absence of a survival difference compared to azithromycin alone do not warrant a routine recommendation for this regimen. • Azithromycin and clarithromycin also each confer protection against respiratory bacterial infections. • If azithromycin or clarithromycin cannot be tolerated, rifabutin is an alternative prophylactic agent for *Mycobacterium avium* complex disease, although drug interactions may make this agent difficult to use. • Primary *Mycobacterium avium* complex disease prophylaxis should be discontinued among adult and adolescent patients who have responded to antiretroviral therapy with an increase in CD4+ counts to >100 cells/µL for ≥3 months. Primary prophylaxis should be reintroduced if the CD4+ count decreases to <50 cells/µL. <u>Treatment of disseminated *Mycobacterium avium* Complex Disease</u> • Initial treatment of *Mycobacterium avium* complex disease should consist of two or more antimycobacterial drugs to prevent or delay the emergence of resistance. • Clarithromycin is the preferred first agent; however, azithromycin can be substituted for clarithromycin when drug interactions or clarithromycin intolerance preclude the use of clarithromycin. • Testing of *Mycobacterium avium* complex disease isolates for susceptibility to clarithromycin or azithromycin is recommended for all patients. <u>Treatment of Penicilliosis marneffei</u> • Penicilliosis is caused by the dimorphic fungus *Penicillium marneffei*, which is known to be endemic in Southeast Asia (especially Northern Thailand and Vietnam) and southern China. • The recommended treatment is liposomal amphotericin B, three to five mg/kg body weight/day intravenously for two weeks, followed by oral itraconazole, 400 mg/day for a subsequent duration of 10 weeks, followed by secondary prophylaxis. • Patients with mild disease can be initially treated with oral itraconazole 400 mg/day for eight weeks, followed by 200 mg/day for prevention of recurrence. • The alternative drug for primary treatment in the hospital is intravenous voriconazole, 6 mg/kg every 12 hours on day one and then 4 mg/kg every 12 hours for at least three days, followed by oral voriconazole, 200 mg twice daily for a maximum of 12 weeks. • Patients with mild disease can be initially treated with oral voriconazole 400 mg twice a day on day one, and then 200 mg twice daily for 12 weeks. The optimal dose of voriconazole for secondary prophylaxis after 12 weeks has not been studied. <u>Primary prophylaxis of *Pneumocystis (carinii) jiroveci* pneumonia</u> • Sulfamethoxazole-trimethoprim is the recommended prophylactic agent. One double-strength tablet daily is the preferred regimen. However, one single-strength tablet daily is also effective and might be better tolerated than one

Clinical Guideline	Recommendation(s)
	double-strength tablet daily. One double-strength tablet three times weekly is also effective. Sulfamethoxazole-trimethoprim at a dose of one double-strength tablet daily confers cross-protection against toxoplasmosis and selected common respiratory bacterial infections. Lower doses of sulfamethoxazole-trimethoprim likely also confer such protection. • For patients who have an adverse reaction that is not life threatening, chemoprophylaxis with sulfamethoxazole-trimethoprim should be continued if clinically feasible; for those who have discontinued such therapy because of an adverse reaction, reinstituting sulfamethoxazole-trimethoprim should be strongly considered after the adverse event has resolved. Patients who have experienced adverse events, including fever and rash, might better tolerate reintroduction of the drug with a gradual increase in dose (i.e., desensitization), according to published regimens or reintroduction of sulfamethoxazole-trimethoprim at a reduced dose or frequency; as many as 70% of patients can tolerate such reinstitution of therapy. • If sulfamethoxazole-trimethoprim cannot be tolerated, alternative prophylactic regimens include dapsone, dapsone/pyrimethamine plus leucovorin, aerosolized pentamidine and atovaquone. • Primary *Pneumocystis (carinii) jiroveci* pneumonia prophylaxis should be discontinued for adult and adolescent patients who have responded to antiretroviral therapy with an increase in CD4+ counts to >200 cells/µL for >3 months. Prophylaxis should be reintroduced if the CD4+ count decreases to <200 cells/µL. <u>Treatment of *Pneumocystis (carinii) jiroveci* pneumonia</u> • Sulfamethoxazole-trimethoprim is the treatment of choice. The dose must be adjusted for abnormal renal function. Multiple randomized clinical trials indicate that sulfamethoxazole-trimethoprim is as effective as parenteral pentamidine and more effective than other regimens. Adding leucovorin to prevent myelosuppression during acute treatment is not recommended because of questionable efficacy and some evidence for a higher failure rate. Oral outpatient therapy of sulfamethoxazole-trimethoprim is highly effective among patients with mild-to-moderate disease. • Patients who have *Pneumocystis (carinii) jiroveci* despite sulfamethoxazole-trimethoprim prophylaxis are usually effectively treated with standard doses of sulfamethoxazole-trimethoprim. • Patients with documented or suspected *Pneumocystis (carinii) jiroveci* and moderate-to-severe disease, as defined by room air pO_2 <70 mm Hg or arterial-alveolar O_2 gradient >35 mm Hg, should receive adjunctive corticosteroids as early as possible, and certainly within 72 hours after starting specific *Pneumocystis (carinii) jiroveci* therapy. • The recommended duration of therapy for *Pneumocystis (carinii) jiroveci* is 21 days. • Patients who have a history of *Pneumocystis (carinii) jiroveci* should be administered chemoprophylaxis for life (i.e., secondary prophylaxis or chronic maintenance therapy) with sulfamethoxazole-trimethoprim unless immune reconstitution occurs as a result of antiretroviral therapy. • Secondary prophylaxis should be discontinued for adult and adolescent patients whose CD4+ count has increased from <200 cells/µL to >200 cells/µL for >3 months as a result of antiretroviral therapy. Prophylaxis should be reintroduced if the CD4+ count decreases to <200 cells/µL. If *Pneumocystis (carinii) jiroveci* recurs at a CD4+ count of ≥200 cells/µL, lifelong prophylaxis should be administered. <u>Primary prophylaxis of *Toxoplasma* encephalitis</u> • The double-strength tablet daily dose of sulfamethoxazole-trimethoprim

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	recommended as the preferred regimen for *Pneumocystis (carinii) jiroveci* prophylaxis is effective against *Toxoplasma* encephalitis as well and is therefore recommended. Sulfamethoxazole-trimethoprim, one double-strength tablet three times weekly, is an alternative.
	• If patients cannot tolerate sulfamethoxazole-trimethoprim, the recommended alternative is dapsone-pyrimethamine plus leucovorin, which is also effective against *Pneumocystis (carinii) jiroveci* pneumonia.
	• Atovaquone with or without pyrimethamine/leucovorin can also be considered.
	• Prophylactic monotherapy with dapsone, pyrimethamine, azithromycin, or clarithromycin cannot be recommended on the basis of available data. Aerosolized pentamidine does not protect against *Toxoplasma* encephalitis and is not recommended.
	• Prophylaxis against *Toxoplasma* encephalitis should be discontinued among adult and adolescent patients who have responded to antiretroviral therapy with an increase in CD4+ counts to >200 cells/µL for >3 months. Prophylaxis for *Toxoplasma* encephalitis should be reintroduced if the CD4+ count decreases to <100–200 cells/µL.
	
	<u>Treatment of *Toxoplasma* encephalitis</u>
	• The initial therapy of choice for *Toxoplasma* encephalitis consists of the combination of pyrimethamine plus sulfadiazine plus leucovorin.
	• The preferred alternative regimen for patients with *Toxoplasma* encephalitis who are unable to tolerate or who fail to respond to first-line therapy is pyrimethamine plus clindamycin plus leucovorin.
	• Sulfamethoxazole-trimethoprim was reported in a small randomized trial to be effective and better tolerated than pyrimethamine-sulfadiazine. On the basis of less in vitro activity and less experience with sulfamethoxazole-trimethoprim, treatment with this drug may be considered an option.
	• Acute therapy for *Toxoplasma* encephalitis should be continued for at least six weeks, if there is clinical and radiologic improvement.
	
	<u>Treatment of latent tuberculosis infection</u>
	• Human immunodeficiency virus-infected persons, regardless of age, should be treated for latent tuberculosis infection if they have no evidence of active tuberculosis and:
	  o A positive diagnostic test for latent tuberculosis infection and no prior history of treatment for active or latent tuberculosis.
	  o A negative diagnostic test for latent tuberculosis infection but are close contacts of persons with infectious pulmonary tuberculosis.
	  o A history of untreated or inadequately treated healed tuberculosis (i.e., old fibrotic lesions on chest radiography) regardless of diagnostic tests for latent tuberculosis infection.
	• Treatment options for latent tuberculosis infection include isoniazid daily or twice weekly for nine months.
	• Due to an increased risk of fatal and severe hepatotoxicity, a two-month regimen of daily rifampin and pyrazinamide is not recommended for latent tuberculosis infection treatment regardless of human immunodeficiency virus status.
	• Human immunodeficiency virus-infected persons receiving isoniazid should receive pyridoxine to minimize the risk of developing peripheral neuropathy. Alternatives for individuals who cannot take isoniazid or who have been exposed to a known isoniazid-resistant index case include either rifampin or rifabutin alone for four months.
	• For persons exposed to isoniazid- and/or rifampin-resistant tuberculosis,

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	decisions to treat with one or two drugs other than isoniazid, rifampin, or rifabutin should be based on the relative risk of exposure to organisms broadly resistant to other antimycobacterial drugs and should be made in consultation with public health authorities. • Directly observed therapy should be used with intermittent dosing regimens when otherwise feasible to maximize regimen completion rates. • There is no evidence to suggest that latent tuberculosis infection treatment should be continued beyond the recommended duration in persons with human immunodeficiency virus infection. Therefore, latent tuberculosis infection treatment should be discontinued after completing the appropriate number of doses. <u>Treatment of active tuberculosis disease</u> • Recommendations for anti-tuberculosis treatment regimens in human immunodeficiency virus -infected adults follow the same principles as for adults without human immunodeficiency virus -infection. • Treatment of drug susceptible tuberculosis disease should include a six-month regimen with an initial phase of isoniazid, rifampin or rifabutin, pyrazinamide, and ethambutol administered for two months followed by isoniazid and rifampin (or rifabutin) for four additional months. • When drug-susceptibility testing confirms the absence of resistance to isoniazid, rifampin, and pyrazinamide, ethambutol may be discontinued before two months of treatment have been completed. • For patients with cavitary lung disease and cultures positive for *Mycobacterium tuberculosis* after completion of two months of therapy, treatment should be extended with isoniazid and rifampin for an additional three months for a total of nine months. • All human immunodeficiency virus-infected patients treated with isoniazid should receive pyridoxine supplementation. • For patients with extrapulmonary tuberculosis, a six- to nine-month regimen (two months of isoniazid, rifampin, pyrazinamide, and ethambutol followed by four to seven months of isoniazid and rifampin) is recommended. • Exceptions to the recommendation for a six- to nine-month regimen for extrapulmonary tuberculosis include central nervous system disease (tuberculoma or meningitis) and bone and joint tuberculosis, for which many experts recommend nine to 12 months. • Adjuvant corticosteroids should be added when treating central nervous system and pericardial disease. • Treatment with corticosteroids should be started intravenously as early as possible with change to oral therapy individualized according to clinical improvement. • Recommended corticosteroid regimens are dexamethasone 0.3 to 0.4 mg/kg tapered over six to eight weeks or prednisone 1 mg/kg for three weeks, then tapered for three to five weeks. <u>Treatment of varicella zoster virus disease</u> • For uncomplicated varicella, the preferred treatment options are valacyclovir (1 gram orally three times daily), or famciclovir (500 mg orally three times daily) for five to seven days. Oral acyclovir (20 mg/kg body weight up to a maximum dose of 800 mg five times daily) can be an alternative. • Prompt antiviral therapy should be instituted in all human immunodeficiency virus-seropositive patients whose herpes zoster is diagnosed within one week of rash onset (or any time before full crusting of lesions). The recommended treatment options for acute localized dermatomal herpes zoster in human immunodeficiency virus-infected patients are oral valacyclovir, famciclovir,

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	or acyclovir (doses as above) for seven to 10 days, although longer durations of therapy should be considered if lesions resolve slowly. Valacyclovir or famciclovir are preferred because of their improved pharmacokinetic properties and simplified dosing schedule. • If cutaneous lesions are extensive or if visceral involvement is suspected, intravenous acyclovir should be initiated and continued until clinical improvement is evident. A switch from intravenous acyclovir to oral antiviral therapy (to complete a 10 to 14 day treatment course) is reasonable when formation of new cutaneous lesions has ceased and the signs and symptoms of visceral varicella zoster virus infection are clearly improving. • Optimal antiviral therapy for progressive outer retinal necrosis remains undefined. Specific treatment should include systemic therapy with at least one intravenous drug (selected from acyclovir, ganciclovir, foscarnet, and cidofovir) coupled with injections of at least one intravitreal drug (selected from ganciclovir and foscarnet). Treatment regimens for progressive outer retinal necrosis recommended by certain specialists include a combination of intravenous ganciclovir and/or foscarnet plus intravitreal injections of ganciclovir and/or foscarnet. The prognosis for visual preservation in involved eyes is poor, despite aggressive antiviral therapy. • Other infectious disease states mentioned within these guidelines note that the treatment guidelines for that disease state should be utilized. • The guideline specifies that detailed recommendations for the treatment of human herpesvirus-8 and associated malignancies are beyond the scope of these guidelines. • Other excluded infectious disease states offer no specific therapy or utilize medications not licensed in the United States.

Centers for Disease Control and Prevention: **Sexually Transmitted Diseases Treatment Guidelines (2010)**[7]	<u>Bacterial vaginosis</u>
	• Recommended regimens:
	  o Metronidazole 500 mg orally twice a day for seven days.
	  o Metronidazole gel 0.75%, one full applicator (5 grams) intravaginally, once a day for five days.
	  o Clindamycin cream 2%, one full applicator (5 grams) intravaginally at bedtime for seven days.
	• Alternative regimens:
	  o Tinidazole 2 grams orally once daily for two days.
	  o Tinidazole 1 gram orally once daily for five days.
	  o Clindamycin 300 mg orally twice daily for seven days.
	  o Clindamycin ovules 100 mg intravaginally once at bedtime for three days.
	
	<u>Cervicitis</u>
	• Recommended regimens for presumptive treatment:
	  o Azithromycin 1 gram orally in a single dose.
	  o Doxycycline 100 mg orally twice a day for seven days.
	
	<u>Chancroid</u>
	• Recommended regimens:
	  o Azithromycin 1 gram orally in a single dose.
	  o Ceftriaxone 250 mg intramuscular in a single dose.
	  o Ciprofloxacin 500 mg orally twice a day for three days.
	  o Erythromycin base 500 mg orally three times a day for seven days.
	
	<u>Chlamydial infections</u>
	• Recommended regimens:

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	o Azithromycin 1 gram orally in a single dose. o Doxycycline 100 mg orally twice a day for seven days. • Alternative regimens: o Erythromycin base 500 mg orally four times a day for seven days. o Erythromycin ethylsuccinate 800 mg orally four times a day for seven days. o Levofloxacin 500 mg orally once daily for seven days. o Ofloxacin 300 mg orally twice a day for seven days. <u>Chlamydial infections among children</u> • Recommended regimen for children <45 kg: o Erythromycin base or ethylsuccinate 50 mg/kg/day orally divided into four doses daily for 14 days. • Recommended regimen for children ≥45 kg and <8 years of age: o Azithromycin 1 gram orally in a single dose. • Recommended regimens for children ≥8 years of age: o Azithromycin 1 gram orally in a single dose. o Doxycycline 100 mg orally twice a day for seven days. <u>Disseminated gonococcal infection</u> • Recommended regimen: o Ceftriaxone 1 gram intramuscular or intravenous every 24 hours. • Alternative regimens: o Cefotaxime 1 gram intravenous every eight hours. o Ceftizoxime 1 gram intravenous every eight hours. <u>Epididymitis</u> • Recommended regimens: o Ceftriaxone 250 mg intramuscular in a single dose plus doxycycline 100 mg orally twice a day for 10 days. • For acute epididymitis most likely caused by enteric organisms: o Levofloxacin 500 mg orally once daily for 10 days. o Ofloxacin 300 mg orally twice a day for 10 days. <u>Genital herpes infection</u> • The use of systemic antivirals including valacyclovir, acyclovir, and famciclovir is encouraged for the treatment of primary and recurrent genital herpes. Topical therapy with antiviral drugs offers minimal clinical benefit, and their use is not recommended. • Systemic antiviral drugs partially control the symptoms and signs of herpes infection when used to treat first clinical episodes and recurrent episodes, or when used as daily suppressive therapy. • However, these drugs neither eradicate latent virus nor affect the risk, frequency, or severity of recurrences after the drug is discontinued. • Randomized trials have indicated that three antiviral medications provide clinical benefit for genital herpes: acyclovir, valacyclovir, and famciclovir. • Topical therapy with antiviral drugs offers minimal clinical benefit, and its use is discouraged. • Foscarnet is frequently effective for treatment of acyclovir-resistant genital herpes in immunocompromised individuals. • Recommended regimens for initial clinical episodes include: o Acyclovir 400 mg three times a day for seven to 10 days or 200 mg five times a day for seven to 10 days. o Famciclovir 250 mg three times a day for seven to 10 days. o Valacyclovir 1 gram twice a day for seven to 10 days.

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	• Recommended regimens for suppressive therapy in recurrent herpes (≥6 episodes/year) include:
	  o Acyclovir 400 mg twice daily.
	  o Famciclovir 250 mg twice daily.
	  o Valacyclovir 500 mg once daily or 1,000 mg once daily.
	• Recommended regimens for episodic therapy in recurrent herpes include:
	  o Acyclovir 400 mg three times a day for five days or 800 mg twice a day for five days or 800 mg three times a day for two days.
	  o Famciclovir 125 mg twice a day for five days or 1 gram twice a day for one day or 500 mg once then 250 mg twice a day for two days.
	  o Valacyclovir 500 mg twice a day for three days or 1 gram once a day for five days.
	• Recommended regimen for severe infections include:
	  o Intravenous acyclovir 5 to 10 mg/kg every eight hours for two to seven days or until clinical improvement is observed, followed by oral antiviral therapy to complete at least 10 days of total therapy.
	• Recommended regimens for suppressive therapy in patients with human immunodeficiency virus include:
	  o Acyclovir 400 to 800 mg twice to three times daily.
	  o Famciclovir 500 mg twice daily.
	  o Valacyclovir 500 mg twice daily.
	• Recommended regimens for episodic therapy in patients with human immunodeficiency virus include:
	  o Acyclovir 400 mg three times daily for five to 10 days.
	  o Famciclovir 500 mg twice daily for five to 10 days.
	  o Valacyclovir 1 gram twice daily for five to 10 days.
	
	<u>Genital warts</u>
	• No evidence exists to identify one treatment as more efficacious than another and no treatment is ideal for all patients with genital warts.
	• Treatment selection may be based on wart size and number, anatomic site of wart, wart morphology, and adverse effects of treatment.
	• Interferon therapy is not recommended as a primary modality because of inconvenient routes of administration, frequent office visits, and the association between its use and a high frequency of adverse effects.
	
	<u>Granuloma inguinale (Donovanosis)</u>
	• Recommended regimen:
	  o Doxycycline 100 mg orally twice a day for at least three weeks and until all lesions have completely healed.
	• Alternative regimens:
	  o Azithromycin 1 gram orally once per week for at least three weeks and until all lesions have completely healed.
	  o Ciprofloxacin 750 mg orally twice a day for at least three weeks and until all lesions have completely healed.
	  o Erythromycin base 500 mg orally four times a day for at least three weeks and until all lesions have completely healed.
	  o Sulfamethoxazole-trimethoprim one double-strength tablet orally twice a day for at least three weeks and until all lesions have completely healed.
	• The addition of an aminoglycoside (e.g., gentamicin 1 mg/kg IV every eight hours) to these regimens can be considered if improvement is not evident within the first few days of therapy.
	
	<u>Gonococcal conjunctivitis</u>

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	• Recommended regimen:
	  o Ceftriaxone 1 gram intramuscular in a single dose.
	
	<u>Gonococcal infections among children</u>
	• Recommended regimen for children >45 kg:
	  o Treat with one of the regimens recommended for adults.
	• Recommended regimen for children who weigh ≤45 kg and who have uncomplicated gonococcal vulvovaginitis, cervicitis, urethritis, pharyngitis, or proctitis:
	  o Ceftriaxone 125 mg intramuscular in a single dose.
	• Recommended regimen for children who weigh ≤45 kg and who have bacteremia or arthritis:
	  o Ceftriaxone 50 mg/kg (maximum dose: 1 gram) intramuscular or intravenous in a single dose daily for seven days.
	• Recommended regimen for children who weigh >45 kg and who have bacteremia or arthritis:
	  o Ceftriaxone 50 mg/kg intramuscular or intravenous in a single dose daily for seven days.
	
	<u>Gonococcal meningitis and endocarditis</u>
	• Recommended regimen:
	  o Ceftriaxone 1 to 2 grams intravenous every 12 hours.
	
	<u>Hepatitis B</u>
	• No specific therapy is available for persons with acute hepatitis B; treatment is supportive.
	• Persons with chronic hepatitis B virus infection should be referred for evaluation to a physician experienced in the management of chronic liver disease.
	• Therapeutic agents approved by Food and Drug Administration for treatment of chronic hepatitis B can achieve sustained suppression of hepatitis B virus replication and remission of liver disease in some persons.
	
	<u>Hepatitis C</u>
	• Combination therapy with pegylated interferon and ribavirin is the treatment of choice for patients with chronic hepatitis C.
	
	<u>Lymphogranuloma venereum</u>
	• Recommended regimen:
	  o Doxycycline 100 mg orally twice a day for 21 days.
	• Alternative regimen:
	  o Erythromycin base 500 mg orally four times a day for 21 days.
	
	<u>Nongonococcal urethritis</u>
	• Recommended regimens:
	  o Azithromycin 1 gram orally in a single dose.
	  o Doxycycline 100 mg orally twice a day for seven days.
	• Alternative regimens:
	  o Erythromycin base 500 mg orally four times a day for seven days.
	  o Erythromycin ethylsuccinate 800 mg orally four times a day for seven days.
	  o Levofloxacin 500 mg orally once daily for seven days.
	  o Ofloxacin 300 mg orally twice a day for seven days.
	
	<u>Ophthalmia neonatorum caused by *Chlamydia trachomatis*</u>

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	• Recommended regimen:
	  o Erythromycin base or ethylsuccinate 50 mg/kg/day orally divided into four doses daily for 14 days.
	
	<u>Pelvic inflammatory disease</u>
	• Recommended parenteral regimen A:
	  o Cefotetan 2 grams intravenous every 12 hours.
	  o Cefoxitin 2 grams intravenous every six hours plus doxycycline 100 mg orally or intravenous every 12 hours.
	• Recommended parenteral regimen B:
	  o Clindamycin 900 mg intravenous every eight hours plus gentamicin loading dose intravenous or intramuscular (2 mg/kg of body weight), followed by a maintenance dose (1.5 mg/kg) every eight hours. Single daily dosing (3 to 5 mg/kg) can be substituted.
	• Alternative parenteral regimens:
	  o Ampicillin-sulbactam 3 grams IV every six hours plus doxycycline 100 mg orally or intravenous every 12 hours.
	• Recommended oral regimen:
	  o Ceftriaxone 250 mg intramuscular in a single dose plus doxycycline 100 mg orally twice a day for 14 days with or without metronidazole 500 mg orally twice a day for 14 days.
	  o Cefoxitin 2 grams intramuscular in a single dose and probenecid, 1 gram orally administered concurrently in a single dose, plus doxycycline 100 mg orally twice a day for 14 days with or without metronidazole 500 mg orally twice a day for 14 days.
	  o Other parenteral third-generation cephalosporin (e.g., ceftizoxime or cefotaxime) plus doxycycline 100 mg orally twice a day for 14 days with or without metronidazole 500 mg orally twice a day for 14 days.
	
	<u>Proctitis, proctocolitis, and enteritis</u>
	• Recommended regimen:
	  o Ceftriaxone 250 mg intramuscular plus doxycycline 100 mg orally twice a day for seven days.
	
	<u>Recurrent and persistent urethritis</u>
	• Recommended regimens:
	  o Metronidazole 2 grams orally in a single dose.
	  o Tinidazole 2 grams orally in a single dose plus azithromycin 1 gram orally in a single dose (if not used for initial episode).
	
	<u>Sexual assault and sexually transmitted diseases</u>
	• Recommended regimen: ceftriaxone plus metronidazole plus azithromycin or doxycycline.
	
	<u>Primary and secondary syphilis</u>
	• Recommended regimen for adults:
	  o Benzathine penicillin G 2.4 million units intramuscular in a single dose.
	• Recommended regimen for infants and children:
	  o Benzathine penicillin G 50,000 units/kg intramuscular, up to the adult dose of 2.4 million units in a single dose.
	
	<u>Early latent syphilis</u>
	• Recommended regimens for adults:
	  o Benzathine penicillin G 2.4 million units intramuscular in a single

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	dose.
	• Recommended regimens for children:
	  o Benzathine penicillin G 50,000 units/kg intramuscular, up to the adult dose of 2.4 million units in a single dose.
	
	<u>Late latent syphilis or latent syphilis of unknown duration</u>
	• Recommended regimens for adults:
	  o Benzathine penicillin G 7.2 million units total, administered as three doses of 2.4 million units intramuscular each at one-week intervals.
	• Recommended regimens for children:
	  o Benzathine penicillin G 50,000 units/kg intramuscular, up to the adult dose of 2.4 million units, administered as three doses at one-week intervals.
	
	<u>Tertiary syphilis</u>
	• Recommended regimen:
	  o Benzathine penicillin G 7.2 million units total, administered as three doses of 2.4 million units intramuscular each at one-week intervals.
	
	<u>Neurosyphilis</u>
	• Recommended regimen:
	  o Aqueous crystalline penicillin G 18 to 24 million units per day, administered as 3 to 4 million units intravenous every four hours or continuous infusion, for 10 to 14 days.
	• Alternative regimen:
	  o Procaine penicillin 2.4 million units intramuscular once daily plus probenecid 500 mg orally four times a day, both for 10 to 14 days.
	
	<u>Trichomoniasis</u>
	• Recommended regimens: metronidazole 2 grams orally in a single dose or tinidazole 2 grams orally in a single dose.
	• Alternative regimen: metronidazole 500 mg orally twice a day for seven days.
	
	<u>Uncomplicated gonococcal infections of the cervix, urethra, and rectum</u>
	• Recommended regimens:
	  o Ceftriaxone 250 mg intramuscular in a single dose.
	  o Cefixime 400 mg orally in a single dose.
	  o Single-dose injectable cephalosporin regimens plus azithromycin 1 gram orally in a single dose or doxycycline 100 mg orally twice a day for seven days.
	
	<u>Uncomplicated gonococcal infections of the pharynx</u>
	• Recommended regimens:
	  o Ceftriaxone 250 mg intermuscular in a single dose plus azithromycin 1 gram orally in a single dose or doxycycline 100 mg orally twice a day for seven days.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the miscellaneous antivirals are noted in Table 3. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 3. FDA-Approved Indications for the Antivirals, Miscellaneous[1-3]

Indication	Foscarnet
Treatment of acyclovir-resistant mucocutaneous herpes simplex virus infections in immunocompromised patients	✔
Treatment of cytomegalovirus retinitis in patients with acquired immunodeficiency syndrome	✔

IV. Pharmacokinetics

The pharmacokinetic parameters of the miscellaneous antivirals are listed in Table 4.

Table 4. Pharmacokinetic Parameters of the Antivirals, Miscellaneous[1-3]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (Hours)
Foscarnet	N/A	14 to17	Not reported	Renal (73 to 94)	3 to 6

V. Drug Interactions

No significant drug interactions with the miscellaneous antivirals have been reported.[1] Since foscarnet decreases serum concentrations of ionized calcium, concurrent treatment with other drugs known to influence serum calcium concentrations should be used with caution.[1-3] Fatalities have been reported in post-marketing surveillance during concomitant therapy with foscarnet and pentamidine. Because of the tendency of foscarnet to cause renal impairment, the use of foscarnet in combination with potentially nephrotoxic drugs (e.g., aminoglycosides, amphotericin B, and intravenous pentamidine) should be avoided unless the potential benefits outweigh the risks to the patient.

VI. Adverse Drug Events

The most common adverse drug events reported with the miscellaneous antivirals are listed in Table 5. The boxed warning for foscarnet is listed in Table 6.

Table 5. Adverse Drug Events (%) Reported with the Antivirals, Miscellaneous[1-5]

Adverse Events	Foscarnet
Cardiovascular	
Cardiac arrest	<1
Chest pain	1 to 5
Edema	1 to 5
Electrocardiogram abnormalities	<5
Flushing	1 to 5
Hypertension	1 to 5
Hypotension	1 to 5
Palpitation	1 to 5
QT_c prolongation	<1
Ventricular arrhythmia	<1
Central Nervous System	
Aggressiveness	1 to 5
Agitation	1 to 5
Amnesia	1 to 5
Anxiety	≥5
Aphasia	1 to 5
Ataxia	1 to 5
Coma	<1

Adverse Events	Foscarnet
Confusion	≥5
Coordination abnormal	1 to 5
Dementia	1 to 5
Depression	≥5
Dizziness	≥5
Electroencephalography abnormal	1 to 5
Fatigue	≥5
Fever	65
Hallucinations	1 to 5
Headache	26
Hypoesthesia	≥5
Insomnia	1 to 5
Malaise	≥5
Meningitis	1 to 5
Nervousness	1 to 5
Paresthesia	≥5
Peripheral neuropathy	≥5
Seizure	8
Somnolence	1 to 5
Stupor	1 to 5
Tremor	1 to5
Dermatological	
Erythema multiforme	<1
Erythematous rash	1 to 5
Maculopapular rash	1 to 5
Pruritus	1 to 5
Seborrhea	1 to 5
Skin discoloration	1 to 5
Skin ulceration	1 to 5
Stevens-Johnson syndrome	<1
Rash	≥5
Toxic epidermal necrolysis	<1
Vesiculobullous eruptions	<1
Gastrointestinal	
Abdominal pain	≥5
Anorexia	≥5
Constipation	1 to 5
Diarrhea	30
Dyspepsia	1 to 5
Dysphasia	1 to 5
Flatulence	1 to 5
Melena	1 to 5
Nausea	47
Pancreatitis	1 to 5
Rectal hemorrhage	1 to 5
Taste perversion	1 to 5
Ulcerative stomatitis	1 to 5
Vomiting	26
Weight loss	1 to 5
Xerostomia	1 to 5
Genitourinary	
Acute renal failure	1 to 5
Albuminuria	1 to 5
Dysuria	1 to 5

Adverse Events	Foscarnet
Hematuria	<1
Nocturia	1 to 5
Polyuria	1 to 5
Renal calculus	<1
Urinary retention	1 to 5
Urinary tract infection	1 to 5
Hematologic	
Anemia	33
Granulocytopenia	17
Leukopenia	≥5
Lymphadenopathy	1 to 5
Neutropenia	<1
Pancytopenia	<1
Thrombocytopenia	1 to 5
Thrombosis	1 to 5
Laboratory Test Abnormalities	
Abnormal hepatic function	1 to 5
Acidosis	1 to 5
Alkaline phosphatase increased	1 to 5
Alanine aminotransferase increased	1 to 5
Amylase increased	<1
Aspartate aminotransferase increased	1 to 5
Blood urea nitrogen increased	1 to 5
Creatine phosphokinase increased	<1
Gamma-glutamyl transpeptidase increased	<1
Hypocalcemia	15 to 30
Hypokalemia	16 to 48
Hypomagnesemia	15 to 30
Hyponatremia	1 to 5
Hypophosphatemia	8 to 26
Hypoproteinemia	<1
Lactate dehydrogenase increased	1 to 5
Musculoskeletal	
Arthralgia	1 to 5
Back pain	1 to 5
Involuntary muscle contractions	≥5
Leg cramps	1 to 5
Myalgia	1 to 5
Myopathy	<1
Myositis	<1
Rhabdomyolysis	<1
Rigors	≥5
Weakness	≥5
Respiratory	
Bronchospasm	1 to 5
Cough	≥5
Dyspnea	≥5
Hemoptysis	1 to 5
Pharyngitis	1 to 5
Pneumonia	1 to 5
Pneumothorax	1 to 5
Rhinitis	1 to 5
Sinusitis	1 to 5
Stridor	1 to 5

Adverse Events	Foscarnet
Other	
Conjunctivitis	1 to 5
Dehydration	<1
Diabetes insipidus	<1
Diaphoresis	≥5
Eye pain	1 to 5
Flu-like syndrome	1 to 5
Hepatic function abnormal	1 to 5
Infection	≥5
Injection site pain	1 to 5
Malignancies	1 to 5
Pain	≥5
Sepsis	≥5
Syndrome of inappropriate antidiuretic hormone secretion	<1
Thirst	1 to 5
Vision abnormalities	≥5

✓ Percent not specified.
- Event not reported or incidence <1%.

Table 6. Boxed Warning for Foscarnet[1]

WARNING
Renal impairment is the major toxicity of foscarnet. Frequent monitoring of serum creatinine, with dose adjustment for changes in renal function, and adequate hydration with administration of foscarnet, is imperative. Seizures, related to alterations in plasma minerals and electrolytes, have been associated with foscarnet treatment. Therefore, patients must be carefully monitored for such changes and their potential sequelae. Mineral and electrolyte supplementation may be required. Foscarnet is indicated for use only in immunocompromised patients with cytomegalovirus retinitis and mucocutaneous acyclovir-resistant herpes simplex virus infections.

VII. Dosing and Administration

The usual dosing regimens for the miscellaneous antivirals are listed in Table 7.

Table 7. Usual Dosing Regimens for the Antivirals, Miscellaneous[1]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Foscarnet	Treatment of acyclovir-resistant mucocutaneous herpes simplex virus infections in immunocompromised patients: Injection: 40 mg/kg every eight or 12 hours for two to three weeks or until healed Treatment of cytomegalovirus retinitis in patients with acquired immunodeficiency syndrome: Injection: induction, 90 mg/kg every 12 hours or 60 mg/kg every eight hours for two to three weeks depending on clinical response; maintenance, 90 to 120 mg/kg/day	Safety and efficacy in children have not been established.	Injection: 24 mg/mL

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the miscellaneous antivirals are summarized in Table 8.

Table 8. Comparative Clinical Trials with the Antivirals, Miscellaneous

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cytomegalovirus Retinitis				
Palestine et al.[8] (1991) Foscarnet 60 mg/kg three times a day for 3 weeks (induction) followed by a maintenance dose of 90 mg/kg once a day vs no therapy (delayed treatment, control group)	MC, RCT Patients with previously untreated AIDS and CMV at low risk for loss of visual acuity were examined weekly to evaluate progression of retinal disease.	N=24 Variable duration	Primary: Progression of retinitis border by 750 microns or development of a new retinal lesion due to CMV Secondary: Changes in visual acuity, CMV shedding in the blood and urine, serum levels of (HIV-1) p24 antigen, and total CD4 T lymphocyte counts	Primary The mean time to progression of retinitis was 3.2 weeks in the control group vs 13.3 weeks in the treatment group (P<0.001). Secondary: Nine patients in the treatment group had positive blood cultures for CMV at entry and had clear cultures by the end of the induction period vs one in the control group (P=0.004). No reductions were seen in p24 levels in the control patients, vs a reduction of more than 50% in p24 levels for all four treated patients for whom follow-up levels were available. Main adverse effects of foscarnet treatment were seizures (two patients), hypomagnesemia (nine), hypocalcemia (11), and elevations in serum creatinine above 2.0 mg/dL (three). The control patients received an average of 0.2 units of blood per week compared to an average of 0.6 units of blood per week for the patients on foscarnet treatment.
Herpes Simplex Virus				
Safrin et al.[9] (1990) Foscarnet 40 mg/kg IV every 8 hours for 10 to 43 days (mean, 18.5)	MC, RCT Patients with HIV, received foscarnet for acyclovir-resistant HSV (34 mucocutaneous, 25 perirectal, 7 orofacial, 1 genital, 1 whitlow) that	N=26 43 days	Primary: Clinical response to foscarnet Secondary: Not reported	Primary: Clinical response was noted in 81% of patients; complete re-epithelialization of HSV lesions occurred in 73%. Cessation of viral shedding was documented in all of the 11 patients who were recultured. Although adverse effects were frequent, only three patients discontinued therapy. Before foscarnet therapy, 14 patients received vidarabine for acyclovir-resistant HSV. The infection did not resolve in any of the vidarabine-treated patients, and therapy was discontinued in four

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	progressed despite therapy with IV(19) or high-dose oral (7) acyclovir, vidarabine (15) or ganciclovir (3)			(29%) patients due to toxicity. Secondary: Not reported
Safrin et al.[10] (1991) Foscarnet (40 mg/kg IV every 8 hours) vs vidarabine* (15 mg/kg/day) IV once daily for 10 to 42 days	MC, RCT Patients with AIDS and mucocutaneous herpetic lesions unresponsive to IV therapy with acyclovir for a minimum of 10 days	N=14 42 days	Primary: Time to lesion resolution, time to complete healing Secondary: Not reported	Primary: The lesions in all eight patients assigned to foscarnet healed completely after 10 to 24 days of therapy. In contrast, vidarabine was discontinued because of treatment failure in all patients. The time to complete healing (P=0.01), time to 50% reductions in the size of the lesions (P=0.01) and the pain score (P=0.004), and time to the end of viral shedding (P=0.006) were all significantly shorter in the patients assigned to foscarnet. Secondary: Not reported

*Agent not currently available in the United States.
Drug regimen abbreviations: IV=intravenous
Study abbreviations: MC=multicenter, RCT=randomized controlled trial
Other abbreviations: AIDS=acquired immunodeficiency virus, CMV=cytomegalovirus, HIV=human immunodeficiency virus, HSV=herpes simplex virus

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 9. Relative Cost of the Antivirals, Miscellaneous

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Foscarnet	injection	N/A	N/A	$$$$$

N/A=Not available.

X. Conclusions

Foscarnet is approved for the treatment of cytomegalovirus (CMV) retinitis in patients with the acquired immunodeficiency syndrome (AIDS).[1-3] It is also approved for the treatment of acyclovir-resistant mucocutaneous herpes simplex virus infections in immunocompromised patients. Foscarnet is available in a generic formulation.

Guidelines for the prevention and treatment of opportunistic infections in human immunodeficiency virus (HIV)-infected adults and adolescents recommend foscarnet as one of several treatment options for CMV retinitis.[6] No one regimen has been proven to have greater efficacy in terms of protecting vision.[6,,8,10] The combination of ganciclovir and foscarnet is generally more effective than systemic therapy with either agent alone for patients with relapsed retinitis, but is accompanied by greater toxicity.[6] After induction therapy, secondary prophylaxis is recommended for life. Foscarnet is considered an effective treatment option for the chronic suppression of CMV retinitis.[6]

Guidelines recommend the use of foscarnet for the treatment of acyclovir-resistant genital herpes in immunocompromised individuals.[5-7] Foscarnet has been shown to be effective for the treatment of herpetic lesions in clinical trials.[9-10]

Therefore, all brand miscellaneous antivirals within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand miscellaneous antiviral is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Amebicides
AHFS Class 083004
November 12, 2014

I. Overview

Amebiasis is an important parasitic infection because of its worldwide distribution and serious gastrointestinal manifestations.[1] *Entamoeba histolytica* is the major pathogen responsible for amebiasis infections. It is transmitted from a human host via the fecal-oral route after ingesting the cyst from contaminated water or food. The incubation period may vary from weeks to years following exposure.[1-4] Once in the lumen of the small intestine, *Entamoeba histolytica* cysts may form into motile trophozoites and penetrate the gastrointestinal mucosa causing either an invasive intestinal infection or extraintestinal disease. Clinical manifestations of the intestinal infection range from mild abdominal discomfort and diarrhea to severe abdominal cramps, flatulence, fever, and bloody or mucoid diarrhea. If the infection spreads to extraintestinal sites, such as the liver, abscesses and other complications may develop. The trophozoite is the metabolically active form responsible for the symptoms; however, it is the *Entamoeba histolytica* cyst that is the infective form of the pathogen due to its ability to survive in the external environment, as well as the acidic conditions of the stomach.

Paromomycin is the only amebicide currently available and it is approved for the treatment of amebiasis. It is an aminoglycoside antibiotic which inhibits protein synthesis by binding to the 30S chromosome.[5-7] Paromomycin is only active against cysts in the intestinal lumen due to its poor absorption from the gastrointestinal tract. It is also approved for use as an adjunctive agent for the treatment of hepatic coma. The decline in neurologic function associated with impaired hepatic function is thought to be due to the accumulation of ammonia.[4-8] Antibiotics have been found to mediate this complication by inhibiting the bacteria associated with ammonia production.

The amebicides that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Paromomycin is available in a generic formulation. This class was last reviewed in May 2012.

Table 1. Amebicides Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Paromomycin	capsule	N/A	paromomycin

N/A=Not available, PDL=Preferred Drug List

The amebicides have been shown to be active against the strains of microorganisms indicated in Table 2. This activity is represented by the Food and Drug Administration (FDA)-approved indications for the amebicides that are noted in Table 4. These agents may also have been found to show activity to other microorganisms in vitro; however, the clinical significance of this is unknown since their safety and efficacy in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials. Although empiric anti-infective therapy may be initiated before culture and susceptibility test results are known, once results become available, appropriate therapy should be selected.

Table 2. Microorganisms Susceptible to the Amebicides[5-7]

Organism	Paromomycin
Entamoeba histolytica	✔

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the amebicides are summarized in Table 3.

Table 3. Treatment Guidelines Using the Amebicides

Clinical Guideline	Recommendation(s)
World	General considerations

Clinical Guideline	Recommendation(s)
Gastroenterology Organization: **Acute Diarrhea (2012)**[9]	• Antimicrobials are the drugs of choice for empirical treatment of traveler's diarrhea and of community-acquired secretory diarrhea when the pathogen is known. • Consider antimicrobial treatment for: o *Shigella*, *Salmonella*, *Campylobacter* (dysenteric form), or parasitic infections. o Nontyphoidal salmonellosis in at-risk populations (malnutrition, infants and elderly, immunocompromised patients and those with liver diseases and lymphoproliferative disorders) and in dysenteric presentation. o Moderate/severe traveler's diarrhea or diarrhea with fever and/or with bloody stools. • Nitazoxanide may be appropriate for *Cryptosporidium* and other infections, including some bacteria. <u>Antimicrobial agents for the treatment of specific causes of diarrhea</u> • Cholera o First-line: doxycycline. o Alternative: azithromycin or ciprofloxacin. • Shigellosis o First-line: ciprofloxacin. o Alternative: pivmecillinam or ceftriaxone. • Amebiasis o First-line: metronidazole. • Giardiasis o First-line: metronidazole. o Alternative: tinidazole, omidazole or secnidazole. • *Campylobacter* o First-line: azithromycin. • Alternative: fluoroquinolones (e.g., ciprofloxacin).
Infectious Diseases Society of America: **The Practice of Travel Medicine (2006)**[10]	<u>Chemoprophylaxis</u> • Bismuth subsalicylate–containing formulations and antibiotics have been proven effective in preventing traveler's diarrhea. • Probiotics, such as lactobacillus, have not demonstrated sufficient efficacy to be recommended. • Widespread drug resistance renders doxycycline and sulfamethoxazole-trimethoprim no longer useful for prevention of traveler's diarrhea. • Chemoprophylaxis can contribute to development of resistant enteric bacteria and potentially predispose the traveler to infection with other deleterious pathogens, such as *Clostridium difficile.* • The routine use of antibiotic prophylaxis for travelers' diarrhea is not generally recommended. • Chemoprophylaxis may be considered in healthy travelers for whom staying well is critical and in special-needs travelers in whom the risk for diarrhea is increased or the consequences of a diarrheal episode may be severe. • When considering chemoprophylaxis, fluoroquinolone antibiotics remain the first choice. • Chemoprophylaxis should be recommended for no more than two to three weeks. <u>Treatment</u> • Fluid replacement and a diet restricted to liquids and bland foods may be appropriate, though they may not provide additional benefits beyond antibiotic treatment. • Symptomatic therapy with bismuth subsalicylate may be recommended in mild cases of diarrhea, but better agents exist for moderate-to-severe disease.

Clinical Guideline	Recommendation(s)
	• Loperamide has become the antimotility agent of choice. It is more efficacious in controlling diarrhea than bismuth subsalicylate and has an onset of action within the first four hours after ingestion. When it is used in combination with an antibiotic, there may be rapid improvement of traveler's diarrhea. • Antibiotics are effective in the treatment of traveler's diarrhea and can reduce the average duration of disease from several days to ~1 day. • Antibiotics that are recommended include fluoroquinolones (norfloxacin, ciprofloxacin, ofloxacin, levofloxacin), azithromycin, and rifaximin. • Fluoroquinolones remain predictably active for empiric therapy in most parts of the world and remain the drugs of first choice. • Antibiotics that are no longer recommended because of drug resistance worldwide are the sulfonamides, neomycin, ampicillin, doxycycline, tetracycline, trimethoprim alone, and sulfamethoxazole-trimethoprim.

Infectious Diseases Society of America: **Practice Guidelines for the Management of Infectious Diarrhea (2001)**[11]	<u>Recommendations for therapy against specific pathogens</u>
	o *Shigella* species:
	  o Sulfamethoxazole-trimethoprim.
	  o Fluoroquinolone.
	  o Nalidixic acid.
	  o Ceftriaxone.
	  o Azithromycin.
	• *Salmonella,* non-typhi species:
	  o Treatment is not routinely recommended; however, consider therapy in patients <6 months old or >50 years old, or patients that have a prosthesis, valvular heart disease, severe atherosclerosis, malignancy, or uremia.
	  o Sulfamethoxazole-trimethoprim.
	  o Fluoroquinolone.
	• *Campylobacter* species:
	  o Erythromycin.
	• *Entamoeba histolytica*
	  o Metronidazole 750 mg three times daily for five to 10 days plus either diiodohydroxyquin 650 mg three times daily for 20 days or paromomycin 500 mg three times daily for seven days.
	• *Escherichia coli* species:
	  o Sulfamethoxazole-trimethoprim.
	  o Fluoroquinolone.
	• *Aeromonas* or *Plesiomonas* species:
	  o Sulfamethoxazole-trimethoprim.
	  o Fluoroquinolone
	• *Yersinia* species:
	  o Antibiotic therapy is not usually required. For severe infections or associated bacteremia, combination therapy with doxycycline, aminoglycosides sulfamethoxazole-trimethoprim or a fluoroquinolone is recommended.
	• *Vibrio cholerae:*
	  o Doxycycline or tetracycline.
	  o Fluoroquinolone.
	• Toxigenic *Clostridium difficile:*
	  o Metronidazole.
	• *Isospora* species:
	  o Sulfamethoxazole-trimethoprim.
	• *Cyclospora* species:
	  o Sulfamethoxazole-trimethoprim.

American College of Gastroenterology:	<u>Bowel cleansing</u> • Bowel cleansing is a standard therapeutic measure in hepatic encephalopathy.

Clinical Guideline	Recommendation(s)
Practice Guidelines: Hepatic Encephalopathy (2001)[12]	• Colonic cleansing reduces the luminal content of ammonia, decreases colonic bacterial counts, and lowers blood ammonia in cirrhotic patients. • Various laxatives may be used, but nonabsorbable disaccharides are preferred. • Alternatively, bowel cleansing can also be achieved after irrigation of the gut with isotonic solution of mannitol. <u>Nonabsorbable disaccharides</u> • Lactulose is a first-line treatment of hepatic encephalopathy. • For acute encephalopathy, lactulose 45 mL is followed by dosing every hour until evacuation occurs. Then dosing is adjusted to achieve two to three soft bowel movements per day (15 to 45 mL every eight to 12 hours). <u>Antibiotics</u> • Antibiotics are a therapeutic alternative to nonabsorbable disaccharides for the treatment of acute and chronic encephalopathy and cirrhosis. • For acute encephalopathy, neomycin (3 to 6 grams/day) should be given for one to two weeks. • For chronic encephalopathy, neomycin (1 to 2 grams/day) should be given. Neomycin can be combined with oral lactulose in problematic cases. • Metronidazole should be started at a dose of 250 mg twice daily.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the amebicides are noted in Table 4. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 4. FDA-Approved Indications for the Amebicides[5-7]

Indication	Paromomycin
Management of hepatic coma as adjunctive therapy	✔
Treatment of acute and chronic intestinal amebiasis	✔

IV. Pharmacokinetics

The pharmacokinetic parameters of the amebicides are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Amebicides[5-7]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (Hours)
Paromomycin	Minimal	Not reported	Not reported	Feces (~100)	Not reported

V. Drug Interactions

Significant drug interactions with the amebicides are listed in Table 6.

Table 6. Significant Drug Interactions with the Amebicides[5]

Generic Name(s)	Significance Level	Interaction	Mechanism
Paromomycin	2	Digoxin	Pharmacologic effects of digoxin may be increased or decreased by paromomycin due to altered bioavailability.

Generic Name(s)	Significance Level	Interaction	Mechanism
Paromomycin	2	Succinylcholine	The neuromuscular blocking effects of succinylcholine may be increased by paromomycin. Prolonged respiratory depression with extended periods of apnea may occur.

Significance level 1=major severity; significance level 2=moderate severity

VI. Adverse Drug Events

The most common adverse drug events reported with the amebicides are listed in Table 7.

Table 7. Adverse Drug Events (%) Reported with the Amebicides[5-7]

Adverse Events	Paromomycin
Central Nervous System	
Headache	<1
Ototoxicity	<1
Vertigo	<1
Dermatological	
Exanthema	<1
Pruritus	<1
Rash	<1
Gastrointestinal	
Abdominal cramps	1 to 10
Diarrhea	1 to 10
Heartburn	1 to 10
Nausea	1 to 10
Secondary enterocolitis	<1
Steatorrhea	<1
Vomiting	1 to 10
Other	
Eosinophilia	<1

VII. Dosing and Administration

The usual dosing regimens for the amebicides are listed in Table 8.

Table 8. Usual Dosing Regimens for the Amebicides[5-7]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Paromomycin	Management of hepatic coma as adjunctive therapy: Capsule: 4 grams daily in divided doses for five to six days Treatment of acute and chronic intestinal amebiasis: Capsule: 25 to 35 mg/kg/day administered in three divided doses for five to 10 days	Treatment of acute and chronic intestinal amebiasis: Capsule: 25 to 35 mg/kg/day administered in three divided doses for five to 10 days	Capsule: 250 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the amebicides are summarized in Table 9.

Table 9. Comparative Clinical Trials with the Amebicides

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Intestinal Amebiasis Infections				
Sullam et al.[13] (1986) Paromomycin 25 to 35 mg/kg per day divided into three times a day doses for 7 days	OL Homosexual men, mean age 30 years, with *Entamoeba histolytica* cysts or trophozoites in stool specimens	N=114 6 weeks	Primary: Improvement or resolution of symptoms, bacteriologic cure rate, adverse effects Secondary: Not reported	Primary: One week post-therapy, 70% of patients on paromomycin therapy reported either an improvement or resolution of symptoms. Four-to-six weeks post-treatment, 80% of patients initially symptomatic were free of symptoms. Four-to-six weeks post-treatment, the cure rate assessed by microbiologic response was 92%, with only seven treatment failures observed in the study. There was no statistically significant difference in cure rate between patients who were symptomatic and nonsymptomatic at the onset of treatment (P>0.5). Patients infected with *Entamoeba histolytica* cysts had a cure rate of 93% compared to a 91% cure rate in patients with a trophozoites infection. The incidence of treatment-related side effects was low and none of the patients discontinued therapy due to adverse events. Gastrointestinal complaints were reported by 69% of patients who were initially asymptomatic, but only one patient had five or more stools per day. Secondary: Not reported
Villamil et al.[14] (1964) Paromomycin 250 mg four times a	OL Adults 16 to 71 years of age with gastrointestinal	N=35 Mean 6 months	Primary: Bacteriologic cure rate, reinfection rate, clinical response	Primary: After therapy with paromomycin, 97% of patients had negative stool samples for *Entamoeba histolytica.* There were no amebas in the stools of 14 patients at three-month

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
day after meals for 12 days	symptoms and stools positive for *Entamoeba histolytica*		(symptomatic relief), adverse effects Secondary: Not reported	follow-up and after six months of observation, the stools of 20 patients were negative for *Entamoeba histolytica*. None of the patients became reinfected during the study period. Clinical response was rated as "good" by 60.0%, "mild" by 25.5%, and "poor" by 14.5% of patients treated with paromomycin. There were no significant adverse effects reported in the study. Secondary: Not reported
Simon et al.[15] (1967) Paromomycin 500 mg and paromomycin 250 mg for 5 days (Group A) vs paromomycin 500 mg and paromomycin 250 mg for 4 days (Group B) vs paromomycin 500 mg and paromomycin 250 mg for 3 days (Group C)	DB, RCT Patients infected with *Entamoeba histolytica*, *Dientamoeba fragilis* or both	N=100 Mean 66 days	Primary: Bacteriological failure rate, adverse effects Secondary: Not reported	Primary: While there were no bacteriological failures in treating *Entamoeba histolytica* infections in the paromomycin groups, the failure rate in the tetracycline group was 100%. While there were no bacteriological failures in treating *Dientamoeba fragilis* infections in groups A and B, the failure rates in the groups C, D, and the tetracycline group were 40, 36, and 87%, respectively. Diarrhea was the most common adverse effect, reported by 15% of patients.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs paromomycin 500 mg and paromomycin 250 mg for 2 days (Group D) vs paromomycin 500 mg and paromomycin 250 mg for 1 day (Group E) vs tetracycline 250 mg for 10 days (Group F)				
Abubakar et al.[16] (2007) Nitazoxanide or paromomycin	MA Immuno-compromised individuals with cryptosporidiosis	N=169 Variable duration	Primary: Durations of diarrhea, mortality, parasitological clearance Secondary: Adverse events	Primary *Nitazoxanide (Two studies)* Two studies showed no evidence that nitazoxanide is more effective in reducing the frequency of diarrhea than placebo (RR, 0.83; 95% CI, 0.36 to 1.94). One study reported data on deaths which showed a RR of 0.61 (95% CI, 0.22 to 1.63) among all 96 children based on five and eight deaths in the intervention and control arms, respectively. Treatment with nitazoxanide led to a significant parasitological response compared to placebo among all children with a RR of 0.52 (95% CI, 0.30 to 0.91). The effect was NS for HIV-seropositive participants (RR, 0.71; 95% CI, 0.36 to 1.37). HIV-seronegative participants on nitazoxanide had a significantly higher RR of achieving parasitological clearance of 0.26 (95% CI, 0.09 to 0.80) based on a

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				single study. *Paromomycin (Two studies)* Two studies showed no evidence that paromomycin is more effective in reducing the frequency of diarrhea than placebo (RR, 0.74; 95% CI, 0.42 to 1.31). The use of paromomycin did not significantly lead to a parasitological response (RR, 0.73; 95% CI, 0.38 to 1.39). Secondary: Adverse events occurred infrequently in all studies.
Blessmann et al.[17] (2002) Paromomycin 500 mg three times a day for 10 days vs diloxanide furoate* 500 mg three times a day for 10 days	RCT Adult patients with asymptomatic intestinal *Entamoeba histolytica* infections, confirmed via a (polymerase-chain-reaction) assay	N=71 30 days	Primary: Cure rate (negative assay 10 and 20 days after the termination of therapy) Secondary: Not reported	Primary: Eradication at 20 days was observed in 85% of patients on paromomycin compared to 51% in the diloxanide furoate group (P=0.003). Secondary: Not reported
Pamba et al.[18] (1990) Aminosidine (paromomycin)† 500 mg twice a day for adults and 15 mg/kg twice a day for children for 5 days vs	RCT Patients between the ages of 6 and 80 with *Entamoeba histolytica* intestinal infection, diagnosed via three microscopic stool examinations	N=417 60 days	Primary: Clinical cure (disappearance of all symptoms present at study onset), parasitological cure (disappearance of all parasitic forms, both invasive and noninvasive forms,	Primary: Eradication of invasive *Entamoeba histolytica* forms was successful in all the treatment groups. At the end of treatment, the incidences of invasive and noninvasive amebic forms identified in stool samples were 0.7 and 7.7%, respectively, compared to baseline. The incidence of parasitological failure with monotherapy was 2.0, 9.9, and 8.0% in patients treated with aminosidine, etophamide, and nimorazole, respectively, and 6.1% the nimorazole-etophamide arm. No cases of parasitological failure occurred in the nimorazole-aminosidine and etophamide-aminosidine combination groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
etophamide‡ 600 mg twice daily for adults and 15 mg/kg twice daily for children for 5 days vs nimorazole§ 1 g twice daily for adults and 20 mg/kg twice daily for children for 5 days vs aminosidine 500 mg twice daily for adults and 15 mg/kg twice daily for children in addition to nimorazole 1 g twice daily for adults and 20 mg/kg twice daily for children for 5 days vs nimorazole 1 g twice daily for adults and 20			from stools or ulcer scrapings), anatomical cure (healing of previous ulceration), tolerance Secondary: Not reported	There were no recurrences of infection in the etophamide-aminosidine combination group, 3.0% in the nimorazole-aminosidine group, 6.0% in the aminosidine, 6.8% in the etophamide, 14.6% in the nimorazole, and 17.3% in the nimorazole-etophamide group. Ulcer cure was achieved in 97.8% in the nimorazole-aminosidine group, 95.5% in the nimorazole, 88.5% in the aminosidine, 87.8% in the nimorazole-etophamide, 87.5% in the etophamide, and 77% in the etophamide-aminosidine group. Clinical cure was achieved in 98 to 100% of patients in all the six treatment groups. All the regimens were well tolerated except the etophamide-aminosidine combination, which was associated with a high incidence of severe diarrhea (76.5%). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/kg twice daily for children in addition to etophamide 600 mg twice daily for adults and 15 mg/kg twice daily for children for 5 days vs etophamide 600 mg BID for adults and 15 mg/kg twice daily for children in addition to aminosidine 500 mg twice daily for adults and 15 mg/kg twice daily for children for 5 days				

*Diloxanide furoate not commercially available in the United States.
†Aminosidine is synonymous with paromomycin.
‡Etophamide (etofamide) is a luminal amebicide, similar to diloxanide furoate, not commercially available in the United States.
§Nimorazole is a 5-nitroimidazole derivative, similar to metronidazole, not commercially available in the United States.
Abbreviations: CI=confidence interval, DB=double-blind, HIV=human immunodeficiency virus, MA=meta-analysis, NS=not significant, RR=relative risk, OL=open-label, RCT=randomized controlled trial

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 10. Relative Cost of the Amebicides

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Paromomycin	capsule	N/A	N/A	$$$$

N/A=Not available.

X. Conclusions

Paromomycin is approved for the treatment of amebiasis, as well as for the adjunctive treatment of hepatic coma.[5-7] It is available in a generic formulation. Guidelines recommend paromomycin in combination with another antiprotozoal agent for the treatment of amebiasis to clear intestinal cysts.[9-11] Clinical trials have demonstrated that paromomycin is effective for the treatment of amebiasis.[13-18] For the treatment of hepatic encephalopathy, guidelines recommend lactulose as initial therapy.[12] Antibiotics are considered an alternative treatment option for acute and chronic encephalopathy.

Paromomycin is generally well tolerated and adverse events are usually limited to the gastrointestinal tract. The most common side effects observed in clinical trials were nausea, vomiting, diarrhea, abdominal cramping, and heartburn. Rare cases of eosinophilia and rash have been reported.

Therefore, all brand amebicides within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand amebicide is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Antimalarials
AHFS Class 083008
November 12, 2014

I. Overview

The antimalarials are approved for the prevention and treatment of malaria.[1-9] This is a common disease worldwide and is caused by protozoan parasites of the genus *Plasmodium*, including *Plasmodium falciparum*, *Plasmodium knowlesi, Plasmodium malariae*, *Plasmodium ovale,* and *Plasmodium vivax*. Transmission occurs after being bitten by an infected female mosquito.[10-14] Once in the systemic circulation, the parasites travel to the liver and divide/mature into schizonts (exoerythrocytic stage). After six to 16 days, the schizonts rupture and release merozoites, which invade red blood cells (erythrocytic stage).[10-14] Symptoms occur following the erythrocytic stage and include fever, chills, headache, nausea and other influenza-like symptoms. Some merozoites may differentiate into gametocytes, which can be ingested by mosquitos followed by reinfection of humans. While malaria can be treated early in the course of the disease, delays in the initiation of therapy can have serious or even fatal consequences. *Plasmodium falciparum* infections can cause rapidly progressive severe disease or death, while the non-falciparum (*Plasmodium vivax, Plasmodium ovale,* or *Plasmodium malariae)* species rarely cause severe complications.[15] In the United States, most cases of malaria occur among individuals who traveled to endemic regions without receiving appropriate prophylactic therapy.[10-11] The incidence of malaria has increased in recent years and drug resistance is an emerging problem.[10-14]

The antimalarials include the quinoline derivatives (chloroquine, hydroxychloroquine, quinine, mefloquine, and primaquine), antifolates (atovaquone-proguanil and pyrimethamine) and artemisinin derivatives (artemether-lumefantrine).[13] The quinoline derivatives inhibit heme polymerase activity, resulting in accumulation of free heme which is toxic to the parasites.[14] The antifolates interfere with enzymes involved in folate synthesis, which is required for parasite deoxyribonucleic acid synthesis. Artemisinin derivatives bind to iron and form free radicals that are toxic to parasite proteins.[13] The majority of the antimalarials target the erythrocytic stage of malaria infection; however, some treatments also target the exoerythrocytic stage and gametocytes.

The antimalarials that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Atovaquone-proguanil, chloroquine, hydroxychloroquine, mefloquine, primaquine, and quinine are available in a generic formulation. This class was last reviewed in May 2012.

Table 1. Antimalarials Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Chloroquine	tablet	N/A	chloroquine
Hydroxychloroquine	tablet	Plaquenil®*	hydroxychloroquine
Mefloquine	tablet	N/A	mefloquine
Primaquine	tablet	N/A	primaquine
Pyrimethamine	tablet	Daraprim®	Daraprim®
Quinine	capsule	Qualaquin®*	quinine
Combination Products			
Artemether and lumefantrine	tablet	Coartem®	none
Atovaquone and proguanil	tablet	Malarone®*	atovaquone and proguanil

*Generic is available in at least one dosage form or strength.
N/A=Not available, PDL=Preferred Drug List

The antimalarials have been shown to be active against the strains of organisms indicated in Tables 2 and 3. This activity has been demonstrated in clinical infections and is represented by the Food and Drug Administration (FDA)-approved indications for the antimalarials that are noted in Tables 6 and 7. These agents may also have been found to show activity to other organisms in vitro; however, the clinical significance of this is unknown since their safety and efficacy in treating clinical infections due to these organisms have not been established in adequate and well-controlled trials. Although empiric antimalarial therapy may be initiated before diagnostic test results are known, once results become available, appropriate therapy should be selected.

Table 2. Microorganisms Susceptible to the Single Entity Antimalarials[1-9]

Organism	Chloroquine	Hydroxychloroquine	Mefloquine	Primaquine	Pyrimethamine	Quinine
Protozoa						
Plasmodium falciparum	✔	✔	✔	✔	✔	✔
Plasmodium malariae	✔	✔			✔	
Plasmodium ovale	✔	✔			✔	
Plasmodium vivax	✔	✔	✔	✔	✔	
Toxoplasma gondii					✔	

Table 3. Microorganisms Susceptible to the Combination Antimalarials[1-9]

Organism	Artemether and Lumefantrine	Atovaquone and Proguanil
Protozoa		
Plasmodium falciparum	✔	✔
Plasmodium malariae		✔
Plasmodium ovale		✔
Plasmodium vivax		✔

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the antimalarials are summarized in Tables 4 and 5.

Table 4. Treatment Guidelines Using the Antimalarials

Clinical Guideline	Recommendation(s)
Centers for Disease Control and Prevention: **Treatment of Malaria (2013)**[15-16]	Treatment – general approach • Treatment for malaria should not be initiated until the diagnosis has been confirmed by laboratory investigations. "Presumptive treatment" without the benefit of laboratory confirmation should be reserved for extreme circumstances (strong clinical suspicion, severe disease, impossibility of obtaining prompt laboratory diagnosis). • Once the diagnosis of malaria has been confirmed, appropriate antimalarial treatment must be initiated immediately. Treatment should be guided by three main factors: the infecting *Plasmodium* species, the clinical status of the patient, and the drug susceptibility of the infecting parasites as determined by the geographic area where the infection was acquired and the previous use of antimalarial medicines. Treatment – uncomplicated malaria • Refer to Table 5 for the 2013 recommendations for the treatment of uncomplicated malaria. Treatment – severe malaria • Patients who are considered to have manifestations of more severe disease should be treated aggressively with parenteral antimalarial therapy regardless of the species of malaria seen on the blood smear. • Oral antimalarial drugs (such as oral quinine, chloroquine, or mefloquine) are not recommended for the initial treatment of severe malaria. If severe malaria is strongly suspected but a laboratory diagnosis cannot be made at that time, blood should be collected for diagnostic testing as soon as it is available and parenteral antimalarial drugs may be started. • In 2013 Centers for Disease Control and Prevention conducted an analysis of cases of severe malaria treated with exchange transfusion and was unable to demonstrate a survival benefit of the procedure and therefore no longer recommends the use of exchange transfusion as an adjunct procedure for the treatment of severe malaria. • Refer to Table 5 for the 2013 recommendations for the treatment of severe malaria.
Centers for Disease Control and Prevention: **Health Information for International Travel (2014)**[17]	Travel to areas with limited malaria transmission • For destinations where malaria cases occur sporadically and risk for infection to travelers is assessed as being low, Centers for Disease Control recommends that travelers use mosquito avoidance measures only, and no chemoprophylaxis should be prescribed. Travel to areas with mainly *Plasmodium vivax* malaria • For destinations where the main species of malaria present is *Plasmodium vivax*, in addition to mosquito avoidance measures, primaquine is a good choice for primary prophylaxis for travelers who are not glucose-6-phosphate dehydrogenase deficient. • For persons unable to take primaquine, other drugs can be used as described below, depending on the presence of antimalarial drug resistance. Travel to areas with chloroquine-sensitive malaria

Clinical Guideline	Recommendation(s)
	• For destinations where chloroquine-sensitive malaria is present, in addition to mosquito avoidance measures, the many effective chemoprophylaxis options include chloroquine, atovaquone-proguanil, doxycycline, mefloquine, and in some instances, primaquine for travelers who are not glucose-6-phosphate dehydrogenase deficient. • Longer-term travelers may prefer weekly chloroquine, while shorter-term travelers may prefer the shorter course of atovaquone-proguanil or primaquine. Travel to areas with chloroquine-resistant malaria • For destinations where chloroquine-resistant malaria is present, in addition to mosquito avoidance measures, chemoprophylaxis options are atovaquone-proguanil, doxycycline, and mefloquine. Travel to areas with mefloquine-resistant malaria • For destinations where mefloquine-resistant malaria is present, in addition to mosquito avoidance measures, chemoprophylaxis options are either atovaquone-proguanil or doxycycline. Chemoprophylaxis for infants, children, and adolescents • Infants of any age or weight or children and adolescents of any age can contract malaria. Therefore, all children traveling to malaria-risk areas should take an antimalarial drug. • Chloroquine and mefloquine are options for use in infants and children of all ages and weights, depending on the presence of drug resistance at their destination. • Primaquine can be used for children who are not glucose-6-phosphate dehydrogenase deficient traveling to areas with principally *Plasmodium vivax*. • Doxycycline may be used for children who are at least eight years of age. • Atovaquone-proguanil may be used for prophylaxis for infants and children weighing at least 5 kg (11 lbs). Chemoprophylaxis during pregnancy and breastfeeding • Malaria infection in pregnant women can be more severe than in nonpregnant women. Malaria can increase the risk for adverse pregnancy outcomes, including prematurity, abortion, and stillbirth. For these reasons, and because no chemoprophylactic regimen is completely effective, women who are pregnant or likely to become pregnant should be advised to avoid travel to areas with malaria transmission if possible. If travel to a malarious area cannot be deferred, use of an effective chemoprophylaxis regimen is essential. • Pregnant women traveling to areas where chloroquine-resistant *Plasmodium falciparum* has not been reported may take chloroquine prophylaxis. Chloroquine has not been found to have any harmful effects on the fetus when used in the recommended doses for malaria prophylaxis; therefore, pregnancy is not a contraindication for malaria prophylaxis with chloroquine phosphate or hydroxychloroquine sulfate. • For travel to areas where chloroquine resistance is present, mefloquine is currently the only medication recommended for malaria chemoprophylaxis during pregnancy. • Because of insufficient data regarding the use during pregnancy, atovaquone-proguanil is not recommended to prevent malaria in

Clinical Guideline	Recommendation(s)
	pregnant women. • Doxycycline is contraindicated for malaria prophylaxis during pregnancy because of the risk for adverse effects seen with tetracycline, a related drug, on the fetus, which include discoloration and dysplasia of the teeth and inhibition of bone growth. • Primaquine should not be used during pregnancy because the drug may be passed transplacentally to a glucose-6-phosphate dehydrogenase deficient fetus and cause hemolytic anemia in utero. Changing medications during chemoprophylaxis as a result of adverse effects • Medications recommended for prophylaxis against malaria have different modes of action that affect the parasites at different stages of the life cycle. Thus, if the medication needs to be changed because of side effects before a full course has been completed, there are some special considerations.
Infectious Diseases Society of America: **The Practice of Travel Medicine (2006)**[18] **(Guideline listed as "retired" per Infectious Diseases Society of America website)**	Prevention of malaria in travelers • Malaria is the most common preventable infectious cause of death among travelers and is the most frequent cause of fever in the returned traveler. • Most travelers who develop malaria do so because they use ineffective or no chemoprophylaxis or are not adherent to an appropriate chemoprophylactic drug regimen. • When considering antimalarial drugs, their potential adverse effects must be weighed against the risk of acquiring malaria and the traveler's access to prompt, reliable medical care. • Therapy with antimalarial drugs should be started prior to travel, and the drugs should be taken regularly during exposure and for a period of time after leaving an area in which malaria is endemic. • Travelers to the following areas should generally take an antimalarial drug: urban and rural risk areas of sub-Saharan Africa (except most of South Africa) and Oceania (including Papua [Indonesian New Guinea], Papua New Guinea, and Vanuatu), India, Bangladesh (except Dhaka), Pakistan, Nepal (Terai region), and Haiti; travelers with evening or overnight exposure in rural, non-resort areas of Southeast Asia, Central and South America, and certain parts of Mexico, North Africa, and the Dominican Republic should also take an antimalarial drug. • Chloroquine-resistant *Plasmodium falciparum* malaria is now widespread in all areas of the world in which malaria is endemic. • All travelers should be well informed about the disease and become advocates for their own care. They should understand that no antimalarial drug guarantees complete protection and that fever during or after travel (particularly in the first two months after travel, but as long as six months to one year after return) is a medical emergency requiring urgent assessment by a health care practitioner. Chemoprophylactic regimens: standard antimalarial drugs • Chloroquine is the drug of choice for travel to areas in which chloroquine resistance has not been described or is minimal. • For travel to areas with chloroquine-resistant *Plasmodium falciparum*, atovaquone-proguanil, mefloquine, and doxycycline are effective standard prophylactic treatments. Chemoprophylactic regimens: alternative antimalarial drugs • Primaquine has been used for decades to prevent relapses from the

Clinical Guideline	Recommendation(s)
	hypnozoite form of *Plasmodium vivax* and *Plasmodium ovale,* either during treatment of clinical cases (radical cure) or as presumptive anti-relapse therapy (terminal prophylaxis) following heavy exposure to these parasites. • Recent studies have demonstrated primaquine to be a very effective and safe chemoprophylactic agent.
National Institutes of Health, the Centers for Disease Control and Prevention, and the Human Immunodeficiency Virus Medicine Association of the Infectious Diseases Society of America: **Guidelines for Prevention and Treatment of Opportunistic Infections in Human Immunodeficiency Virus - Infected Adults and Adolescents (2013)[19]**	Aspergillosis • Voriconazole is the drug of choice but should be used cautiously with human immunodeficiency virus protease inhibitors and efavirenz. Amphotericin B deoxycholate at 1 mg/kg daily or lipid-formulation amphotericin B at 5 mg/kg daily are alternatives, as is caspofungin at 50 mg daily and posaconazole. • Other echinocandins, such as micafungin and anidulafungin, are reasonable alternatives. • For treatment failure (if voriconazole was used initially) substitution with amphotericin B, posaconazole, or echinocandins might be considered; the amphotericin B or echinocandins would be rational for those who began therapy with voriconazole or posaconazole. Candidiasis (mucocutaneous) • Oral fluconazole is as effective as topical therapy for oropharyngeal candidiasis and is considered the drug of choice. Initial episodes of oropharyngeal candidiasis can be adequately treated with topical therapy, including clotrimazole troches, nystatin suspension or pastilles, or miconazole mucoadhesive tablets. Itraconazole oral solution for seven to 14 days is as effective as oral fluconazole but less well tolerated. Posaconazole oral solution is also as effective as fluconazole and is generally better tolerated than itraconazole. Intravenous amphotericin B is usually effective and can be used among patients with refractory disease. Both conventional amphotericin B and lipid complex and liposomal amphotericin B have been used. • Systemic antifungals are required for effective treatment of esophageal candidiasis. A 14 to 21-day course of either fluconazole (oral or intravenous) or oral itraconazole solution is highly effective. Oral ketoconazole or itraconazole capsules are less effective than fluconazole because of variable absorption. Although intravenous caspofungin or intravenous voriconazole are effective in treating esophageal candidiasis among human immunodeficiency virus - infected patients, oral or intravenous fluconazole remain the preferred therapies. Azole-refractory esophageal candidiasis can be treated with posaconazole, amphotericin B, anidulafungin, caspofungin, micafungin, or voriconazole. • Vulvovaginal candidiasis in human immunodeficiency virus -infected women is usually uncomplicated (90%) and responds readily to short-course oral or topical treatment with any of several therapies, including oral fluconazole, topical azoles, and itraconazole oral solution. Severe or recurrent episodes of vaginitis require oral fluconazole or topical antifungal therapy for ≥7 days. Coccidioidomycosis • For patients with clinically mild infection, such as focal pneumonia or a positive coccidioidal serologic test alone, initial therapy with a triazole antifungal is appropriate. • For patients with either diffuse pulmonary involvement or severely ill patients with extrathoracic disseminated disease, amphotericin B is the preferred initial therapy. Therapy with amphotericin B should continue

Clinical Guideline	Recommendation(s)
	until clinical improvement is observed. Some specialists would use a triazole antifungal concurrently with amphotericin B and continue the triazole once amphotericin B is stopped. Cryptococcosis • The recommended initial standard treatment is amphotericin B combined with flucytosine for ≥2 weeks for those with normal renal function. • The combination of amphotericin B with fluconazole is less effective than amphotericin B combined with flucytosine in terms of clearing *Cryptococcus* from the cerebrospinal fluid but is better than amphotericin B alone. • Fluconazole combined with flucytosine is an alternative to amphotericin B plus flucytosine, but is less effective than amphotericin B and is recommended only for persons unable to tolerate or unresponsive to standard treatment. • After at least a two-week period of successful induction therapy, amphotericin B and flucytosine may be discontinued and follow-up therapy initiated with fluconazole. This should continue for eight weeks. Itraconazole is an acceptable though less effective alternative. • The optimal therapy for those with treatment failure is not established. For those initially treated with fluconazole, therapy should be changed to amphotericin B, with or without flucytosine, and continued until a clinical response occurs. Liposomal amphotericin B may have improved efficacy over the deoxycholate formulation and should be considered in treatment failures. Higher doses of fluconazole in combination with flucytosine might also be useful. Cryptosporidiosis • In the setting of severe immunosuppression, antiretroviral therapy with immune restoration to a CD4+ count >100 cells/µL leads to resolution of clinical cryptosporidiosis and is the mainstay of treatment. • All patients with cryptosporidiosis should be offered antiretroviral therapy as part of the initial management of their infection. • Management should include symptomatic treatment of diarrhea. Rehydration and repletion of electrolyte losses by either the oral or intravenous route are important. Severe diarrhea can exceed >10 L/day among patients with acquired immunodeficiency syndrome, often requiring intensive support. Aggressive efforts at oral rehydration should be made with oral rehydration solutions. Prevention of Cytomegalovirus • Cytomegalovirus end-organ disease is best prevented by using antiretroviral therapy to maintain the CD4+ count >100 cells/µL. • Although oral valganciclovir would likely prevent the occurrence of cytomegalovirus retinitis in patients with CD4+ counts <50 cells/µL, such therapy is not generally recommended because of the potential to induce cytomegalovirus resistance, the utility of treating disease when it occurs, and the lack of demonstrated survival advantage. Treatment of Cytomegalovirus disease • Oral valganciclovir, intravenous ganciclovir, intravenous ganciclovir followed by oral valganciclovir, intravenous foscarnet, and intravenous cidofovir are all effective treatments for cytomegalovirus retinitis. • The ganciclovir implant, a surgically-implanted reservoir of

Clinical Guideline	Recommendation(s)
	ganciclovir, which lasts approximately six months, also is very effective but it no longer is being manufactured. In its absence, some clinicians will use intravitreal injections of ganciclovir or foscarnet in conjunction with oral valganciclovir, at least initially, to provide immediate high intraocular levels of drug and presumably faster control of the retinitis. • Systemic therapy has been shown to reduce morbidity in the contralateral eye. This should be considered when choosing between the oral, intravenous, and local options. • The choice of initial therapy for cytomegalovirus retinitis should be individualized based on the location and severity of the lesion(s), the level of underlying immune suppression, and other factors such as concomitant medications and ability to adhere to treatment. • No one regimen has been proven in a clinical trial to have greater efficacy in terms of protecting vision, and thus clinical judgment must be used when choosing a regimen. • In studies conducted in the pre-antiretroviral therapy era, ganciclovir intraocular implant plus oral ganciclovir was superior to once-daily intravenous ganciclovir for treatment of cytomegalovirus retinitis; however, the implant is no longer manufactured. Assuming that this observation can be extended to other combinations of systemically and locally administered drugs, human immunodeficiency virus-specialists often recommend intravitreal ganciclovir or foscarnet injections plus oral valganciclovir as the preferred initial therapy for patients with immediate sight-threatening lesions. Intravitreal injections deliver high concentrations of the drug to the target organ immediately while steady-state concentrations in the eye are achieved with systemically delivered medications. For patients with small peripheral lesions, oral valganciclovir alone often is adequate. • After induction therapy, secondary prophylaxis (i.e., chronic maintenance therapy) should be continued until immune reconstitution occurs as a result of antiretroviral therapy. Regimens demonstrated to be effective for chronic suppression in randomized, controlled clinical trials include parenteral ganciclovir, oral valganciclovir, parenteral foscarnet, combined parenteral ganciclovir and foscarnet, and parenteral cidofovir. <u>Management of Cytomegalovirus retinitis treatment failures</u> • When patients relapse while receiving maintenance therapy, induction with the same drug followed by reinstitution of maintenance therapy can control the retinitis, although for progressively shorter periods of time with each relapse. • Ganciclovir and foscarnet in combination appear to be superior in efficacy to either agent alone and should be considered for patients whose disease does not respond to single-drug therapy, and for patients with multiple relapses of retinitis. This drug combination, however, is associated with substantial toxicity. <u>Treatment of Hepatitis B Virus coinfection in patients not receiving antiretroviral therapy</u> • For patients with CD4+ counts >350 cells/µL who are not receiving antiretroviral therapy but meet criteria for hepatitis B virus treatment, adefovir or peginterferon alfa-2a monotherapy for 48 weeks might be considered, with close monitoring of hepatitis B virus deoxyribonucleic acid levels and follow-up to evaluate for hepatitis B e antigen seroconversion. However, early initiation of antiretroviral

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	therapy should also be considered for human immunodeficiency virus/hepatitis B virus -coinfected persons with CD4+ counts >350 cells/µL.
	
	Treatment of Hepatitis B Virus coinfection in patients who require antiretroviral therapy
	• For human immunodeficiency virus-infected persons, some experts recommend combination therapy with two agents active against hepatitis B virus to reduce the risk of hepatitis B virus drug resistance; although, there are no results from controlled trials as yet to support this strategy.
	• Among patients infected with hepatitis B virus, hepatitis C virus, and human immunodeficiency virus, consideration of the need for antiretroviral therapy should be the first priority. If antiretroviral therapy is not required, interferon-based therapy, which suppresses both hepatitis C virus and hepatitis B virus, should be considered. If interferon-based therapy for hepatitis C virus has failed, treatment of chronic hepatitis B with nucleoside or nucleotide analogs is recommended.
	
	Treatment of Hepatitis C coinfection
	• Antiviral treatment for hepatitis C virus infection should be considered for all human immunodeficiency virus-infected persons with acute or chronic hepatitis C virus infection.
	• The combination of peginterferon alfa (PegIFN) plus ribavirin is the recommended backbone of therapy for HIV/HCV-co-infected patients regardless of HCV genotype.
	• Antiviral treatment with PegIFN is not recommended in patients with decompensated liver disease.
	• For HCV-genotype-1-infected patients who are not co-infected with HIV, a HCV NS3/4A protease inhibitor (PI), either boceprevir or telaprevir, in combination with PegIFN/ribavirin is recommended on the basis of large clinical trials demonstrating significantly higher SVR rates with an acceptable safety/tolerability profile compared to PegIFN/ribavirin alone.
	• For HIV/HCV co-infected patients, preliminary data from small, ongoing clinical trials of boceprevir or telaprevir plus PegIFN/ribavirin for the treatment of HCV genotype 1 infection in HIV/HCV co-infected patients demonstrate greater efficacy than PegIFN/ribavirin alone, with a safety and tolerability profile similar to that observed in HCV monoinfected patients treated with boceprevir or telaprevir plus PegIFN/ribavirin. Preliminary recommendations are as follows:
	  o PegIFN is recommended for use for all HCV genotypes
	  o Ribavirin is recommended for use with PegIFN for all HCV genotypes.
	  o Boceprevir is approved for use in combination with PegIFN/ribavirin in HCV-genotype-1-monoinfected-patients. For HIV/HCV-co-infected patients, the regimen being evaluated is PegIFN/ribavirin administered for four weeks (lead-in phase) followed by boceprevir 800 mg orally every 7 to 9 hours (with a light snack) added to PegIFN/ribavirin for an additional 44 weeks.
	  o Telaprevir is approved for use in combination with PegIFN/ribavirin in HCV-genotype-1-monoinfected-patients. Dosing regimens lasting 48 weeks are being evaluated.
	• Patients with contraindications to the use of ribavirin can be treated

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	with peginterferon alfa (2a or 2b) monotherapy. However, substantially lower sustained viral response rates are expected in persons not receiving ribavirin. HCV PIs should not be administered without ribavirin because of the high likelihood of virologic failure. Treatment of herpes simplex virus disease • Orolabial lesions can be treated with oral valacyclovir, famciclovir, or acyclovir for five to 10 days. • Severe mucocutaneous herpes simplex virus lesions are best treated initially with intravenous acyclovir. Patients may be switched to oral therapy after the lesions have begun to regress. Therapy should be continued until the lesions have completely healed. • Genital herpes simplex virus infection should be treated with oral valacyclovir, famciclovir, or acyclovir for five to 14 days. Short-course therapy (one, two, or three days) should not be used in patients with human immunodeficiency virus infection. • Most recurrences of genital herpes can be prevented by use of daily anti- herpes simplex virus therapy, and this is recommended for persons who have frequent or severe recurrences. • Suppressive therapy with oral acyclovir, valacyclovir, or famciclovir is effective in preventing recurrences. Suppressive therapy with valacyclovir should be 500 mg twice daily in human immunodeficiency virus -infected persons or twice-daily regimens with acyclovir or famciclovir should be used. Management of herpes simplex virus treatment failure • The treatment of choice for acyclovir-resistant herpes simplex virus is intravenous foscarnet. Topical trifluridine, cidofovir, and imiquimod also have been used successfully for lesions on external surfaces, although prolonged application for 21 to 28 days or longer might be required. Histoplasmosis • Patients with moderately severe to severe disseminated histoplasmosis should be treated with an intravenous lipid formulation of amphotericin B for ≥2 weeks or until they clinically improve followed by oral itraconazole (200 mg three times daily for three days and then 200 mg twice daily for a total of ≥12 months). • In patients with less severe disseminated histoplasmosis, oral itraconazole at 200 mg three times daily for three days followed by 200 mg twice daily is appropriate initial therapy. Treatment of Isosporiasis (also known as Cystoisosporiasis) • Sulfamethoxazole-trimethoprim is the antimicrobial agent of choice for treatment of isosporiasis. It is the only agent whose use is supported by substantial published data and clinical experience. Therefore, potential alternative therapies should be reserved for patients with documented sulfa intolerance or in whom treatment fails. The traditional treatment regimen has been a 10-day course of Sulfamethoxazole-trimethoprim (800-160 mg) administered orally four times daily. • Intravenous administration of Sulfamethoxazole-trimethoprim should be considered for patients with potential or documented malabsorption. • Single-agent therapy with pyrimethamine has been used, with anecdotal success for treatment and prevention of isosporiasis.

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	Pyrimethamine (50 to 75 mg/day) plus leucovorin (10 to 25 mg/day) to prevent myelosuppression may be an effective treatment alternative; it is the option for sulfa-intolerant patients. Leishmaniasis • Due to similar efficacy and a better toxicity profile, clinicians consider liposomal amphotericin B as the drug of choice for visceral leishmaniasis in human immunodeficiency virus-coinfected patients. The optimal amphotericin B dosage has not been determined. • Regimens with efficacy include conventional amphotericin B 0.5 to 1.0 mg/kg body weight/day intravenous to achieve a total dose of 1.5 to 2.0 g, or liposomal or lipid complex preparations of two to four mg/kg body weight administered on consecutive days or in an interrupted schedule (e.g., 4 mg/kg on Days 1 to 5, 10, 17, 24, 31, and 38) to achieve a total cumulative dose of 20 to 60 mg/kg body weight. A higher daily dosage is recommended for liposomal or lipid complex preparations than for conventional amphotericin B. Preventing disseminated *Mycobacterium avium* complex disease • Human immunodeficiency virus-infected adults and adolescents should receive chemoprophylaxis against disseminated *Mycobacterium avium* complex disease if they have a CD4+ count <50 cells/µL. • Azithromycin or clarithromycin are the preferred prophylactic agents. • The combination of clarithromycin and rifabutin is no more effective than clarithromycin alone for chemoprophylaxis, is associated with a higher rate of adverse effects than either drug alone, and should not be used. • The combination of azithromycin with rifabutin is more effective than azithromycin alone; however, the additional cost, increased occurrence of adverse effects, potential for drug interactions, and absence of a survival difference compared to azithromycin alone do not warrant a routine recommendation for this regimen. • Azithromycin and clarithromycin also each confer protection against respiratory bacterial infections. • If azithromycin or clarithromycin cannot be tolerated, rifabutin is an alternative prophylactic agent for *Mycobacterium avium* complex disease, although drug interactions may make this agent difficult to use. • Primary *Mycobacterium avium* complex disease prophylaxis should be discontinued among adult and adolescent patients who have responded to antiretroviral therapy with an increase in CD4+ counts to >100 cells/µL for ≥3 months. Primary prophylaxis should be reintroduced if the CD4+ count decreases to <50 cells/µL. Treatment of disseminated *Mycobacterium avium* Complex Disease • Initial treatment of *Mycobacterium avium* complex disease should consist of two or more antimycobacterial drugs to prevent or delay the emergence of resistance. • Clarithromycin is the preferred first agent; however, azithromycin can be substituted for clarithromycin when drug interactions or clarithromycin intolerance preclude the use of clarithromycin. • Testing of *Mycobacterium avium* complex disease isolates for susceptibility to clarithromycin or azithromycin is recommended for all patients.

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	Treatment of Penicilliosis marneffei • Penicilliosis is caused by the dimorphic fungus *Penicillium marneffei*, which is known to be endemic in Southeast Asia (especially Northern Thailand and Vietnam) and southern China. • The recommended treatment is liposomal amphotericin B, three to five mg/kg body weight/day intravenously for two weeks, followed by oral itraconazole, 400 mg/day for a subsequent duration of 10 weeks, followed by secondary prophylaxis. • Patients with mild disease can be initially treated with oral itraconazole 400 mg/day for eight weeks, followed by 200 mg/day for prevention of recurrence. • The alternative drug for primary treatment in the hospital is intravenous voriconazole, 6 mg/kg every 12 hours on day one and then 4 mg/kg every 12 hours for at least three days, followed by oral voriconazole, 200 mg twice daily for a maximum of 12 weeks. • Patients with mild disease can be initially treated with oral voriconazole 400 mg twice a day on day one, and then 200 mg twice daily for 12 weeks. The optimal dose of voriconazole for secondary prophylaxis after 12 weeks has not been studied. Primary prophylaxis of *Pneumocystis (carinii) jiroveci* pneumonia • Sulfamethoxazole-trimethoprim is the recommended prophylactic agent. One double-strength tablet daily is the preferred regimen. However, one single-strength tablet daily is also effective and might be better tolerated than one double-strength tablet daily. One double-strength tablet three times weekly is also effective. Sulfamethoxazole-trimethoprim at a dose of one double-strength tablet daily confers cross-protection against toxoplasmosis and selected common respiratory bacterial infections. Lower doses of sulfamethoxazole-trimethoprim likely also confer such protection. • For patients who have an adverse reaction that is not life threatening, chemoprophylaxis with sulfamethoxazole-trimethoprim should be continued if clinically feasible; for those who have discontinued such therapy because of an adverse reaction, reinstituting sulfamethoxazole-trimethoprim should be strongly considered after the adverse event has resolved. Patients who have experienced adverse events, including fever and rash, might better tolerate reintroduction of the drug with a gradual increase in dose (i.e., desensitization), according to published regimens or reintroduction of sulfamethoxazole-trimethoprim at a reduced dose or frequency; as many as 70% of patients can tolerate such reinstitution of therapy. • If sulfamethoxazole-trimethoprim cannot be tolerated, alternative prophylactic regimens include dapsone, dapsone/pyrimethamine plus leucovorin, aerosolized pentamidine and atovaquone. • Primary *Pneumocystis (carinii) jiroveci* pneumonia prophylaxis should be discontinued for adult and adolescent patients who have responded to antiretroviral therapy with an increase in CD4+ counts to >200 cells/µL for >3 months. Prophylaxis should be reintroduced if the CD4+ count decreases to <200 cells/µL. Treatment of *Pneumocystis (carinii) jiroveci* pneumonia • Sulfamethoxazole-trimethoprim is the treatment of choice. The dose must be adjusted for abnormal renal function. Multiple randomized clinical trials indicate that sulfamethoxazole-trimethoprim is as effective as parenteral pentamidine and more effective than other

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	regimens. Adding leucovorin to prevent myelosuppression during acute treatment is not recommended because of questionable efficacy and some evidence for a higher failure rate. Oral outpatient therapy of sulfamethoxazole-trimethoprim is highly effective among patients with mild-to-moderate disease. • Patients who have *Pneumocystis (carinii) jiroveci* despite sulfamethoxazole-trimethoprim prophylaxis are usually effectively treated with standard doses of sulfamethoxazole-trimethoprim. • Patients with documented or suspected *Pneumocystis (carinii) jiroveci* and moderate-to-severe disease, as defined by room air pO_2 <70 mm Hg or arterial-alveolar O_2 gradient >35 mm Hg, should receive adjunctive corticosteroids as early as possible, and certainly within 72 hours after starting specific *Pneumocystis (carinii) jiroveci* therapy. • The recommended duration of therapy for *Pneumocystis (carinii) jiroveci* is 21 days. • Patients who have a history of *Pneumocystis (carinii) jiroveci* should be administered chemoprophylaxis for life (i.e., secondary prophylaxis or chronic maintenance therapy) with sulfamethoxazole-trimethoprim unless immune reconstitution occurs as a result of antiretroviral therapy. • Secondary prophylaxis should be discontinued for adult and adolescent patients whose CD4+ count has increased from <200 cells/µL to >200 cells/µL for >3 months as a result of antiretroviral therapy. Prophylaxis should be reintroduced if the CD4+ count decreases to <200 cells/µL. If *Pneumocystis (carinii) jiroveci* recurs at a CD4+ count of ≥200 cells/µL, lifelong prophylaxis should be administered. <u>Primary prophylaxis of *Toxoplasma* encephalitis</u> • The double-strength tablet daily dose of sulfamethoxazole-trimethoprim recommended as the preferred regimen for *Pneumocystis (carinii) jiroveci* prophylaxis is effective against *Toxoplasma* encephalitis as well and is therefore recommended. Sulfamethoxazole-trimethoprim, one double-strength tablet three times weekly, is an alternative. • If patients cannot tolerate sulfamethoxazole-trimethoprim, the recommended alternative is dapsone-pyrimethamine plus leucovorin, which is also effective against *Pneumocystis (carinii) jiroveci* pneumonia. • Atovaquone with or without pyrimethamine/leucovorin can also be considered. • Prophylactic monotherapy with dapsone, pyrimethamine, azithromycin, or clarithromycin cannot be recommended on the basis of available data. Aerosolized pentamidine does not protect against *Toxoplasma* encephalitis and is not recommended. • Prophylaxis against *Toxoplasma* encephalitis should be discontinued among adult and adolescent patients who have responded to antiretroviral therapy with an increase in CD4+ counts to >200 cells/µL for >3 months. Prophylaxis for *Toxoplasma* encephalitis should be reintroduced if the CD4+ count decreases to <100–200 cells/µL. <u>Treatment of *Toxoplasma* encephalitis</u> • The initial therapy of choice for *Toxoplasma* encephalitis consists of the combination of pyrimethamine plus sulfadiazine plus leucovorin. • The preferred alternative regimen for patients with *Toxoplasma*

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	encephalitis who are unable to tolerate or who fail to respond to first-line therapy is pyrimethamine plus clindamycin plus leucovorin.
	• Sulfamethoxazole-trimethoprim was reported in a small randomized trial to be effective and better tolerated than pyrimethamine-sulfadiazine. On the basis of less in vitro activity and less experience with sulfamethoxazole-trimethoprim, treatment with this drug may be considered an option.
	• Acute therapy for *Toxoplasma* encephalitis should be continued for at least six weeks, if there is clinical and radiologic improvement.
	
	<u>Treatment of latent tuberculosis infection</u>
	• Human immunodeficiency virus-infected persons, regardless of age, should be treated for latent tuberculosis infection if they have no evidence of active tuberculosis and:
	  o A positive diagnostic test for latent tuberculosis infection and no prior history of treatment for active or latent tuberculosis.
	  o A negative diagnostic test for latent tuberculosis infection but are close contacts of persons with infectious pulmonary tuberculosis.
	  o A history of untreated or inadequately treated healed tuberculosis (i.e., old fibrotic lesions on chest radiography) regardless of diagnostic tests for latent tuberculosis infection.
	• Treatment options for latent tuberculosis infection include isoniazid daily or twice weekly for nine months.
	• Due to an increased risk of fatal and severe hepatotoxicity, a two-month regimen of daily rifampin and pyrazinamide is not recommended for latent tuberculosis infection treatment regardless of human immunodeficiency virus status.
	• Human immunodeficiency virus-infected persons receiving isoniazid should receive pyridoxine to minimize the risk of developing peripheral neuropathy. Alternatives for individuals who cannot take isoniazid or who have been exposed to a known isoniazid-resistant index case include either rifampin or rifabutin alone for four months.
	• For persons exposed to isoniazid- and/or rifampin-resistant tuberculosis, decisions to treat with one or two drugs other than isoniazid, rifampin, or rifabutin should be based on the relative risk of exposure to organisms broadly resistant to other antimycobacterial drugs and should be made in consultation with public health authorities.
	• Directly observed therapy should be used with intermittent dosing regimens when otherwise feasible to maximize regimen completion rates.
	• There is no evidence to suggest that latent tuberculosis infection treatment should be continued beyond the recommended duration in persons with human immunodeficiency virus infection. Therefore, latent tuberculosis infection treatment should be discontinued after completing the appropriate number of doses.
	
	<u>Treatment of active tuberculosis disease</u>
	• Recommendations for anti-tuberculosis treatment regimens in human immunodeficiency virus -infected adults follow the same principles as for adults without human immunodeficiency virus -infection.
	• Treatment of drug susceptible tuberculosis disease should include a six-month regimen with an initial phase of isoniazid, rifampin or rifabutin, pyrazinamide, and ethambutol administered for two months followed by isoniazid and rifampin (or rifabutin) for four additional

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	months. • When drug-susceptibility testing confirms the absence of resistance to isoniazid, rifampin, and pyrazinamide, ethambutol may be discontinued before two months of treatment have been completed. • For patients with cavitary lung disease and cultures positive for *Mycobacterium tuberculosis* after completion of two months of therapy, treatment should be extended with isoniazid and rifampin for an additional three months for a total of nine months. • All human immunodeficiency virus-infected patients treated with isoniazid should receive pyridoxine supplementation. • For patients with extrapulmonary tuberculosis, a six- to nine-month regimen (two months of isoniazid, rifampin, pyrazinamide, and ethambutol followed by four to seven months of isoniazid and rifampin) is recommended. • Exceptions to the recommendation for a six- to nine-month regimen for extrapulmonary tuberculosis include central nervous system disease (tuberculoma or meningitis) and bone and joint tuberculosis, for which many experts recommend nine to 12 months. • Adjuvant corticosteroids should be added when treating central nervous system and pericardial disease. • Treatment with corticosteroids should be started intravenously as early as possible with change to oral therapy individualized according to clinical improvement. • Recommended corticosteroid regimens are dexamethasone 0.3 to 0.4 mg/kg tapered over six to eight weeks or prednisone 1 mg/kg for three weeks, then tapered for three to five weeks. <u>Treatment of varicella zoster virus disease</u> • For uncomplicated varicella, the preferred treatment options are valacyclovir (1 gram orally three times daily), or famciclovir (500 mg orally three times daily) for five to seven days. Oral acyclovir (20 mg/kg body weight up to a maximum dose of 800 mg five times daily) can be an alternative. • Prompt antiviral therapy should be instituted in all human immunodeficiency virus-seropositive patients whose herpes zoster is diagnosed within one week of rash onset (or any time before full crusting of lesions). The recommended treatment options for acute localized dermatomal herpes zoster in human immunodeficiency virus-infected patients are oral valacyclovir, famciclovir, or acyclovir (doses as above) for seven to 10 days, although longer durations of therapy should be considered if lesions resolve slowly. Valacyclovir or famciclovir are preferred because of their improved pharmacokinetic properties and simplified dosing schedule. • If cutaneous lesions are extensive or if visceral involvement is suspected, intravenous acyclovir should be initiated and continued until clinical improvement is evident. A switch from intravenous acyclovir to oral antiviral therapy (to complete a 10 to 14 day treatment course) is reasonable when formation of new cutaneous lesions has ceased and the signs and symptoms of visceral varicella zoster virus infection are clearly improving. • Optimal antiviral therapy for progressive outer retinal necrosis remains undefined. Specific treatment should include systemic therapy with at least one intravenous drug (selected from acyclovir, ganciclovir, foscarnet, and cidofovir) coupled with injections of at least one intravitreal drug (selected from ganciclovir and foscarnet). Treatment

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	regimens for progressive outer retinal necrosis recommended by certain specialists include a combination of intravenous ganciclovir and/or foscarnet plus intravitreal injections of ganciclovir and/or foscarnet. The prognosis for visual preservation in involved eyes is poor, despite aggressive antiviral therapy. • Other infectious disease states mentioned within these guidelines note that the treatment guidelines for that disease state should be utilized. • The guideline specifies that detailed recommendations for the treatment of human herpesvirus-8 and associated malignancies are beyond the scope of these guidelines. • Other excluded infectious disease states offer no specific therapy or utilize medications not licensed in the United States.
American College of Rheumatology: **2012 Update of the 2008 American College of Rheumatology Recommendations for the Use of Nonbiologic and Biologic Disease-Modifying Antirheumatic Drugs in Rheumatoid Arthritis (2012)**[20]	<u>Monotherapy recommendations</u> • Initiation of methotrexate or leflunomide monotherapy for patients with all disease durations and for all degrees of disease activity, irrespective of poor prognostic features. • Hydroxychloroquine monotherapy for patients without poor prognostic features, with low disease activity, and with disease duration ≤24 months. • Minocycline monotherapy for patients without poor prognostic features, with low disease activity, and with short disease duration. • Sulfasalazine monotherapy for patients with all disease durations and without poor prognostic features and those with all degrees of disease activity. <u>Two-drug combination therapy recommendations</u> • Methotrexate plus hydroxychloroquine for patients with moderate to high disease activity irrespective of disease duration or poor prognostic features and for patients with longer disease duration and low disease activity, independent of prognostic features. • Methotrexate plus leflunomide for patients with intermediate or longer disease duration (≥6 months), regardless of prognostic features as long as disease activity is high. • Methotrexate plus sulfasalazine for patients with all disease durations if they have high disease activity and poor prognostic features. • Hydroxychloroquine plus sulfasalazine for patients with intermediate disease duration (six to 24 months) and high disease activity but without poor prognostic features. <u>Three-drug combination therapy recommendations</u> • Sulfasalazine plus hydroxychloroquine plus methotrexate for all patients with poor prognostic features and moderate or high levels of disease activity, regardless of disease duration. <u>Biologic therapy recommendations</u> • Patients with early rheumatoid arthritis and only low or moderate disease activity are not considered candidates for biologic therapy. • The use of an anti-TNFα agent in combination with methotrexate is recommended if high disease activity was present for <3 months with features of both a poor prognosis and an absence of either barriers related to treatment cost and no insurance restrictions to accessing medical care. • In intermediate-duration and longer-duration rheumatoid arthritis, the

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	use of an anti-TNFα agent is recommended in patients for whom prior methotrexate monotherapy led to an inadequate response, with moderate disease activity and features of a poor prognosis, and for patients with high disease activity, irrespective of prognostic features. • The use of an anti-TNFα agent is recommended in patients for whom prior methotrexate therapy was used in combination, or if sequential administration of other nonbiologic disease-modifying antirheumatic drugs led to an inadequate response with at least moderate residual disease activity irrespective of prognostic features. • The anti-TNFα agents (etanercept, infliximab, and adalimumab) are efficacious in improving disease activity, function, and quality of life and/or retarding radiographic progression when used alone, in combination with methotrexate, or in patients for whom treatment with disease-modifying antirheumatic drugs other than methotrexate led to an inadequate response.
British Society for Rheumatology: **Guideline for the Management of Rheumatoid Arthritis (The First Two Years) (2006)**[21]	• Patients with rheumatoid arthritis should be established on disease-modifying antirheumatic drug therapy as soon as possible after the diagnosis. • There is clear evidence of disease-modifying effect for methotrexate, sulfasalazine, leflunomide and intramuscular gold, with less compelling, controlled data supporting reduction of erosions with hydroxychloroquine, penicillamine, oral gold, cyclosporine and azathioprine, although these agents do improve symptoms and some objective measures of inflammation. • Choice of the first agent is based on the risk to benefit ratio with hydroxychloroquine an option in disease perceived as mild and methotrexate or sulfasalazine in those adjudged moderate-to-severe, or likely to progress.
American College of Rheumatology: **Guidelines for Referral and Management of Systemic Lupus Erythematosus in Adults (1999)**[22]	• Treatment usually consists of nonsteroidal anti-inflammatory drugs as needed, topical steroids for rash, antimalarial medications (e.g., hydroxychloroquine 200 to 400 mg daily), and low dose oral corticosteroids (prednisone ≤10 mg daily). • For severe life-threatening or organ-threatening disease, high dose steroids (prednisone 40 to 60 mg daily) may be used. • Additional treatment options that may be used depending upon severity include immunomodulators such as azathioprine, cyclophosphamide, methotrexate, chlorambucil, or cyclosporine.

Table 5. CDC Guidelines for Treatment of Malaria in the United States[16]

Clinical Diagnosis/ *Plasmodium* species	Region Infection Acquired	Recommended Drug and Adult Dose[1]	Recommended Drug and Pediatric Dose[1] *Pediatric dose should NEVER exceed adult dose*
Uncomplicated malaria/ *P. falciparum* or Species not identified If "species not identified" is subsequently diagnosed as *P. vivax* or *P ovale:* see *P. vivax* and *P ovale* (below) re. treatment with primaquine	**Chloroquine-resistant or unknown resistance[2]** (All malarious regions except those specified as chloroquine-sensitive listed in the box below.)	**A. Atovaquone-proguanil (Malarone®)[3]** **Adult tab = 250 mg atovaquone/ 100 mg proguanil** 4 tabs po qd x 3 days	**A. Atovaquone-proguanil (Malarone®)[3]** **Adult tab = 250 mg atovaquone/ 100 mg proguanil** **Peds tab = 62.5 mg atovaquone/ 25 mg proguanil** 5 - 8kg: 2 peds tabs po qd x 3 d 9-10kg: 3 peds tabs po qd x 3 d 11-20kg: 1adult tab po qd x 3 d 21-30kg: 2 adult tabs po qd x 3d 31-40kg: 3 adult tabs po qd x 3d >40 kg: 4 adult tabs po qd x 3d
		B. Artemether-lumefantrine (Coartem®)[3] **1 tablet = 20 mg artemether and 120 mg lumefantrine** A 3-day treatment schedule with a total of 6 oral doses is recommended for both adult and pediatric patients based on weight. The patient should receive the initial dose, followed by the second dose 8 hours later, then 1 dose po bid for the following 2 days. 5 - <15 kg: 1 tablet per dose 15 - <25 kg: 2 tablets per dose 25 - <35 kg: 3 tablets per dose ≥35 kg: 4 tablets per dose	
		C. Quinine sulfate plus one of the following: Doxycycline, Tetracycline, or Clindamycin **Quinine sulfate:** 542 mg base (=650 mg salt)[4] po tid x 3 or 7 days[5] **Doxycycline:** 100 mg po bid x 7 days **Tetracycline:** 250 mg po qid x 7 days **Clindamycin:** 20 mg base/kg/day po divided tid x 7 days	**C. Quinine sulfate[4] plus one of the following: Doxycycline[5], Tetracycline[6] or Clindamycin** **Quinine sulfate:** 8.3 mg base/kg (=10 mg salt/kg) po tid x 3 or 7 days[5] **Doxycycline:** 2.2 mg/kg po every 12 hours x 7 days **Tetracycline:** 25 mg/kg/day po divided qid x 7 days **Clindamycin:** 20 mg base/kg/day po divided tid x 7 days
		D. Mefloquine (Lariam® and generics)[7] 684 mg base (=750 mg salt) po as initial dose, followed by 456 mg base (=500 mg salt) po given 6-12 hours after initial dose. Total dose= 1,250 mg salt	**D. Mefloquine (Lariam® and generics)[7]** 13.7 mg base/kg (=15 mg salt/kg) po as initial dose, followed by 9.1 mg base/kg (=10 mg salt/kg) po given 6-12 hours after initial dose. Total dose= 25 mg salt/kg

1 If a person develops malaria despite taking chemoprophylaxis, that particular medicine should not be used as a part of their treatment regimen. Use one of the other options instead.
2 NOTE: There are 4 options (A, B, C, or D) available for treatment of uncomplicated malaria caused by chloroquine-resistant *P. falciparum*. Options A, B, and C are equally recommended. Because of a higher rate of severe neuropsychiatric reactions seen at treatment doses, we do not recommend option D (mefloquine) unless the other options cannot be used. For option C, because there is more data on the efficacy of quinine in combination with doxycycline or tetracycline, these treatment combinations are generally preferred to quinine in combination with clindamycin.
3 Take with food or whole milk. If patient vomits within 30 minutes of taking a dose, then they should repeat the dose.
4 US manufactured quinine sulfate capsule is in a 324mg dosage; therefore 2 capsules should be sufficient for adult dosing. Pediatric dosing may be difficult due to unavailability of non-capsule forms of quinine.
5 For infections acquired in Southeast Asia, quinine treatment should continue for 7 days. For infections acquired elsewhere, quinine treatment should continue for 3 days.
6 Doxycycline and tetracycline are not indicated for use in children less than 8 years old. For children less than 8 years old with chloroquine-resistant *P. falciparum*, atovaquone-proguanil and artemether-lumefantrine are recommended treatment options; mefloquine can be considered if no other options are available. For children less than 8 years old with chloroquine-resistant *P. vivax,* mefloquine is the recommended treatment. If it is not available or is not being tolerated and if the treatment benefits outweigh the risks, atovaquone-proguanil or artemether-lumefantrine should be used instead.
7Treatment with mefloquine is not recommended in persons who have acquired infections from Southeast Asia due to drug resistance.
8When treating chloroquine-sensitive infections, chloroquine and hydroxychloroquine are recommended options. However, regimens used to treat chloroquine-resistant infections may also be used if available, more convenient, or preferred.
9Primaquine is used to eradicate any hypnozoites that may remain dormant in the liver, and thus prevent relapses, in *P. vivax* and *P. ovale* infections. Because primaquine can cause hemolytic anemia in G6PD-deficient persons, G6PD screening must occur prior to starting treatment with primaquine. For persons with borderline G6PD deficiency or as an alternate to the above regimen, primaquine may be given 45 mg orally one time per week for 8 weeks; consultation with an expert in infectious disease and/or tropical medicine is advised if this alternative regimen is considered in G6PD-deficient persons. Primaquine must not be used during pregnancy.

Table 5. CDC Guidelines for Treatment of Malaria in the United States (Cont.)[16]

Clinical Diagnosis/ *Plasmodium* species	Region Infection Acquired	Recommended Drug and Adult Dose[1]	Recommended Drug and Pediatric Dose[1] *Pediatric dose should NEVER exceed adult dose*
Uncomplicated malaria/ *P. falciparum* or ***Species not identified***	**Chloroquine-sensitive** (Central America west of Panama Canal; Haiti; the Dominican Republic; and most of the Middle East)	**Chloroquine phosphate (Aralen® and generics)[8]** 600 mg base (=1,000 mg salt) po immediately, followed by 300 mg base (=500 mg salt) po at 6, 24, and 48 hours Total dose: 1,500 mg base (=2,500 mg salt) **OR** **Hydroxychloroquine (Plaquenil® and generics)** 620 mg base (=800 mg salt) po immediately, followed by 310 mg base (=400 mg salt) po at 6, 24, and 48 hours Total dose: 1,550 mg base (=2,000 mg salt)	**Chloroquine phosphate (Aralen® and generics)[8]** 10 mg base/kg po immediately, followed by 5 mg base/kg po at 6, 24, and 48 hours Total dose: 25 mg base/kg **OR** **Hydroxychloroquine (Plaquenil® and generics)** 10 mg base/kg po immediately, followed by 5 mg base/kg po at 6, 24, and 48 hours Total dose: 25 mg base/kg
Uncomplicated malaria/ *P. malariae or P. knowlesi*	**All regions**	**Chloroquine phosphate:[8]** Treatment as above **OR** **Hydroxychloroquine:** Treatment as above	**Chloroquine phosphate:[8]** Treatment as above **OR** **Hydroxychloroquine:** Treatment as above
Uncomplicated malaria/ *P. vivax* or ***P. ovale***	**All regions** Note: for suspected chloroquine-resistant *P. vivax,* see row below	**Chloroquine phosphate[8] plus Primaquine phosphate[9]** **Chloroquine phosphate:** Treatment as above **Primaquine phosphate:** 30 mg base po qd x 14 days **OR** **Hydroxychloroquine plus Primaquine phosphate[9]** **Hydroxychloroquine:** Treatment as above **Primaquine phosphate:** 30 mg base po qd x 14 days	**Chloroquine phosphate[8] plus Primaquine phosphate[9]** **Chloroquine phosphate:** Treatment as above **Primaquine:** 0.5mg base/kg po qd x 14 days **OR** **Hydroxychloroquine plus Primaquine phosphate[9]** **Hydroxychloroquine:** Treatment as above **Primaquine phosphate:** 0.5mg base/kg po qd x 14 days
Uncomplicated malaria/ *P. vivax*	**Chloroquine-resistant[10]** (Papua New Guinea and Indonesia)	**A. Quinine sulfate plus either Doxycycline or Tetracycline plus Primaquine phosphate[9]** **Quinine sulfate:** Treatment as above **Doxycycline or Tetracycline:** Treatment as above **Primaquine phosphate:** Treatment as above	**A. Quinine sulfate plus either Doxycycline[6] or Tetracycline[6] plus Primaquine phosphate[9]** **Quinine sulfate:** Treatment as above **Doxycycline or Tetracycline:** Treatment as above **Primaquine phosphate:** Treatment as above
		B. Atovaquone-proguanil plus Primaquine phosphate[9] **Atovaquone-proguanil:** Treatment as above **Primaquine phosphate:** Treatment as above	**B. Atovaquone-proguanil plus Primaquine phosphate[9]** **Atovaquone-proguanil:** Treatment as above **Primaquine phosphate:** Treatment as above
		C. Mefloquine plus Primaquine phosphate[9] **Mefloquine:** Treatment as above **Primaquine phosphate:** Treatment as above	**C. Mefloquine plus Primaquine phosphate[9]** **Mefloquine:** Treatment as above **Primaquine phosphate:** Treatment as above
Uncomplicated malaria: alternatives for pregnant women[11,12,13]	**Chloroquine-sensitive** (see uncomplicated malaria sections above for chloroquine-sensitive species by region)	**Chloroquine phosphate:** Treatment as above **OR** **Hydroxychloroquine:** Treatment as above	Not applicable
	Chloroquine resistant (see sections above for regions with chloroquine resistant ***P. falciparum and P. vivax***)	**Quinine sulfate plus Clindamycin** **Quinine sulfate:** Treatment as above **Clindamycin:** Treatment as above **OR** **Mefloquine:** Treatment as above	Not applicable

10 NOTE: There are three options (A, B, or C) available for treatment of uncomplicated malaria caused by chloroquine-resistant *P. vivax.* High treatment failure rates due to chloroquine-resistant *P. vivax* have been well documented in Papua New Guinea and Indonesia. Rare case reports of chloroquine-resistant *P. vivax* have also been documented in Burma (Myanmar), India, and Central and South America. Persons acquiring *P. vivax* infections outside of Papua New Guinea or Indonesia should be started on chloroquine. If the patient does not respond, the treatment should be changed to a chloroquine-resistant *P. vivax* regimen and CDC should be notified (Malaria Hotline number listed above). For treatment of chloroquine-resistant *P. vivax* infections, options A, B, and C are equally recommended.

11 For pregnant women diagnosed with uncomplicated malaria caused by chloroquine-resistant *P. falciparum* or chloroquine-resistant *P. vivax* infection, treatment with doxycycline or tetracycline is generally not indicated. However, doxycycline or tetracycline may be used in combination with quinine (as recommended for non-pregnant adults) if other treatment options are not available or are not being tolerated, and the benefit is judged to outweigh the risks.

12 Atovaquone-proguanil and artemether-lumefantrine are generally not recommended for use in pregnant women, particularly in the first trimester due to lack of sufficient safety data. For pregnant women diagnosed with uncomplicated malaria caused by chloroquine-resistant *P. falciparum* infection, atovaquone-proguanil or artemether-lumefantrine may be used if other treatment options are not available or are not being tolerated, and if the potential benefit is judged to outweigh the potential risks.

13 For *P. vivax* and *P. ovale* infections, primaquine phosphate for radical treatment of hypnozoites should not be given during pregnancy. Pregnant patients with *P. vivax* and *P. ovale* infections should be maintained on chloroquine prophylaxis for the duration of their pregnancy. The chemoprophylactic dose of chloroquine phosphate is 300 mg base (=500 mg salt) orally once per week. After delivery, pregnant patients who do not have G6PD deficiency should be treated with primaquine.

Table 5. CDC Guidelines for Treatment of Malaria in the United States (Cont.)[16]

Clinical Diagnosis/ *Plasmodium* species	Region Infection Acquired	Recommended Drug and Adult Dose[1]	Recommended Drug and Pediatric Dose[1] *Pediatric dose should NEVER exceed adult dose*
Severe malaria[14,15,16]	**All regions**	**Quinidine gluconate[14] plus one of the following: Doxycycline, Tetracycline, or Clindamycin** **Quinidine gluconate:** 6.25 mg base/kg (=10 mg salt/kg) loading dose IV over 1 to 2 hrs, then 0.0125 mg base/kg/min (=0.02 mg salt/kg/min) continuous infusion for at least 24 hours. An alternative regimen is 15 mg base/kg (=24 mg salt/kg) loading dose IV infused over 4 hours, followed by 7.5 mg base/kg (=12 mg salt/kg) infused over 4 hours every 8 hours, starting 8 hours after the loading dose (see package insert). Once parasite density <1% and patient can take oral medication, complete treatment with oral quinine, dose as above. Quinidine/quinine course = 7 days in Southeast Asia; = 3 days in Africa or South America. **Doxycycline:** Treatment as above. If patient not able to take oral medication, give 100 mg IV every 12 hours and then switch to oral doxycycline (as above) as soon as patient can take oral medication. For IV use, avoid rapid administration. Treatment course = 7 days. **Tetracycline:** Treatment as above **Clindamycin:** Treatment as above. If patient not able to take oral medication, give 10 mg base/kg loading dose IV followed by 5 mg base/kg IV every 8 hours. Switch to oral clindamycin (oral dose as above) as soon as patient can take oral medication. For IV use, avoid rapid administration. Treatment course = 7 days. ***Investigational new drug (contact CDC for information):*** **Artesunate followed by one of the following: Atovaquone-proguanil (Malarone®), Doxycycline (Clindamycin in pregnant women), or Mefloquine**	**Quinidine gluconate[14] plus one of the following: Doxycycline[4], Tetracycline[4], or Clindamycin** **Quinidine gluconate:** Same mg/kg dosing and recommendations as for adults. **Doxycycline:** Treatment as above. If patient not able to take oral medication, may give IV. For children <45 kg, give 2.2 mg/kg IV every 12 hours and then switch to oral doxycycline (dose as above) as soon as patient can take oral medication. For children ≥45 kg, use same dosing as for adults. For IV use, avoid rapid administration. Treatment course = 7 days. **Tetracycline:** Treatment as above **Clindamycin:** Treatment as above. If patient not able to take oral medication, give 10 mg base/kg loading dose IV followed by 5 mg base/kg IV every 8 hours. Switch to oral clindamycin (oral dose as above) as soon as patient can take oral medication. For IV use, avoid rapid administration. Treatment course = 7 days. ***Investigational new drug (contact CDC for information):*** **Artesunate followed by one of the following: Atovaquone-proguanil (Malarone®), Clindamycin, or Mefloquine**

14 Persons with a positive blood smear OR history of recent possible exposure and no other recognized pathology who have one or more of the following clinical criteria (impaired consciousness/coma, severe normocytic anemia, renal failure, pulmonary edema, acute respiratory distress syndrome, circulatory shock, disseminated intravascular coagulation, spontaneous bleeding, acidosis, hemoglobinuria, jaundice, repeated generalized convulsions, and/or parasitemia of > 5%) are considered to have manifestations of more severe disease. Severe malaria is most often caused by *P. falciparum.*
15 Patients diagnosed with severe malaria should be treated aggressively with parenteral antimalarial therapy. Treatment with IV quinidine should be initiated as soon as possible after the diagnosis has been made. Patients with severe malaria should be given an intravenous loading dose of quinidine unless they have received more than 40 mg/kg of quinine in the preceding 48 hours or if they have received mefloquine within the preceding 12 hours. Consultation with a cardiologist and a physician with experience treating malaria is advised when treating malaria patients with quinidine. During administration of quinidine, blood pressure monitoring (for hypotension) and cardiac monitoring (for widening of the QRS complex and/or lengthening of the QTc interval) should be monitored continuously and blood glucose (for hypoglycemia) should be monitored periodically. Cardiac complications, if severe, may warrant temporary discontinuation of the drug or slowing of the intravenous infusion.
16 Pregnant women diagnosed with severe malaria should be treated aggressively with parenteral antimalarial therapy.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the antimalarials are noted in Tables 6 and 7. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 6. FDA-Approved Indications for the Single Entity Antimalarials[1-9]

Indication	Chloroquine	Hydroxychloroquine	Mefloquine	Primaquine	Pyrimethamine	Quinine
Prophylaxis of malaria	✔	✔	✔		✔ ‡	
Radical cure (prevention of relapse) of vivax malaria				✔		
Treatment of acute malaria	✔	✔	✔		✔ *	✔ §
Treatment of extraintestinal amebiasis	✔					
Treatment of lupus erythematosus		✔ ^				
Treatment of rheumatoid arthritis		✔ ^				
Treatment of toxoplasmosis when used conjointly with a sulfonamide					✔	

*Should not be used alone to treat acute malaria. Fast-acting schizonticides such as chloroquine or quinine are indicated and preferable for the treatment of acute malaria. However, conjoint use of pyrimethamine with a sulfonamide will initiate transmission control and suppression of susceptible strains of plasmodia.
‡Resistance to pyrimethamine is prevalent worldwide.
§Not routinely recommended; should only be considered for travelers to areas where chloroquine-resistant malaria is endemic and when alternative drugs are not available or contraindicated.
^Useful in patients who have not responded satisfactorily to drugs with less potential for serious side effects.

Table 7. FDA-Approved Indications for the Combination Antimalarials[1-9]

Indication	Artemether and Lumefantrine	Atovaquone and Proguanil
Prophylaxis of malaria		✔ †
Treatment of acute malaria	✔	✔

†Including in areas where chloroquine resistance has been reported.

IV. Pharmacokinetics

The pharmacokinetic parameters of the antimalarials are listed in Table 8.

Table 8. Pharmacokinetic Parameters of the Antimalarials[1-9]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life
Single Entity Agents					
Chloroquine	89	55 to 60	Liver	Renal (65 to 70)	3 to 5 days
Hydroxychloroquine	Not reported	55	Liver	Renal (16 to 25)	32 to 50 days
Mefloquine	85	98	Liver	Renal (1 to 8)	13 to 30 days
Primaquine	Not reported	Not reported	Not reported	Renal (1)	4 to 7 hours
Pyrimethamine	Not reported	87	Not reported	Not reported	87 to 187 hours
Quinine	76 to 88	93 to 95	Not reported	Renal (12 to 30)	4 to 11 hours
Combination Products					
Artemether and lumefantrine	Artemether: Not reported Lumefantrine: Not reported	Artemether: 95.0 Lume-fantrine: 99.7	Liver	Not reported	Artemether: 1.6 to 2.2 hours Lumefantrine: 101 to 119 hours
Atovaquone and proguanil	Atovaquone: 23 Proguanil: Not reported	Atovaquone: 99 Proguanil: 75	Liver	Renal (40 to 60)	Atovaquone: 32 to 84 hours Proguanil: 12 to 21 hours

V. Drug Interactions

Significant drug interactions with the antimalarials are listed in Table 9.

Table 9. Significant Drug Interactions with the Antimalarials[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Single Entity Agents			
Chloroquine	1	Class IA and III antiarrhythmics	Prolonged QT interval and cardiac arrhythmias are a potential when antiarrhythmics and chloroquine are used concomitantly.
Chloroquine	1	H_1 antagonists	Use of chloroquine and H_1 antagonists may increase the risk of cardiovascular toxicity, including potentially fatal cardiac arrhythmias (torsade de pointes).
Chloroquine	1	Macrolides, ketolides and fluoroquinolones	Cardiac arrhythmias resulting from the potential for additive QT prolongation should be considered as a possibility when these agents are coadministered.
Chloroquine	1	Mefloquine	Convulsions are a potential when mefloquine and chloroquine are used concomitantly.
Chloroquine	1	Methadone	Coadministration of methadone and chloroquine may cause significant prolongation of the cardiac QT interval, and possibly lead to torsades de pointes arrhythmias, especially in

Generic Name(s)	Significance Level	Interaction	Mechanism
			high doses, female sex, hypokalemia, or patients with a history of cardiac conduction disease.
Chloroquine	1	Nilotinib	Additive QT prolongation may occur during coadministration of nilotinib and chloroquine.
Hydroxychloroquine	1	Mefloquine	The combination of hydroxychloroquine and mefloquine may result in an increased risk of cardiac arrhythmias due to prolonged QT intervals.
Hydroxychloroquine	1	Natalizumab	Hydroxychloroquine may increase the plasma concentration and toxicity of natalizumab resulting in an increased occurrence of concurrent infection.
Mefloquine	1	Antipsychotics	The combination of mefloquine and quetiapine/ziprasidone may result in an increased risk of cardiac arrhythmias due to prolonged QT intervals.
Mefloquine	1	Dronedarone	Coadministration of dronedarone and mefloquine may increase the risk of cardiovascular toxicity, including potentially fatal cardiac arrhythmias (torsade de pointes).
Mefloquine	1	Halofantrine	The combination of mefloquine and halofantrine may result in an increased incidence of cardiac arrhythmias.
Mefloquine	1	Ketoconazole	The combination of mefloquine or within 15 weeks of the last dose of mefloquine and ketoconazole may result in an increased incidence of cardiac arrhythmias.
Mefloquine	1	Quinidine or quinine	Prolonged QT interval and convulsions are a potential when mefloquine and quinidine/quinine are used concomitantly.
Mefloquine	1	Tetrabenazine	Additive QT prolongation may occur during coadministration of tetrabenazine and mefloquine.
Mefloquine	1	Toremifene	Prolonged QT interval and cardiac arrhythmias are a potential when toremifene and mefloquine are used concomitantly.
Mefloquine	1	Vandetanib	Prolonged QT interval and cardiac arrhythmias are a potential when vandetanib and mefloquine are used concomitantly.
Mefloquine	1	Vemurafenib	Prolonged QT interval and cardiac arrhythmias are a potential when vemurafenib and mefloquine are used concomitantly.
Primaquine	1	Mefloquine	Prolonged QT interval and convulsions are a potential when mefloquine and primaquine are used

Generic Name(s)	Significance Level	Interaction	Mechanism
			concomitantly.
Pyrimethamine	1	Methotrexate	Coadministration of pyrimethamine and methotrexate may increase the risk of bone marrow suppression.
Pyrimethamine	1	Sulfonamides	Coadministration of pyrimethamine and sulfonamides or sulfamethoxazole-trimethoprim may increase the risk of bone marrow suppression.
Pyrimethamine	1	Zidovudine	Coadministration of pyrimethamine and zidovudine may increase the risk of bone marrow suppression.
Quinine	1	Anticoagulants	Quinine derivatives may inhibit the hepatically synthesized clotting factors resulting in potentiation of anticoagulation and possible hemorrhage.
Quinine	1	Astemizole	Quinine may inhibit the metabolism of astemizole and result in torsades de pointes.
Quinine	1	Class IA and III antiarrhythmics	Coadministration of quinine with other antiarrhythmic agents may result in QT prolongation.
Quinine	1	Halofantrine	The combination of quinine and halofantrine may result in an increased incidence of cardiac arrhythmias.
Quinine	1	Macrolides	Coadministration of macrolides and quinine may increase the serum concentration of quinine.
Quinine	1	Mefloquine	The combination of quinine and mefloquine may result in an increased incidence of cardiac arrhythmias.
Quinine	1	Nondepolarizing muscle relaxants	The neuromuscular blocking effects of non-depolarizing muscle relaxants may be increased. Prolonged respiratory depression with extended periods of apnea may occur.
Quinine	1	Rifamycins	Rifamycins increase the hepatic metabolism of quinine may result in reduced therapeutic effects of quinine.
Chloroquine	2	Antacids	Coadministration of chloroquine and antacids can reduce the absorption and efficacy of chloroquine.
Chloroquine	2	Cyclosporine	Chloroquine may increase the plasma concentration and toxicity of cyclosporine.
Chloroquine	2	Dapsone	Dapsone may increase the risk of hemolytic reactions; closely monitor patients who are taking dapsone and chloroquine, particularly patients deficient in glucose-6-phosphate dehydrogenase, methemoglobin reductase, or with hemoglobin M.
Chloroquine	2	Flecainide	Additive QT prolongation may occur during coadministration of flecainide

Generic Name(s)	Significance Level	Interaction	Mechanism
			and chloroquine.
Chloroquine	2	Perflutren	Additive QT prolongation may occur during coadministration of perflutren and chloroquine.
Chloroquine	2	Propafenone	Additive QT prolongation may occur during coadministration of propafenone and chloroquine.
Chloroquine	2	Tetrabenazine	Additive QT prolongation may occur during coadministration of tetrabenazine and chloroquine.
Hydroxychloroquine	2	Dapsone	Dapsone may increase the risk of hemolytic reactions; closely monitor patients who are taking dapsone and hydroxychloroquine, particularly patients deficient in glucose-6-phosphate dehydrogenase, methemoglobin reductase, or with hemoglobin M.
Hydroxychloroquine	2	Digoxin	Hydroxychloroquine appears to decrease the biliary clearance of digoxin resulting in increased digoxin serum levels with possible toxicity.
Hydroxychloroquine	2	Leflunomide	Pancytopenia, agranulocytosis, and/or thrombocytopenia may occur during coadministration of hydroxychloroquine and leflunomide.
Hydroxychloroquine	2	Roflumilast	Coadministration of hydroxychloroquine and roflumilast may enhance immunosuppression.
Mefloquine	2	Anticonvulsants	Coadministration of mefloquine and anticonvulsants may reduce seizure control by lowering the plasma levels of anticonvulsants.
Mefloquine	2	Beta-adrenergic blockers	Coadministration of mefloquine and beta-adrenergic blockers may cause cardiovascular toxicity, including electrocardiographic abnormalities such as QT interval prolongation.
Primaquine	2	Dapsone	Dapsone may increase the risk of hemolytic reactions; closely monitor patients who are taking dapsone and primaquine, particularly patients deficient in glucose-6-phosphate dehydrogenase, methemoglobin reductase, or with hemoglobin M.
Pyrimethamine	2	Dapsone	Dapsone may increase the risk of hemolytic reactions; closely monitor patients who are taking dapsone and pyrimethamine, particularly patients deficient in glucose-6-phosphate dehydrogenase, methemoglobin reductase, or with hemoglobin M.
Quinine	2	Anti-cholinesterases	The beneficial effects of anticholinesterases in the treatment of myasthenia gravis may be reversed by quinine.

Generic Name(s)	Significance Level	Interaction	Mechanism
Quinine	2	Digoxin	Quinine appears to decrease the biliary clearance of digoxin resulting in increased digoxin serum levels with possible toxicity.
Quinine	2	Succinylcholine	Quinine may produce a decrease in plasma cholinesterase activity resulting in a slowed metabolic rate for succinylcholine. This may result in prolongation of the neuromuscular blockade produced by succinylcholine.
Combination Products			
Artemether/lumefantrine	1	Antipsychotics	The combination may increase the additive effect on the QT interval and incidence of cardiac arrhythmias.
Artemether/lumefantrine	1	Antiretroviral agents	The combination may increase lumefantrine concentrations causing QT prolongation, decreased concentration of antiretroviral resulting in loss of efficacy, or decrease in artemether/lumefantrine concentrations resulting in loss of efficacy.
Artemether/lumefantrine	1	Class IA antiarrhythmics	Prolonged QT interval and cardiac arrhythmias are a potential when class IA antiarrhythmics and artemether/lumefantrine are used concomitantly.
Artemether/lumefantrine	1	Class III antiarrhythmics	Prolonged QT interval and cardiac arrhythmias are a potential when class III antiarrhythmics and artemether/lumefantrine are used concomitantly.
Artemether/lumefantrine	1	Dronedarone	Coadministration of dronedarone and artemether/lumefantrine may increase the risk of cardiovascular toxicity, including potentially fatal cardiac arrhythmias (torsade de pointes).
Artemether/lumefantrine	1	Halofantrine	The combination of artemether/lumefantrine and halofantrine may result in an increased incidence of cardiac arrhythmias.
Artemether/lumefantrine	1	Macrolides, fluoroquinolones, triazole antifungals	Use of these agents may increase the additive effect on the QT interval and incidence of cardiac arrhythmias.
Artemether/lumefantrine	1	Nilotinib	Additive QT prolongation may occur during coadministration of nilotinib and artemether/lumefantrine.
Artemether/lumefantrine	1	Nonsedating antihistamines	Use of artemether/lumefantrine and astemizole/terfenadine may increase the additive effect on the QT interval and incidence of cardiac arrhythmias.
Artemether/lumefantrine	1	Tetrabenazine	Additive QT prolongation may occur during coadministration of

Generic Name(s)	Significance Level	Interaction	Mechanism
			tetrabenazine and artemether/lumefantrine.
Artemether/lumefantrine	1	Toremifene	Prolonged QT interval and cardiac arrhythmias are a potential when toremifene and artemether/lumefantrine are used concomitantly.
Artemether/lumefantrine	1	Vandetanib	Prolonged QT interval and cardiac arrhythmias are a potential when vandetanib and artemether/lumefantrine are used concomitantly.
Artemether/lumefantrine	1	Vemurafenib	Prolonged QT interval and cardiac arrhythmias are a potential when vemurafenib and artemether/lumefantrine are used concomitantly.
Atovaquone/proguanil	1	Anticoagulants	Proguanil may inhibit the hepatically synthesized clotting factors resulting in potentiation of anticoagulation.
Artemether/lumefantrine	2	Dapsone	Dapsone may increase the risk of hemolytic reactions; closely monitor patients who are taking dapsone and artemether/lumefantrine, particularly patients deficient in glucose-6-phosphate dehydrogenase, methemoglobin reductase, or with hemoglobin M.
Artemether/lumefantrine	2	Hormonal contraceptives	Serum concentrations of hormonal contraceptives may be decreased by artemether
Atovaquone/proguanil	2	Etoposide	Plasma concentrations of etoposide may be increased by atovaquone.
Atovaquone/proguanil	2	Rifamycins	Plasma concentrations of atovaquone may be decreased by rifamycins.
Atovaquone/proguanil	2	Tetracyclines	Tetracyclines may decrease the plasma concentrations and pharmacologic effects of atovaquone.

Significance level 1=major severity; significance level 2=moderate severity

VI. Adverse Drug Events

The most common adverse drug events reported with the antimalarials are listed in Tables 10 and 11. The boxed warnings for the antimalarials are listed in Tables 12 and 13.

Table 10. Adverse Drug Events (%) Reported with the Single Entity Antimalarials[1-9]

Adverse Events	Chloroquine	Hydroxychloroquine	Mefloquine	Primaquine	Pyrimethamine	Quinine
Cardiovascular						
Arrhythmia	-	-	-	✔	✔	✔
Atrial fibrillation	-	-	-	-	-	✔
Atrioventricular block	-	-	-	-	-	✔
Bradycardia	-	-	<1	-	-	✔
Cardiac arrest	-	-	-	-	-	✔
Cardiomyopathy	✔	✔	-	-	-	-
Chest pain	-	-	✔	-	-	✔
Electrocardiogram changes	✔	-	✔	-	-	✔
Flushing	-	-	✔	-	-	✔
Hypotension	✔	-	✔	-	-	✔
Hypertension	-	-	✔	-	-	-
Palpitations	-	-	✔	-	-	✔
Syncope	-	-	✔	-	-	✔
Tachycardia	-	-	✔	-	-	✔
Torsades de pointes	-	-	-	-	-	✔
Central Nervous System						
Agitation	✔	-	✔	-	-	-
Altered mental status	-	-	-	-	-	✔
Aphasia	-	-	-	-	-	✔
Asthenia	-	-	<1	-	-	✔
Ataxia	-	✔	-	-	-	✔
Clonus	-	-	-	-	-	-
Coma	-	-	-	-	-	✔
Confusion	-	-	✔	-	-	✔
Convulsions	-	-	✔	-	-	-
Delirium	✔	-	-	-	-	-
Depression	✔	-	✔	-	-	-
Dizziness	-	✔	✔	-	✔	✔
Dystonic reaction	-	-	-	-	-	✔
Fine motor delay	-	-	-	-	-	-
Gait disturbance	-	-	-	-	-	-

Adverse Events	Chloroquine	Hydroxychloroquine	Mefloquine	Primaquine	Pyrimethamine	Quinine
Fatigue	-	-	1 to 10	-	-	-
Fever	-	-	1 to 10	-	-	✔
Headache	✔	✔	1 to 10	✔	-	✔
Hyperreflexia	-	-	-	-	-	-
Hypoesthesia	-	-	-	-	-	-
Insomnia	✔	-	✔	-	✔	-
Irritability	-	✔	-	-	-	-
Lightheadedness	-	-	-	-	✔	-
Malaise	-	-	-	-	✔	-
Mood swings	-	-	✔	-	-	-
Nervousness	-	✔	-	-	-	-
Nightmares	-	✔	-	-	-	-
Nystagmus	-	-	-	-	-	-
Personality changes	✔	✔	<1	-	-	-
Psychosis	✔	✔	-	-	-	-
Restlessness	-	-	✔	-	-	✔
Seizures	✔	✔	<1	-	-	✔
Sleep disorder	-	-	-	-	-	-
Somnolence	-	-	✔	-	-	-
Syncope	-	-	✔	-	-	-
Tremor	-	-	-	-	-	-
Vertigo	-	✔	✔	-	-	✔
Dermatological						
Acrodermatitis	-	-	-	-	-	-
Allergic skin reactions	-	-	-	-	-	✔
Angioedema	-	✔	-	-	-	-
Dermatitis	-	-	-	-	✔	-
Edema	-	-	✔	-	-	-
Erythema multiforme	-	-	✔	-	✔	✔
Exfoliative dermatitis	-	✔	✔	-	-	✔
Hair loss	✔	✔	<1	-	-	-
Impetigo	-	-	-	-	-	-
Micropapular eruptions	-	✔	-	-	-	✔
Photosensitivity	✔	-	-	-	-	✔
Pigmentation	✔	✔	-	-	✔	-
Pruritus	✔	✔	<1	✔	-	✔
Rash	-	-	1 to 10	-	✔	✔

Adverse Events	Chloroquine	Hydroxychloroquine	Mefloquine	Primaquine	Pyrimethamine	Quinine
Skin and hair bleaching	✔	✔	-	-	-	-
Stevens-Johnson syndrome	-	✔	✔	-	✔	✔
Sweating	-	-	✔	-	-	✔
Toxic epidermal necrosis	-	-	-	-	✔	✔
Urticaria	-	✔	-	-	-	✔
Endocrine and Metabolic						
Cholestatic jaundice	-	-	-	-	-	✔
Elevated liver enzyme levels	-	-	-	-	-	✔
Hepatitis	-	-	-	-	-	✔
Hypersensitivity reactions	-	-	-	-	✔	✔
Hypoglycemia	-	-	-	-	-	✔
Gastrointestinal						
Abdominal cramps/pain	✔	✔	1 to 10	✔	✔	✔
Abnormal liver function	-	✔	-	-	-	✔
Anorexia	✔	✔	✔	-	✔	✔
Atopic glossitis	-	-	-	-	✔	-
Constipation	-	-	-	-	-	-
Diarrhea	✔	✔	1 to 10	-	✔	✔
Dyspepsia	-	-	-	✔	-	-
Dysphagia	-	-	-	-	-	-
Epigastric distress	-	-	-	✔	-	-
Gastroenteritis	-	-	-	-	-	-
Hepatic failure	-	✔	-	-	-	-
Nausea	✔	✔	1 to 10	✔	-	✔
Peptic ulcer	-	-	-	-	-	-
Vomiting	✔	✔	3	✔	✔	✔
Weight loss	-	✔	-	-	-	-
Genitourinary						
Hematuria	-	-	-	-	✔	-
Proteinuria	-	-	-	-	-	-
Renal failure	-	-	-	-	-	✔
Renal impairment	-	-	-	-	-	✔
Urinary tract infection	-	-	-	-	-	-
Hematologic						
Agranulocytosis	✔	✔	-	✔	-	✔
Anemia	-	✔	-	✔	-	-
Aplastic anemia	✔	✔	-	-	-	✔

Adverse Events	Chloroquine	Hydroxychloroquine	Mefloquine	Primaquine	Pyrimethamine	Quinine
Coagulopathy	-	-	-	-	-	✔
Eosinophilia	-	-	-	-	✔	-
Hematocrit decreased	-	-	✔	-	-	-
Hemolytic anemia	-	-	-	✔	-	✔
Leukocytosis	-	-	-	✔	-	-
Leukopenia	-	✔	✔	✔	✔	-
Lymphocyte morphology abnormal	-	-	-	-	-	-
Megaloblastic anemia	-	-	-	-	✔	-
Methemoglobinemia	-	-	-	✔	-	-
Neutropenia	✔	-	-	-	-	✔
Pancytopenia	✔	-	-	-	✔	✔
Thrombocytopenia	✔	✔	✔	-	-	✔
Thrombocytosis	-	-	-	-	-	-
Hepatic						
Hepatitis	-	-	-	-	-	-
Hepatomegaly	-	-	-	-	-	-
Laboratory Test Abnormalities						
Alanine aminotransferase increased	✔	-	-	-	-	-
Aspartate aminotransferase increased	✔	-	-	-	-	-
Hypokalemia	-	-	-	-	-	-
Hypoprothrombinemia	-	-	-	-	-	✔
Transaminases elevated	-	-	✔	-	-	-
Musculoskeletal						
Asthenia	-	-	-	-	-	-
Atrophy	✔	✔	-	-	-	-
Arthralgia	-	-	✔	-	-	-
Back pain	-	-	-	-	-	-
Muscle cramps	-	-	✔	-	-	-
Myalgia	-	-	1 to 10	-	-	✔
Myopathy	✔	✔	-	-	-	-
Reflex depression	✔	✔	-	-	-	-
Sensory changes	✔	✔	-	-	-	-
Weakness	✔	-	✔	-	-	✔
Respiratory						
Asthma	-	-	-	-	-	✔
Bronchospasm	-	✔	-	-	-	-
Cough	-	-	-	-	-	-

Adverse Events	Chloroquine	Hydroxychloroquine	Mefloquine	Primaquine	Pyrimethamine	Quinine
Dyspnea	-	-	✔	-	-	✔
Influenza	-	-	-	-	-	-
Nasopharyngitis	-	-	-	-	-	-
Pneumonia	-	-	-	-	-	-
Pulmonary edema	-	-	-	-	-	✔
Respiratory tract infection	-	-	-	-	-	-
Rhinitis	-	-	-	-	-	-
Other						
Abnormal color vision	-	✔	-	-	-	✔
Abscess	-	-	-	-	-	-
Anaphylaxis	-	-	-	✔	-	-
Angioedema	-	-	-	-	-	-
Blindness	-	-	-	-	-	✔
Blurred vision	✔	✔	-	-	-	✔
Changes in accommodation	✔	✔	-	✔	-	✔
Chills	-	-	1 to 10	-	-	✔
Conjunctivitis	-	-	-	-	-	-
Corneal deposits	-	✔	-	-	-	-
Deafness/hearing impairment	✔	✔	✔	-	-	✔
Diplopia	-	-	-	-	-	✔
Ear infection	-	-	-	-	-	-
Helminthic infection	-	-	-	-	-	-
Hookworm infection	-	-	-	-	-	-
Hypersensitivity reactions	-	-	-	-	-	-
Lupus-like syndrome	-	-	-	-	-	✔
Ocular edema	-	✔	-	-	-	-
Oral herpes	-	-	-	-	-	-
Photophobia	-	✔	-	-	-	-
Retinopathy	✔	✔	-	-	-	-
Scotomas	✔	✔	-	-	-	✔
Splenomegaly	-	-	-	-	-	-
Suicide	-	-	-	-	-	✔
Tinnitus	✔	✔	✔	-	-	✔

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 11. Adverse Drug Events (%) Reported with the Combination Antimalarials[1-9]

Adverse Events	Artemether and Lumefantrine	Atovaquone and Proguanil
Cardiovascular		
Palpitations	18	-
Central Nervous System		
Agitation	<3	-
Asthenia	5 to 38	8
Ataxia	<3	-
Clonus	<3	-
Depression	-	<1
Dizziness	4 to 39	5
Fine motor delay	<3	-
Gait disturbance	<3	-
Fatigue	3 to 17	-
Fever	25 to 29	<1
Headache	13 to 56	10
Hyperreflexia	<3	-
Hypoesthesia	<3	-
Insomnia	5	2-3
Malaise	3	-
Mood swings	<3	-
Nystagmus	<3	-
Seizures	-	✔
Sleep disorder	22	-
Tremor	<3	-
Vertigo	3	-
Dermatological		
Acrodermatitis	<3	-
Erythema multiforme	-	✔
Impetigo	<3	-
Photosensitivity	-	✔
Pruritus	4	1 to 6
Rash	3	✔
Stevens-Johnson syndrome	-	✔
Urticaria	<3	✔
Gastrointestinal		
Abdominal cramps/pain	8 to 17	17
Anorexia	13 to 40	≥5
Constipation	<3	-

Adverse Events	Artemether and Lumefantrine	Atovaquone and Proguanil
Diarrhea	7 to 8	5 to 8
Dyspepsia	<3	-
Dysphagia	<3	-
Gastroenteritis	<3	-
Nausea	5 to 26	12
Peptic ulcer	<3	-
Stomatitis	-	✔
Vomiting	17 to 18	12
Genitourinary		
Hematuria	<3	-
Proteinuria	<3	-
Urinary tract infection	<3	-
Hematologic		
Anemia	4 to 9	✔
Eosinophilia	<3	-
Hematocrit decreased	<3	-
Leukocytosis	<3	-
Leukopenia	<3	-
Lymphocyte morphology abnormal	<3	-
Neutropenia	-	✔
Pancytopenia	-	✔
Thrombocytopenia	<3	-
Thrombocytosis	<3	-
Hepatic		
Cholestasis	-	✔
Hepatitis	-	✔
Hepatomegaly	6 to 9	-
Laboratory Test Abnormalities		
Alanine aminotransferase increased	<3	✔
Aspartate aminotransferase increased	4	✔
Hypokalemia	<3	-
Musculoskeletal		
Atrophy	-	-
Arthralgia	3 to 34	-
Back pain	<3	-
Myalgia	3 to 32	-
Respiratory		

Adverse Events	Artemether and Lumefantrine	Atovaquone and Proguanil
Asthma	<3	-
Bronchitis	<3	-
Cough	6 to 23	-
Influenza	<3	-
Nasopharyngitis	≤3	-
Pneumonia	<3	-
Respiratory tract infection	<3	-
Rhinitis	4	-
Other		
Abscess	<3	-
Anaphylaxis	-	✔
Angioedema	✔	✔
Chills	5 to 23	-
Conjunctivitis	<3	-
Ear infection	<3	-
Helminthic infection	<3	-
Hookworm infection	<3	-
Hypersensitivity reactions	✔	✔
Lupus-like syndrome	-	-
Ocular edema	-	-
Oral herpes	<3	-
Scotomas	-	-
Splenomegaly	9	-
Tinnitus	<3	-
Visual difficulties	-	✔

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 12. Boxed Warning for Chloroquine, Hydroxychloroquine and Primaquine[1]

WARNING
Physicians should completely familiarize themselves with the complete contents of the monograph before prescribing chloroquine, hydroxychloroquine, and primaquine.

Table 13. Boxed Warning for Quinine[1]

WARNING
Quinine use for the treatment or prevention of nocturnal leg cramps may result in serious and life-threatening hematologic reactions, including thrombocytopenia and hemolytic uremic syndrome/thrombotic thrombocytopenic purpura. Chronic renal impairment associated with the development of thrombotic thrombocytopenic purpura has been reported. The risk associated with quinine use in the absence of evidence of its effectiveness in the treatment or prevention of nocturnal leg cramps outweighs any potential benefit.

VII. Dosing and Administration

The usual dosing regimens for the antimalarials are listed in Table 14.

Table 14. Usual Dosing Regimens for the Antimalarials[1-9]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Chloroquine	Treatment of extraintestinal amebiasis: Tablet: 1 g (600 mg base) daily for two days, followed by 500 mg (300 mg base) daily for at least two to three weeks; treatment is usually combined with an effective amebicide Prophylaxis of malaria: Tablet: 500 mg (300 mg base) on the same day each week; begin two weeks prior to exposure; if therapy cannot begin two weeks before exposure, an initial loading dose of 1 g (600 mg base) should be given in two divided doses, six hours apart; continue for eight weeks after leaving endemic area Treatment of acute malaria: Tablet: 1 g (600 mg base), followed by an additional 500 mg (300 mg base) after six to eight hours, and a single dose of 500 mg (300 mg base) on each of two consecutive days; this represents a total dose of 2.5 g chloroquine phosphate	Prophylaxis of malaria: Tablet: 5 mg/kg (calculated as base) on the same day each week, but should not exceed the adult dose regardless of weight; begin two weeks prior to exposure; if therapy cannot begin two weeks before exposure, an initial loading dose of 10 mg/kg (calculated as base) should be given in two divided doses, six hours apart; continue for eight weeks after leaving endemic area Treatment of acute malaria: Tablet: First dose, 10 mg/kg (calculated as base but not to exceed 600 mg base); Second dose, 5 mg/kg (calculated as base but not to exceed 300 mg base) given 6 hours after first dose; Third dose, 5 mg/kg (calculated as base) given 24 hours after first dose; Fourth dose, 5 mg/kg (calculated as base) given 36 hours after first dose	Tablet: 250 mg 500 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	or 1.5 g base in three days		
Hydroxychloroquine	Treatment of lupus erythematosus: Tablet: initial, 400 mg once or twice daily continued for several weeks or months; maintenance: 200 to 400 mg daily Prophylaxis of Malaria: Tablet: 400 mg (310 mg base) weekly on the exact same day; begin two weeks prior to exposure; if therapy cannot begin two weeks before exposure, an initial loading dose of 800 mg (620 mg base) should be given in two divided doses, six hours apart; continue for 8 weeks after leaving endemic area Treatment of rheumatoid arthritis: Tablet: initial, 400 to 600 mg daily; maintenance: 200 to 400 mg daily Treatment of Acute Malaria: Tablet: 800 mg (620 mg base) initially, followed by 400 mg (310 mg base) in six to eight hours and 400 mg (310 mg base) on each of two consecutive days; an alternative method, employing a single dose of 800 mg (620 mg base) has also proved effective	Prophylaxis of Malaria: Tablet: 5 mg base/kg (calculated as base) weekly on the exact same day; begin two weeks prior to exposure; if therapy cannot begin two weeks before exposure, an initial loading dose of 10 mg/kg (calculated as base) should be given in two divided doses, six hours apart. Continue for eight weeks after leaving endemic area Treatment of Acute Malaria: Tablet: First dose, 10 mg/kg (calculated as base but not to exceed 620 mg base); Second dose, 5 mg/kg (calculated as base but not to exceed 310 mg base) 6 hours after first dose; Third dose, 5 mg/kg (calculated as base but not to exceed 310 mg base) 18 hours after second dose; Fourth dose, 5 mg/kg (calculated as base but not to exceed 310 mg base) 24 hours after third dose.	Tablet: 200 mg
Mefloquine	Prophylaxis of Malaria: Tablet: 250 mg once weekly; begin one week before arrival in an endemic area and continue for four additional weeks after leaving endemic area Treatment of Acute Malaria: Tablet: 1,250 mg given as a single dose	Prophylaxis of Malaria: Tablet: ≥6 months of age, 20 to 30 kg: ½ tablet once weekly; 30 to 45 kg, ¾ tablet once weekly; >45 kg, 1 tablet once weekly; begin one week before arrival in an endemic area and continue for four additional weeks after leaving endemic area Treatment of Acute Malaria: Tablet: ≥6 months of age: 20 to 25 mg/kg, which may be split into two doses separated by six to eight hours	Tablet: 250 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Primaquine	Radical Cure of Vivax Malaria, Prevention of Relapse of Vivax Malaria: Tablet: one tablet (15 mg base) daily for 14 days	Safety and efficacy in children have not been established	Tablet: 26.3 mg
Pyrimethamine	Prophylaxis of Malaria: Tablet: 25 mg once weekly Treatment of Acute Malaria: Tablet: 25 mg daily for two days in combination with a sulfonamide; if used alone, use 50 mg daily for two days Treatment of toxoplasmosis when used conjointly with a sulfonamide: Tablet: initial, 50 to 75 mg daily (with 1 to 4 grams of sulfadoxine) for one to three weeks, then reduce dose by half and continue for an additional four to five weeks	Prophylaxis of Malaria: Tablet: <4 years of age: 6.25 mg once weekly; 4 to 10 years of age, 12.5 mg once weekly; >10 years of age, 25 mg once weekly Treatment of Acute Malaria: Tablet: four to 10 years of age, 25 mg daily for two days in combination with a sulfonamide Treatment of toxoplasmosis when used conjointly with a sulfonamide: Tablet: 1 mg/kg divided into two daily doses; after two to four days, may reduce dose by half and continue for one month	Tablet: 25 mg
Quinine	Treatment of Acute Malaria: Capsule: 648 mg every eight hours for seven days	Treatment of acute malaria in patients ≥16 years of age: Capsule: 648 mg every eight hours for seven days	Capsule: 324 mg
Combination Products			
Artemether and lumefantrine	Treatment of Acute Malaria: Tablet: a three-day treatment schedule with a total of six doses is recommended for adult patients with a bodyweight of ≥35 kg: 4 tablets as a single initial dose, 4 tablets again after 8 hours, and then 4 tablets twice daily for the following two days (total course of 24 tablets)	Treatment of Acute Malaria: Tablet: 5 to <15 kg: 1 tablet as an initial dose, 1 tablet again after 8 hours, and then 1 tablet twice daily for the following two days 15 to <25 kg: 2 tablets as an initial dose, 2 tablets again after 8 hours, and then 2 tablets twice daily for the following two days 25 to <35 kg: 3 tablets as an initial dose, 3 tablets again after 8 hours, and then 3 tablets twice daily for the following two days ≥35 kg: 4 tablets as an initial dose, 4 tablets again after 8 hours, and then 4 tablets twice daily for the following two days	Tablet: 20-120 mg
Atovaquone and proguanil	Prophylaxis of Malaria:	Prophylaxis of Malaria:	Tablet:

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Tablet: 250-100 mg once daily. Begin one to two days before entering an endemic area and continue daily during stay and for seven days after return Treatment of Acute Malaria: Tablet: four tablets (total daily dose 1 g atovaquone and 400 mg proguanil) as a single daily dose for three consecutive days	Tablet: 11 to 20 kg, 62.5-25 mg daily; 21 to 30 kg, 125-50 mg daily as a single dose; 31 to 40 kg, 187.5-75 mg daily as a single dose; >40 kg: 250-100 mg daily as a single dose; begin one to two days before entering an endemic area and continue daily during stay and for seven days after return Treatment of Acute Malaria: Tablet: 5 to 8 kg, 125-50 mg daily for three consecutive days; 9 to 10 kg, 187.5-75 mg daily for three consecutive days; 11 to 20 kg, 250-100 mg daily for three consecutive days; 21 to 30 kg, 500-200 mg daily for three consecutive days; 31 to 40 kg, 750-300 mg daily for three consecutive days; >40 kg, 1,000-400 mg daily for three consecutive days	62.5-25 mg 250-100 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the antimalarials are summarized in Table 15.

Table 15. Comparative Clinical Trials with the Antimalarials

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Prophylaxis of Malaria				
Overbosch et al.[23] (2001) Atovaquone-proguanil vs mefloquine	DB, MC, RCT Nonimmune patients who traveled to malaria-endemic areas for up to 28 days	N=966 60 days following return from endemic area	Primary: Frequency of adverse events Secondary: Frequency of treatment-limiting adverse events, efficacy of prophylaxis	Primary: At least one adverse event was reported in 352 (71.4%) of 493 subjects in the atovaquone-proguanil group and 325 (67.3%) of 483 subjects in the mefloquine group seven days after returning from a malaria-endemic area (4.1% difference; 95% CI, –1.7 to 9.9). The total number of adverse events reported was 1,037 (38.4 per 100 person-weeks) in the atovaquone-proguanil group and 1,163 (43.4 per 100 person weeks) in the mefloquine group. Adverse events were reported in 318 (64.5%) of 493 subjects who received atovaquone-proguanil and 324 (67.1%) of 483 subjects who received mefloquine (-2.6% difference; 95% CI, –8.5 to 3.4). Of the 2,120 treatment-associated adverse events, 1,310 (62%) were considered to be unrelated to the study drug. Treatment-associated adverse events occurred in a significantly higher proportion of subjects on mefloquine compared to those on atovaquone-proguanil (42 vs 30%; P=0.01). Adverse events associated with the study drug were described as moderate or severe in 51 (10%) of 493 subjects (96 events) who received atovaquone-proguanil and in 92 (19%) of 483 subjects (194 events) who received mefloquine (difference, 9%; P=0.01). These events were severe in 19 subjects (4%; 31 events) who received atovaquone-proguanil and in 29 subjects (6%; 55 events) who received mefloquine. Secondary: More patients in the mefloquine group discontinued treatment due to adverse effects compared to the atovaquone-proguanil group (26 subjects vs 16 subjects). The event was attributed to treatment in 37 subjects. Twenty-eight events occurred in 13 subjects in the atovaquone-proguanil arm, and 79 events occurred in 24 subjects in the mefloquine arm.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Four subjects were evaluated for malaria, but serologic testing indicated that none had malaria. A total of 963 subjects completed the 60-day follow-up period.
Høgh et al.[24] (2000) Atovaquone-proguanil vs chloroquine and proguanil	DB, PC, RCT Patients planning to travel for up to 28 days to a *Plasmodium falciparum*-endemic area	N=1,008 60 days after leaving a malaria-endemic area	Primary: Overall frequency of adverse events assessed at seven days and 28 days after leaving the malaria-endemic area Secondary: Frequency of treatment-limiting adverse events	Primary: At least one adverse event was reported by 311 of 511 (61%) participants in the atovaquone-proguanil group and 329 of 511 (64%) in the chloroquine-proguanil group at seven days after return from a malaria-endemic area (-3.5% difference; 95% CI, –9.5 to 2.4). Adverse events not attributable to placebo were reported by 296 of 511 (58%) of those receiving atovaquone-proguanil and 329 of 511 (64%) receiving chloroquine-proguanil (–6.5%, 95% CI, –12.4 to –0.5). Adverse events attributed to study drug occurred in more participants in the chloroquine-proguanil arm than in the atovaquone-proguanil arm (28 vs 22%; P=0.024). Moderate-to-severe adverse events attributable to the study drug occurred in 37 (7%) participants (54 events) receiving atovaquone-proguanil and 56 (11%) (97 events) on chloroquine-proguanil experienced (difference, 4%; P=0.05). Secondary: Eleven people in the atovaquone-proguanil arm and 16 in the chloroquine-proguanil arm discontinued study drug prematurely because of adverse events. Study drugs were not thought to be associated with any serious adverse events.
Camus et al.[25] (2004) Atovaquone-proguanil vs chloroquine and proguanil	MC, OL, RCT Nonimmune pediatric travelers (2 to 17 years of age) to areas where there was a substantial risk of acquiring *Plasmodium*	N=221 60 days after travel	Primary: Frequency of adverse events (during travel plus seven days after and while subjects were receiving study drug) Secondary:	Primary: No serious adverse events or deaths occurred in the study. A similar proportion of subjects in each treatment group (35 and 37% of atovaquone-proguanil and chloroquine-proguanil recipients, respectively) reported adverse events during travel and 7 days after returning (–0.015; 95% CI, –0.14 to 0.11). There was a lower incidence of abdominal pain and vomiting in the atovaquone-proguanil group than in the chloroquine-proguanil group (6 vs

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	falciparum infection		Not reported	13% for both events; between-group difference in proportions, –0.062; 95% CI, –0.14 to 0.01). Thirty-five percent of subjects in the atovaquone-proguanil group reported experiencing at least one adverse event compared to 41% of subjects in the chloroquine-proguanil group (between-group difference in proportions, –0.060; 95% CI, –0.19 to 0.07). There was a similar frequency of adverse events between the atovaquone-proguanil group through day seven after travel (7 vs 8%, respectively, between-group difference in proportions, –0.008; 95% CI, –0.08 to 0.06). Throughout treatment, a lower proportion of atovaquone-proguanil recipients experienced drug-related adverse events (8 vs 14%; between-group difference in proportions, –0.062; 95% CI, –0.15 to 0.02). This difference was primarily the result of a greater number of chloroquine-proguanil recipients with digestive tract complaints (10 vs 5%; between-group difference in proportions, –0.045; 95% CI, –0.11 to 0.03). Secondary: Not reported
Shanks et al.[26] (1998) Atovaquone-proguanil 250-100 mg daily vs atovaquone-proguanil 500-200 mg daily vs placebo	DB, PC, RCT Adult volunteers in a highly malarious area of western Kenya where chloroquine resistance is widespread	N=198 10 weeks	Primary: Development of parasitemia confirmed by blood smear during prophylaxis, symptoms were also tracked Secondary: Adverse events	Primary: All patients in the low-dose and high-dose atovaquone-proguanil groups remained malaria-free during the 10-week prophylaxis period, compared to only 48% in the placebo group (P<0.001). Secondary: Both atovaquone-proguanil prophylactic treatments were well tolerated when compared to placebo. The most commonly reported adverse events were dyspepsia and gastritis, which occurred with a frequency of 6 to 12% and 7 to 9%, respectively, in the atovaquone-proguanil treatment groups and 13 and 7%, respectively, in the placebo group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Sukwa et al.[27] (1999) Atovaquone-proguanil 250 mg/100 mg daily vs placebo	DB, PC, RCT Adult volunteers in a highly malarious area of Zambia	N=274 10 weeks	Primary: Development of parasitemia, as confirmed by blood smear Secondary: Adverse events	Primary: The prophylaxis success rates in the atovaquone-proguanil and placebo groups were 98 and 63%, respectively (P<0.001). Secondary: The most commonly reported adverse events were headache (4% treatment group compared to 9% placebo) and abdominal pain (3% treatment group compared to 5% placebo).
Lell et al.[28] (1998) Atovaquone-proguanil (weight-based dosing) daily vs placebo	DB, PC, RCT Gabonese children 4 to 16 years old who lived in a hyperendemic area for chloroquine-resistant *Plasmodium falciparum* malaria	N=320 12 weeks + 4 weeks of medication-free follow-up	Primary: Positive blood smear, adverse events Secondary: Not reported	Primary: After 12 weeks, a positive blood smear was identified in 25 children in the placebo group and none of the children in the atovaquone-proguanil group (P<0.001). During follow-up weeks 12 to 14, during which the children did not receive medication, positive blood smears were found in 6 placebo-group children and in none of the children on atovaquone plus proguanil (P=0.012). At week 16, the group who had received atovaquone-proguanil and the group who had received placebo did not differ significantly in rates of parasitemia (P=0.252). Adverse events during the chemosuppression phase did not differ between the groups. Secondary: Not reported
Berman et al.[29] (2001) Atovaquone-proguanil 250-100 mg daily for 8 days	DB, PC, RCT Healthy, HIV-negative volunteers in the United States (US) aged 18 to 50 years	N=16 8 weeks	Primary: Rates of parasitemia measured from blood films and by polymerase chain reaction (PCR), symptoms	Primary: Patent parasitemia (i.e., confirmed by blood film) developed in four of four placebo recipients and zero of 12 atovaquone-proguanil recipients (P<0.00l). Protective efficacy of atovaquone-proguanil was 100%. Evaluation of sub-patent parasitemia by PCR analysis of blood obtained on day eight and day nine (six and seven days after challenge) was positive in two of four placebo recipients on day nine and negative on both

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	Volunteers were challenged through the bites of mosquitoes infected with *Plasmodium falciparum.*		suggestive of malaria, adverse events not due to malaria Secondary: Not reported	days for all 12 atovaquone-proguanil recipients. Each placebo recipient was symptomatic within six hours of initial parasitemia, with symptoms including fever, chills, vomiting, and other symptoms. Mild gastrointestinal events were attributed to drug administration in two placebo recipients and one atovaquone-proguanil recipient. Secondary: Not reported
Nakato et al.[30] (2006) Atovaquone–proguanil vs antimalarial chemoprophylaxis (chloroquine–proguanil or mefloquine) vs placebo	MA Patients at risk for malaria	N=4539 (10 trials) Variable duration	Primary: Prevention of malaria, adverse events and tolerability Secondary: Not reported	Primary: <u>Atovaquone–proguanil vs placebo (five studies)</u> The pooled relative risk of malaria in the intervention arm was 0.0423 (95% CI, 0.021 to 0.0853). The protective efficacy of atovaquone–proguanil was 95.8% (95% CI, 91.5 to 97.9). <u>Atovaquone–proguanil vs alternative antimalarial prophylactic agents (three studies)</u> In only one of these three studies were any subjects diagnosed with malaria. In this one study, three subjects in the chloroquine–proguanil group developed *Plasmodium falciparum* malaria compared to none in the atovaquone–proguanil group. Although all three malaria cases were in the chloroquine–proguanil group, this was not statistically significant (P=0.25). There was no greater reporting of adverse effects in those taking atovaquone–proguanil compared to those taking placebo. Serious adverse events were rare. Only one adverse event related to atovaquone–proguanil was reported, and this was repeated vomiting requiring hospitalization. Patients on atovaquone–proguanil had fewer self-reported adverse effects (RR, 0.8234; 95% CI, 0.67 to 1.01) and severe adverse effects (RR, 0.61; 95% CI, 0.42 to 0.89) than those using other antimalarials, whereas neuropsychiatric adverse effects were similar (RR, 0.74; 95% CI, 0.47 to 1.14).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was no significant difference in the proportion of study participants who completed their prescribed course (RR, 0.88; 95% CI, 0.69 to 1.1). Secondary: Not reported
Lobel et al.[31] (1993) Chloroquine 300 mg weekly vs mefloquine 250 mg weekly vs mefloquine 250 mg every other week vs chloroquine 300 mg weekly and proguanil 200 mg daily	OS US Peace Corps volunteers in sub-Saharan Africa while taking prophylactic therapy	N=1,322 3 years	Primary: Long term efficacy and tolerability (incidence of *Plasmodium falciparum* infections and of adverse reactions) Secondary: Not reported	Primary: Weekly mefloquine was 94% more effective compared to chloroquine (95% CI, 86 to 97; P<0.0001), 86% more effective compared to chloroquine plus proguanil (95% CI, 67 to 94; P<0.0001), and 82% more effective compared to mefloquine every other week (95% CI, 68 to 90; P<0.0001). No serious adverse events were observed and mild adverse events were equally frequent in mefloquine- and chloroquine-treated patients. The frequency of these events declined with the increasing duration of prophylaxis. Secondary: Not reported
Tukur et al.[32] (2007) Chloroquine 600 mg base on days 1 and 2, followed by 300 mg base on day 3, then weekly pyrimethamine 25	PRO Pregnant women between 12 and 28 weeks of gestation	N=500 Variable follow-up	Primary: Acute uncomplicated or severe malaria during pregnancy, infants born with congenital malaria parasitemia, and	Primary: Of the women who completed at least four antenatal visits, 26 (5.9%) had a febrile illness during follow-up: four (1.8%) in the SP group and 22 (9.8%) in the CQ + P group (P=0.005). None of the women in the SP group developed severe malaria, but three (1.3%) in the CQ + P group had severe malaria (P=0.25). Of those who completed at least four antenatal visits, no woman in the SP

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg until delivery (CQ+P) vs pyrimethamine-sulfadoxine 1,500 mg/75 mg as a single dose, then a second dose was administered in the third trimester a minimum of 4 weeks after the first dose but not after 34 weeks gestation as chemoprophylaxis (SP)			infants with low birth weight Secondary: Not reported	group but 11 women (4.9%) in the CQ + P group had peripheral parasitemia prior to or during delivery (P=0.002). Uncomplicated malaria was no more likely to occur in women in their first or second pregnancies than in women with two or more prior pregnancies (P=0.60). Of those who completed at least four visits, five (2.3%) in the SP group had minor reactions to the drug, most commonly vomiting and dizziness. Eleven (4.9%) in the CQ + P group had minor reactions, most commonly pruritus and vomiting. No woman discontinued prophylaxis because of side effects. By delivery, the proportion of women with anemia decreased in both treatment groups. Significantly fewer women in the SP group had anemia (1.2%) than in the CQ + P group (5.0%; P=0.04). The mean hematocrit at delivery was 34.4% in the SP group compared to 33.7% in the CQ + P group (P=0.02). Two women in the CQ + P group delivered very low birth weight infants (<1,500 gm) at a gestational age of 30 weeks. Twelve subjects delivered low birth weight infants (<2,500 gm) between 30 and 35 weeks of gestation, six (3.5%) in the SP group and six (3.3%) in the CQ + P group (P=0.63). Low birth weight was not associated with maternal or cord blood parasitemia. The mean ± SD birth weight in the SP group was 3.12 ± 0.51 kg compared to 3.17 ± 0.56 kg in the CQ + P group (P=0.38). Secondary: Not reported
Steffen et al.[33] (1993) Mefloquine vs pyrimethamine-	OS Tourists to East Africa; all passengers returning on charter flights from Mombasa, Kenya to Europe	N=145,003 1985 to 1991	Primary: Efficacy and side-effects of malaria prophylaxis Secondary: Not reported	Primary: Among the 139,164 who stayed in East Africa for less than one year, 296 cases of confirmed malaria were reported (275 due to *Plasmodium falciparum*). In people who used no chemoprophylaxis, the incidence of *Plasmodium falciparum* malaria was 1.2% per month.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
sulfadoxine vs chloroquine-proguanil vs chloroquine vs no therapy	received an in-flight questionnaire and a second one was sent three months later. Respondents were excluded if they had spent more than a year abroad or if the majority of their stay was outside of East Africa.			Prophylactic effectiveness was 91% (95% CI, 85 to 94) for mefloquine, 82% (95% CI, 71 to 89) for pyrimethamine and sulfadoxine, 72% (95% CI, 56 to 82) for chloroquine plus proguanil, and 10 to 42% for chloroquine at various doses. Rates of side effects, which were usually mild, were 18.8% for mefloquine users, 17.1 and 18.6% for chloroquine 300 and 600 mg base per week users, 30.1% for chloroquine plus proguanil users, and 11.7% for sulfadoxine and pyrimethamine users. Secondary: Not reported
Ohrt et al.[34] (1997) Mefloquine 250 mg daily for 3 days, then 250 mg once weekly vs doxycycline 100 mg daily vs placebo	DB, PC, RCT Soldiers from military posts in areas of Indonesia where drug-resistant malaria is prevalent	N=204 13 weeks	Primary: First occurrence of malaria as documented by positive lab test Secondary: Tolerability of study drugs	Primary: In the placebo group, 53 of 69 soldiers developed malaria (9.1 person-years), resulting in an attack rate of 5.8 cases per person-year (95% CI, 4.3 to 7.7). No malaria occurred in the 68 soldiers (16.9 person-years) in the mefloquine group resulting in 100% (95% CI, 96 to 100) protective efficacy. In the doxycycline group, *Plasmodium falciparum* malaria occurred in one of 67 soldiers (16.0 person-years), yielding a protective efficacy of 99% (95% CI, 94 to 100). Secondary: Both doxycycline and mefloquine were significantly better tolerated than placebo (P<0.001 and P=0.005, respectively) and doxycycline was better tolerated than mefloquine (P=0.006).
Sonmez et al.[35] (2005) Mefloquine 250 mg per week	RCT Prophylaxis in Turkish soldiers assigned to service in Kabul,	N=1,400 9 months (12 weeks prophylaxis and 6 months	Primary: Safety and efficacy of mefloquine and doxycycline Secondary:	Primary: No malaria case was observed and there were no severe adverse events in either group. The most frequent side effects in both groups were gastrointestinal, for which the frequency was significantly higher with doxycycline (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs doxycycline 100 mg daily	Afghanistan	of monitoring after returning to Turkey)	Not reported	Neurological side effects were higher with doxycycline by the 2nd week compared to mefloquine (P=0.001). The compliance rate with mefloquine was greater than with doxycycline (P<0.05). Secondary: Not reported
Soto et al.[36] (1998) Primaquine 30 mg daily vs placebo	DB, PC, RCT Male Colombian soldiers assigned to patrol a malaria-endemic area (Uraba province, Columbia) receiving required prophylactic therapy as nonimmune persons	N=176 19 weeks	Primary: Efficacy of primaquine prophylaxis Secondary: Not reported	Primary: Protective efficacy in the primaquine group (122 participants) was 89% (95% CI, 75 to 96) against all types of malaria, 94% (95% CI, 78 to 99) against *Plasmodium falciparum* malaria, and 85% (95% CI, 57 to 95) against *Plasmodium vivax* malaria. Secondary: Not reported
Treatment of Malaria				
Smithuis et al.[37] (2010) Artemether 3.3 mg/kg/day plus lumefantrine 19.8 mg/day (treatment 4) vs artesunate 4 mg/kg/day for 3 days plus mefloquine 25	RCT, OL, MC Patients with acute uncomplicated *Plasmodium falciparum* malaria or mixed infection	N=800 63 days	Primary: Efficacy and safety Secondary: Not reported	Primary: Patients on artesunate-amodiaquine had a higher reoccurrence of *Plasmodium falciparum* infections (9.4%; 95% CI, 5.7 to 15.3) than for artemether- lumefantrine (1.4%; 95% CI, 0.3 to 5.3%; P=0.0013), fixed-dose artesunate-mefloquine (0%; 95% CI, 0 to 2.3%; P<0.001), loose dose artesunate-mefloquine (1.3%; 95% CI, 0.3 to 5.3%; P=0.0018), and dihydroartemisinin-piperaquine (1.3%; 95% CI, 0.3 to 5.2%; P=0.0012). Artesunate-amodiaquine compared to artesunate-mefloquine treatment groups (HR, 3.2; 95% CI, 1.3 to 8.0; P=0.04). Artesunate-amodiaquine compared to artemether-lumefantrine (HR, 2.6; 95% CI, 1.0 to 6.0; P=0.08). Artesunate-amodiaquine compared to dihydroartemisinin-piperaquine (HR, 2.3; 95% CI, 0.9 to 6.0; P=0.08). Mixed *falciparum* and *vivax* infection were common: 16% had mixed infection at study initiation and 41% of patients had *Plasmodium vivax*

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/kg on day 0 (treatment 1a loose dose) vs artesunate 4 mg/kg/day for 3 days plus mefloquine 8.8 mg/kg/day for 3 days (treatment 1b fixed dose) vs artesunate 4 mg/kg/day plus amodiaquine 10.8 mg/kg/day (treatment 2) vs dihydroartemisinin 2.5 mg/kg/day plus piperaquine 20 mg/kg/day (treatment 3) Patients were also randomly assigned to receive primaquine 0.75 mg/kg as a single dose.				infection at follow-up. The addition of single dose primaquine reduced *Plasmodium falciparum* significantly (RR, 11.9; 95% CI, 7.4 to 20.5). Adverse events reported by 599 patients; most common included vomiting and dizziness. Secondary: Not reported
Achan et al.[38]	RCT, OL	N=175	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2009) Artemether-lumefantrine (weight-based dosing) at baseline, then 8 hours after the first dose, then twice daily for the following two days vs quinine 10 mg/kg three times daily for 7 days	Children aged 6 to 59 months with uncomplicated malaria	28 days	Cure rates Secondary: Adherence to study drug, presence of gametocytes, recovery of hemoglobin concentration from baseline at day 28, and safety profiles	Cure rates were 96% for the artemether-lumefantrine group and 64% for the quinine group (P<0.001). Participants were 10 times more likely to fail treatment with oral quinine than with artemether-lumefantrine (HR, 10.7; 95% CI, 3.3 to 35.5; P=0.001). The risk of treatment failure was significantly higher in the quinine group than in the artemether-lumefantrine group (35.3 vs 4.1%; P<0.001). Secondary: Mean adherence in the artemether-lumefantrine group was 95% and in the quinine group was 85% (P=0.0008). Non-adherence to treatment was higher in the quinine group than in the artemether-lumefantrine group (55 vs 17%; P=0.001). Gametocytemia was more common in the quinine group at day 7 compared to the artemether- lumefantrine group (14 vs 1%; P=0.001). By day 28 the groups did not differ. Total person time with gametocytes was 20 weeks for quinine compared to five weeks for artemether-lumefantrine (P<0.01). Hemoglobin concentrations improved equally in both groups during 28 days of follow-up. Reported adverse events did not differ between the groups. Common side effects of quinine such as nausea, headache, tinnitus, and blurred vision were not noted.
Gürkov et al.[39] (2008) Artemether-lumefantrine (AL) (weight-based dosing) at 0, 8, 24, 36, 48 and 60 hours (6 doses)	RCT, SB Patients ≥5 years of age with parasitologically proven uncomplicated *Plasmodium falciparum* malaria	N=97 90 days	Primary: Clinical and parasitological efficacy, tolerability, and ototoxicity Secondary: Not reported	Primary: On day seven, no treatment failure was detected in any group. Until day 28, three patients in the Q group and one in the AP group presented with *Plasmodium falciparum* malaria. The parasitological failure rate on day 28 was 9 and 6% in the Q and AP group, respectively. There was no treatment failure in the AL group. Between day 28 and day 90, seven patients with *falciparum* malaria were diagnosed. Nine patients (five treated with Q, two with AP, and two with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs atovaquone-proguanil (AP) 20 mg/8mg/kg (<40 kg) or 1000 mg/400 mg (adults and children ≥40 kg) per day for 3 days vs quinine (Q) 10 mg/kg (children) or 600 mg (adults and children ≥50 kg) three times daily for 7 days				AL) showed *Plasmodium vivax* infection during follow-up. No vomiting occurred after ingestion of the antimalarial drugs, and no serious adverse events were reported during treatment and follow-up. Hearing problems and tinnitus were more common on day seven with nine of thirty patients complaining of hearing problems in the Q group. In seven of these, audiometry and otoacoustic emissions (OAE) testing confirmed significant hearing loss. Patients reporting subjective hearing impairment in the AL group did not have abnormal hearing test results. In the AP group, only the reported hearing loss by one patient on day 90 corresponded to significantly impaired audiometry and OAE results. In the Q group, a hearing loss affecting all frequencies was evident on day seven and has disappeared by day 28. Otherwise, no significant changes of the mean hearing thresholds compared to day zero were evident. There was no evidence of persistent hearing loss in any treatment group. The average distortion product (DP) threshold level of the Q group on day seven was elevated from baseline. Multivariate analysis reveals a significant effect of time on the DP threshold levels for day seven and day 28. The three treatment groups did not behave differently, except on day seven when a significant combined effect of time and group is visible as the Q ototoxicity. There was no evidence of drug-induced brain stem lesions by brain stem evoked response audiometry measurements. Secondary: Not reported
Thapa et al.[40] (2007) Artemether-lumefantrine (AL) (based on body weight) given as 6	RCT, OL, PG Patients >5 years of age who had uncomplicated *falciparum* or mixed *falciparum/vivax*	N=99 28 days	Primary: Treatment failure Secondary: Not reported	Primary: Assessed by microscopy, 12.1% of SP-treated patients redeveloped parasitemia during the 28-day follow-up period compared to 0% in the AL group (P=0.011). An additional six patients (two SP and four AL) with sub-microscopic gametocytemia or breakthrough parasitemia between Days 14 and 28,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
doses over 3 days vs pyrimethamine-sulfadoxine (SP) (based on body weight) as a single dose	malaria infection			suggesting that AL efficacy was lower than estimated by microscopy. Apart from fever, the most frequent symptoms at presentation were headache (97 and 88% in AL and SP groups, respectively), nausea (42 and 64%, respectively), and vomiting (39 and 46%, respectively). Other gastrointestinal, neurologic, musculoskeletal, respiratory, and dermatologic complaints were less frequent. Secondary: Not reported
Bustos et al.[41] (1999) Atovaquone-proguanil (weight-based dosing) daily for 3 days vs chloroquine (total dose over the course of 3 days: if >40 kg, received 1,500 mg, if 30-40 kg received 10 mg/kg) vs chloroquine (dosed as above) plus pyrimethamine-sulfadoxine (>50 kg 1,500 mg/75 mg; ≤50 kg 1,000 mg/50 mg)	OL, RCT Patients with acute uncomplicated *Plasmodium falciparum* malaria treated at a hospital in the Philippines between October 1994 and February 1995, 12 to 65 years old and >30 kg Patients were hospitalized for 28 days to ensure medication compliance and prevent reinfection.	N=110 28 days	Primary: Cure rate including parasite clearance time (PCT) and fever clearance time (FCT); symptoms were also assessed using an interview Secondary: Not reported	Primary: Atovaquone-proguanil produced a significantly higher cure rate (100%) compared to chloroquine (30.4%; P<0.001) or the chloroquine-sulfadoxine-pyrimethamine regimen (87.5%; P<0.05). There were significant differences between the treatment groups regarding parasite clearance time (mean: 46.7 hours for atovaquone-proguanil, 60 hours for chloroquine, and 42.8 hours for chloroquine plus sulfadoxine-pyrimethamine) or fever clearance time (mean, 38.8, 46.8, and 34.5 hours, respectively). The most frequently reported adverse events were consistent with malaria infection and included vomiting (18% with atovaquone-proguanil, 17% with chloroquine, and 9% with chloroquine-sulfadoxine-pyrimethamine), abdominal pain (15, 17, and 3%, respectively), anorexia (11, 13, and 0%, respectively), and headache (6, 17, and 3%, respectively). Adverse events did not differ significantly between treatment groups. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
as a single dose				
Looareesuwan et al.[42] (1999) Atovaquone-proguanil 4 tablets by mouth daily for 3 days vs mefloquine 750 mg by mouth initially, then 500 mg 6 hours later	OL, RCT Adult patients with acute *Plasmodium falciparum* malaria treated at a hospital in Thailand between August 1993 and July 1994 Patients were treated for 1 to 3 days and followed for 28 days.	N=158 28 days	Primary: Cure rate, calculated using World Health Organization (WHO) classifications as R1, R2 or R3 Secondary: Parasite clearance time (PCT), fever clearance time (FCT), safety	Primary: Atovaquone-proguanil was significantly more efficacious compared to mefloquine (cure rate 100 vs 86%; P<0.002). Secondary: The treatments did not differ with respect to PCT (mean 65 hours compared to 74 hours) or FCT (mean 59 hours compared to 51 hours). Adverse events occurred in 36% of the patients in the atovaquone-proguanil group and 35% of those in the mefloquine group, with the chief difference observed being vomiting which was found to be more common in the atovaquone-proguanil group (10 vs 2%).
Hitani et al.[43] (2006) Atovaquone-proguanil 250-100 mg 4 tablets daily for 3 successive days (children received one tablet daily for 3 successive days) vs mefloquine 15-25 mg/kg divided into 1-3 doses	RCT Nonimmune patients with uncomplicated *Plasmodium falciparum*	N=73 Follow-up period was 7 to 10 days	Primary: Cure rate, parasite clearance time (PCT), fever clearance time (FCT), and adverse events Secondary: Not reported	Primary: All 20 atovaquone-proguanil adult patients (100%) and 49 of the 50 mefloquine-treated patients (98%) were cured (P=0.71). In the atovaquone-proguanil group, the FCT and PCT appeared to be longer than those of the mefloquine group (3.7 and 3.3 days compared to 2.9 and 2.8 days; P=0.13 and 0.28). Transient elevations in liver enzymes were noted in 15% of the atovaquone-proguanil-treated patients while 38% of mefloquine-treated patients experienced other adverse events such as dizziness, nausea, and vomiting. Secondary: Not reported
de Alencar et al.[44] (1997) Atovaquone 1g	OL, R Adult men (ages 18 to 65 years) with	N=175 10 months (study	Primary: Fever clearance times, parasite clearance times,	Primary: All patients in the quinine plus tetracycline group were cured, and one patient had recrudescence in the atovaquone plus proguanil group. This gave a cure rate of 100% (95% CI, 95 to 100) for the quinine plus

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
plus proguanil 400 mg, both once daily for 3 days vs quinine 600 mg 3 times daily plus tetracycline 250 mg 4 times daily, both for 7 days	smear-confirmed *Plasmodium falciparum* malaria undergoing treatment for malaria at a hospital in the southern Brazilian Amazon region	duration) 28 days (per-patient treatment and follow-up)	cure rates, adverse events Secondary: Not reported	tetracycline group and 98.7% (95% CI, 92 to 99) for the atovaquone plus proguanil group. The mean parasite clearance times were shorter in the atovaquone plus proguanil group (56.1 hours) than in the quinine plus tetracycline group (64 hours; P=0.008). The mean fever clearance times were shorter in the atovaquone plus proguanil group (18.8 hours) than in the quinine plus tetracycline group (28.5 hours; P=0.05). Approximately 62% of patients had side effects in the atovaquone plus proguanil group vs 89% in the quinine plus tetracycline group. There were more patients complaining about tinnitus (55 vs 3; P=0.01), dizziness (39 vs 10; P=0.01), nausea (22 vs 12; P=0.05), and anorexia (13 vs 5; P=0.04) in the quinine plus tetracycline group than in the atovaquone plus proguanil group. Secondary: Not reported
Llanos-Cuentas et al.[45] (2001) <u>Phase I</u> Atovaquone-proguanil vs chloroquine <u>Phase II</u> pyrimethamine-sulfadoxine as a single dose	OL, RCT Patients with acute *falciparum* malaria in northern Peru	N=43 Duration not reported	Primary: 28-day cure rate (RIII=no significant reduction in parasitemia in first 48 hours, RII= marked reduction of parasitemia without clearance in 7 days, RI= clearance of parasitemia within 7 days followed by recrudescence in 28 days)	Primary: <u>Phase I</u> Significantly more patients in the atovaquone-proguanil group were cured (100 vs 8%; P<0.0001). <u>Phase II</u> There were no significant differences in cure rates between the treatment groups (100 vs 100%). Secondary: There were no significant differences in parasite clearance times or fever clearance times between groups in either phase of the study.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs atovaquone-proguanil			Secondary: Fever clearance time and parasite clearance time	
Krudsood et al.[46] (2007) Atovaquone-proguanil 1,000 mg/400 mg once a day for three days	OL Individuals greater than 14 years of age with confirmed acute, uncomplicated *Plasmodium falciparum*	N=140 3 treatment days followed by 3 weeks in a non-transmission area	Primary: 28 day cure rate, parasite clearance time (PCT), and fever clearance time (FCT) Secondary: Not reported	Primary: The overall cure rate at the 28-day follow-up was 97.8% (95% CI, 95.4 to 100). Mean PCT was 41.9 hours while the FCT was 37.1 hours. Secondary: Not reported
Mulenga et al.[47] (1999) Atovaquone-proguanil vs pyrimethamine-sulfadoxine	OL, PG, RCT Inpatients at the Central Hospital of the Tropical Disease Research Centre in Ndola, Zambia with acute *Plasmodium falciparum* malaria (parasite counts between 1,000 and 200,000/µL of blood)	N=163 28 days after treatment ended	Primary: 28 day cure rate, parasite clearance time (PCT) and fever clearance time (FCT) Secondary: Not reported	Primary: There was no significant difference in cure rates between the atovaquone-proguanil group and the sulfadoxine-pyrimethamine group after 28 days (100 vs 98.8%, respectively). FCT was significantly shorter in the atovaquone-proguanil group compared to the sulfadoxine-pyrimethamine group (mean, 30.4 vs 44.9 hours; 95% CI, 8.3 to 26.5; P<0.05). PCT was significantly longer in the atovaquone-proguanil group compared to the sulfadoxine-pyrimethamine group (mean, 64.0 vs 51.4 hours; 95% CI, 12 to 24; P<0.05). Secondary: Not reported
Mulenga et al.[48] (2006) Atovaquone–proguanil (AP) 17 mg/kg and 7 mg/kg of atovaquone and proguanil,	DB, RCT Children 6 to 119 months of age with moderately severe anemia (packed cell volume of <21% and >9%) and *Plasmodium*	N=128	Primary: Treatment failure (defined as a need for blood transfusion or treatment with quinine, persistent anemia or death within 14	Primary: By day 14, 22% of children who had received SP as compared to 8% of children who had received AP met the criteria for treatment failure (OR, 3.34; 95% CI, 1.54 to 7.21). Secondary: The fever clearance time (FCT) was faster in the AP group than in the SP group (P=0.0001). The median FCT in the AP group was 12 hours compared to 29 hours in the SP group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
respectively once daily for 3 days plus placebo vs pyrimethamine-sulfadoxine (SP) 25 mg/kg of sulfadoxine as single dose plus placebo Folic acid 1 mg was given daily for 14 days.	*falciparum* parasitemia		days) Secondary: Fever clearance time, parasitemia at days three, seven, 14 and 28 after the start of treatment, hematological findings 14 or 28 days after the start of treatment, and adverse events	At each time point, parasitemia was less frequent in children who received AP than in those who received SP, but the difference was only statistically significant at day 28 when the failure rate in the SP group was 22% (P=0.001). There were no significant differences in hematological measurements between the treatment groups. The occurrence of non-serious adverse events (AEs) such as cough, vomiting, anorexia and weakness was comparable in the two treatment groups with the exception of vomiting. More patients in the AP group (19%) vomited between day one and two than those in the SP group (7%; P=0.003). AEs were mild and self-limiting and required no intervention.
Ursing et al.[49] (2011) Chloroquine 50 mg/kg given as 2 daily doses over 3 days vs artemether-lumefantrine 1-4 tablets per dose according to weight were given at 0, 8, 24, 36, 48, and 60 hours	OL, MC, RCT Children aged 6 months to 15 years with uncomplicated *falciparum* malaria	N=378 1.5 years	Primary: PCR-adjusted adequate clinical and parasitological response (ACPR) on day 42; PCR-adjusted ACPR on days 28 and 70; selection of resistance-associated alleles and drug tolerability Secondary: Not reported	Primary: Day 28 and 42 treatment efficacies were 97 and 97%, respectively, for artemether-lumefantrine; 95 and 94% respectively, for chloroquine. Parasite clearance was faster with artemether-lumefantrine than with chloroquine (P<0.001). Symptoms resolved similarly in both treatment arms during days zero to three. In the artemether-lumefantrine arm, dizziness (P=0.03) and headache (P=0.01) were more common on day one. Sleeping disorders were more common in the chloroquine arm on day two (P=0.003). Fever was cleared by 130 of 181 and 143 of 188 children by the second dose in the chloroquine and artemether-lumefantrine arms, respectively (P=0.78). When parasites with resistance-associated *Plasmodium falciparum* Chloroquine Resistance Transporter 76T were treated, the day 28 efficacy of chloroquine was 87%. No severe drug-related adverse events were detected for either treatment. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Lederman et al.[50] (2006) Chloroquine 25 mg/kg for 3 days vs chloroquine (same dose) and sulfadoxine 25 mg/kg (single dose) and pyrimethamine 1.25 mg/kg (single dose) (SP) vs above therapy and primaquine 45 mg on day 0 vs above therapy and primaquine 45 mg on day 2	MC, RCT Patients with uncomplicated *falciparum* malaria in Indonesia	N=117 28 days	Primary: Clearance rates and reinfection adjusted cure rates Secondary: Not reported	Primary: After 28 days, 58% of subjects receiving chloroquine had cleared parasitemia and remained aparasitemic compared to 94% receiving chloroquine plus SP (P<0.001). Genotyping was used to confirm that no new infections had intervened to influence cure rates. The demonstrated reinfection-adjusted cure rates for chloroquine compared to chloroquine plus SP were 70 and 99%, respectively (P=0.0006). The difference in clearance rates between the two primaquine groups was insignificant (P=0.025). Secondary: Not reported
Yeshiwondim et al.[51] (2010) Chloroquine 10 mg/kg on day 0 and day 1 and 5 mg/kg on day 2	OL, PRO, RCT Ethiopian patients ≥1 year of age who were positive for *Plasmodium vivax* infections	N=290 8 months	Primary: Treatment failure and relapse rates Secondary: Not reported	Primary: A total of 98.6% patients cleared parasitemia on day three. There was no difference in mean parasite clearance time between treatment groups (chloroquine: 48.3 hours and chloroquine+ primaquine 50.67 hours; P=0.25). The cumulative incidence for therapeutic failure at day 28 was 5.76%, (95% CI, 2.2 to 14.61) with chloroquine treatment and 0.75% (95% CI,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
plus primaquine 0.25 mg/kg from day 29 to day 41 vs chloroquine 10 mg/kg on day 0 and day 1, and 5 mg/kg on day 2 plus primaquine 0.25 mg/kg from day 3 to day 16				0.11 to 5.2) with chloroquine + primaquine treatment (P=0.19). The relapse rate was 8% for chloroquine treatment and 3% for chloroquine + primaquine treatment (P=0.07). The cumulative risk of relapse at day 157 was 61.8% (95% CI, 20.1 to 98.4) with chloroquine treatment compared to 26.3% (95% CI, 7.5 to 29.4) with chloroquine + primaquine treatment (P=0.0038). Secondary: Not reported
Adam et al.[52] (2004) Chloroquine 10 mg/kg for 2 days then 5 mg/kg on day 3 vs pyrimethamine-sulfadoxine as a single dose of 25 mg/kg of the sulfadoxine component (SP) vs quinine 10 mg/kg three times a day for 1 week	OL, RCT Patients with uncomplicated *Plasmodium falciparum* malaria in Sudan	N=96 28 days	Primary: Clinical response according to WHO criteria and parasitological response (levels RIII, RII, and RI), gauged by readings taken on days 0 to 7, 14, 21 and 28 (RIII if day two parasitemia was >25% of day 0; RII if positive smear on day 2 and parasitemia <25% of day 0 value or smear-positive on days 2 to 7; RI if clearance of parasitemia for at least two consecutive days followed by the	Primary: No treatment failures were observed among the patients given sulfadoxine and pyrimethamine. In the chloroquine group, 23.1% had an adequate clinical response; however, 15.4% had early failure (severe malaria symptoms on day three, day-two parasitemia was >25% of day zero, or day-three parasitemia was >25% of day zero) and 61.5% late treatment failure (fever or severe malaria symptoms or any parasitemia after day three). Regarding, parasitological failure, 54.1% in the chloroquine group showed early resistance, 7.7% showed late RI, and 15.1% showed RIII. Adequate treatment responses were achieved in 90.6% of the quinine group. The frequency of treatment failure was significantly higher with chloroquine compared to quinine (76.9 vs 9.3%; P=0.0008). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			reappearance of parasitemia either on days 7 or 14 [early RI] or on days 21 or 28 [late RI]) Secondary: Not reported	
Ezedinachi et al.[53] (1999) Mefloquine 250 mg, sulfadoxine 500 mg and 25 mg pyrimethamine as a single-dose tablet; 0.5-2 tablets were taken daily based on body weight (MSP) vs chloroquine 10mg/kg for 2 days then 5 mg/kg on day 3 (CQ)	MC, RCT Patients with malaria in Nigeria, each treatment was divided into two groups (Group 1 was treated presumptively, based on symptoms while Group 2 was treated based on a parasitological diagnosis)	N=1,935 12 months	Primary: Efficacy and tolerability of treatments Secondary: Not reported	Primary: Low-dose MSP had day-7 response rates of 95 and 91% for Group 1 and Group 2. CQ had day-7 response rates of 82 and 66% in Group 1 and Group 2, respectively. The low-dose MSP was significantly more efficacious, with faster fever and parasite clearance times compared to CQ (P<0.0001). Adverse events were generally more common among those treated with MSP (29%) than those treated with CQ (17%; P<0.0001); however, the adverse events caused by both drugs were mild to moderate and self-limited. Secondary: Not reported
Maguire et al.[54] (2006) Mefloquine 15 mg/kg as a single dose vs chloroquine	OL, PRO, RCT A malaria-naïve population of Javanese adults and children were monitored after arriving in a malaria-endemic region of Papua,	N=243 3 years	Primary: Curative efficacy at 28 days Secondary: Not reported	Primary: The cumulative 28-day curative efficacy with mefloquine was 96% against *Plasmodium falciparum* malaria and 99.6% against *Plasmodium vivax* malaria compared to 26 and 82% with chloroquine against *Plasmodium falciparum* malaria and *Plasmodium vivax* malaria, respectively (P<0.05). The relative rates of treatment failure with chloroquine compared to mefloquine were 20 for *Plasmodium falciparum* (95% CI, 10 to 41) and 52 for *Plasmodium vivax* (95% CI, 7 to 376).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
150 mg base in 3 doses over 48 hours: 10 mg/kg on day 0, then 10 mg/kg on day 1, then 5 mg/kg on day 2 Subjects with confirmed *Plasmodium vivax* malaria also received primaquine.	Indonesia; all subjects who contracted uncomplicated malaria within this group were included in the study			Secondary: Not reported
de Radigues et al.[55] (2006) Pyrimethamine-sulfadoxine as a single dose of 25 mg/kg of the sulfadoxine component (SP) vs chloroquine 10 mg/kg day 0 and day 1, and 5 mg/kg day 2 (CQ)	RCT Children 6 to 59 months with *Plasmodium falciparum* malaria	N=210 28 days	Primary: Therapy failure Secondary: Not reported	Primary: Not taking into account reinfections the global failure rate at day 14 was 2.0 (95% CI, 0.0 to 4.8) in the SP group and 44.2% (95% CI, 34.9 to 96.2) in the CQ group. At day 28 adjusted failure proportions were 7.0% (95% CI, 1.9 to 12.1) in the SP group and 90.5% (95% CI, 84.8 to 96.2) in the CQ group. Secondary: Not reported
MacArthur et al.[56] (2001) Pyrimethamine-sulfadoxine as a single dose of 25 mg/kg of the	RCT Children 6 to 59 months with *Plasmodium falciparum* malaria	N=102 14 days	Primary: Clinical response, parasitological response, hematologic response, and adverse events	Primary: There was no significant difference in clinical, parasitological, and hematologic response between the two treatment groups (P=0.43, 0.69, and 0.70). Significantly more children vomited while on SP compared to MQ on day two (P=0.047) and between days three and seven (P=0.039).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
sulfadoxine component (SP) vs mefloquine 15 mg/kg (MQ)			Secondary: Not reported	Secondary: Not reported
Marquiño et al.[57] (2003) Pyrimethamine-sulfadoxine as a single dose of 25 mg/kg of the sulfadoxine component (SP) vs chloroquine 10 mg/kg day 0 and day 1, and 5 mg/kg day 2 (CQ) vs mefloquine single dose of 15 mg/kg (MQ)	MC, RCT Patients 2 to 50 years of age with *Plasmodium falciparum* malaria	N=198 14 days	Primary: Treatment failures Secondary: Not reported	Primary: An early treatment failure was noted in 27.1% of the CQ group compared to 0% in the SP or MQ. A late treatment failure was noted in 59.3% of the CQ group, 6.4% in the SP groups and 0% in the MQ group. Secondary: Not reported
Bell et al.[58] (2008) Pyrimethamine-sulfadoxine as a single dose of 25 mg/kg of the sulfadoxine component (SP)	DB, RCT Children aged 1 to 5 years with an illness suggesting *falciparum* malaria	N=455 42 days	Primary: Day 28 ‘‘adequate clinical and parasitological response’’ (ACPR) rate Secondary: Day 14 and 42	Primary: The day 28 ACPR rate was 25% with SP alone, which was less effective than each of the three SP combination regimens (P<0.001). AQ+SP had an ACPR rate of 97%, which was higher than CQ+SP and ART+SP (P<0.001). There was no significant difference in the day 28 ACPR rate between CQ+SP and ART+SP.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs chloroquine 10 mg/kg (CQ) on days 0 and 1, and 5 mg/kg on day 2 plus SP vs artesunate 4 mg/kg (ART) once daily for 3 days plus SP vs amodiaquine 10 mg/kg (AQ) daily for 3 days plus SP			ACPR rates, time to fever resolution, time to parasite clearance, change in hemoglobin from day 0 to day 14, appearance of gametocytes by day 28 after treatment, and adverse events	Secondary: Ninety-five percent of children had cleared their parasite by day 2 in the ART+SP group compared to 35% for SP, 47% for CQ+SP, and 55% for AQ+SP (P<0.001 for each comparison with AQ+SP). By days three and seven, there were no differences between the three combination therapies and they were all more effective than SP alone (P=0.005). In the SP group, there was no association between the day zero parasitemia and time to parasite clearance or between day zero parasitemia and clinical outcome. Fever resolution was slower with SP alone; the percentage of children who still had fever on day one were 18% for SP, 5% for CQ+SP, 6% for ART+SP and 5% for AQ+SP (P<0.008 for each comparison with SP). Mean hemoglobin concentration rose in all treatment groups. Compared to SP alone, the adjusted mean on day 14 was greater after CQ+SP (P=0.03) and AQ+SP (P=0.002) but not after ART+SP (P=0.81). Gametocytes were present on day zero in 16% of children. There were no differences between the groups in the percentage of children with gametocytes on day 28; 4% after SP, 7% after CQ+SP, 5% after ART+SP and 7% after AQ+SP. Cough was the most common adverse event (45% of all AEs). Compared to SP alone, cough was more commonly reported after ART+SP (P=0.04). No other statistically significant differences were found.
Achan et al.[59] (2009) Quinine 10 mg/kg/day 3 times daily for 7 days	OL, RCT Ugandan children 6 to 59 months with uncomplicated malaria	N=175 240 days	Primary: Parasitological cure rates after 28 days of follow-up Secondary: Adherence to study	Primary: Unadjusted cure rate by genotyping was 96% for the artemether-lumefantrine group compared to 64% in the quinine group (P=0.001). In the quinine group, 69% of parasitological failures were due to reoccurrence compared to none in the artemether-lumefantrine group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs artemether-lumefantrine: 1 tablet per dose for body weight 10-14.9 kg, 2 tablets for 15-24.9 kg, 3 tablets for 25-34.9 kg, 4 tablets for ≥ 35kg for 7 days			drug, presence of gametocytes, recovery of hemoglobin concentration from baseline at day 28 and incidence of adverse effects	Secondary: The mean adherence to artemether-lumefantrine was 94.5% compared to 85.4% to quinine (P=0.0008). Adherence levels ≥80% was associated with a decreased risk of treatment failure (P=0.06). Adverse events did not differ between treatment groups.
Piola et al.[60] (2010) Quinine 10 mg/kg every 8 hours for 7 days vs artemether-lumefantrine (fixed-dose combination of 20-120 mg) 4 tablets at 0, 8, 24, 36, 48, and 60 hours for 3 days	RCT, OL Pregnant Ugandan women with uncomplicated *Plasmodium falciparum* malaria	N=304 2.5 years	Primary: Adjusted cure rate at day 42 Secondary: Not reported	Primary: At day 42, 99.3% of patients taking artemether–lumefantrine and 97.6% taking quinine were cured (lower limit of 95% CI, 0.9). The median time to first *Plasmodium falciparum* reappearance was 65 days for quinine and 70 for artemether–lumefantrine (P=0.4). On day two, parasite clearance was lower in the quinine group than in the artemether–lumefantrine group (P<0.0001), but increased on day three. Artemether–lumefantrine was more effective than quinine in gametocyte clearance by day two (P=0.03) and day seven (P=0.04). A total of 290 adverse events in the quinine group and 141 in the artemether–lumefantrine group. Secondary: Not reported
Malaria (Relapse Prevention)				
Galappaththy et al.[61] (2007) Trial Group 1: Primaquine	MA Studies evaluating relapse prevention	N=3,423 (9 trial) 5-14 days	Primary: Relapse prevention Secondary: Not reported	Primary: Compared to chloroquine alone, five-day primaquine plus chloroquine was no better at preventing relapses (OR 1.04); however, the 14-day primaquine plus chloroquine treatment regimen was significantly better (OR, 0.24; 95% CI, 0.12 to 0.45) at preventing relapse.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
5mg/kg/day plus chloroquine 25 mg/kg/day vs chloroquine alone Trial Group 2: Primaquine 15 mg/kg daily plus chloroquine for 5 vs 14 days				Direct comparisons of the 14-day and five-day primaquine plus chloroquine regimens also confirmed the greater efficacy of the longer course (OR, 13.33; 95% CI, 3.45 to 51.44). Secondary: Not reported
Treatment of Lupus Erythematosus				
Tsakonas et al.[62] (1998) Hydroxy-chloroquine 400 mg daily (HCQ) vs placebo	PC, RCT Patients with quiescent SLE	N=47 42 months	Primary: Time to major flare-up Secondary: Specific subtype flares (glomerulo-nephritis, vasculitis, etc) and hospitalization for an SLE exacerbation	Primary: Over the 42 months of study, 50% in the placebo group and 28% of patients in the treatment group experienced a major flare. The relative risk of major flare for those randomized to continue HCQ vs placebo was 0.43 (95% CI, 0.17 to 1.12). Secondary: The relative risks for subtypes of flares were 0.26 (95% CI, 0.03 to 2.54) for nephritis, 0.51 (95% CI, 0.09 to 3.08) for vasculitis and 0.65 (95% CI, 0.17 to 2.41) for flares characterized by other symptoms. The relative risk of hospitalization for major flare for patients randomized to continue hydroxychloroquine was 0.58 (95% CI, 0.13 to 2.60).
Molad et al.[63] (2002) Hydroxy-chloroquine (as a component of ongoing therapy for SLE)	OBS Patients with SLE	N=151 Variable duration	Primary: Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR DI)	Primary: Mean score of SLICC/ACR DI at the first and last encounters were 0.17 and 1.64, respectively (P<0.0001). Hydroxychloroquine therapy was significantly associated with lower SLICC/ACR DI (P=0.015). Hydroxychloroquine treatment significantly prolonged damage-free survival in the lupus patients (P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs non-hydroxy-chloroquine-containing regimens			Secondary: Not reported	Secondary: Not reported
Ruiz-Irastorza et al.[64] (2010) Hydroxy-chloroquine treatment vs chloroquine treatment	MA Patients with SLE	95 trials Variable duration	Primary: Efficacy and safety Secondary: Not reported	Primary: High levels of evidence were found that antimalarials prevent lupus flares and increase long-term survival of patients with SLE. Moderate evidence of protection from antimalarials against irreversible organ damage, thrombosis and bone mass loss. High levels of evidence were found that hydroxychloroquine decreases lupus activity without harming pregnant women or their baby. Evidence supporting an effect on severe lupus activity, lipid levels and subclinical atherosclerosis was weak. Secondary: Not reported
Prophylaxis for *Pneumocystis* Pneumonia				
Green et al.[65] (2007) Atovaquone vs pentamidine vs sulfamethoxazole-trimethoprim (SMX-TMP)	MA Immuno-compromised patients with cancer, bone marrow transplant patients, solid organ transplant patients, patients receiving corticosteroids, patients receiving other immune suppressive medications,	N=1,155 (11 trials) Variable duration	Primary: Documented Pneumocystis infections Secondary: All-cause mortality at end of study follow-up, PCP-related mortality at end of study follow-up, infections other than Pneumocystis	Primary: There was a significant reduction in the occurrence of PCP infections in the SMX-TMP prophylaxis group compared to others (RR, 0.09; 95% CI, 0.02 to 0.32). The corresponding number of patients needed to treat to prevent one episode of PCP was 15 patients (95% CI, 13 to 20). Five trials compared daily-administrated SMX-TMP prophylaxis vs no intervention or placebo. Prophylaxis resulted in a significant decrease in the occurrence of PCP infections (RR, 0.08; 95% CI, 0.02 to 0.38). Three trials compared SMX-TMP prophylaxis vs a non anti-PCP antibiotic (quinolones). Prophylaxis with SMX-TMP was better than quinolones in the prevention of PCP (RR, 0.09; 95% CI, 0.01 to 1.57). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs dapsone vs pyrimethamine vs clindamycin vs mycophenolate mofetil	severe malnutrition, primary immune-deficiency diseases			All-cause mortality was reported in five trials. Three trials compared SMX-TMP to placebo (RR, 0.79; 95% CI, 0.18 to 3.46), and two trials compared SMX-TMP vs quinolones (RR, 0.49; 95% CI, 0.02 to 10.73). SMX-tmp prophylaxis reduced PCP-related mortality (RR, 0.17; 95% CI, 0.03 to 0.94).Four trials compared SMX-TMP vs no intervention or placebo. PCP related mortality was reduced in the prophylaxis group (RR, 0.18; 95% CI, 0.02 to 1.56). Three studies compared SMX-TMP vs quinolones. PCP related mortality was reduced in the SMX-TMP group (RR, 0.14; 95% CI, 0.01 to 2.65). In the analysis of any infection other than PCP, one study comparing SMX-TMP prophylaxis vs no intervention or placebo found no statistically significant difference between the groups (RR, 0.86; 95% CI, 0.68 to 1.08). Three studies that compared SMX-TMP prophylaxis vs quinolones found significantly more infections other than PCP in the SMX-TMP arm compared to quinolones (RR, 1.59; 95% CI, 1.17 to 2.14).
Treatment of Rheumatoid Arthritis				
Suarez-Almazor et al.[66] (2000) Hydroxy-chloroquine 400 mg daily vs placebo	MA Patients with recently diagnosed, mild rheumatoid arthritis with no prior treatment with a disease-modifying antirheumatic drug (DMARD)	N=571 (4 trials) ≥6 months	Primary: End-of-trial results were pooled as standardized mean differences (SMDs) for joint scores, pain, global, and functional assessments Secondary: Not reported	Primary: The standardized mean differences (SMDs) for the various outcome measures were as follows: tender joints: –0.33 (95% CI, –0.50 to –0.17); swollen joints: –0.52 (95% CI, –0.69 to –0.36); pain: –0.45 (95% CI, –0.63 to –0.27); physician global assessment: –0.45 (95% CI, –0.66 to –0.24); patient global assessment: –0.39 (95% CI, –0.59 to –0.18). A weighted mean difference (WMD) of 6 mm (95% CI, –8.51 to –4.24) favoring hydroxychloroquine was observed for erythrocyte sedimentation rate. Only one study measured functional status: no significant differences were observed between hydroxychloroquine and placebo in Health Assessment Questionnaire scores. Another study reported radiological progression but no significant differences were observed between groups. Patients receiving hydroxychloroquine were less likely to discontinue

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				treatment, overall (OR 0.59; 95% CI, 0.41 to 0.86), or because of insufficient response (OR 0.55; 95% CI, 0.33 to 0.91). Withdrawals due to adverse reactions were rare (4.7% in the antimalarial group and 5.5% in the placebo group). None of the three studies which conducted ophthalmologic evaluations reported withdrawals due to ocular toxicity. Secondary: Not reported
Matteson et al.[67] (2004) Hydroxy-chloroquine 200 mg twice daily, nonsteroidal anti-inflammatory drug, and prednisone up to 10 mg daily	OL Patients with early rheumatoid arthritis (less than 1 year); all patients had never taken any standard disease-modifying anti-rheumatic drug (DMARD) prior to enrollment	N=111 24 weeks	Primary: Baseline factors associated with initial response to treatment; if patients needed to add methotrexate (MTX) or prednisone >10 mg/day they were also classified as nonresponders Secondary: Not reported	Primary: After 24 months of follow-up, a majority of patients (56/94) were either still on solo DMARD therapy with HCQ (N=49) or off DMARD therapy with controlled/quiescent disease (N=4), and 38 patients were taking MTX (including 11 in combination with other DMARDs). Features present at enrollment which were predictors of MTX therapy at month 24 weeks were high pain score, baseline rheumatoid factor titer >1:40, higher number of swollen joints, and poor patient global assessment (P<0.001). Secondary: Not reported
Verstappen et al.[68] (2005) Hydroxy-chloroquine 400 mg/day vs intramuscular gold 50 mg/week	MC, RCT Patients with recent onset of rheumatoid arthritis (within 1 year)	N=562 62 months	Primary: Remission rates (duration of morning stiffness <15 minutes, visual analog scale pain <10 mm, Thompson joint score=10, and ESR=30 mm/hour) for at least 6	Primary: Thirty-six percent of patients achieved at least one period of remission. The percentage of patients in remission during follow-up was not significantly different between the four treatment groups: 42% in the gold group, 36% in the methotrexate group, 31% in the hydroxychloroquine group, and 38% in the pyramid group (P=0.28). Median duration between diagnosis and the first remission period was 15 months for the intramuscular gold group, 18 months for the methotrexate and hydroxychloroquine groups, and 24 months for the pyramid group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs methotrexate 7.5 to 15 mg/week vs NSAIDS			months Secondary: Not reported	(NS). Predictors of remission were early response to initial treatment, less pain, rheumatoid factor negativity, and lower joint score at baseline (P<0.0001). Secondary: Not reported
Das et al.[69] (2007) Hydroxy-chloroquine 400 mg daily for 8 weeks (HCQ) vs placebo for 8 weeks After 8 weeks, all patients received hydroxy-chloroquine 200 mg daily for 4 weeks. All patients received nimesulide 100 mg twice daily.	RCT, DB, MC, PC Patients between 18 and 60 years of age suffering from rheumatoid arthritis (RA) who had failed to respond to at least 2 weeks of NSAID therapy	N=122 12 weeks	Primary: Assessment of response at 12 weeks using modified ACR 20 (American College of Rheumatology 20) criteria Secondary: Not reported	Primary: A significant improvement was recorded in the HCQ group as compared to placebo in swollen joint count (57.9 vs 37.9%; P=0.03), tender joint count (52.6 vs 29.3%; P=0.01) and VAS pain score (57.9 vs 31.0%; P=0.004). There were no significant differences between the treatment groups in physician global assessment (49.1 vs 32.8%; P=0.07), ARA functional class (45.6 vs 29.3%; P=0.07), patient global assessment (50.9 vs 37.9%; P=0.16), or ESR (42.1 vs 34.5%; P=0.4). Overall improvement (Modified ACR 20 Response) was observed in 40.4% of patients in the HCQ group as compared to only 20.7% of patients in the placebo group (P=0.02). At 12 weeks of study, no clinically significant biochemical changes from baseline were observed in patients treated with HCQ. The ophthalmic examination carried out also did not show any abnormal findings in any of the patients. Only minimal adverse events were seen in the study and the most common were gastrointestinal. Secondary: Not reported
Saunders et al.[70] (2008)	RCT Patients between 18	N=96 1 year	Primary: Disease activity and functional	Primary: After 12 months of follow-up, both groups demonstrated substantial improvements in the mean DAS28 score from baseline. The mean

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Methotrexate (MTX) 7.5 mg/week, sulfasalazine (SSZ) 500 mg twice daily, and hydroxy-chloroquine (HCQ) 200 mg daily (parallel triple therapy) vs sulfasalazine (SSZ) 40mg/kg/day in divided doses. After 3 months, (if DAS28 ≥3.2) methotrexate (MTX) 7.5 mg/week was added. After the maximum tolerated dose of MTX was reached, 400 mg/day of hydroxy-chloroquine (HCQ) was added in patients with persistent disease activity (step-up therapy)	and 80 years of age who were newly diagnosed as having active rheumatoid arthritis (defined as symptom duration of <5 years, Disease Activity Score in 28 joints (DAS28) of >5.1) and who had not previously been treated with DMARDs other than hydroxychloroquine		outcome Secondary: Not reported	decrease in the DAS28 score was -4.0 (step-up therapy group) vs -3.3 (parallel therapy group; P=0.163). No significant differences in the percentages of patients with DAS28 remission (45% with step-up therapy group vs 33% parallel triple therapy group 33%), DAS28 good response (60 vs 41%, respectively) or American College of Rheumatology criteria for 20% improvement (ACR20; 77 vs 76%, respectively), ACR50 (60 vs 51%, respectively), or ACR70 (30 vs 20%, respectively) responses were seen. Improvements were seen in both groups in all disease activity variables, as well as in physical function and quality of life, but there were no significant differences between groups. There was no difference between the groups in radiologic progression over 12 months. Patients in both treatment groups reported adverse events with similar frequency. A total of 135 adverse events were reported in the step-up therapy group (48 gastrointestinal, six abnormal liver function tests, 27 infective, 16 mucocutaneous, eight hematologic, 13 neurologic, and 17 other events). There were 141 adverse events reported in the parallel triple therapy group (52 gastrointestinal, five abnormal findings on liver function tests, 29 infective, 19 mucocutaneous, eight hematologic, six neurologic, and 22 others). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Treatment of Toxoplasmosis				
Dedicoat et al.[71] (2006) Pyrimethamine and clindamycin (P+C) vs pyrimethamine and sulfadiazine (P+S) vs sulfamethoxazole and trimethoprim (SMX-TMP)	MA Patients with the acquired immunodeficiency syndrome and toxoplasmosis	N=475 (3 trials) Variable duration	Primary: Mortality, clinical response to treatment, (neurological outcome, and serious adverse events) Secondary: Radiological response and minor adverse events	Primary: <u>P+C vs P+S</u> One of the trials showed complete or partial clinical response in 46.2% of the patients receiving P+C compared to 48.5% of the patients receiving P+S (RR, 0.95; 95% CI, 0.55 to 1.64). The second trial was excluded due to lack of data. For both of the trials, the two treatment arms did not differ for death (RR, 1.41; 95% CI, 0.88 to 2.28). <u>P+S vs SMX-TMP</u> Seventy percent of subjects in each group had a good clinical response. Secondary: Sixty-eight percent of patients in the SMX-TMP group compared to 62% in the P+S group had a good radiological outcome (RR, 1.09; 95% CI, 0.78 to 1.51). Twelve percent of patients randomized to SMX-TMP and 22% patients randomized to P+S experienced an adverse event (RR, 0.58; 95% CI, 0.21 to 1.61). There were no statistically significant differences between all of the treatment groups (SMX-TMP, P+C or P+S; RR, 1.51; 95% CI, 0.86 to 2.67).

Study abbreviations: CI=confidence interval, DB=double-blind, HR=hazard ratio, MA=meta-analysis, MC=multicenter, NS=not significant, OL=open-label, OR=odds ratio, OS=observational, PC=placebo-controlled, PG=parallel-group, PRO=prospective, R=randomized, RCT=randomized controlled trial, Retro=retrospective, RR=relative risk
Miscellaneous abbreviations: PCP=Pneumocystis carinii pneumonia, SLE= systemic lupus erythematosus, SMX-TMP=sulfamethoxazole-trimethoprim

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 16. Relative Cost of the Antimalarials

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Chloroquine	tablet	N/A	N/A	$$
Hydroxychloroquine	tablet	Plaquenil®*	$$$$$	$
Mefloquine	tablet	N/A	N/A	$$
Primaquine	tablet	N/A	N/A	$$
Pyrimethamine	tablet	Daraprim®	$$$$$	N/A
Quinine	capsule	Qualaquin®*	$$$$	$$$$
Combination Products				
Artemether and lumefantrine	tablet	Coartem®	$$$	N/A
Atovaquone and proguanil	tablet	Malarone®*	$$$-$$$$	$$$$$

*Generic is available in at least one dosage form or strength.
N/A=Not available

X. Conclusions

The antimalarials are approved for the prevention and treatment of malaria.[1-9] In the United States, most cases of malaria occur among individuals who traveled to endemic regions without receiving appropriate prophylactic therapy. Treatment for malaria should not be initiated until the diagnosis has been confirmed by laboratory investigations.[15] Once the diagnosis of malaria has been confirmed, appropriate antimalarial treatment must be initiated immediately. Treatment decisions are based upon the infecting *Plasmodium* species, the clinical status of the patient, and the drug susceptibility of the infecting parasites as determined by the geographic area where the infection was acquired.[15] Atovaquone-proguanil, chloroquine, hydroxychloroquine, mefloquine, primaquine, and quinine are available in a generic formulation.

In July 2013, the Centers for Disease Control (CDC) published updated guidelines for the treatment of malaria based on drugs currently available in the United States.[16] For chloroquine-sensitive infections due to *Plasmodium falciparum*, *Plasmodium malariae, and Plasmodium knowlesi*, initial treatment with chloroquine or hydroxychloroquine is recommended.[16] For the treatment of chloroquine-resistant infections due to *Plasmodium falciparum*, the CDC recommends the use of atovaquone-proguanil, artemether-lumefantrine, or quinine (in combination with doxycycline, tetracycline, or clindamycin) and does not give preference to one treatment regimen over another. Mefloquine is considered an alternative treatment option; however, due to higher rates of severe neuropsychiatric reactions seen at treatment doses, it is not recommended unless other options cannot be used.[16] For the treatment of chloroquine-resistant *Plasmodium vivax*, the CDC recommends the use of quinine (plus primaquine and doxycycline/tetracycline), atovaquone-proguanil (plus primaquine), or mefloquine (plus primaquine) and does not give preference to one treatment regimen over another.[16]

Chemoprophylaxis is recommended for individuals who will be traveling to areas where malaria transmission is expected. For travel to destinations where chloroquine-sensitive malaria is present, guidelines recommend the use of chloroquine, atovaquone-proguanil, doxycycline, mefloquine, and primaquine (for travelers who are not glucose-6-phosphate dehydrogenase deficient).[17-18] For destinations where chloroquine-resistant malaria is present, chemoprophylaxis options are limited to atovaquone-proguanil, doxycycline, and mefloquine.[17-18] Guidelines do not give preference to one chemoprophylactic agent over another.[17-18]

The agents in this class are also approved for the treatment of non-malarial diseases, including extraintestinal amebiasis (chloroquine), systemic lupus erythematosus, and rheumatoid arthritis (hydroxychloroquine), as well as toxoplasmosis (pyrimethamine). Guidelines for the use of disease-modifying antirheumatic drugs (DMARDs) in rheumatoid arthritis recommend the use of hydroxychloroquine monotherapy for patients without poor prognostic features, with low disease activity, and with disease duration ≤24 months.[20] It is also recommended in combination with other DMARDs for patients with intermediate to high disease activity. For the treatment of systemic lupus erythematosus, hydroxychloroquine is recommended as one of several initial treatment options.[22] In patients with HIV infection, the recommended initial treatment for toxoplasmosis encephalitis consists of the combination of pyrimethamine, sulfadiazine, and leucovorin.[19]

There is insufficient evidence to support that one brand antimalarial is more efficacious than another within its given indication. Since the antimalarials are not used for the management of common infectious diseases that would be seen in general use, formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand antimalarials within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand antimalarial is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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AHFS Class 083092
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I. Overview

The miscellaneous antiprotozoals are approved for the treatment of various infectious diseases, including amebiasis, anaerobic bacterial infections, bacterial vaginosis, cryptosporidiosis, giardiasis, *Pneumocystis* pneumonia, and trichomoniasis.[1-11] Amebiasis is a parasitic infection caused by *Entamoeba histolytica* which may or may not be symptomatic and can remain latent in an infected person for several years.[12-14] While the most frequent clinical manifestations are gastrointestinal, the parasite can spread to extraintestinal sites resulting in liver abscesses and other complications. Cryptosporidiosis is a parasitic infection caused by *Cryptosporidium* which results in self-limiting diarrhea in immunocompetent persons, but may lead to potentially life-threatening complications in immunocompromised persons.[12,15] Giardiasis is a parasitic infection caused by *Giardia lamblia,* which may result in acute self-limiting diarrhea or chronic diarrhea associated with malabsorption and weight loss.[12,16] All three parasitic infections can be transmitted from person-to-person, via the fecal-oral route, or by ingesting microbial cysts from contaminated food and water.[12-16]

Pneumocystis pneumonia is caused by *Pneumocystis jiroveci* (formerly known as *Pneumocystis carinii*), which is classified as a fungus, but also shares characteristics with protozoa.[17,18] *Pneumocystis* is commonly found in the lungs of healthy people and rarely causes disease. However, Pneumocystis pneumonia is common among immunocompromised persons, including human immunodeficiency virus-infected individuals, people taking immunosuppressant medications, as well as in those who have undergone bone marrow or solid organ transplantation.

Bacterial vaginosis results from replacement of the normal hydrogen peroxide-producing *Lactobacillus* species in the vagina with anaerobic bacteria.[19] Untreated vaginitis is associated with numerous health risks, such as pelvic inflammatory disease, cervicitis, postoperative infection, preterm delivery, postpartum endometritis, posthysterectomy infections, intrauterine infections, and other sexually transmitted infections.[20] Trichomoniasis is caused by the protozoan *Trichomonas vaginalis* and is primarily a sexually transmitted disease.[19] However, the organism can survive for short periods of time on moist surfaces, such as bathing or toilet articles, and can be transmitted by nonsexual contact. Symptoms include vaginal discharge, odor, itching, dysuria, and dyspareunia.

The miscellaneous antiprotozoals differ in their mechanism of action.[1-11] Atovaquone is thought to inhibit electron transport, which may lead to the inhibition of nucleic acid and adenosine triphosphate synthesis. Metronidazole and tinidazole are antiprotozoal and antibacterial agents. They are reduced by intracellular proteins, which produce free radicals that results in the death of the microorganism. The antiprotozoal activity of nitazoxanide is thought to be due to interference with the pyruvate:ferredoxin oxidoreductase enzyme-dependent electron transfer reaction, which is essential to anaerobic energy metabolism. Pentamidine interferes with protozoal nuclear metabolism by inhibition of deoxyribonucleic acid, ribonucleic acid, phospholipid, and protein synthesis.

The miscellaneous antiprotozoals that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Atovaquone, metronidazole, and tinidazole are available in a generic formulation. This class was last reviewed in May 2012.

Table 1. Antiprotozoals, Miscellaneous Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Atovaquone	suspension	Mepron®*	atovaquone
Metronidazole	capsule, extended-release tablet, injection, tablet	Flagyl®*, Flagyl ER®	metronidazole
Nitazoxanide	suspension, tablet	Alinia®	none
Pentamidine	inhalation, injection	NebuPent®, Pentam 300®	none
Tinidazole	tablet	Tindamax®*	tinidazole

*Generic is available in at least one dosage form or strength.
PDL=Preferred Drug List.

The miscellaneous antiprotozoals have been shown to be active against the strains of microorganisms indicated in Table 2. This activity has been demonstrated in clinical infections and is represented by the Food and Drug Administration (FDA)-approved indications for the miscellaneous antiprotozoals that are noted in Table 4. These agents may also have been found to show activity to other microorganisms in vitro; however, the clinical significance of this is unknown since their safety and efficacy in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials. Although empiric anti-infective therapy may be initiated before culture and susceptibility test results are known, once results become available, appropriate therapy should be selected.

Table 2. Microorganisms Susceptible to the Antiprotozoals, Miscellaneous[1-11]

Organism	Atovaquone	Metronidazole	Nitazoxanide	Pentamidine	Tinidazole
Gram-Positive Anaerobes					
Clostridium species		✔			
Eubacterium species		✔			
Peptococcus niger		✔			
Peptostreptococcus species		✔			
Gram-Negative Anaerobes					
Bacteroides fragilis		✔			
Bacteroides distasonis		✔			
Bacteroides ovatus		✔			
Bacteroides thetaiotaomicron		✔			
Bacteroides vulgatus		✔			
Fusobacterium species		✔			
Protozoal Parasites					
Cryptosporidium parvum			✔		
Entamoeba histolytica		✔			✔
Giardia lamblia			✔		✔
Trichomonas vaginalis		✔			✔
Other Microorganisms					
Gardnerella vaginalis					✔
Haemophilus vaginalis					✔
Pneumocystis jiroveci	✔			✔	

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the miscellaneous antiprotozoals are summarized in Table 3.

Table 3. Treatment Guidelines Using the Antiprotozoals, Miscellaneous

Clinical Guideline	Recommendation(s)
Society for Healthcare Epidemiology of America/Infectious Diseases Society of America: **Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults (2010)[21]**	Treatment of *Clostridium difficile* infections • Discontinue therapy with the inciting antimicrobial agent(s) as soon as possible, as this may influence the risk of *Clostridium difficile* infections recurrence. • When severe or complicated *Clostridium difficile* infections is suspected, initiate empirical treatment as soon as the diagnosis is suspected. • If possible, avoid use of antiperistaltic agents, as they may obscure symptoms and precipitate toxic megacolon. • Metronidazole is the drug of choice for the initial episode of mild-to-moderate *Clostridium difficile* infections. The dosage is 500 mg orally three times per day for 10 to 14 days. • Vancomycin is the drug of choice for an initial episode of severe *Clostridium difficile* infections. The dosage is 125 mg orally four times per day for 10 to 14 days. • Vancomycin administered orally with or without intravenously administered

Clinical Guideline	Recommendation(s)
	metronidazole is the regimen of choice for the treatment of severe, complicated *Clostridium difficile* infections. The vancomycin dosage is 500 mg orally four times per day and 500 mg in approximately 100 mL normal saline per rectum every six hours as a retention enema, and the metronidazole dosage is 500 mg intravenously every eight hours. • Treatment of the first recurrence of *Clostridium difficile* infections is usually with the same regimen as for the initial episode but should be stratified by disease severity (mild-to-moderate, severe, or severe complicated), as is recommended for treatment of the initial *Clostridium difficile* infections episode. • Do not use metronidazole beyond the first recurrence of *Clostridium difficile* infections or for long-term chronic therapy because of potential for cumulative neurotoxicity. • Treatment of the second or later recurrence of *Clostridium difficile* infections with vancomycin therapy using a tapered and/or pulse regimen is the preferred next strategy. • No recommendations can be made regarding prevention of recurrent *Clostridium difficile* infections in patients who require continued antimicrobial therapy for the underlying infection.

European Society of Clinical Microbiology and Infectious Diseases: **Update of the Treatment Guidance Document for *Clostridium difficile* Infection (2014)**[22]	Treatment of *Clostridium difficile* infection
	o Treatment for an initial, non-severe episode of *Clostridium difficile* infections:
	  o Metronidazole 500 mg three times a day for 10 days is strongly recommended.
	  o Alternatives with moderately supported recommendation include vancomycin 125 mg four times daily for 10 days and fidaxomicin 200 mg twice daily for 10 days.
	• Treatment for an initial, severe episode of *Clostridium difficile* infections:
	  o Vancomycin 125 mg four times a day for 10 days is strongly recommended.
	  o Fidaxomicin 200 mg twice daily for 10 days is a moderately supported recommendation.
	  o It is recommended against using metronidazole 500 mg three times a day for 10 days.
	• Treatment (or risk of) first recurrence of *Clostridium difficile* infections:
	  o Vancomycin 125 mg four times daily for 10 days and fidaxomicin 200 mg twice daily or 10 days are moderately supported as a recommendation.
	  o Metronidazole 500 mg three times daily for 10 days is marginally supported as a recommendation.
	• Treatment for multiple recurrences of *Clostridium difficile* infections:
	  o Vancomycin 125 mg four times a day for 10 days followed by pulse or taper strategy and fidaxomicin 200 mg twice daily for 10 days are moderately supported recommendations.
	  o Vancomycin 500 mg four times daily for 10 days is marginally recommended.
	  o It is recommended against using metronidazole 500 mg three times daily for 10 days.
	• Oral treatment is not possible:
	  o Metronidazole 500 mg intravenously three times a day for 10 days is recommended for non-severe *Clostridium difficile* infections.
	  o For severe *Clostridium difficile* infections, metronidazole 500 mg intravenously three times a day for 10 days is strongly recommended. Vancomycin 500 mg enterally four times daily is moderately recommended. Tigecycline 50 mg intravenously twice daily is marginally recommended for use.

World Gastroenterology Organization: **Acute Diarrhea**	General considerations • Antimicrobials are the drugs of choice for empirical treatment of traveler's diarrhea and of community-acquired secretory diarrhea when the pathogen is known.

Clinical Guideline	Recommendation(s)
(2012)[23]	• Consider antimicrobial treatment for: o *Shigella*, *Salmonella*, *Campylobacter* (dysenteric form), or parasitic infections. o Nontyphoidal salmonellosis in at-risk populations (malnutrition, infants and elderly, immunocompromised patients and those with liver diseases and lymphoproliferative disorders) and in dysenteric presentation. o Moderate/severe traveler's diarrhea or diarrhea with fever and/or with bloody stools. • Nitazoxanide may be appropriate for *Cryptosporidium* and other infections, including some bacteria. <u>Antimicrobial agents for the treatment of specific causes of diarrhea</u> • Cholera o First-line: doxycycline. o Alternative: azithromycin or ciprofloxacin. • Shigellosis o First-line: ciprofloxacin. o Alternative: pivmecillinam or ceftriaxone. • Amebiasis o First-line: metronidazole. • Giardiasis o First-line: metronidazole. o Alternative: tinidazole, omidazole or secnidazole. • *Campylobacter* o First-line: azithromycin. o Alternative: fluoroquinolones (e.g., ciprofloxacin).
Infectious Diseases Society of America: **The Practice of Travel Medicine (2006)**[24]	<u>Chemoprophylaxis</u> • Bismuth subsalicylate–containing formulations and antibiotics have been proven effective in preventing traveler's diarrhea. • Probiotics, such as lactobacillus, have not demonstrated sufficient efficacy to be recommended. • Widespread drug resistance renders doxycycline and sulfamethoxazole-trimethoprim no longer useful for prevention of traveler's diarrhea. • Chemoprophylaxis can contribute to development of resistant enteric bacteria and potentially predispose the traveler to infection with other deleterious pathogens, such as *Clostridium difficile.* • The routine use of antibiotic prophylaxis for travelers' diarrhea is not generally recommended. • Chemoprophylaxis may be considered in healthy travelers for whom staying well is critical and in special-needs travelers in whom the risk for diarrhea is increased or the consequences of a diarrheal episode may be severe. • When considering chemoprophylaxis, fluoroquinolone antibiotics remain the first choice. • Chemoprophylaxis should be recommended for no more than two to three weeks. <u>Treatment</u> • Fluid replacement and a diet restricted to liquids and bland foods may be appropriate, though they may not provide additional benefits beyond antibiotic treatment. • Symptomatic therapy with bismuth subsalicylate may be recommended in mild cases of diarrhea, but better agents exist for moderate-to-severe disease. • Loperamide has become the antimotility agent of choice. It is more efficacious in controlling diarrhea than bismuth subsalicylate and has an onset of action within the first four hours after ingestion. When it is used in combination with an antibiotic, there may be rapid improvement of traveler's diarrhea.

Clinical Guideline	Recommendation(s)
	• Antibiotics are effective in the treatment of traveler's diarrhea and can reduce the average duration of disease from several days to ~1 day. • Antibiotics that are recommended include fluoroquinolones (norfloxacin, ciprofloxacin, ofloxacin, levofloxacin), azithromycin, and rifaximin. • Fluoroquinolones remain predictably active for empiric therapy in most parts of the world and remain the drugs of first choice. • Antibiotics that are no longer recommended because of drug resistance worldwide are the sulfonamides, neomycin, ampicillin, doxycycline, tetracycline, trimethoprim alone, and sulfamethoxazole-trimethoprim.

Infectious Diseases Society of America: **Practice Guidelines for the Management of Infectious Diarrhea (2001)**[25]	<u>Recommendations for therapy against specific pathogens</u>
	o *Shigella* species:
	  o Sulfamethoxazole-trimethoprim.
	  o Fluoroquinolone.
	  o Nalidixic acid.
	  o Ceftriaxone.
	  o Azithromycin.
	• *Salmonella,* non-typhi species:
	  o Treatment is not routinely recommended; however, consider therapy in patients <6 months old or >50 years old, or patients that have a prosthesis, valvular heart disease, severe atherosclerosis, malignancy, or uremia.
	  o Sulfamethoxazole-trimethoprim.
	  o Fluoroquinolone.
	• *Campylobacter* species:
	  o Erythromycin.
	• *Entamoeba histolytica*
	  o Metronidazole 750 mg three times daily for five to 10 days plus either diiodohydroxyquin 650 mg three times daily for 20 days or paromomycin 500 mg three times daily for seven days.
	• *Escherichia coli* species:
	  o Sulfamethoxazole-trimethoprim.
	  o Fluoroquinolone.
	• *Aeromonas* or *Plesiomonas* species:
	  o Sulfamethoxazole-trimethoprim.
	  o Fluoroquinolone
	• *Yersinia* species:
	  o Antibiotic therapy is not usually required. For severe infections or associated bacteremia, combination therapy with doxycycline, aminoglycosides sulfamethoxazole-trimethoprim or a fluoroquinolone is recommended.
	• *Vibrio cholerae:*
	  o Doxycycline or tetracycline.
	  o Fluoroquinolone.
	• Toxigenic *Clostridium difficile:*
	  o Metronidazole.
	• *Isospora* species:
	  o Sulfamethoxazole-trimethoprim.
	• *Cyclospora* species:
	  o Sulfamethoxazole-trimethoprim.

Centers for Disease Control and Prevention: **Sexually Transmitted Diseases Treatment Guidelines**	<u>Bacterial vaginosis</u>
	• Recommended regimens:
	  o Metronidazole 500 mg orally twice a day for seven days.
	  o Metronidazole gel 0.75%, one full applicator (5 grams) intravaginally, once a day for five days.
	  o Clindamycin cream 2%, one full applicator (5 grams) intravaginally at

Clinical Guideline	Recommendation(s)
(2010)[19]	bedtime for seven days. • Alternative regimens: o Tinidazole 2 grams orally once daily for two days. o Tinidazole 1 gram orally once daily for five days. o Clindamycin 300 mg orally twice daily for seven days. o Clindamycin ovules 100 mg intravaginally once at bedtime for three days. <u>Cervicitis</u> • Recommended regimens for presumptive treatment: o Azithromycin 1 gram orally in a single dose. o Doxycycline 100 mg orally twice a day for seven days. <u>Chancroid</u> • Recommended regimens: o Azithromycin 1 gram orally in a single dose. o Ceftriaxone 250 mg intramuscular in a single dose. o Ciprofloxacin 500 mg orally twice a day for three days. o Erythromycin base 500 mg orally three times a day for seven days. <u>Chlamydial infections</u> • Recommended regimens: o Azithromycin 1 gram orally in a single dose. o Doxycycline 100 mg orally twice a day for seven days. • Alternative regimens: o Erythromycin base 500 mg orally four times a day for seven days. o Erythromycin ethylsuccinate 800 mg orally four times a day for seven days. o Levofloxacin 500 mg orally once daily for seven days. o Ofloxacin 300 mg orally twice a day for seven days. <u>Chlamydial infections among children</u> • Recommended regimen for children <45 kg: o Erythromycin base or ethylsuccinate 50 mg/kg/day orally divided into four doses daily for 14 days. • Recommended regimen for children ≥45 kg and <8 years of age: o Azithromycin 1 gram orally in a single dose. • Recommended regimens for children ≥8 years of age: o Azithromycin 1 gram orally in a single dose. o Doxycycline 100 mg orally twice a day for seven days. <u>Disseminated gonococcal infection</u> • Recommended regimen: o Ceftriaxone 1 gram intramuscular or intravenous every 24 hours. • Alternative regimens: o Cefotaxime 1 gram intravenous every eight hours. o Ceftizoxime 1 gram intravenous every eight hours. <u>Epididymitis</u> • Recommended regimens: o Ceftriaxone 250 mg intramuscular in a single dose plus doxycycline 100 mg orally twice a day for 10 days. • For acute epididymitis most likely caused by enteric organisms: o Levofloxacin 500 mg orally once daily for 10 days. o Ofloxacin 300 mg orally twice a day for 10 days.

Clinical Guideline	Recommendation(s)

	Genital herpes infection
	• The use of systemic antivirals including valacyclovir, acyclovir, and famciclovir is encouraged for the treatment of primary and recurrent genital herpes. Topical therapy with antiviral drugs offers minimal clinical benefit, and their use is not recommended.
	• Systemic antiviral drugs partially control the symptoms and signs of herpes infection when used to treat first clinical episodes and recurrent episodes, or when used as daily suppressive therapy.
	• However, these drugs neither eradicate latent virus nor affect the risk, frequency, or severity of recurrences after the drug is discontinued.
	• Randomized trials have indicated that three antiviral medications provide clinical benefit for genital herpes: acyclovir, valacyclovir, and famciclovir.
	• Topical therapy with antiviral drugs offers minimal clinical benefit, and its use is discouraged.
	• Foscarnet is frequently effective for treatment of acyclovir-resistant genital herpes in immunocompromised individuals.
	• Recommended regimens for initial clinical episodes include:
	  o Acyclovir 400 mg three times a day for seven to 10 days or 200 mg five times a day for seven to 10 days.
	  o Famciclovir 250 mg three times a day for seven to 10 days.
	  o Valacyclovir 1 gram twice a day for seven to 10 days.
	• Recommended regimens for suppressive therapy in recurrent herpes (≥6 episodes/year) include:
	  o Acyclovir 400 mg twice daily.
	  o Famciclovir 250 mg twice daily.
	  o Valacyclovir 500 mg once daily or 1,000 mg once daily.
	• Recommended regimens for episodic therapy in recurrent herpes include:
	  o Acyclovir 400 mg three times a day for five days or 800 mg twice a day for five days or 800 mg three times a day for two days.
	  o Famciclovir 125 mg twice a day for five days or 1 gram twice a day for one day or 500 mg once then 250 mg twice a day for two days.
	  o Valacyclovir 500 mg twice a day for three days or 1 gram once a day for five days.
	• Recommended regimen for severe infections include:
	  o Intravenous acyclovir 5 to 10 mg/kg every eight hours for two to seven days or until clinical improvement is observed, followed by oral antiviral therapy to complete at least 10 days of total therapy.
	• Recommended regimens for suppressive therapy in patients with human immunodeficiency virus include:
	  o Acyclovir 400 to 800 mg twice to three times daily.
	  o Famciclovir 500 mg twice daily.
	  o Valacyclovir 500 mg twice daily.
	• Recommended regimens for episodic therapy in patients with human immunodeficiency virus include:
	  o Acyclovir 400 mg three times daily for five to 10 days.
	  o Famciclovir 500 mg twice daily for five to 10 days.
	  o Valacyclovir 1 gram twice daily for five to 10 days.
	
	Genital warts
	• No evidence exists to identify one treatment as more efficacious than another and no treatment is ideal for all patients with genital warts.
	• Treatment selection may be based on wart size and number, anatomic site of wart, wart morphology, and adverse effects of treatment.
	• Interferon therapy is not recommended as a primary modality because of

Clinical Guideline	Recommendation(s)

	inconvenient routes of administration, frequent office visits, and the association between its use and a high frequency of adverse effects.
	
	Granuloma inguinale (Donovanosis)
	• Recommended regimen:
	  o Doxycycline 100 mg orally twice a day for at least three weeks and until all lesions have completely healed.
	• Alternative regimens:
	  o Azithromycin 1 gram orally once per week for at least three weeks and until all lesions have completely healed.
	  o Ciprofloxacin 750 mg orally twice a day for at least three weeks and until all lesions have completely healed.
	  o Erythromycin base 500 mg orally four times a day for at least three weeks and until all lesions have completely healed.
	  o Sulfamethoxazole-trimethoprim one double-strength tablet orally twice a day for at least three weeks and until all lesions have completely healed.
	• The addition of an aminoglycoside (e.g., gentamicin 1 mg/kg IV every eight hours) to these regimens can be considered if improvement is not evident within the first few days of therapy.
	
	Gonococcal conjunctivitis
	• Recommended regimen:
	  o Ceftriaxone 1 gram intramuscular in a single dose.
	
	Gonococcal infections among children
	• Recommended regimen for children >45 kg:
	  o Treat with one of the regimens recommended for adults.
	• Recommended regimen for children who weigh ≤45 kg and who have uncomplicated gonococcal vulvovaginitis, cervicitis, urethritis, pharyngitis, or proctitis:
	  o Ceftriaxone 125 mg intramuscular in a single dose.
	• Recommended regimen for children who weigh ≤45 kg and who have bacteremia or arthritis:
	  o Ceftriaxone 50 mg/kg (maximum dose: 1 gram) intramuscular or intravenous in a single dose daily for seven days.
	• Recommended regimen for children who weigh >45 kg and who have bacteremia or arthritis:
	  o Ceftriaxone 50 mg/kg intramuscular or intravenous in a single dose daily for seven days.
	
	Gonococcal meningitis and endocarditis
	• Recommended regimen:
	  o Ceftriaxone 1 to 2 grams intravenous every 12 hours.
	
	Hepatitis B
	• No specific therapy is available for persons with acute hepatitis B; treatment is supportive.
	• Persons with chronic hepatitis B virus infection should be referred for evaluation to a physician experienced in the management of chronic liver disease.
	• Therapeutic agents approved by Food and Drug Administration for treatment of chronic hepatitis B can achieve sustained suppression of hepatitis B virus replication and remission of liver disease in some persons.
	
	Hepatitis C

Clinical Guideline	Recommendation(s)

	• Combination therapy with pegylated interferon and ribavirin is the treatment of choice for patients with chronic hepatitis C.
	
	<u>Lymphogranuloma venereum</u>
	• Recommended regimen:
	  o Doxycycline 100 mg orally twice a day for 21 days.
	• Alternative regimen:
	  o Erythromycin base 500 mg orally four times a day for 21 days.
	
	<u>Nongonococcal urethritis</u>
	• Recommended regimens:
	  o Azithromycin 1 gram orally in a single dose.
	  o Doxycycline 100 mg orally twice a day for seven days.
	• Alternative regimens:
	  o Erythromycin base 500 mg orally four times a day for seven days.
	  o Erythromycin ethylsuccinate 800 mg orally four times a day for seven days.
	  o Levofloxacin 500 mg orally once daily for seven days.
	  o Ofloxacin 300 mg orally twice a day for seven days.
	
	<u>Ophthalmia neonatorum caused by *Chlamydia trachomatis*</u>
	• Recommended regimen:
	  o Erythromycin base or ethylsuccinate 50 mg/kg/day orally divided into four doses daily for 14 days.
	
	<u>Pelvic inflammatory disease</u>
	• Recommended parenteral regimen A:
	  o Cefotetan 2 grams intravenous every 12 hours.
	  o Cefoxitin 2 grams intravenous every six hours plus doxycycline 100 mg orally or intravenous every 12 hours.
	• Recommended parenteral regimen B:
	  o Clindamycin 900 mg intravenous every eight hours plus gentamicin loading dose intravenous or intramuscular (2 mg/kg of body weight), followed by a maintenance dose (1.5 mg/kg) every eight hours. Single daily dosing (3 to 5 mg/kg) can be substituted.
	• Alternative parenteral regimens:
	  o Ampicillin-sulbactam 3 grams IV every six hours plus doxycycline 100 mg orally or intravenous every 12 hours.
	• Recommended oral regimen:
	  o Ceftriaxone 250 mg intramuscular in a single dose plus doxycycline 100 mg orally twice a day for 14 days with or without metronidazole 500 mg orally twice a day for 14 days.
	  o Cefoxitin 2 grams intramuscular in a single dose and probenecid, 1 gram orally administered concurrently in a single dose, plus doxycycline 100 mg orally twice a day for 14 days with or without metronidazole 500 mg orally twice a day for 14 days.
	  o Other parenteral third-generation cephalosporin (e.g., ceftizoxime or cefotaxime) plus doxycycline 100 mg orally twice a day for 14 days with or without metronidazole 500 mg orally twice a day for 14 days.
	
	<u>Proctitis, proctocolitis, and enteritis</u>
	• Recommended regimen:
	  o Ceftriaxone 250 mg intramuscular plus doxycycline 100 mg orally twice a day for seven days.
	
	<u>Recurrent and persistent urethritis</u>

Clinical Guideline	Recommendation(s)

	• Recommended regimens:
	  o Metronidazole 2 grams orally in a single dose.
	  o Tinidazole 2 grams orally in a single dose plus azithromycin 1 gram orally in a single dose (if not used for initial episode).
	
	<u>Sexual assault and sexually transmitted diseases</u>
	• Recommended regimen: ceftriaxone plus metronidazole plus azithromycin or doxycycline.
	
	<u>Primary and secondary syphilis</u>
	• Recommended regimen for adults:
	  o Benzathine penicillin G 2.4 million units intramuscular in a single dose.
	• Recommended regimen for infants and children:
	  o Benzathine penicillin G 50,000 units/kg intramuscular, up to the adult dose of 2.4 million units in a single dose.
	
	<u>Early latent syphilis</u>
	• Recommended regimens for adults:
	  o Benzathine penicillin G 2.4 million units intramuscular in a single dose.
	• Recommended regimens for children:
	  o Benzathine penicillin G 50,000 units/kg intramuscular, up to the adult dose of 2.4 million units in a single dose.
	
	<u>Late latent syphilis or latent syphilis of unknown duration</u>
	• Recommended regimens for adults:
	  o Benzathine penicillin G 7.2 million units total, administered as three doses of 2.4 million units intramuscular each at one-week intervals.
	• Recommended regimens for children:
	  o Benzathine penicillin G 50,000 units/kg intramuscular, up to the adult dose of 2.4 million units, administered as three doses at one-week intervals.
	
	<u>Tertiary syphilis</u>
	• Recommended regimen:
	  o Benzathine penicillin G 7.2 million units total, administered as three doses of 2.4 million units intramuscular each at one-week intervals.
	
	<u>Neurosyphilis</u>
	• Recommended regimen:
	  o Aqueous crystalline penicillin G 18 to 24 million units per day, administered as 3 to 4 million units intravenous every four hours or continuous infusion, for 10 to 14 days.
	• Alternative regimen:
	  o Procaine penicillin 2.4 million units intramuscular once daily plus probenecid 500 mg orally four times a day, both for 10 to 14 days.
	
	<u>Trichomoniasis</u>
	• Recommended regimens: metronidazole 2 grams orally in a single dose or tinidazole 2 grams orally in a single dose.
	• Alternative regimen: metronidazole 500 mg orally twice a day for seven days.
	
	<u>Uncomplicated gonococcal infections of the cervix, urethra, and rectum</u>
	• Recommended regimens:
	  o Ceftriaxone 250 mg intramuscular in a single dose.
	  o Cefixime 400 mg orally in a single dose.

Clinical Guideline	Recommendation(s)
	o Single-dose injectable cephalosporin regimens plus azithromycin 1 gram orally in a single dose or doxycycline 100 mg orally twice a day for seven days. <u>Uncomplicated gonococcal infections of the pharynx</u> • Recommended regimens: o Ceftriaxone 250 mg intermuscular in a single dose plus azithromycin 1 gram orally in a single dose or doxycycline 100 mg orally twice a day for seven days.
Infectious Diseases Society of America: **Diagnosis and Management of Complicated Intra-abdominal Infection in Adults and Children (2010)**[26]	<u>Community-acquired infection in adults: mild to moderate severity</u> • Antibiotics selected should be active against enteric gram-negative aerobic and facultative bacilli, and enteric gram-positive streptococci. • Coverage for obligate anaerobic bacilli should be provided for distal small bowel, appendiceal, and colon-derived infection, and for more proximal gastrointestinal perforations in the presence of obstruction or paralytic ileus. • The use of ticarcillin-clavulanate, cefoxitin, ertapenem, moxifloxacin, or tigecycline as single-agent therapy or combinations of metronidazole with cefazolin, cefuroxime, ceftriaxone, cefotaxime, levofloxacin, or ciprofloxacin are preferable to regimens with substantial anti-*Pseudomonal* activity. • Because of increasing resistance, the following are not recommended for use (resistant bacteria also listed): Ampicillin-sulbactam (*Escherichia coli*), cefotetan and clindamycin (*Bacteroides fragilis*). • Aminoglycosides are not recommended for routine use due to availability of less toxic agents. • Empiric coverage for *Enterococcus* or antifungal therapy for *Candida* is not recommended in adults or children with community-acquired intra-abdominal infections. <u>Community-acquired infection in adults: high severity</u> • Antimicrobial regimens should be adjusted according to culture and susceptibility reports to ensure activity against the predominant pathogens isolated. Empiric use of antimicrobial regimens with broad-spectrum activity against gram-negative organisms, including meropenem, imipenem-cilastatin, doripenem, piperacillin-tazobactam, ciprofloxacin or levofloxacin in combination with metronidazole, or ceftazidime or cefepime in combination with metronidazole, is recommended. • Quinolone-resistant *Escherichia coli* have become common in some communities, and quinolones should not be used unless hospital surveys indicate >90% susceptibility of *Escherichia coli* to quinolones. • Aztreonam plus metronidazole is an alternative, but addition of an agent effective against gram-positive cocci is recommended. • In adults, routine use of an aminoglycoside or another second agent effective against gram-negative facultative and aerobic bacilli is not recommended in the absence of evidence that the patient is likely to harbor resistant organisms that require such therapy. • Empiric use of agents effective against enterococci is recommended. • Use of agents effective against methicillin-resistant Staphylococcus aureus or yeast is not recommended in the absence of evidence of infection due to such organisms. <u>Community-acquired infection in pediatric patients</u> • Selection of antimicrobial therapy should be based on origin of infection, severity of illness, and safety of the antimicrobial agents in specific pediatric age groups. • Acceptable broad spectrum agents include an aminoglycoside-based regimen, a

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	carbapenem (imipenem, meropenem, or ertapenem), a β-lactam-β-lactamase-inhibitor combination (piperacillin-tazobactam or ticarcillin-clavulanate), or an advanced-generation cephalosporin (cefotaxime, ceftriaxone, ceftazidime, or cefepime) with metronidazole. It is not recommended in all patients with fever and abdominal pain if there is low suspicion of complicated appendicitis or other acute intra-abdominal infection. • Ciprofloxacin plus metronidazole or an aminoglycoside-based regimen, are recommended for children with severe reactions to β-lactam antibiotics. • Fluid resuscitation, bowel decompression and broad-spectrum intravenous antibiotics should be used in neonates with necrotizing enterocolitis. These antibiotics include ampicillin, gentamicin, and metronidazole; ampicillin, cefotaxime, and metronidazole; or meropenem. Vancomycin may be used instead of ampicillin for suspected methicillin-resistant *Staphylococcus aureus* or ampicillin-resistant enterococcal infection. Fluconazole or amphotericin B should be used if the gram stain or cultures of specimens obtained at operation are consistent with a fungal infection. Health care-associated infection: • Therapy should be based on microbiologic results. To achieve empiric coverage, multi-drug regimens that include agents with expanded spectra of activity against gram-negative aerobic and facultative bacilli may be needed. These agents include meropenem, imipenem, imipenem-cilastatin, doripenem, piperacillin-tazobactam, or ceftazidime or cefepime in combination with metronidazole. Aminoglycosides or colistin may be required. • Broad spectrum therapy should be tailored upon microbiologic results to reduce number and spectra of administered agents. Cholecystitis and cholangitis: • Patients with suspected infection should receive antimicrobial therapy, but should have it discontinued within 24 hours after undergoing cholecystectomy unless evidence of infection outside the gallbladder wall.

Infectious Diseases Society of America: **Practice Guidelines for the Diagnosis and Management of Skin and Soft-Tissue Infections (2005)**[27]	Overview
	• Minor skin and soft-tissue infections may be empirically treated with semisynthetic penicillins, first- or second-generation oral cephalosporins, macrolides, or clindamycin; however, resistance to clindamycin has been found in almost 50% of methicillin-resistant S*taphylococcus aureus* strains.
	
	Animal bites
	• Oral treatment options:
	  o Amoxicillin-clavulanate is recommended.
	  o Alternative oral agents include doxycycline, as well as penicillin VK plus dicloxacillin.
	  o First-generation cephalosporins, penicillinase-resistant penicillins, macrolides, and clindamycin all have poor in vitro activity against *Pasteurella multocida* and should be avoided.
	• Intravenous treatment options:
	  o β-lactam-β-lactamase combinations, piperacillin-tazobactam, second-generation cephalosporins, and carbapenems.
	
	Animal contact
	• Erysipeloid:
	  o For cutaneous infection, penicillin or amoxicillin for seven to 10 days seems to be rational.
	
	Cellulitis

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	• A large percentage of patients can receive oral medications from the start. Suitable agents include dicloxacillin, cephalexin, clindamycin, or erythromycin, unless streptococci or staphylococci. • For parenteral therapy, which is indicated for severely ill patients or for those unable to tolerate oral medications, reasonable choices include a penicillinase-resistant penicillin such as nafcillin, a first-generation cephalosporin such as cefazolin, or, for patients with life-threatening penicillin allergies, clindamycin or vancomycin. • In cases of uncomplicated cellulitis, five days of antibiotic treatment is as effective as a 10-day course. <u>Erysipelas</u> • Penicillin, given either parenterally or orally depending on clinical severity, is the treatment of choice. • If staphylococcal infection is suspected, a penicillinase-resistant semisynthetic penicillin or a first-generation cephalosporin should be selected. <u>Human bites</u> • Clenched-fist injuries often require hospitalization and intravenous antimicrobial therapy with agents such as cefoxitin, ampicillin-sulbactam, ertapenem, or some combination that covers *Staphylococcus aureus, Haemophilus* species, *Eikenella corrodens,* and β-lactamase–producing anaerobes. <u>Impetigo</u> • The decision of how to treat impetigo depends on the number of lesions, their location (face, eyelid, or mouth), and the need to limit spread of infection to others. • Patients who have numerous lesions or who are not responding to topical agents should receive oral antimicrobials effective against both *Staphylococcus aureus* and *Streptococcus pyogenes.* • Because *Staphylococcus aureus* currently accounts for most cases of bullous impetigo, as well as for a substantial portion of nonbullous infections, penicillinase-resistant penicillins or first generation cephalosporins are preferred. • Additional therapies include clindamycin or amoxicillin-clavulanate. <u>Necrotizing infections</u> • Antimicrobial therapy must be directed at the pathogens and used in appropriate doses until repeated operative procedures are no longer needed, the patient has demonstrated obvious clinical improvement, and fever has been absent for 48 to 72 hours. • The best choice of antibiotics for community-acquired mixed infections is a combination of ampicillin-sulbactam plus clindamycin plus ciprofloxacin. The carbapenems, or a combination of cefotaxime plus metronidazole or clindamycin, are also appropriate. In cases of penicillin allergy, alternatives include clindamycin or metronidazole plus an aminoglycoside or fluoroquinolone. • *Staphylococcus aureus* infection, often associated with pyomyositis, should be treated with nafcillin, oxacillin, or cefazolin. Vancomycin should be reserved for resistant strains or can be used in cases of severe penicillin allergy, as well as linezolid, quinupristin-dalfopristin or daptomycin. Clindamycin is limited by its potential of cross-resistance. <u>Surgical site infections</u> • If there is minimal surrounding evidence of invasive infection (<5 cm of erythema and induration), and if the patient has minimal systemic signs of

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	infection (a temperature of <38.5°C and a pulse rate of <100 beats/minute), antibiotics are unnecessary. • For patients with a temperature of >38.5°C or a pulse rate of >100 beats/minute, a short course of antibiotics, usually for a duration of 24 to 48 hours, may be indicated. The antibiotic choice is usually empirical but can be supported by findings of gram stain and results of culture of the wound contents. • For intestinal or genital tract surgical site infections, single agents such as cefoxitin, ceftizoxime, ampicillin-sulbactam, ticarcillin-clavulanate, piperacillin-tazobactam, or carbapenems are indicated. In cases where facultative and aerobic activity is desired, fluoroquinolones, third-generation cephalosporins, aztreonam, or aminoglycosides are recommended. When anaerobic activity is desired, appropriate treatment includes clindamycin, metronidazole, chloramphenicol or a penicillin agent plus a β-lactamase inhibitor. • In axillary or perineum surgical site infections, cefoxitin, ampicillin-sulbactam or agents indicated for intestinal and genital sites are appropriate.
Surgical Infection Prevention Guideline Writers Workgroup: **Antimicrobial Prophylaxis for Surgery: An Advisory Statement from the National Surgical Infection Prevention Project (2004)**[28]	General considerations • There is published evidence to support the use of many prophylactic antimicrobial regimens besides those included in this advisory statement or in existing guidelines. • Factors such as cost, half-life, safety, and antimicrobial resistance favor the use of older agents with a relatively narrow spectrum. • The use of newer, broad-spectrum drugs that are front-line therapeutic agents should be avoided in surgical prophylaxis to reduce emergence of bacterial strains that are resistant to these antimicrobials. Gynecologic and obstetrical surgery • For abdominal or vaginal hysterectomy, cefotetan is preferred, but reasonable alternatives are cefazolin and cefoxitin. In cases of β-lactam allergy, the workgroup recommends the use of one of the following regimens: clindamycin combined with gentamicin, aztreonam, or ciprofloxacin; metronidazole combined with gentamicin or ciprofloxacin; or clindamycin monotherapy. A single 750 mg dose of levofloxacin can be substituted for ciprofloxacin. • For cesarean section, a narrow-spectrum antimicrobial regimen similar to that recommended for hysterectomy provides adequate prophylaxis. Orthopedic total joint (hip and knee) arthroplasty • The preferred antimicrobials for prophylaxis in patients undergoing hip or knee arthroplasty are cefazolin and cefuroxime. • Vancomycin or clindamycin may be used in patients with serious allergy or adverse reactions to β-lactams. Cardiothoracic and vascular surgery • The recommended antimicrobials for cardiothoracic and vascular operations include cefazolin or cefuroxime. • For patients with serious allergy or adverse reaction to β-lactams, vancomycin is appropriate, and clindamycin may be an acceptable alternative. Colorectal surgery • Antimicrobial prophylaxis for colorectal operations can consist of an orally administered antimicrobial bowel preparation, a preoperative parenteral antimicrobial, or the combination of both. • Recommended oral prophylaxis consists of neomycin plus erythromycin or neomycin plus metronidazole, initiated no more than 18 to 24 hours before the operation, along with administration of a mechanical bowel preparation. • Cefotetan or cefoxitin are recommended for parenteral prophylaxis, and the

Clinical Guideline	Recommendation(s)
	combination of parenteral cefazolin and metronidazole is also recommended as an alternative. • For patients with confirmed allergy or adverse reaction to β-lactams, use of one of the following regimens is recommended: clindamycin combined with gentamicin, aztreonam, or ciprofloxacin; or metronidazole combined with gentamicin or ciprofloxacin. A single 750 mg dose of levofloxacin can be substituted for ciprofloxacin.
National Institutes of Health, the Centers for Disease Control and Prevention, and the Human Immunodeficiency Virus Medicine Association of the Infectious Diseases Society of America: **Guidelines for Prevention and Treatment of Opportunistic Infections in Human Immunodeficiency Virus -Infected Adults and Adolescents (2013)**[18]	Aspergillosis • Voriconazole is the drug of choice but should be used cautiously with human immunodeficiency virus protease inhibitors and efavirenz. Amphotericin B deoxycholate at 1 mg/kg daily or lipid-formulation amphotericin B at 5 mg/kg daily are alternatives, as is caspofungin at 50 mg daily and posaconazole. • Other echinocandins, such as micafungin and anidulafungin, are reasonable alternatives. • For treatment failure (if voriconazole was used initially) substitution with amphotericin B, posaconazole, or echinocandins might be considered; the amphotericin B or echinocandins would be rational for those who began therapy with voriconazole or posaconazole. Candidiasis (mucocutaneous) • Oral fluconazole is as effective as topical therapy for oropharyngeal candidiasis and is considered the drug of choice. Initial episodes of oropharyngeal candidiasis can be adequately treated with topical therapy, including clotrimazole troches, nystatin suspension or pastilles, or miconazole mucoadhesive tablets. Itraconazole oral solution for seven to 14 days is as effective as oral fluconazole but less well tolerated. Posaconazole oral solution is also as effective as fluconazole and is generally better tolerated than itraconazole. Intravenous amphotericin B is usually effective and can be used among patients with refractory disease. Both conventional amphotericin B and lipid complex and liposomal amphotericin B have been used. • Systemic antifungals are required for effective treatment of esophageal candidiasis. A 14 to 21-day course of either fluconazole (oral or intravenous) or oral itraconazole solution is highly effective. Oral ketoconazole or itraconazole capsules are less effective than fluconazole because of variable absorption. Although intravenous caspofungin or intravenous voriconazole are effective in treating esophageal candidiasis among human immunodeficiency virus -infected patients, oral or intravenous fluconazole remain the preferred therapies. Azole-refractory esophageal candidiasis can be treated with posaconazole, amphotericin B, anidulafungin, caspofungin, micafungin, or voriconazole. • Vulvovaginal candidiasis in human immunodeficiency virus -infected women is usually uncomplicated (90%) and responds readily to short-course oral or topical treatment with any of several therapies, including oral fluconazole, topical azoles, and itraconazole oral solution. Severe or recurrent episodes of vaginitis require oral fluconazole or topical antifungal therapy for ≥7 days. Coccidioidomycosis • For patients with clinically mild infection, such as focal pneumonia or a positive coccidioidal serologic test alone, initial therapy with a triazole antifungal is appropriate. • For patients with either diffuse pulmonary involvement or severely ill patients with extrathoracic disseminated disease, amphotericin B is the preferred initial therapy. Therapy with amphotericin B should continue until clinical improvement is observed. Some specialists would use a triazole antifungal concurrently with amphotericin B and continue the triazole once amphotericin B is stopped.

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	Cryptococcosis • The recommended initial standard treatment is amphotericin B combined with flucytosine for ≥2 weeks for those with normal renal function. • The combination of amphotericin B with fluconazole is less effective than amphotericin B combined with flucytosine in terms of clearing *Cryptococcus* from the cerebrospinal fluid but is better than amphotericin B alone. • Fluconazole combined with flucytosine is an alternative to amphotericin B plus flucytosine, but is less effective than amphotericin B and is recommended only for persons unable to tolerate or unresponsive to standard treatment. • After at least a two-week period of successful induction therapy, amphotericin B and flucytosine may be discontinued and follow-up therapy initiated with fluconazole. This should continue for eight weeks. Itraconazole is an acceptable though less effective alternative. • The optimal therapy for those with treatment failure is not established. For those initially treated with fluconazole, therapy should be changed to amphotericin B, with or without flucytosine, and continued until a clinical response occurs. Liposomal amphotericin B may have improved efficacy over the deoxycholate formulation and should be considered in treatment failures. Higher doses of fluconazole in combination with flucytosine might also be useful. Cryptosporidiosis • In the setting of severe immunosuppression, antiretroviral therapy with immune restoration to a CD4+ count >100 cells/µL leads to resolution of clinical cryptosporidiosis and is the mainstay of treatment. • All patients with cryptosporidiosis should be offered antiretroviral therapy as part of the initial management of their infection. • Management should include symptomatic treatment of diarrhea. Rehydration and repletion of electrolyte losses by either the oral or intravenous route are important. Severe diarrhea can exceed >10 L/day among patients with acquired immunodeficiency syndrome, often requiring intensive support. Aggressive efforts at oral rehydration should be made with oral rehydration solutions. Prevention of Cytomegalovirus • Cytomegalovirus end-organ disease is best prevented by using antiretroviral therapy to maintain the CD4+ count >100 cells/µL. • Although oral valganciclovir would likely prevent the occurrence of cytomegalovirus retinitis in patients with CD4+ counts <50 cells/µL, such therapy is not generally recommended because of the potential to induce cytomegalovirus resistance, the utility of treating disease when it occurs, and the lack of demonstrated survival advantage. Treatment of Cytomegalovirus disease • Oral valganciclovir, intravenous ganciclovir, intravenous ganciclovir followed by oral valganciclovir, intravenous foscarnet, and intravenous cidofovir are all effective treatments for cytomegalovirus retinitis. • The ganciclovir implant, a surgically-implanted reservoir of ganciclovir, which lasts approximately six months, also is very effective but it no longer is being manufactured. In its absence, some clinicians will use intravitreal injections of ganciclovir or foscarnet in conjunction with oral valganciclovir, at least initially, to provide immediate high intraocular levels of drug and presumably faster control of the retinitis. • Systemic therapy has been shown to reduce morbidity in the contralateral eye. This should be considered when choosing between the oral, intravenous, and local options. • The choice of initial therapy for cytomegalovirus retinitis should be

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	individualized based on the location and severity of the lesion(s), the level of underlying immune suppression, and other factors such as concomitant medications and ability to adhere to treatment. • No one regimen has been proven in a clinical trial to have greater efficacy in terms of protecting vision, and thus clinical judgment must be used when choosing a regimen. • In studies conducted in the pre-antiretroviral therapy era, ganciclovir intraocular implant plus oral ganciclovir was superior to once-daily intravenous ganciclovir for treatment of cytomegalovirus retinitis; however, the implant is no longer manufactured. Assuming that this observation can be extended to other combinations of systemically and locally administered drugs, human immunodeficiency virus-specialists often recommend intravitreal ganciclovir or foscarnet injections plus oral valganciclovir as the preferred initial therapy for patients with immediate sight-threatening lesions. Intravitreal injections deliver high concentrations of the drug to the target organ immediately while steady-state concentrations in the eye are achieved with systemically delivered medications. For patients with small peripheral lesions, oral valganciclovir alone often is adequate. • After induction therapy, secondary prophylaxis (i.e., chronic maintenance therapy) should be continued until immune reconstitution occurs as a result of antiretroviral therapy. Regimens demonstrated to be effective for chronic suppression in randomized, controlled clinical trials include parenteral ganciclovir, oral valganciclovir, parenteral foscarnet, combined parenteral ganciclovir and foscarnet, and parenteral cidofovir. <u>Management of Cytomegalovirus retinitis treatment failures</u> • When patients relapse while receiving maintenance therapy, induction with the same drug followed by reinstitution of maintenance therapy can control the retinitis, although for progressively shorter periods of time with each relapse. • Ganciclovir and foscarnet in combination appear to be superior in efficacy to either agent alone and should be considered for patients whose disease does not respond to single-drug therapy, and for patients with multiple relapses of retinitis. This drug combination, however, is associated with substantial toxicity. <u>Treatment of Hepatitis B Virus coinfection in patients not receiving antiretroviral therapy</u> • For patients with CD4+ counts >350 cells/µL who are not receiving antiretroviral therapy but meet criteria for hepatitis B virus treatment, adefovir or peginterferon alfa-2a monotherapy for 48 weeks might be considered, with close monitoring of hepatitis B virus deoxyribonucleic acid levels and follow-up to evaluate for hepatitis B e antigen seroconversion. However, early initiation of antiretroviral therapy should also be considered for human immunodeficiency virus/hepatitis B virus -coinfected persons with CD4+ counts >350 cells/µL. <u>Treatment of Hepatitis B Virus coinfection in patients who require antiretroviral therapy</u> • For human immunodeficiency virus-infected persons, some experts recommend combination therapy with two agents active against hepatitis B virus to reduce the risk of hepatitis B virus drug resistance; although, there are no results from controlled trials as yet to support this strategy. • Among patients infected with hepatitis B virus, hepatitis C virus, and human immunodeficiency virus, consideration of the need for antiretroviral therapy should be the first priority. If antiretroviral therapy is not required, interferon-based therapy, which suppresses both hepatitis C virus and hepatitis B virus, should be considered. If interferon-based therapy for hepatitis C virus has failed, treatment of chronic hepatitis B with nucleoside or nucleotide analogs is

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	recommended.
	
	Treatment of Hepatitis C coinfection
	• Antiviral treatment for hepatitis C virus infection should be considered for all human immunodeficiency virus-infected persons with acute or chronic hepatitis C virus infection.
	• The combination of peginterferon alfa (PegIFN) plus ribavirin is the recommended backbone of therapy for HIV/HCV-co-infected patients regardless of HCV genotype.
	• Antiviral treatment with PegIFN is not recommended in patients with decompensated liver disease.
	• For HCV-genotype-1-infected patients who are not co-infected with HIV, a HCV NS3/4A protease inhibitor (PI), either boceprevir or telaprevir, in combination with PegIFN/ribavirin is recommended on the basis of large clinical trials demonstrating significantly higher SVR rates with an acceptable safety/tolerability profile compared to PegIFN/ribavirin alone.
	• For HIV/HCV co-infected patients, preliminary data from small, ongoing clinical trials of boceprevir or telaprevir plus PegIFN/ribavirin for the treatment of HCV genotype 1 infection in HIV/HCV co-infected patients demonstrate greater efficacy than PegIFN/ribavirin alone, with a safety and tolerability profile similar to that observed in HCV monoinfected patients treated with boceprevir or telaprevir plus PegIFN/ribavirin. Preliminary recommendations are as follows:
	  o PegIFN is recommended for use for all HCV genotypes
	  o Ribavirin is recommended for use with PegIFN for all HCV genotypes.
	  o Boceprevir is approved for use in combination with PegIFN/ribavirin in HCV-genotype-1-monoinfected-patients. For HIV/HCV-co-infected patients, the regimen being evaluated is PegIFN/ribavirin administered for four weeks (lead-in phase) followed by boceprevir 800 mg orally every 7 to 9 hours (with a light snack) added to PegIFN/ribavirin for an additional 44 weeks.
	  o Telaprevir is approved for use in combination with PegIFN/ribavirin in HCV-genotype-1-monoinfected-patients. Dosing regimens lasting 48 weeks are being evaluated.
	• Patients with contraindications to the use of ribavirin can be treated with peginterferon alfa (2a or 2b) monotherapy. However, substantially lower sustained viral response rates are expected in persons not receiving ribavirin. HCV PIs should not be administered without ribavirin because of the high likelihood of virologic failure.
	
	Treatment of herpes simplex virus disease
	• Orolabial lesions can be treated with oral valacyclovir, famciclovir, or acyclovir for five to 10 days.
	• Severe mucocutaneous herpes simplex virus lesions are best treated initially with intravenous acyclovir. Patients may be switched to oral therapy after the lesions have begun to regress. Therapy should be continued until the lesions have completely healed.
	• Genital herpes simplex virus infection should be treated with oral valacyclovir, famciclovir, or acyclovir for five to 14 days. Short-course therapy (one, two, or three days) should not be used in patients with human immunodeficiency virus infection.
	• Most recurrences of genital herpes can be prevented by use of daily anti- herpes simplex virus therapy, and this is recommended for persons who have frequent or severe recurrences.
	• Suppressive therapy with oral acyclovir, valacyclovir, or famciclovir is effective in preventing recurrences. Suppressive therapy with valacyclovir should be 500 mg twice daily in human immunodeficiency virus -infected persons or twice-

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	daily regimens with acyclovir or famciclovir should be used. Management of herpes simplex virus treatment failure • The treatment of choice for acyclovir-resistant herpes simplex virus is intravenous foscarnet. Topical trifluridine, cidofovir, and imiquimod also have been used successfully for lesions on external surfaces, although prolonged application for 21 to 28 days or longer might be required. Histoplasmosis • Patients with moderately severe to severe disseminated histoplasmosis should be treated with an intravenous lipid formulation of amphotericin B for ≥2 weeks or until they clinically improve followed by oral itraconazole (200 mg three times daily for three days and then 200 mg twice daily for a total of ≥12 months). • In patients with less severe disseminated histoplasmosis, oral itraconazole at 200 mg three times daily for three days followed by 200 mg twice daily is appropriate initial therapy. Treatment of Isosporiasis (also known as Cystoisosporiasis) • Sulfamethoxazole-trimethoprim is the antimicrobial agent of choice for treatment of isosporiasis. It is the only agent whose use is supported by substantial published data and clinical experience. Therefore, potential alternative therapies should be reserved for patients with documented sulfa intolerance or in whom treatment fails. The traditional treatment regimen has been a 10-day course of Sulfamethoxazole-trimethoprim (800-160 mg) administered orally four times daily. • Intravenous administration of Sulfamethoxazole-trimethoprim should be considered for patients with potential or documented malabsorption. • Single-agent therapy with pyrimethamine has been used, with anecdotal success for treatment and prevention of isosporiasis. Pyrimethamine (50 to 75 mg/day) plus leucovorin (10 to 25 mg/day) to prevent myelosuppression may be an effective treatment alternative; it is the option for sulfa-intolerant patients. Leishmaniasis • Due to similar efficacy and a better toxicity profile, clinicians consider liposomal amphotericin B as the drug of choice for visceral leishmaniasis in human immunodeficiency virus-coinfected patients. The optimal amphotericin B dosage has not been determined. • Regimens with efficacy include conventional amphotericin B 0.5 to 1.0 mg/kg body weight/day intravenous to achieve a total dose of 1.5 to 2.0 g, or liposomal or lipid complex preparations of two to four mg/kg body weight administered on consecutive days or in an interrupted schedule (e.g., 4 mg/kg on Days 1 to 5, 10, 17, 24, 31, and 38) to achieve a total cumulative dose of 20 to 60 mg/kg body weight. A higher daily dosage is recommended for liposomal or lipid complex preparations than for conventional amphotericin B. Preventing disseminated *Mycobacterium avium* complex disease • Human immunodeficiency virus-infected adults and adolescents should receive chemoprophylaxis against disseminated *Mycobacterium avium* complex disease if they have a CD4+ count <50 cells/µL. • Azithromycin or clarithromycin are the preferred prophylactic agents. • The combination of clarithromycin and rifabutin is no more effective than clarithromycin alone for chemoprophylaxis, is associated with a higher rate of adverse effects than either drug alone, and should not be used. • The combination of azithromycin with rifabutin is more effective than

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	azithromycin alone; however, the additional cost, increased occurrence of adverse effects, potential for drug interactions, and absence of a survival difference compared to azithromycin alone do not warrant a routine recommendation for this regimen. • Azithromycin and clarithromycin also each confer protection against respiratory bacterial infections. • If azithromycin or clarithromycin cannot be tolerated, rifabutin is an alternative prophylactic agent for *Mycobacterium avium* complex disease, although drug interactions may make this agent difficult to use. • Primary *Mycobacterium avium* complex disease prophylaxis should be discontinued among adult and adolescent patients who have responded to antiretroviral therapy with an increase in CD4+ counts to >100 cells/µL for ≥3 months. Primary prophylaxis should be reintroduced if the CD4+ count decreases to <50 cells/µL. <u>Treatment of disseminated *Mycobacterium avium* Complex Disease</u> • Initial treatment of *Mycobacterium avium* complex disease should consist of two or more antimycobacterial drugs to prevent or delay the emergence of resistance. • Clarithromycin is the preferred first agent; however, azithromycin can be substituted for clarithromycin when drug interactions or clarithromycin intolerance preclude the use of clarithromycin. • Testing of *Mycobacterium avium* complex disease isolates for susceptibility to clarithromycin or azithromycin is recommended for all patients. <u>Treatment of Penicilliosis marneffei</u> • Penicilliosis is caused by the dimorphic fungus *Penicillium marneffei*, which is known to be endemic in Southeast Asia (especially Northern Thailand and Vietnam) and southern China. • The recommended treatment is liposomal amphotericin B, three to five mg/kg body weight/day intravenously for two weeks, followed by oral itraconazole, 400 mg/day for a subsequent duration of 10 weeks, followed by secondary prophylaxis. • Patients with mild disease can be initially treated with oral itraconazole 400 mg/day for eight weeks, followed by 200 mg/day for prevention of recurrence. • The alternative drug for primary treatment in the hospital is intravenous voriconazole, 6 mg/kg every 12 hours on day one and then 4 mg/kg every 12 hours for at least three days, followed by oral voriconazole, 200 mg twice daily for a maximum of 12 weeks. • Patients with mild disease can be initially treated with oral voriconazole 400 mg twice a day on day one, and then 200 mg twice daily for 12 weeks. The optimal dose of voriconazole for secondary prophylaxis after 12 weeks has not been studied. <u>Primary prophylaxis of *Pneumocystis (carinii) jiroveci* pneumonia</u> • Sulfamethoxazole-trimethoprim is the recommended prophylactic agent. One double-strength tablet daily is the preferred regimen. However, one single-strength tablet daily is also effective and might be better tolerated than one double-strength tablet daily. One double-strength tablet three times weekly is also effective. Sulfamethoxazole-trimethoprim at a dose of one double-strength tablet daily confers cross-protection against toxoplasmosis and selected common respiratory bacterial infections. Lower doses of sulfamethoxazole-trimethoprim likely also confer such protection. • For patients who have an adverse reaction that is not life threatening, chemoprophylaxis with sulfamethoxazole-trimethoprim should be continued if

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	clinically feasible; for those who have discontinued such therapy because of an adverse reaction, reinstituting sulfamethoxazole-trimethoprim should be strongly considered after the adverse event has resolved. Patients who have experienced adverse events, including fever and rash, might better tolerate reintroduction of the drug with a gradual increase in dose (i.e., desensitization), according to published regimens or reintroduction of sulfamethoxazole-trimethoprim at a reduced dose or frequency; as many as 70% of patients can tolerate such reinstitution of therapy. • If sulfamethoxazole-trimethoprim cannot be tolerated, alternative prophylactic regimens include dapsone, dapsone/pyrimethamine plus leucovorin, aerosolized pentamidine and atovaquone. • Primary *Pneumocystis (carinii) jiroveci* pneumonia prophylaxis should be discontinued for adult and adolescent patients who have responded to antiretroviral therapy with an increase in CD4+ counts to >200 cells/µL for >3 months. Prophylaxis should be reintroduced if the CD4+ count decreases to <200 cells/µL. <u>Treatment of *Pneumocystis (carinii) jiroveci* pneumonia</u> • Sulfamethoxazole-trimethoprim is the treatment of choice. The dose must be adjusted for abnormal renal function. Multiple randomized clinical trials indicate that sulfamethoxazole-trimethoprim is as effective as parenteral pentamidine and more effective than other regimens. Adding leucovorin to prevent myelosuppression during acute treatment is not recommended because of questionable efficacy and some evidence for a higher failure rate. Oral outpatient therapy of sulfamethoxazole-trimethoprim is highly effective among patients with mild-to-moderate disease. • Patients who have *Pneumocystis (carinii) jiroveci* despite sulfamethoxazole-trimethoprim prophylaxis are usually effectively treated with standard doses of sulfamethoxazole-trimethoprim. • Patients with documented or suspected *Pneumocystis (carinii) jiroveci* and moderate-to-severe disease, as defined by room air pO_2 <70 mm Hg or arterial-alveolar O_2 gradient >35 mm Hg, should receive adjunctive corticosteroids as early as possible, and certainly within 72 hours after starting specific *Pneumocystis (carinii) jiroveci* therapy. • The recommended duration of therapy for *Pneumocystis (carinii) jiroveci* is 21 days. • Patients who have a history of *Pneumocystis (carinii) jiroveci* should be administered chemoprophylaxis for life (i.e., secondary prophylaxis or chronic maintenance therapy) with sulfamethoxazole-trimethoprim unless immune reconstitution occurs as a result of antiretroviral therapy. • Secondary prophylaxis should be discontinued for adult and adolescent patients whose CD4+ count has increased from <200 cells/µL to >200 cells/µL for >3 months as a result of antiretroviral therapy. Prophylaxis should be reintroduced if the CD4+ count decreases to <200 cells/µL. If *Pneumocystis (carinii) jiroveci* recurs at a CD4+ count of ≥200 cells/µL, lifelong prophylaxis should be administered. <u>Primary prophylaxis of *Toxoplasma* encephalitis</u> • The double-strength tablet daily dose of sulfamethoxazole-trimethoprim recommended as the preferred regimen for *Pneumocystis (carinii) jiroveci* prophylaxis is effective against *Toxoplasma* encephalitis as well and is therefore recommended. Sulfamethoxazole-trimethoprim, one double-strength tablet three times weekly, is an alternative. • If patients cannot tolerate sulfamethoxazole-trimethoprim, the recommended alternative is dapsone-pyrimethamine plus leucovorin, which is also effective against *Pneumocystis (carinii) jiroveci* pneumonia.

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	• Atovaquone with or without pyrimethamine/leucovorin can also be considered.
	• Prophylactic monotherapy with dapsone, pyrimethamine, azithromycin, or clarithromycin cannot be recommended on the basis of available data. Aerosolized pentamidine does not protect against *Toxoplasma* encephalitis and is not recommended.
	• Prophylaxis against *Toxoplasma* encephalitis should be discontinued among adult and adolescent patients who have responded to antiretroviral therapy with an increase in CD4+ counts to >200 cells/µL for >3 months. Prophylaxis for *Toxoplasma* encephalitis should be reintroduced if the CD4+ count decreases to <100–200 cells/µL.
	
	<u>Treatment of *Toxoplasma* encephalitis</u>
	• The initial therapy of choice for *Toxoplasma* encephalitis consists of the combination of pyrimethamine plus sulfadiazine plus leucovorin.
	• The preferred alternative regimen for patients with *Toxoplasma* encephalitis who are unable to tolerate or who fail to respond to first-line therapy is pyrimethamine plus clindamycin plus leucovorin.
	• Sulfamethoxazole-trimethoprim was reported in a small randomized trial to be effective and better tolerated than pyrimethamine-sulfadiazine. On the basis of less in vitro activity and less experience with sulfamethoxazole-trimethoprim, treatment with this drug may be considered an option.
	• Acute therapy for *Toxoplasma* encephalitis should be continued for at least six weeks, if there is clinical and radiologic improvement.
	
	<u>Treatment of latent tuberculosis infection</u>
	• Human immunodeficiency virus-infected persons, regardless of age, should be treated for latent tuberculosis infection if they have no evidence of active tuberculosis and:
	  o A positive diagnostic test for latent tuberculosis infection and no prior history of treatment for active or latent tuberculosis.
	  o A negative diagnostic test for latent tuberculosis infection but are close contacts of persons with infectious pulmonary tuberculosis.
	  o A history of untreated or inadequately treated healed tuberculosis (i.e., old fibrotic lesions on chest radiography) regardless of diagnostic tests for latent tuberculosis infection.
	• Treatment options for latent tuberculosis infection include isoniazid daily or twice weekly for nine months.
	• Due to an increased risk of fatal and severe hepatotoxicity, a two-month regimen of daily rifampin and pyrazinamide is not recommended for latent tuberculosis infection treatment regardless of human immunodeficiency virus status.
	• Human immunodeficiency virus-infected persons receiving isoniazid should receive pyridoxine to minimize the risk of developing peripheral neuropathy. Alternatives for individuals who cannot take isoniazid or who have been exposed to a known isoniazid-resistant index case include either rifampin or rifabutin alone for four months.
	• For persons exposed to isoniazid- and/or rifampin-resistant tuberculosis, decisions to treat with one or two drugs other than isoniazid, rifampin, or rifabutin should be based on the relative risk of exposure to organisms broadly resistant to other antimycobacterial drugs and should be made in consultation with public health authorities.
	• Directly observed therapy should be used with intermittent dosing regimens when otherwise feasible to maximize regimen completion rates.
	• There is no evidence to suggest that latent tuberculosis infection treatment should be continued beyond the recommended duration in persons with human immunodeficiency virus infection. Therefore, latent tuberculosis infection

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	treatment should be discontinued after completing the appropriate number of doses. Treatment of active tuberculosis disease • Recommendations for anti-tuberculosis treatment regimens in human immunodeficiency virus -infected adults follow the same principles as for adults without human immunodeficiency virus -infection. • Treatment of drug susceptible tuberculosis disease should include a six-month regimen with an initial phase of isoniazid, rifampin or rifabutin, pyrazinamide, and ethambutol administered for two months followed by isoniazid and rifampin (or rifabutin) for four additional months. • When drug-susceptibility testing confirms the absence of resistance to isoniazid, rifampin, and pyrazinamide, ethambutol may be discontinued before two months of treatment have been completed. • For patients with cavitary lung disease and cultures positive for *Mycobacterium tuberculosis* after completion of two months of therapy, treatment should be extended with isoniazid and rifampin for an additional three months for a total of nine months. • All human immunodeficiency virus-infected patients treated with isoniazid should receive pyridoxine supplementation. • For patients with extrapulmonary tuberculosis, a six- to nine-month regimen (two months of isoniazid, rifampin, pyrazinamide, and ethambutol followed by four to seven months of isoniazid and rifampin) is recommended. • Exceptions to the recommendation for a six- to nine-month regimen for extrapulmonary tuberculosis include central nervous system disease (tuberculoma or meningitis) and bone and joint tuberculosis, for which many experts recommend nine to 12 months. • Adjuvant corticosteroids should be added when treating central nervous system and pericardial disease. • Treatment with corticosteroids should be started intravenously as early as possible with change to oral therapy individualized according to clinical improvement. • Recommended corticosteroid regimens are dexamethasone 0.3 to 0.4 mg/kg tapered over six to eight weeks or prednisone 1 mg/kg for three weeks, then tapered for three to five weeks. Treatment of varicella zoster virus disease • For uncomplicated varicella, the preferred treatment options are valacyclovir (1 gram orally three times daily), or famciclovir (500 mg orally three times daily) for five to seven days. Oral acyclovir (20 mg/kg body weight up to a maximum dose of 800 mg five times daily) can be an alternative. • Prompt antiviral therapy should be instituted in all human immunodeficiency virus-seropositive patients whose herpes zoster is diagnosed within one week of rash onset (or any time before full crusting of lesions). The recommended treatment options for acute localized dermatomal herpes zoster in human immunodeficiency virus-infected patients are oral valacyclovir, famciclovir, or acyclovir (doses as above) for seven to 10 days, although longer durations of therapy should be considered if lesions resolve slowly. Valacyclovir or famciclovir are preferred because of their improved pharmacokinetic properties and simplified dosing schedule. • If cutaneous lesions are extensive or if visceral involvement is suspected, intravenous acyclovir should be initiated and continued until clinical improvement is evident. A switch from intravenous acyclovir to oral antiviral therapy (to complete a 10 to 14 day treatment course) is reasonable when formation of new cutaneous lesions has ceased and the signs and symptoms of

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	visceral varicella zoster virus infection are clearly improving. • Optimal antiviral therapy for progressive outer retinal necrosis remains undefined. Specific treatment should include systemic therapy with at least one intravenous drug (selected from acyclovir, ganciclovir, foscarnet, and cidofovir) coupled with injections of at least one intravitreal drug (selected from ganciclovir and foscarnet). Treatment regimens for progressive outer retinal necrosis recommended by certain specialists include a combination of intravenous ganciclovir and/or foscarnet plus intravitreal injections of ganciclovir and/or foscarnet. The prognosis for visual preservation in involved eyes is poor, despite aggressive antiviral therapy. • Other infectious disease states mentioned within these guidelines note that the treatment guidelines for that disease state should be utilized. • The guideline specifies that detailed recommendations for the treatment of human herpesvirus-8 and associated malignancies are beyond the scope of these guidelines. • Other excluded infectious disease states offer no specific therapy or utilize medications not licensed in the United States.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the miscellaneous antiprotozoals are noted in Table 4. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 4. FDA-Approved Indications for the Antiprotozoals, Miscellaneous[1-11]

Indication	Atovaquone	Metronidazole	Nitazoxanide	Pentamidine	Tinidazole
Acute intestinal amebiasis (amebic dysentery)		✔			✔
Amebic liver abscess		✔			✔
Bacterial septicemia		✔			
Bacterial vaginosis		✔ §			✔
Bone and joint infections		✔			
Central nervous system infections		✔			
Diarrhea caused by *Cryptosporidium parvum* or *Giardia lamblia*			✔		
Endocarditis		✔			
Giardiasis					✔
Gynecologic infections		✔			
Intra-abdominal infections		✔			
Lower respiratory tract infections		✔			
Perioperative prophylaxis, contaminated or potentially contaminated colorectal surgery		✔ ‡			
Skin and skin-structure infections		✔			
Prevention of *Pneumocystis carinii* pneumonia in high-risk, human immunodeficiency virus-infected patients				✔ †	
Prevention of *Pneumocystis carinii* pneumonia in patients who are intolerant to sulfamethoxazole-trimethoprim	✔				
Treatment of mild-to-moderate *Pneumocystis carinii* pneumonia in patients who are intolerant to sulfamethoxazole-trimethoprim	✔				
Treatment of *Pneumocystis carinii* pneumonia				✔ ‡	
Trichomoniasis		✔			✔

†Inhalation formulation only.
‡Intravenous formulation only.
§Extended-release formulation only.

IV. Pharmacokinetics

The pharmacokinetic parameters of the miscellaneous antiprotozoals are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Antiprotozoals, Miscellaneous[1-11]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (Hours)
Atovaquone	47	99.9	Limited	Renal (0.6) Feces (>94.0)	67 to 78
Metronidazole	100	<20	Liver	Renal (60 to 80) Feces (6 to 15)	6 to 12
Nitazoxanide	70	>99	Conjugation	Renal (33) Feces (67)	1.0 to 1.6
Pentamidine	Not reported	69	Not reported	Renal (12)	5 to 8
Tinidazole	100	12	Liver	Renal (20 to 25) Feces (12)	12 to 14

V. Drug Interactions

Significant drug interactions with the miscellaneous antiprotozoals are listed in Table 6.

Table 6. Significant Drug Interactions with the Antiprotozoals, Miscellaneous[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Metronidazole, tinidazole	1	Anticoagulants	The anticoagulant effect of warfarin may be enhanced; hemorrhage could occur. Liver metabolism of the S (−) enantiomorph of racemic warfarin may be decreased by metronidazole.
Metronidazole, tinidazole	1	Busulfan	Busulfan trough concentrations may be elevated, increasing the risk of serious toxicity (e.g., veno-occlusive disease, hemorrhagic cystitis).
Metronidazole, tinidazole	1	Disulfiram	Acute toxic psychosis may occur during the coadministration of metronidazole and disulfiram.
Metronidazole	1	Ergot alkaloids	Plasma concentrations and pharmacologic effects of ergot alkaloids may be increased by metronidazole. The potential for the development of ergotism exists.
Pentamidine	1	Nilotinib, vandetanib	Additive QT prolongation may occur during coadministration of nilotinib or vandetanib and pentamidine.
Pentamidine	1	QTC-prolonging agents	Additive QT prolongation may occur during coadministration with pentamidine.
Pentamidine (injection)	1	Class III antiarrhythmics	Prolongation of the QT interval with possible development of cardiac arrhythmias, including torsades de pointes, should be considered when class III antiarrhythmics are co-administered with pentamidine.
Pentamidine (injection)	1	Dofetilide	The risk of cardiovascular toxicity, including torsade de pointes, may be increased by co-administration of pentamidine and dofetilide.
Pentamidine	1	H1-antagonists	Co-administration of pentamidine and H1-

Generic Name(s)	Significance Level	Interaction	Mechanism
(injection)			antagonists may cause cardiovascular toxicity, including excessive prolongation of the QT interval and, rarely, fatal cardiac arrhythmias (torsades de pointes).
Pentamidine inhalation	1	Toremifene	Additive QT prolongation may occur during coadministration of toremifene and pentamidine.
Tinidazole	1	H-1 antagonists	Tinidazole may decrease the hepatic metabolism of H-1 antagonists. Elevated H-1 antagonists plasma concentrations with severe cardiac toxicity may occur.
Tinidazole	1	Cyclosporine	Tinidazole may increase plasma concentrations and pharmacologic effects of cyclosporine. Renal toxicity possibly associated with elevated cyclosporine blood or plasma concentrations may occur.
Metronidazole, tinidazole	2	Barbiturates	Therapeutic failure of metronidazole may occur by means of barbiturate induction of metronidazole metabolism, resulting in more rapid elimination and lower serum concentrations.
Metronidazole, tinidazole	2	Macrolide immunosuppressants	Pharmacologic and toxic effects of macrolide immunosuppressants may be increased by metronidazole. Elevated plasma concentrations of macrolide immunosuppressants with nephrotoxicity may occur.
Metronidazole, tinidazole	2	Protease inhibitors	Co-administration of metronidazole and human immunodeficiency virus protease inhibitors may cause an alcohol intolerance reaction.
Atovaquone	2	Rifamycins	Plasma concentrations of atovaquone may be decreased by rifamycins.
Atovaquone	2	Tetracyclines	Tetracyclines may decrease the plasma concentrations and pharmacologic effects of atovaquone.
Atovaquone	2	Zidovudine	Concurrent administration of atovaquone and zidovudine may result in inhibition of zidovudine glucuronidation, thereby increasing zidovudine concentrations and the risk of zidovudine toxicity. If an interaction is suspected, a dose reduction of zidovudine may be indicated.
Pentamidine (injection)	2	Flecainide	Additive QT interval prolongation may occur during coadministration of pentamidine and flecainide.
Pentamidine (injection)	2	Lapatinib	Additive QT interval prolongation is listed in the manufacturer's package labeling for lapatinib as a possibility when lapatinib and pentamidine are co-administered.
Pentamidine (injection)	2	Perflutren	Additive QT interval prolongation may occur during coadministration of perflutren and pentamidine.
Pentamidine (injection)	2	Propafenone	Additive QT interval prolongation may occur during coadministration of pentamidine and propafenone.

Generic Name(s)	Significance Level	Interaction	Mechanism
Pentamidine (injection)	2	Tetrabenazine	Additive QT prolongation may occur during coadministration of tetrabenazine and pentamidine.

Significance level 1=major severity; significance level 2=moderate severity

VI. Adverse Drug Events

The most common adverse drug events reported with the miscellaneous antiprotozoals are listed in Table 7. The boxed warning for metronidazole is listed in Table 8. The boxed warning for tinidazole is listed in Table 9.

Table 7. Adverse Drug Events (%) Reported with the Antiprotozoals, Miscellaneous[1-11]

Adverse Events	Atovaquone	Metronidazole	Nitazoxanide	Pentamidine	Tinidazole
Cardiovascular					
Cardiac arrhythmias	-	-	-	✔	-
Chest pain	-	-	-	✔	-
Hypertension	-	-	<1	✔	-
Hypotension	<1	-	-	5	-
Palpitations	-	-	-	✔	✔
Syncope	-	✔	<1	✔	-
T-wave flattening	-	✔	-	-	-
Tachycardia	-	-	<1	✔	-
Torsades de pointes	-	-	-	✔	-
Sinus arrhythmia	✔	-	-	-	-
Central Nervous System					
Anxiety	≤7	-	-	✔	-
Aseptic meningitis	-	✔	-	-	-
Asthenia	≤22	✔	<1	-	✔
Ataxia	-	✔	-	-	✔
Coma	-	-	-	-	✔
Confusion	-	✔	-	2	✔
Convulsions	-	✔	-	-	✔
Dementia	✔	-	-	-	-
Depression	✔	✔	-	✔	✔
Dizziness	≤8	✔	<1	✔	2
Drowsiness	-	-	<1	✔	✔
Encephalopathy	-	✔	-	-	-
Fatigue	-	✔	-	✔	2
Fever	14 to 40	✔	<1	✔	✔
Giddiness	-	-	-	-	✔
Hallucinations	-	-	-	2	-
Headache	16 to 31	✔	3	✔	1
Hearing loss	-	✔	-	-	-
Hypesthesia	-	-	<1	-	-
Insomnia	10 to 19	✔	<1	✔	✔
Irritability	-	✔	-	-	-
Malaise	-	✔	-	✔	2
Peripheral neuropathy	≤22	✔	<1	-	✔
Seizure	-	✔	-	✔	✔
Tremor	-	-	<1	✔	-
Vertigo	-	✔	-	✔	✔
Weakness	-	✔	-	✔	2
Dermatological					
Burning sensation	-	-	-	-	✔

Adverse Events	Atovaquone	Metronidazole	Nitazoxanide	Pentamidine	Tinidazole
Erythema multiforme	✔	-	-	-	-
Pruritus	5 to 10	✔	<1	✔	✔
Rash	22 to 46	✔	<1	3	✔
Stevens-Johnson syndrome	✔	✔	-	-	-
Sweating	>10	-	-	-	✔
Toxic epidermal necrolysis	-	✔	-	-	-
Urticaria	✔	✔	-	✔	✔
Gastrointestinal					
Abdominal pain	4 to 21	✔	7	✔	✔
Appetite decreased	7	✔	<1	6	2
Appetite increased	✔	-	-	-	-
Colitis	-	-	-	✔	-
Constipation	3	✔	<1	-	<1
Cramps	5	✔	<1	✔	2
Diarrhea	19 to 42	1 to 4	4	✔	✔
Dry mouth	-	✔	<1	✔	✔
Dyspepsia	5	✔	<1	✔	2
Epigastric distress	5	✔	<1	✔	2
Esophagitis	-	-	-	✔	-
Flatulence	-	-	<1	-	-
Glossitis	-	✔	-	-	✔
Hematochezia	-	-	-	✔	-
Nausea	21 to 32	4 to 10	3	6	3
Pseudomembranous colitis	-	✔	-	-	-
Salivation	-	-	-	✔	✔
Stomatitis	-	✔	-	-	✔
Taste perversion	3	2 to 9	-	2	4 to 6
Thirst	-	-	<1	-	✔
Tongue discoloration	-	-	-	-	✔
Vomiting	14 to 22	✔	<1	✔	2
Genitourinary					
Impaired renal function	✔	-	-	29	-
Azotemia	-	-	-	9	-
Cystitis	-	✔	-	-	-
Dryness of vagina	-	✔	-	-	-
Dyspareunia	-	✔	-	-	-
Dysuria	-	✔	<1	-	-
Incontinence	-	✔	-	-	-
Libido decrease	-	✔	-	-	-
Menstrual irregularities	-	✔	<1	-	-
Polyuria	-	✔	-	-	-
Proctitis	-	✔	-	-	-
Sense of pelvic pressure	-	✔	-	-	-
Urethral discomfort	-	✔	-	-	-
Urine discoloration	-	✔	<1	-	✔
Vaginal discharge	-	12	-	-	✔
Vaginal irritation	-	✔	-	-	-
Vaginitis	-	✔	-	-	-
Vulvovaginal candidiasis	-	✔	-	-	✔
Hematologic					
Anemia	4 to 6	-	<1	1	-
Bone marrow aplasia	-	✔	-	-	-
Eosinophilia	-	-	-	✔	-
Leukocytosis	-	-	<1	-	-

Adverse Events	Atovaquone	Metronidazole	Nitazoxanide	Pentamidine	Tinidazole
Leukopenia	-	✔	-	10	✔
Methemoglobinemia	✔	-	-	-	-
Neutropenia	3 to 5	✔	-	✔	✔
Pancytopenia	-	-	-	✔	-
Thrombocytopenia	✔	✔	-	3	✔
Hepatic					
Alkaline phosphatase increase	8	-	-	-	-
Alanine aminotransferase increased	6	-	-	-	✔
Aspartate aminotransferase increased	4	-	-	-	✔
Bilirubin increased	✔	-	-	-	-
Liver function tests abnormal	-	-	-	9	-
Laboratory Test Abnormalities					
Amylase increased	7 to 8	-	-	-	-
Blood urea nitrogen increased	<1	-	-	7	-
Hypercalcemia	-	-	-	✔	-
Hyperglycemia	9	-	-	✔	-
Hypoglycemia	<1	-	-	6	-
Hyponatremia	7 to 10	-	-	-	-
Serum creatinine increased	<1	-	-	24	-
Serum glutamic-pyruvic transaminase increased	-	-	<1	-	-
Musculoskeletal					
Arthralgias	-	-	-	-	✔
Arthritis	-	-	-	-	✔
Bone fracture	-	-	<1	-	-
Joint pain	-	✔	-	-	-
Leg cramps	-	-	<1	-	-
Myalgias	-	-	<1	-	✔
Pain	≤10	-	<1	-	-
Paresthesia	-	-	-	-	✔
Respiratory					
Bronchitis	-	-	-	✔	-
Bronchospasm	2 to 4	-	-	✔	✔
Cough	14 to 25	-	-	✔	-
Dyspnea	15 to 21	-	-	✔	✔
Epistaxis	-	-	<1	-	-
Nasal congestion	-	✔	-	-	-
Pharyngitis	-	✔	<1	✔	✔
Rhinitis	5 to 24	✔	-	-	-
Sinusitis	7 to 10	✔	-	✔	-
Tachypnea	-	-	-	✔	-
Upper respiratory tract infections	-	✔	-	✔	-
Wheezing	-	-	-	✔	-
Special Senses					
Ear ache	-	-	<1	-	-
Eye discoloration	-	-	<1	-	-
Ototoxicity	-	✔	-	-	-
Tinnitus	-	✔	-	-	-

Adverse Events	Atovaquone	Metronidazole	Nitazoxanide	Pentamidine	Tinidazole
Vision abnormalities	-	-	-	✔	-
Other					
Allergic reaction	1	-	<1	-	-
Anaphylaxis	-	-	-	✔	-
Angioedema	✔	-	-	-	✔
Candidiasis	5 to 10	✔	-	✔	✔
Diabetes mellitus	-	-	-	✔	-
Flu-like syndrome	>10	-	<1	-	-
Flushing	-	✔	-	-	✔
Herpes zoster	-	-	-	✔	-
Hypersensitivity	-	-	-	-	✔
Infection	18 to 22	✔	-	✔	-
Infiltration	-	-	-	✔	-
Injection site reaction	-	-	-	11	-
Ketoacidosis	-	-	-	✔	-
Nephrotoxicity	-	-	-	✔	-
Night sweats	-	-	-	✔	-
Non-specific herpes	-	-	-	✔	-
Non-specific influenza	-	✔	-	✔	-
Pancreatitis	✔	✔	-	✔	-
Syndrome of inappropriate antidiuretic hormone	-	-	-	✔	-
Thrombophlebitis	-	✔	-	-	-
Vortex keratopathy	✔	-	-	-	-

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 8. Boxed Warning for Metronidazole[1]

WARNING
Metronidazole has been shown to be carcinogenic in mice and rats. Unnecessary use of the drug should be avoided. Its use should be reserved for the conditions for which this drug is indicated.

Table 9. Boxed Warning for Tinidazole[1]

WARNING
Carcinogenicity has been seen in mice and rats treated chronically with metronidazole, another nitroimidazole agent. Although such data have not been reported for tinidazole, the two drugs are structurally related and have similar biologic effects. Reserve its use only for the conditions for which it is indicated.

VII. Dosing and Administration

The usual dosing regimens for the miscellaneous antiprotozoals are listed in Table 10.

Table 10. Usual Dosing Regimens for the Antiprotozoals, Miscellaneous[1-11]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Atovaquone	Prevention of *Pneumocystis carinii* pneumonia in patients who are intolerant to sulfamethoxazole-trimethoprim: Suspension: 1,500 mg once daily with a meal	Prevention of *Pneumocystis carinii* pneumonia in patients who are intolerant to sulfamethoxazole-trimethoprim for patients 13 to 16 years of age: Suspension: 1,500 mg once	Suspension: 750 mg/5 mL

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Treatment of mild-to-moderate *Pneumocystis carinii* pneumonia in patients who are intolerant to sulfamethoxazole-trimethoprim: Suspension: 750 mg twice daily for 21 days	daily with a meal Treatment of mild-to-moderate *Pneumocystis carinii* pneumonia in patients who are intolerant to sulfamethoxazole-trimethoprim: Suspension: 750 mg twice daily for 21 days	
Metronidazole	Acute intestinal amebiasis (amebic dysentery): Capsules, extended-release tablets, tablets: 750 mg three times daily for five to 10 days Amebic liver abscess: Capsules, extended-release tablets, tablets: 500 to 750 mg three times daily for five to 10 days Anaerobic bacterial infections: Capsules, extended-release tablets, tablets: 7.5 mg/kg every six hours for seven to 10 days Injection: 15 mg/kg intravenous loading dose, followed by 7.5 mg/kg intravenously every six hours Bacterial vaginosis: Extended-release tablets: 750 mg once daily for seven days Perioperative prophylaxis, contaminated or potentially contaminated colorectal surgery: Injection: 15 mg/kg intravenously one hour prior to procedure and if necessary, 7.5 mg/kg intravenously at six and 12 hours after the initial dose Trichomoniasis (females): Capsules, extended-release tablets, tablets: one-day regimen, 2 g as a single dose or two divided doses of 1 g each given in the same day; seven-day regimen, 250 mg three times daily for seven days or 375 mg twice for seven days Trichomoniasis (males): Treatment should be individualized	Amebiasis: Capsules, extended-release tablets, tablets: 35 to 50 mg/kg per 24 hours, divided into three doses, orally for 10 days	Capsule: 375 mg Extended-release tablet: 750 mg Injection: 500 mg/500 mL Tablet: 250 mg 500 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Nitazoxanide	Diarrhea caused by *Cryptosporidium parvum* or *Giardia lamblia*: Suspension, tablets: 500 mg every 12 hours for three days	Diarrhea Caused by *Giardia lamblia* or *Cryptosporidium parvum* in patients one to three years of age: Suspension, tablets: 100 mg every 12 hours for three days Diarrhea Caused by *Giardia lamblia* or *Cryptosporidium parvum* in patients four to 11 years of age: Suspension, tablets: 200 mg every 12 hours for three days Diarrhea Caused by *Giardia lamblia* or *Cryptosporidium parvum* in patients >12 years of age: Suspension, tablets: 500 mg every 12 hours for three days	Suspension: 100 mg/5 mL Tablet: 500 mg
Pentamidine	Prevention of *Pneumocystis carinii* pneumonia in high-risk, human immunodeficiency virus-infected patients: Inhalation: 300 mg once every four weeks Treatment of *Pneumocystis carinii* pneumonia: Injection: 4 mg/kg intravenously once daily for 14 to 21 days	Treatment of *Pneumocystis carinii* pneumonia in patients ≥4 months of age: Injection: 4 mg/kg intravenously once daily for 14 to 21 days	Inhalation: 300 mg Injection: 300 mg
Tinidazole	Acute intestinal amebiasis (amebic dysentery): Tablets: 2 g as a single dose for three days Amebic liver abscess: Tablets: 2 g as a single dose for three to five days Bacterial vaginosis: Tablets: 2 g once daily for two days or 1 g once daily for five days Giardiasis: Tablets: 2 g as a single dose Trichomoniasis: Tablets: 2 g as a single dose; treat sexual partners with same dose and at the same time	Acute intestinal amebiasis (amebic dysentery) in patients ≥3 years of age: Tablets: 50 mg/kg/day as a single dose (up to 2 g per day) for three days Amebic liver abscess in patients ≥3 years of age: Tablets: 50 mg/kg/day as a single dose (up to 2 g per day) for three to five days Giardiasis in patients ≥3 years of age: Tablets: 50 mg/kg as a single dose (up to 2 g)	Tablet: 250 mg 500 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the miscellaneous antiprotozoals are summarized in Table 11.

Table 11. Comparative Clinical Trials with the Antiprotozoals, Miscellaneous

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Amebiasis				
Kokhani et al.[29] (1977) Metronidazole 2 g per day for two days vs tinidazole 2 g per day for two days	RCT Patients with amebic liver abscess	N=19 30 days	Primary: Efficacy rate Secondary: Not reported	Primary: Efficacy rates were reported to be 56 and 100% in the metronidazole and tinidazole groups, respectively (P<0.05). Secondary: Not reported
Mathur et al.[30] (1977) Metronidazole 2 g per day for two days vs tinidazole 2 g per day for two days	RCT Adult patients with amebic liver abscess (India)	N=22 30 days	Primary: Efficacy rate Secondary: Not reported	Primary: Efficacy rates were reported to be 91 and 100% in the metronidazole and tinidazole groups, respectively (P=NS). Secondary: Not reported
Misra et al.[31] (1977) Metronidazole 2 g per day for three days vs	RCT Patients with symptomatic intestinal amebiasis	N=60 30 days	Primary: Cure rates (relief of symptoms, healing of colonic ulcers and absence of *Entamoeba histolytica* in stools and sigmoidoscopic	Primary: After 30 days, cure rates were 53.3 and 90.0% in the metronidazole and tinidazole groups, respectively (P<0.01). The most frequently reported adverse events were gastrointestinal and were experienced in 53.3 and 26.7% of patients receiving metronidazole and tinidazole, respectively (P<0.05). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
tinidazole 2 g per day for three days			scrapings), adverse events Secondary: Not reported	Not reported
Baksih et al.[32] (1978) Metronidazole 2 g per day for three days vs tinidazole 2 g per day for three days	RCT Patients diagnosed with symptomatic intestinal amebiasis	N=257 30 days	Primary: Cure rate, adverse events Secondary: Not reported	Primary: Cure rate was reported in 53.7 and 91.8% of patients in the metronidazole and tinidazole treatment groups, respectively (P<0.001). Overall, adverse events were reported in 54.4 and 31.3% of patients receiving metronidazole and tinidazole, respectively (P<0.01). The most frequently reported side effects with metronidazole were nausea (43.1%), anorexia (27.6%), vomiting (11.4%) and abdominal pain (11.4%). The most frequently reported side effects with tinidazole were bitter taste (14.9%), nausea (10.4%) and anorexia (8.2%). Secondary: Not reported
Swami et al.[33] (1977) Metronidazole 2 g per day for three days vs tinidazole 2 g per day for three days	PG, RCT Patients diagnosed with symptomatic intestinal amebiasis and *Entamoeba histolytica* present in stools (India)	N=56 30 days	Primary: Cure rate, adverse events Secondary: Not reported	Primary: Cure rates were reported in 55.5 and 96.5% of patients in the metronidazole and tinidazole treatment groups, respectively (P<0.01). Overall, adverse events were reported in 37.0 and 51.7% of patients receiving metronidazole and tinidazole, respectively. Of patients reporting side effects, eight of 10 patients and two of 15 patients reported the side effects to be of moderate severity with metronidazole and tinidazole, respectively. The most frequently reported side effects with metronidazole were nausea (21.2%), abdominal pain (12.1%) and colored urine (12.1%). The most frequently reported side effects with tinidazole were metallic taste (40.9%) and bitter taste (18.2%). Secondary: Not reported
Singh et al.[34] (1977)	RCT	N=56	Primary: Cure rate, adverse	Primary: Combined clinical and parasitological cure rate was reported in 58.6 and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Metronidazole 2 g per day for three days vs tinidazole 2 g per day for three days	Patients diagnosed with symptomatic intestinal amebiasis and *Entamoeba histolytica* present in stools (India)	30 days	events Secondary: Not reported	92.6% of patients in the metronidazole and tinidazole treatment groups, respectively (P<0.01). The most frequently reported adverse events were gastrointestinal and were experienced in 75.9 and 51.9% of patients receiving metronidazole and tinidazole, respectively. Secondary: Not reported
Scragg et al.[35] (1977) Metronidazole 2 g for three days vs tinidazole 2 g for three days	RCT Patients with amebic liver abscess	N=31 7 days	Primary: Success rates Secondary: Not reported	Primary: Success rates were reported as 80.0% with metronidazole for an average of seven days and 93.8% with tinidazole for an average of four days. Secondary: Not reported
Kundu et al.[36] (1977) Metronidazole 2 g per day for three days vs tinidazole 2 g per day for three days	RCT Patients with amebic liver abscesses	N=18 30 days	Primary: Cure rate, adverse events Secondary: Not reported	Primary: Marked improvement within one week or after one week, followed by clinical cure by day 30 with no other specific treatment required was reported in 33.3 and 88.9% of patients in the metronidazole and tinidazole treatment groups, respectively (P<0.05). Mild gastrointestinal side effects were reported in 44.4 and 11.1% of patients receiving metronidazole and tinidazole, respectively. Two patients died, one in the metronidazole group due to adrenal insufficiency and one in the tinidazole group due to hepatic coma. Neither death was considered drug related. Secondary: Not reported
Islam et al.[37] (1978) Metronidazole 2 g	RCT Patients with amebic liver	N=31 30 days	Primary: Efficacy rate Secondary:	Primary: Efficacy rates were reported to be 80 and 93% in the metronidazole and tinidazole groups, respectively (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
per day for 3 to 10 days vs tinidazole 2 g per day for three to six days	abscess		Not reported	Secondary: Not reported
Simjee et al.[38] (1985) Metronidazole 2 g per day for five days vs tinidazole 2 g per day for five days A second course of the same study drug could be given if the patient showed no improvement after five days.	RCT Patients with amebic liver abscesses	N=48 8 weeks	Primary: Clinical cure, adverse events Secondary: Not reported	Primary: Cure rate was reported in 100% of patients in both the metronidazole and tinidazole treatment groups (P=NS), although 7.4 and 19.0% of patients in the metronidazole and tinidazole treatment groups, respectively, required a second course of treatment. The most frequently reported adverse event was oral candidiasis and it was observed in 7.4 and 9.5% of patients receiving metronidazole and tinidazole, respectively. Secondary: Not reported
Mendis et al.[39] (1984) Metronidazole 400 mg TID for five days vs tinidazole 2 g per day for three days	DB, RCT Patients with amebic liver abscess	N=34 30 days	Primary: Efficacy rate Secondary: Not reported	Primary: Efficacy rates were reported to be 33 and 81% in the metronidazole and tinidazole groups, respectively (P<0.01). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Simjee et al.[40] (1985) Metronidazole 2 g daily for five days vs tinidazole 2 g daily for five days Treatment was repeated after five days if there was no improvement.	PG, PRO Patients with uncomplicated amebic liver abscess in South Africa	N=48 8 weeks	Primary: Time to pain disappearance, time for temperature to settle, time for tenderness to disappear Secondary: Not reported	Primary: Two patients treated with metronidazole and four patients treated with tinidazole required a second course of therapy. There was no difference between metronidazole and tinidazole in the time for pain to disappear (4.2 vs 5.2 days, respectively); time for temperature to "settle" (5.2 vs 5.2 days, respectively); or time for tenderness to disappear (7.9 vs 7.9 days, respectively). Secondary: Not reported
Bassily et al.[41] (1987) Metronidazole 1.5 g daily for 10 days vs tinidazole 1.5 g daily for 10 days vs ornidazole* 1 g daily for 10 days	RCT Patients diagnosed with *Entamoeba histolytica* intestinal infection	N=53 3 weeks	Primary: Microbiological cure Secondary: Not reported	Primary: Microbiological cure rates at three weeks were 88% with metronidazole, 67% with tinidazole and 94% with ornidazole (P=0.0438). Secondary: Not reported
Gonzales et al.[42] (2009) Metronidazole vs	MA Adults and children with clinical symptoms of amoebic colitis	N=4,487 (37 trials) Variable duration	Primary: Clinical and parasitological failures, relapse, adverse events Secondary:	Primary: *Tinidazole vs metronidazole (nine trials)* Treatment with tinidazole reduced clinical failure by 72% compared to metronidazole (RR, 0.28; 95% CI, 0.15 to 0.51). Results for parasitological failure did not show that tinidazole was more effective in eradicating *Entamoeba histolytica* compared to metronidazole.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
tinidazole vs other amebic therapies vs placebo			Not reported	No data on relapse were reported. There were no serious adverse events or adverse events that necessitated drug withdrawal in the three trials that reported on this. For the other adverse events, they were more common in those given metronidazole compared to those given tinidazole (RR, 0.65; 95% CI, 0.46 to 0.92). The most common adverse events reported were nausea, vomiting, decreased appetite, altered taste or metallic taste, and abdominal discomfort. *Other drugs vs metronidazole (five trials)* Other alternative drugs tested were ornidazole, panidazole, and satranidazole. The number of trials was too small to detect any difference in clinical failure or parasitological failure compared to metronidazole. For relapse, data were reported for two trials, and both compared ornidazole with metronidazole. There were more relapses in those given ornidazole compared to metronidazole (RR, 4.74; 95% CI, 1.07 to 20.99), but there were insufficient data to draw definite conclusions. There were no serious adverse events or withdrawals resulting from adverse events in two trials that reported on this. *Combination regimen vs metronidazole alone (three trials*) Combination therapy reduced clinical failure one to 14 days after the end of treatment by 67% compared to monotherapy with metronidazole (RR, 0.33; 95% CI, 0.11 to 0.98). The combinations included dehydroemetine, tetracycline, and diloxanide furoate; a fixed-drug combination suspension of metronidazole and furazolidone; and a fixed-drug combination tablet of metronidazole and diiodohydroxyquinoline. For parasitological failure, results showed a 64% reduction in parasitological failures one to 14 days after the end of treatment in those given the combination compared to metronidazole alone (RR, 0.36; 95% CI, 0.15 to 0.86). Only one trial reported details for adverse events. One participant given a

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				fixed-drug combination tablet of metronidazole and diiodohydroxyquinoline developed an unspecified allergic reaction on the first day necessitating withdrawal from the trial. Secondary: Not reported
Bacterial Vaginosis				
Brandt et al.[43] (2008) Metronidazole 2,000 mg orally as a single dose vs metronidazole 1,000 mg intravaginally once daily for two days	DB, MC, PC, RCT Patients ≥18 years of age with bacterial vaginosis	N=263 12 weeks	Primary: Cure of bacterial vaginosis and recurrence Secondary: Adverse events and tolerability	Primary: The cure rate in patients treated with intravaginal metronidazole was slightly higher compared to patients treated with oral metronidazole (92.5 vs 89.9%); however, there was no significant difference between the treatment groups. Recurrences occurred in 10.0% of patients receiving oral metronidazole and 13.9% of patients receiving intravaginal metronidazole. There was no statistical significant difference between the groups Secondary: The physician's rating of the overall tolerability was better with intravaginal metronidazole compared to oral metronidazole (P=0.048). The patients' overall satisfaction with the intravaginal administration of metronidazole was higher as compared to the oral administration (P=0.046). Significantly more adverse events were reported after oral administration of metronidazole as compared to the intravaginal administration (71.1 vs 57.7%; P=0.023). The most common adverse events were nausea (30.4% with oral therapy vs 10.2% for vaginal therapy; P<0.001), abdominal pain (31.9% with oral therapy vs 16.8% for vaginal therapy; P=0.005), and headache (24.1% with oral therapy vs 31.1% for vaginal therapy; P=0.047). Nausea, abdominal pain and metallic taste as adverse events occurred significantly less often in patients treated with intravaginal metronidazole as compared to the orally treated patients.
Fischbach et al.[44] (1992) Metronidazole 500	AC, DB, MC, RCT Women ≥18 years of age diagnosed	N=407 39 days	Primary: Cure rate, post-treatment vulvovaginal	Primary: There was no significant difference in cure rate for oral metronidazole (78%) and clindamycin vaginal cream (83%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg BID for seven days vs clindamycin phosphate vaginal cream 2% once daily for seven days	with bacterial vaginosis		candidiasis Secondary: Not reported	The incidence of drug-related adverse effects was similar in both groups, approximately 12%. There was no significant difference in the rates of post-treatment vulvovaginal candidiasis associated with oral metronidazole (4.7%), and clindamycin vaginal cream (8.5%). Secondary: Not reported
Arredondo et al.[45] (1992) Metronidazole 500 mg capsules BID for seven days vs clindamycin vaginal cream 2% BID for seven days	DB, MC, RCT Women with symptomatic bacterial vaginosis	N=184 50 days	Primary: Total healing rate, relapse rate, failure rate, adverse events Secondary: Not reported	Primary: Improvement in total healing was 87% for clindamycin and 79% for metronidazole (P>0.22). While 7% of patients randomized to the metronidazole group developed relapse of the disease following treatment, none of the patients receiving topical clindamycin experienced a relapse. While clindamycin had a failure rate of 3%, 15% of patients in the metronidazole group failed treatment. Both drugs were well tolerated, with the most serious side effect, generalized rash, reported by a patient on metronidazole therapy. Secondary: Not reported
Andres et al.[46] (1992) Metronidazole 500 mg capsules BID for seven days vs clindamycin vaginal cream 2% BID for seven days	DB, PC, PRO, RCT Non-pregnant women 18 to ≤60 years of age diagnosed with bacterial vaginosis	N=60 30 days	Primary: Cure rate, improvement rate, clinical failure assessed at the one-week and four-week follow-up visits, adverse events Secondary: Not reported	Primary: There was no statistically significant difference between the metronidazole (82%) and clindamycin (97%) study groups at the one-week follow-up visit in terms of patients who have either improved or were cured post-treatment. There was no statistically significant difference between the metronidazole (94.1%) and clindamycin (89.5%) study groups at the four-week follow-up visit in terms of patients who had either improved or were cured post-treatment. There was no statistically significant difference in terms of clinical failure

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				rate among patients randomized to receive either of the two study drugs. There was no statistically significant difference in side effects among patients randomized to receive either of the two study drugs. Secondary: Not reported
Schmitt et al.[47] (1993) Metronidazole 500 mg capsules BID for seven days vs clindamycin vaginal cream 2% daily for seven days	DB, PC, RCT Nonpregnant women 18 to ≤60 years of age diagnosed with bacterial vaginosis	N=61 30 days	Primary: Overall healing rate (clinical and microbiological), symptomatic failure rate at the one-week and four-week follow-up visits, adverse events, *Candida* infections Secondary: Not reported	Primary: There was no statistically significant difference in the overall cure rate between the metronidazole (87%) and clindamycin (72%) study groups at the one-week follow-up visit (P=0.32). One month later, 61% of patients in both groups remained cured. Symptomatic failure occurred in one patient receiving clindamycin and in no one on metronidazole therapy. There were fewer asymptomatic failures in the metronidazole group compared to the clindamycin treatment arm; however this difference was not statistically significant (P=0.16). Symptomatic *Candida* yeast infections developed in 12% of clindamycin-treated patients and 9% of patients on metronidazole therapy. There was no statistically significant difference in side effects among patients randomized to receive either of the two study drugs. Secondary: Not reported
Ferris et al.[48] (1993) Metronidazole 500 mg BID for seven days vs	AC, DB, RCT Women ≥18 years of age diagnosed with bacterial vaginosis	N=101 14 days	Primary: Cure rate, post-treatment vulvovaginal candidiasis Secondary: Not reported	Primary: There was no significant difference in cure rates for oral metronidazole (84.2%), metronidazole vaginal cream (75%), or clindamycin vaginal cream (86.2%; P=0.548). There was no significant difference in the rates of post-treatment vulvovaginal candidiasis associated with oral metronidazole (12.5%), metronidazole vaginal cream (30.4%), or clindamycin vaginal cream (14.8%; P=0.272).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
metronidazole vaginal gel BID for five days vs clindamycin vaginal cream 2% daily for seven days				Secondary: Not reported
Higuera et al.[49] (2002) Metronidazole 500 mg capsules BID for seven days vs clindamycin vaginal cream 2% daily for seven days	DB, PC, RCT Women 16 to ≤60 years of age diagnosed with bacterial vaginosis	N=82 50 days	Primary: Cure rate, improvement, clinical failure rate, relapse rate Secondary: Microbiological cure rate, vaginal fluid description, patient's efficacy evaluation, adverse effects	Primary: There was no statistically significant difference between the metronidazole (82%) and clindamycin (86%) study groups at the one-week follow-up visit in terms of patients who have either improved or were cured post-treatment. There was no statistically significant difference in cure rate between the metronidazole (88%) and the clindamycin (90%) groups at the four-week follow-up visit. There was no statistically significant difference in failure rate between the metronidazole (17.9%) and clindamycin (14.3%) treatment groups at the one-week and four-week follow-up visits. Secondary: There was no statistically significant difference in microbiological cure rate between the metronidazole (82%) and the clindamycin (86%) groups at the first follow-up visit. There was no statistically significant difference in patient self-reported cure rate between the metronidazole (82%) and clindamycin (86%) groups. There was a higher percentage of patients in the clindamycin group (10%) with a gram stain compatible with bacterial vaginosis at the second follow-up visit compared to the metronidazole group (4%; P<0.04). At the second follow-up visit, there were a greater number of patients in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				the clindamycin group (14%) exhibiting vaginal fluid odor compared to the metronidazole group (4%). There was no significant difference in the incidence of side effects between the metronidazole group (22%) and clindamycin (15%) group.
Paavonen et al.[50] (2005) Metronidazole 500 mg capsules BID for seven days vs clindamycin 100 mg ovules administered intravaginally for three consecutive days	AC, DB, MC, RCT Women diagnosed with bacterial vaginosis	N=399 52 days	Primary: Overall clinical outcome, reported as cure, failure, and non-assessable efficacy rate Secondary: Clinical status, symptoms of vaginitis or cervicitis at each follow-up visit, patient evaluation of efficacy at second follow-up visit, adverse effects	Primary: No statistically significant difference between the two treatment groups was observed regarding the primary endpoint (95% CI, –10.6 to 13.4; P=0.810). There was no statistically significant difference in clinical status, at either the first or second follow-up visit, between the two treatment groups (P>0.5). There was no significant difference in the proportion of patients in the metronidazole treatment group who rated their vaginal infection as cured (79.6%) vs the proportion of patients randomized to clindamycin therapy who considered themselves cured (78.3%). Secondary: There was no difference in the number of patients reporting symptoms of vaginitis and cervicitis at either the first or second follow-up visit. Treatment-related adverse effects were more frequent in the metronidazole group (16.3%), compared to the clindamycin treatment group (10.3%), but this difference was not statistically significant (P=0.104).
Mohanty et al.[51] (1987) Metronidazole 2 g single dose vs tinidazole 2 g single dose	RCT Women with bacterial vaginosis associated with *Gardnerella vaginalis*	N=280 6 weeks	Primary: Cure (defined as negative culture for *Gardnerella vaginalis s* and absence of three or more of four criteria), recurrence (positive result after two weeks),	Primary: Cure was achieved in 79.4, 88.0 and 92.3% of patients receiving metronidazole, nimorazole and tinidazole, respectively. There were no significant differences between the treatment groups. The overall recurrence rate was 21% with metronidazole, 26% with nimorazole and 14% with tinidazole and was believed to be due to reinfection from the untreated partners rather than to relapse. Mild adverse effects were reported in 46.3% of patients receiving metronidazole, 28.0% of patients receiving nimorazole and 32.7% of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs nimorazole* 2 g single dose			adverse events Secondary: Not reported	patients receiving tinidazole. Secondary: Not reported
Schwebke et al.[52] (2011) Metronidazole 500 mg BID for seven days vs tinidazole 500 mg BID for seven days vs tinidazole 1 g BID for seven days	OL, PRO, RCT Women with bacterial vaginitis with no evidence of STDs	N=593 28 days	Primary: Microbiologic cure Secondary: Clinical improvement; cure; clinical failure	Primary: At the 14-day follow-up, failures (Nugent score ≥7) were not different between the metronidazole group (17.7%), the tinidazole 1 g group (27.0%) or the tinidazole 500 mg group (24.7%; P=0.16). At the 14-day follow-up, there was no difference in the microbiologic cure (Nugent score <7) in the metronidazole group (82.4%), the tinidazole 1 g group (73.0%), or the tinidazole 500 mg group (75.3%; P=0.08). At the 28-day follow-up, the microbiologic cure or improvement rate (Nugent score <7) was not different between the metronidazole group (55.2%), the tinidazole 1 g group (62.3%), or the tinidazole 500 mg group (58.0%; P=0.08). Secondary: There was no difference in recurrence rates between the treatment groups at the one- or two-month follow-up visits. There were no differences in adverse events between groups, except for a higher incidence of taste perversion (41.8%) in the tinidazole 1 g group compared to metronidazole (11.0%) and tinidazole 500 mg (15.2%; P<0.001).
Ekgren et al.[53] (1988) Tinidazole 2 g for one or two days vs placebo	DB, PC, RCT Women with nonspecific bacterial vaginosis	N=247 2 weeks	Primary: Cure (defined as absence of both clue cells and *Gardnerella vaginalis* Secondary: Not reported	Primary: Cure rates were 74% for the two-day regimen and 51% for the single-dose regimen and 4% for placebo (P<0.001 vs placebo for both active treatments; P<0.02 tinidazole two-day regimen vs single-dose regimen). Secondary: Not reported
Carmona et al.[54] (1983)	OL	N=30	Primary: Bacteriologic cure,	Primary: Bacteriologic and clinical cure rates after one week were 90 and 93%,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Tinidazole 2 g as a single dose	Women with bacteriologic and clinical diagnosis of *Gardnerella vaginalis* vaginitis	30 days	clinical cure Secondary: Not reported	respectively. Secondary: Not reported
Livengood et al.[55] (2007) Tinidazole 1 g once daily for five days or tinidazole 2 g once daily for two days vs placebo	DB, PC, RCT Women ≥18 years of age with bacterial vaginosis	N=235 10 days	Primary: Cure rates Secondary: Adverse events	Primary: Treatment with tinidazole 1 g once daily for five days resulted in a cure rate of 36.8% (P<0.001; number needed to treat 3.2) and a cure rate of 27.4% with tinidazole 2 g once daily for two days (P<0.001; number needed to treat 4.5) as compared to placebo (5.1% cured). Secondary: Adverse events occurred with comparable frequency in tinidazole and placebo recipients, except for dysgeusia, which was significantly more common in the tinidazole arms. However, no difference was seen between the tinidazole and placebo groups in the number of participants experiencing one or more gastrointestinal symptoms.
Cryptosporidiosis				
Rossignol et al.[56] (2001) Nitazoxanide 500 mg BID (12 to 65 years), 200 mg BID (4 to 11 years) or 100 mg BID (1 to 3 years) for three days vs placebo	DB, PC, RCT Immunocompetent adults and children with diarrhea and *Cryptosporidium parvum* oocysts in stool (Egypt)	N=98 7 to 10 days	Primary: Clinical response at day seven, parasitological response seven to 10 days after treatment initiation Secondary: Time to passage of last unformed stool, adverse events	Primary: At seven days after initiation of therapy, diarrhea had resolved in 39 (80%) of the 49 patients in the nitazoxanide treatment group, compared to 20 (41%) of 49 in the placebo group (P<0.0001). Parasitological response (no oocysts in either of the two posttreatment stool samples) was reported in 33 (67%) of patients in the nitazoxanide group compared to 11 (22%) in the placebo group (P<0.0001). Nitazoxanide treatment reduced the duration of both diarrhea (P<0.0001) and oocyst shedding (P<0.0001). Secondary: Diarrhea was resolved in most patients receiving nitazoxanide within three or four days of treatment initiation. In the placebo group, 59% of patients still had diarrhea at the end of the follow-up period. Safety and tolerance data were similar among the nitazoxanide and placebo treatment groups, with no serious adverse event occurring. Therapy was discontinued due to dizziness in one patient receiving

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				nitazoxanide and one patient receiving placebo.
Rossignol et al.[57] (2006) Nitazoxanide 500 mg tablets BID for three days vs nitazoxanide 500 mg suspension BID for three days vs placebo	DB, PC, RCT Immunocompetent patients 12 years and older with *Cryptosporidium* as the sole cause of diarrhea (Egypt)	N=86 7 to 10 days	Primary: Clinical response at day seven Secondary: Microbiologic response at day seven to 10 after treatment initiation	Primary: The proportion of patients reporting a well response (no symptoms, no watery stools and no more than two soft stools, and no hematochezia within the past 24 hours or no symptoms and no unformed stools within the past 48 hours) was 96, 87 and 41% for the nitazoxanide tablets (P<0.0001), nitazoxanide suspension (P=0.0003) and placebo, respectively. Secondary: The proportion of patients with no *Cryptosporidium* oocysts detected in posttreatment stool samples was 93% (P<0.0001), 90% (P<0.0001) and 37% for nitazoxanide tablets, nitazoxanide suspension and placebo, respectively.
Amadi et al.[58] (2002) Nitazoxanide 100 mg BID for three days vs placebo	PC, RCT Zambian children >1 year of age with diarrhea due to *Cryptosporidium parvum*, stratified by HIV serology	N=100 10 days	Primary: Clinical response on day seven after start of treatment Secondary: Parasitological response by day 10, mortality by day eight, adverse events	Primary: In HIV-negative children, diarrhea resolved in 56 and 23% of patients receiving nitazoxanide and placebo, respectively (difference, 33%; 95% CI, 7 to 59; P=0.037). In HIV-positive children, diarrhea resolved in 8 and 25% of patients receiving nitazoxanide and placebo, respectively (difference, –17%; 95% CI, –37 to 3; P=0.14). Secondary: *Cryptosporidium parvum* was eradicated from stool in 52 and 14% of HIV-negative children receiving nitazoxanide and placebo, respectively (38%; 95% CI, 14 to 63; P=0.007). There was no difference in parasitological response in HIV-positive children receiving nitazoxanide (16%) or placebo (21%) (P=1.0). None of the HIV-negative children in the nitazoxanide group died compared to 18% of children in the placebo group (–8%; 95% CI, –34% to 2; P=0.041). There was no difference in mortality rate among HIV-positive children receiving nitazoxanide (20%) or placebo (17%) (P=1.0).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Nitazoxanide was not significantly associated with adverse events in either stratum.
Rossignol et al.[59] (1998) Group 1 Nitazoxanide 500 mg plus placebo BID for 14 days, then placebo for 14 days vs Group 2 nitazoxanide 1,000 mg BID for 14 days, then placebo for 14 days vs Group 3 placebo for 14 days, then randomized to one of the above nitazoxanide regimens for 14 days	DB, PC, RCT Adult HIV-positive patients 18 to 65 years of age with *Cryptosporidium parvum* diarrhea (Mexico)	N=54 7 to 10 days	Primary: Parasitological cure (no *Cryptosporidium parvum* oocysts observed in three consecutive stool samples at seven-day intervals, starting on day 15 of the trial), clinical cure (assessed on days 15 and 29 and defined as diarrhea completely resolved and no longer suffered from accompanying symptoms) Secondary: Not reported	Primary: Parasitological cure was reported in 12 patients in Group 1 (63%; P=0.016 vs placebo) and 10 patients in Group 2 (67%; P=0.013 vs placebo) but only in five patients (25%) receiving placebo (Group 3). There was a correlation between parasitological cure and patient CD4 count. Pooled data taken from the 10 patients with a CD4 count <50 cells/mm^3 showed that only 30% achieved parasitological cure, which was not significantly different than patients receiving placebo (40%). In patients with a CD4 count >50 cells/mm^3, nitazoxanide yielded a 79% (N=19) parasitological cure rate as opposed to 20% (N=3) for patients receiving placebo. Thus, the lower the CD4 count of patients, the less likely they are to respond to nitazoxanide therapy. Upon follow-up on days 15 and 29, 92 and 80% of patients achieving parasitological cure also demonstrated clinical cure in Groups 1 and 2, respectively. There were a total of 53 adverse reactions reported in the study, none of which were labeled as related or probably related to treatment with nitazoxanide. There were, however, 16 adverse reactions that were categorized as possibly related to nitazoxanide therapy, the most common being vomiting (10), anemia (4), jaundice (1), and hematuria (1). Secondary: Not reported
Rossignol et al.[60] (2006) Nitazoxanide 500 to 1,500 mg BID in adults and 8 mg/kg–23 mg/kg BID in	MC, OL Patients ≥3 years of age who were HIV-positive and had at least two weeks of diarrhea	N=357 1 day to 4 years	Primary: Clinical response (changes in global assessment of symptoms and global assessment of overall health	Primary: Among the 357 patients included in the intent-to-treat analysis, 209 (59%) achieved a sustained clinical response while on treatment. Mean time to clinical response was two weeks. Among the 202 patients who submitted at least one stool sample, 116 patients (57% of evaluable patients) had *Cryptosporidium*-negative stool at

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
children	(four weeks if CD4 count >200/mm3) and positive stool for *Cryptosporidium parvum* oocysts		over time) and parasitological response at weeks one, two, four, and monthly thereafter while patients was on treatment, adverse events Secondary: Not reported	the last examination before completing the study while 86 (43%) patients had *Cryptosporidium*-positive stool. The mean time to first negative stool examination was seven weeks. Clinical responses were closely associated with Cryptosporidium-negative stools (P<0.0001). Among the evaluable patients, relationships between CD4 count and last parasitology result were apparent (P=0.072 and P=0.0051, respectively), and those with higher CD4 counts were more likely to achieve both the sustained clinical response and negative parasitology results. Twenty-seven nonserious adverse events were considered possibly related to the use of the study drug. Most of these events were associated with the digestive tract (nausea, vomiting, diarrhea, abdominal pain and dyspepsia). No safety issues were identified at doses up to 3,000 mg/day or for long durations of treatment. Nitazoxanide can be considered useful therapy for treatment of patients with AIDS-related cryptosporidiosis. Secondary: Not reported
Abubakar et al.[61] (2007) Nitazoxanide or paromomycin	MA Immuno-compromised individuals with cryptosporidiosis	N=169 Variable duration	Primary: Durations of diarrhea, mortality, parasitological clearance Secondary: Adverse events	Primary *Nitazoxanide (Two studies)* Two studies showed no evidence that nitazoxanide is more effective in reducing the frequency of diarrhea than placebo (RR, 0.83; 95% CI, 0.36 to 1.94). One study reported data on deaths which showed a RR of 0.61 (95% CI, 0.22 to 1.63) among all 96 children based on five and eight deaths in the intervention and control arms, respectively. Treatment with nitazoxanide led to a significant parasitological response compared to placebo among all children with a RR of 0.52 (95% CI, 0.30 to 0.91). The effect was NS for HIV-seropositive participants (RR, 0.71; 95% CI, 0.36 to 1.37). HIV-seronegative participants on nitazoxanide had

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				a significantly higher RR of achieving parasitological clearance of 0.26 (95% CI, 0.09 to 0.80) based on a single study. *Paromomycin (Two studies)* Two studies showed no evidence that paromomycin is more effective in reducing the frequency of diarrhea than placebo (RR, 0.74; 95% CI, 0.42 to 1.31). The use of paromomycin did not significantly lead to a parasitological response (RR, 0.73; 95% CI, 0.38 to 1.39). Secondary: Adverse events occurred infrequently in all studies.
Giardiasis				
Ortiz et al.[62] (2001) Metronidazole 125 mg BID (5 to 6 years of age) or 250 mg BID (6 to 11 years of age) for five days vs nitazoxanide 100 mg BID (2 to 3 years of age) or 200 mg BID (4 to 11 years of age) for three days	RCT Children 2 to 11 years of age with acute or chronic diarrhea and cysts of *Giardia intestinalis* in a stool sample seven days prior to the start of the study (Peru)	N=110 7 to 10 days	Primary: Clinical response at day seven follow-up visit Secondary: Parasitological response at seven to 10 days, adverse events	Primary: Diarrhea had resolved in 80 and 85% of the children treated with metronidazole and nitazoxanide, respectively, before day seven follow-up visit (P=0.6148). Diarrhea resolved within four days in 75 and 87% of children treated with metronidazole and nitazoxanide, respectively. Secondary: The proportions of children with no cysts of *Giardia intestinalis* collected seven to 10 days following metronidazole and nitazoxanide were 75 and 71%, respectively (P=0.8307). Fourteen children, seven in the metronidazole group and seven in the nitazoxanide group reported that they had missed one or more doses of study medication (range one to nine doses, mean 4.57 for metronidazole; range one to five doses, mean three for nitazoxanide). Only mild, transient adverse events were reported.
Gazder et al.[63] (1978) Metronidazole 50	OL, PG, RCT Children mean age 5.5 years with	N=100 16 days	Primary: Clinical success (relief of all symptoms and	Primary: Symptom relief and parasitic clearance were obtained in 36.0% (18/50) of patients receiving metronidazole and 80.0% (40/50) of patients treated with tinidazole (P<0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/kg as a single dose vs tinidazole 50 mg/kg as a single dose	symptoms of giardiasis and stools positive for cysts or trophozoites of *Giardia duodenalis* (India)		stools negative for *Giardia*), adverse events Secondary: Not reported	Adverse events, including mild nausea, vomiting and bitter taste were reported in 4.0% of patients receiving metronidazole and 12.0% of patients receiving tinidazole. Secondary: Not reported
Bakshi et al.[64] (1978) Metronidazole 50 mg/kg as a single dose vs tinidazole 50 mg/kg as a single dose	PG, RCT Children mean age 5.8 years with abdominal symptoms and *Giardia* cysts in stool (India)	N=186 16 days	Primary: Clinical success (relief of all symptoms and stools negative for *Giardia*), adverse events Secondary: Not reported	Primary: Clinical success was achieved in 46.7% (43/92) of patients given metronidazole vs 88.3% (83/94) of patients given tinidazole (P<0.01). Mild gastrointestinal adverse events were reported in 2.2 and 8.8% of patients receiving metronidazole and tinidazole. Secondary: Not reported
Krishnamurthy et al.[65] (1978) Metronidazole 50 mg/kg as a single dose vs tinidazole 50 mg/kg as a single dose	PG, RCT Pediatric patients with symptomatic giardiasis	N=60 12 days	Primary: Cure Secondary: Not reported	Primary: Cure was reported in 50.0 and 96.7% of patients receiving metronidazole and tinidazole, respectively (P<0.01). Secondary: Not reported
Nigam et al.[66] (1991) Metronidazole 50 mg/kg as a single dose	PG, RCT Young adults with giardiasis (India)	N=75 12 days	Primary: Cure (negative stools and symptoms), adverse effects Secondary:	Primary: Cure was reported in 54.3 and 97.5% of patients receiving metronidazole and tinidazole, respectively (P<0.01). Overall adverse events were reported in 5.7 and 12.5% of patients receiving metronidazole and tinidazole, respectively. The most frequently reported adverse events were gastrointestinal discomfort, nausea,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs tinidazole 50 mg/kg as a single dose			Not reported	vomiting, and bitter metallic taste. Secondary: Not reported
Jokipii et al.[67] (1979) Metronidazole 2.4 g as a single dose vs metronidazole 2.4 g per day for two days vs tinidazole 2 g as a single dose	OL, PG Adults with symptoms of giardiasis and stools positive for cysts or trophozoites of *Giardia duodenalis* (Finland)	N=85 8 weeks	Primary: Cure rates (clinical assessment and stool samples at one, two, four, and eight weeks after completion of treatment), adverse events Secondary: Not reported	Primary: Cure rates were 50.0% in those who received metronidazole single dose, 77.4% in those who received metronidazole multiple dose and 92.9% in patients who received tinidazole single dose (P<0.001 metronidazole single dose vs tinidazole single dose; P=NS metronidazole multiple dose vs tinidazole single dose; P<0.05 metronidazole multiple dose vs single dose). Adverse effects were mild across groups and included metallic taste, nausea and fatigue occurring in 92.3% metronidazole single dose, and 90.3% metronidazole multiple dose, and 75.0% tinidazole single dose. Secondary: Not reported
Kyronseppa et al.[68] (1981) Metronidazole 2 g per day for two days vs tinidazole 2 g as a single dose	PG, RCT Adults with symptoms of giardiasis and stools positive for *Giardia* (Finland)	N=50 4 weeks	Primary: Cure (disappearance of symptoms), adverse events Secondary: Not reported	Primary: Cure was reported in 76.0 and 88.0% of patients receiving metronidazole and tinidazole, respectively (P=NS). A one-week course of metronidazole (200 mg TID) was successful in 8/9 failures. Overall adverse events were reported in 28.0% of patients receiving metronidazole and 17.9% of patients receiving tinidazole with nausea, fatigue, drowsiness and gastrointestinal discomfort (metronidazole) most frequently reported. Secondary: Not reported
Speelman et al.[69] (1985)	RCT Infants through	Study 1 N=33 4 weeks	Primary: Parasitological cure (no *Giardia*	Primary: After four weeks, the eradication rates following single doses of metronidazole and tinidazole in Study 1 were 56% (9/16) and 94%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Study 1 Metronidazole 60 mg/kg single dose up to 2.4 g vs tinidazole 50 mg/kg single dose up to 2 g Study 2 Metronidazole 50 mg/kg single dose up to 2 g for three days vs tinidazole 50 mg/kg single dose up to 2 g	adults infected with *Giardia lamblia* (Bangladesh)	Study 2 N=30 4 weeks	*lamblia* cysts or trophozoites in fecal specimens), adverse events (only Study 2) Secondary: Not reported	(16/17), respectively (P<0.02). In Study 2, eradication rates were 93.3% (14/15) with metronidazole three-day regimen vs 100% (15/15) with tinidazole single dose. No serious side effects were encountered in either group. There were no statistically significant differences in side effects reported in patients receiving tinidazole single dose vs the metronidazole three-day regimen. Problems with the administration of the syrup to children, because of an unpleasant taste, were only reported in the tinidazole group (P<0.05). Secondary: Not reported
Suntornpoch et al.[70] (1981) Metronidazole 20 mg/kg for five days vs ornidazole* 50 mg/kg single dose (maximum 2 g) vs tinidazole 50 mg/kg	RCT Children with *Giardia lamblia* (cysts or trophozoites) in stool specimens (Thailand)	N=121 21 days	Primary: Cure (negative stools and relief of symptoms) Secondary: Not reported	Primary: Cure was reported in 32/33 patients receiving metronidazole, 38/40 ornidazole and 45/48 of tinidazole (P>0.05). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
single dose (maximum 2 g)				
Rossignol et al.[71] (2001) Nitazoxanide 500 mg BID for three days vs placebo	DB, PC, RCT Patients 12 to 65 years of age with diarrhea caused by *Giardia intestinalis* and/or *Entamoeba histolytica* and/or *Entamoeba dispar* (Egypt)	N=89 7 to 10 days	Primary: Clinical response at day seven, parasitological response (no cysts observed in two posttreatment stool examinations) at seven to 10 days Secondary: Date of last unformed stool, adverse events	Primary: After initiation of treatment, diarrhea resolved within seven days in 81% of patients in the nitazoxanide group vs 40% in the placebo group (P=0.0002). The parasitological response rate for *G intestinalis* was 71% for the nitazoxanide group vs 0% for the placebo group (P<0.0001). For *Entamoeba histolytica* and/or *Entamoeba dispar*, the parasitological response rate for the nitazoxanide group was 69 vs 39% for the placebo group (P=0.0148). Secondary: The median time from initiation of therapy to passage of the last unformed stool was three days in the nitazoxanide group, but could not be calculated in the placebo group since 60% of the patients still had diarrhea at the end of the follow-up period. All of the adverse events were mild and transient in nature, with none resulting in discontinuation of therapy.
Escobedo et al.[72] (2008) Nitazoxanide 7.5 mg/kg BID for three days vs tinidazole 50 mg/kg as a single dose	OL, RCT Children 5 to 15 years of age infected with *Giardia lamblia* with or without diarrhea	N=166 7 days following treatment	Primary: Response to treatment and adverse events Secondary: Not reported	Primary: The frequency of parasitological cure seen in children given tinidazole was significantly higher than that obtained with nitazoxanide (90.5 vs 78.4%; P<0.05). Diarrhea stopped within six days of completing treatment in all 33 children in the nitazoxanide group who had diarrhea at enrollment and in 19 of the 20 children in the tinidazole group who had diarrhea at enrollment. The median times taken for diarrhea to resolve were four days after completing nitazoxanide treatment and three days after completing tinidazole treatment. Both treatments were well tolerated. Adverse events occurred in 43.2% of patients in the nitazoxanide group and in 22.2% of patients in the tinidazole group. All adverse events were graded as mild and transient and did not require medication or discontinuation of treatment. Apart from a

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				bitter taste (reported by 17.5% of the children given tinidazole and none of those given nitazoxanide; P<0.05) and unusually yellowish urine (reported by 36.5% of the children given nitazoxanide and none of those given tinidazole; P<0.05), there were no significant differences in the incidences of any of the adverse events among the treatment groups. Secondary: Not reported
Prevention of *Pneumocystis* Pneumonia				
El-Sadr et al.[73] (1998) Atovaquone 1,500 mg daily vs dapsone 100 mg daily	MC, OL, RCT Patients ≥13 years old with a history of PCP, or with a CD4 cell count no higher than 200 per mm^3 or no more than 15% of the total lymphocyte count, and a history of treatment-limiting reaction to sulfonamides or trimethoprim	N=1,057 Mean 27 months	Primary: Onset of probable or micro-biologically confirmed PCP Secondary: Confirmed or probable toxoplasmosis, death, combined end point of death or PCP, discontinuation of the drug due to intolerable adverse events	Primary: There was no statistically significant difference in PCP development between the dapsone- and atovaquone-treated groups (RR, 0.85; 95% CI, 0.67 to 1.09; P=0.20). Secondary: There was no statistically significant difference in toxoplasmosis development between the dapsone- and atovaquone-treated groups (RR, 1.18; 95% CI, 0.26 to 5.30; P=0.83). There was no statistically significant difference in mortality between the dapsone- and atovaquone-treated groups (RR, 1.07; 95% CI, 0.89 to 1.30; P=0.45). There was no statistically significant difference in the cumulative endpoint between the two groups (RR, 0.98; 95% CI, 0.89 to 1.16; P=0.80). There was no statistically significant difference in the number of patients discontinuing treatment because of intolerable toxicity between the two groups (RR, 0.94; 95% CI, 0.74 to 1.19; P=0.59). Among patients receiving a dapsone-based prophylactic regimen at baseline, the risk of discontinuation due to adverse effects was higher in the atovaquone group (RR, 3.78; 95% CI, 2.37 to 6.01; P<0.001). Among patients not receiving a dapsone-based prophylactic regimen at baseline, the risk of discontinuation due to adverse effects was lower in the atovaquone group (RR, 0.42; 95% CI, 0.30 to 0.58; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Among patients who cannot tolerate SMX-TMP, atovaquone and dapsone are similarly effective for the prevention of PCP. Our results support the continuation of dapsone prophylaxis among patients who are already receiving it. However, among those not receiving dapsone, atovaquone is better tolerated and may be the preferred choice for prophylaxis against PCP.
Chan et al.[74] (1999) Atovaquone 750 mg or 1,500 mg once daily vs pentamidine aerosolized 300 mg once a month	OL, PG, RCT Patients with HIV who met standard criteria for PCP prophylaxis, were intolerant to sulfonamides and/or trimethoprim, did not have evidence of active PCP, were at least 13 years of age, and did not have marked abnormalities in laboratory tests of hematologic, renal, hepatic and pancreatic function	N=549 Median time using assigned therapy was 6.6 months and median follow-up was 11.3 months	Primary: Incidence of PCP Secondary: Mortality, combined end point of PCP or death, incidence of adverse events	Primary: There was no significant difference in the incidence of PCP in patients receiving atovaquone 750 mg, atovaquone 1,500 mg or aerosolized pentamidine (25, 22, and 17%, respectively). Compared to aerosolized pentamidine, the RR were 1.41 (95% CI, 0.90 to 2.22) and 1.26 (95% CI, 0.78 to 2.03) for atovaquone 750 and 1,500 mg, respectively. Secondary: There were no statistically significant differences among subjects with regard to mortality (22, 15 and 19%, respectively). Compared to aerosolized pentamidine, the RR was 1.12 (95% CI, 0.72 to 1.75) and 0.75 (95% CI, 0.46 to 1.24) for atovaquone 750 and 1,500 mg, respectively. The combined occurrence of PCP or death was not significantly different among the subjects (37, 30, and 30%, respectively). The incidence of adverse events was significantly higher with atovaquone than aerosolized pentamidine (P<0.01). The most frequent adverse events in both atovaquone groups were rash, diarrhea, vomiting, and nausea. In the aerosolized pentamidine group, respiratory events (bronchospasm, cough, and dyspnea) were the most frequent adverse events.
Hughes et al.[75] (1993) Atovaquone 750 mg TID for 21 days vs SMX-TMP 1,600 to	DB Patients with AIDS and mild (alveolar-arterial oxygen gradient <35 mm Hg) or moderately severe (alveolar-arterial oxygen	N=322 8 weeks	Primary: Therapeutic failure due to lack of efficacy, treatment limiting adverse events, successful therapy, survival Secondary:	Primary: SMX-TMP was more effective than atovaquone in treating PCP with 7 and 20%, respectively, of patients considered to have therapeutic failure measured one month after therapy (P=0.0002). Treatment limiting adverse events requiring a change in therapy occurred more frequently in patients receiving SMX-TMP (20%) than atovaquone (7%) (P=0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
320 mg TID for 21 days	gradient 35 to 45 mm Hg) PCP		Not reported	Significantly higher rates (P<0.05) were reported in the SMX-TMP group than in the atovaquone group for nausea (44 vs 20%), vomiting (35 vs 14%), constipation (17 vs 3%), dizziness (8 vs 3%), fever (25 vs 14%) and rash (34 vs 23%). Diarrhea occurred more frequently during treatment with atovaquone (19%) than SMX-TMP (7%) (P<0.05), but it was not associated with lack of efficacy or treatment-limiting adverse effects. Within four weeks of the completion of treatment, there were 11 deaths in the atovaquone group (four due to PCP) and one death in the SMX-TMP group (due to AIDS wasting syndrome) (P=0.003). Diarrhea at entry was associated with lower plasma drug concentrations (P=0.009), therapeutic failure (P<0.001), and death (P<0.001) in the atovaquone group but not in the SMX-TMP group. Atovaquone was less effective than SMX-TMP, but had fewer treatment-limiting adverse effects. Secondary: Not reported
Ioannidis et al.[76] (1996) Pentamidine, aerosolized vs dapsone-based regimens vs SMX-TMP vs	MA Trials comparing dapsone, aerosolized pentamidine, or SMX-TMP in preventing PCP	N=6,583 (35 trials) Variable duration	Primary: Number of *Pneumocystis jiroveci* episodes, *Pneumocystis jiroveci*-related deaths, toxoplasmosis episodes, all-cause mortality Secondary: Not reported	Primary: There was a significant decrease in the incidence of *Pneumocystis jiroveci* events in patients on any primary or secondary prophylactic regimen compared to placebo (RR, 0.39; 95% CI, 0.27 to 0.55 and RR, 0.16; 95% CI, 0.08 to 0.35, respectively). There was no significant difference in mortality between the different prophylactic regimens in all 35 trials. Oral prophylactic regimens were significantly more effective in reducing *Pneumocystis jiroveci* events compared to aerosolized pentamidine (RR, 0.39; 95% CI, 0.27 to 0.55). Oral prophylactic regimens were significantly more effective in reducing toxoplasmosis events compared to aerosolized pentamidine (RR, 0.67; 95% CI, 0.50 to 0.88).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo				There was no statistically significant difference in the occurrence of *P jiroveci* and toxoplasmosis events between patients receiving SMX-TMP or dapsone-based regimens (RR, 0.61; 95% CI, 0.34 to 1.10 and RR, 1.26; 95% CI, 0.68 to 2.34, respectively). While SMX-TMP exhibited greater efficacy in reducing *Pneumocystis jiroveci* events (RR, 0.58; 95% CI, 0.45 to 0.75), dapsone-based regimens were comparable to the aerosolized pentamidine regimen (RR, 0.93; 95% CI, 0.72 to 1.19). Compared to aerosolized pentamidine, oral regimens were overall 5 times more likely to be discontinued due to adverse events (RR, 5.38; 95% CI, 3.69 to 7.83). There was no significant difference between the SMX-TMP and dapsone-based regimens in the patient attrition rate as a result of treatment-related adverse effects (RR, 1.30; 95% CI, 1.04 to 1.62). SMX-TMP-treated groups exhibited the smallest prophylaxis failure rates, 0.5% for both primary and secondary prophylaxis. Secondary: Not reported
Bucher et al.[77] (1997) Pentamidine, aerosolized vs dapsone vs dapsone-pyrimethamine	MA Trials comparing dapsone, dapsone-pyrimethamine, aerosolized pentamidine or SMX-TMP in preventing PCP events	N=4,870 (22 trials) Variable duration	Primary: Opportunistic infections with PCP, *Toxoplasma* encephalitis, or both, mortality, drug-limiting toxicity requiring a change in therapy Secondary: Not reported	Primary: Compared to aerosolized pentamidine, dapsone-based regimens were more effective in preventing PCP events (RR, 0.90; 95% CI, 0.71 to 1.15) but not significantly different in terms of *Toxoplasma* encephalitis prevention (RR, 0.78; 95% CI, 0.55 to 1.11). Compared to dapsone-based regimens, SMX-TMP was more effective in preventing PCP events (RR, 0.49; 95% CI, 0.26 to 0.92) but not significantly different in terms of *Toxoplasma* encephalitis prevention (RR, 1.17; 95% CI, 0.68 to 2.04). SMX-TMP was significantly more effective compared to aerosolized pentamidine in preventing PCP events (RR, 0.59; 95% CI, 0.45 to 0.76).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs SMX-TMP				Drug-limiting toxicity was experienced by 29.7% of patients treated with a dapsone-based regimen, 6.8% of patients treated with aerosolized pentamidine, and 31.5% of patients on SMX-TMP therapy. There was no significant difference in mortality between the dapsone-based regimen and SMX-TMP (RR, 0.98; 95% CI, 0.80 to 1.08; P>0.20) or the aerosolized pentamidine regimen (RR, 1.07; 95% CI, 0.90 to 1.27; P>0.18). The mortality risk ratio in patients with CD4 cell count <100 cells/mm^3 treated with SMX-TMP compared to dapsone-based regimen was 0.43 (95% CI, 0.21 to 0.88). Mortality was lower in the SMX-TMP-treated group compared to patients on the aerosolized pentamidine therapy (RR, 0.88; 95% CI, 0.74 to 1.06; P=0.04). Secondary: Not reported
Green et al.[78] (2007) Atovaquone vs pentamidine vs sulfamethoxazole-trimethoprim (SMX-TMP) vs dapsone	MA Immuno-compromised patients with cancer, bone marrow transplant patients, solid organ transplant patients, patients receiving corticosteroids, patients receiving other immune suppressive medications, severe malnutrition, primary immune-	N=1,155 (11 trials) Variable duration	Primary: Documented Pneumocystis infections Secondary: All-cause mortality at end of study follow-up, PCP-related mortality at end of study follow-up, infections other than Pneumocystis	Primary: There was a significant reduction in the occurrence of PCP infections in the SMX-TMP prophylaxis group compared to others (RR, 0.09; 95% CI, 0.02 to 0.32). The corresponding number of patients needed to treat to prevent one episode of PCP was 15 patients (95% CI, 13 to 20). Five trials compared daily-administrated SMX-TMP prophylaxis vs no intervention or placebo. Prophylaxis resulted in a significant decrease in the occurrence of PCP infections (RR, 0.08; 95% CI, 0.02 to 0.38). Three trials compared SMX-TMP prophylaxis vs a non anti-PCP antibiotic (quinolones). Prophylaxis with SMX-TMP was better than quinolones in the prevention of PCP (RR, 0.09; 95% CI, 0.01 to 1.57). Secondary: All-cause mortality was reported in five trials. Three trials compared SMX-TMP to placebo (RR, 0.79; 95% CI, 0.18 to 3.46), and two trials compared SMX-TMP vs quinolones (RR, 0.49; 95% CI, 0.02 to 10.73).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs pyrimethamine vs clindamycin vs mycophenolate mofetil	deficiency diseases			SMX-tmp prophylaxis reduced PCP-related mortality (RR, 0.17; 95% CI, 0.03 to 0.94).Four trials compared SMX-TMP vs no intervention or placebo. PCP related mortality was reduced in the prophylaxis group (RR, 0.18; 95% CI, 0.02 to 1.56). Three studies compared SMX-TMP vs quinolones. PCP related mortality was reduced in the SMX-TMP group (RR, 0.14; 95% CI, 0.01 to 2.65). In the analysis of any infection other than PCP, one study comparing SMX-TMP prophylaxis vs no intervention or placebo found no statistically significant difference between the groups (RR, 0.86; 95% CI, 0.68 to 1.08). Three studies that compared SMX-TMP prophylaxis vs quinolones found significantly more infections other than PCP in the SMX-TMP arm compared to quinolones (RR, 1.59; 95% CI, 1.17 to 2.14).
Treatment of *Pneumocystis* Pneumonia				
Dohn et al.[79] (1994) Atovaquone 750 mg orally with meals TID vs pentamidine IV 3 to 4 mg/kg once daily	OL, RCT Patients with HIV infection and clinical presentations consistent with mild or moderate PCP, 75% of patients were intolerant of sulfonamides or trimethoprim	N=109 8 weeks	Primary: Therapy success (sustained clinical improvement four weeks after therapy was discontinued), therapy failure because of absence of response or due to adverse events Secondary: Not reported	Primary: Fifty-seven percent of patients treated with atovaquone and 40% of patients treated with pentamidine were clinically improved four weeks after therapy was discontinued (P=0.085). Twenty-nine percent of patients treated with atovaquone were considered treatment failures compared to 17% of patients treated with pentamidine (P=0.18). Discontinuation of treatment due to adverse events was more common with pentamidine (36%) than with atovaquone (4%; P<0.001). The most common adverse events for pentamidine were hypoglycemia (11%), vomiting (8%), nausea (7%), elevated creatinine level (6%) and rash (6%). Rash (4%) was the most common treatment limiting adverse events in patients receiving atovaquone. Nine patients in each treatment group died during the study (P=0.65), with death attributed to PCP in four patients receiving atovaquone and three patients receiving pentamidine. Secondary: Not reported
Kim et al.[80]	RETRO	N=23	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2009) Pentamidine vs clindamycin-primaquine	Korean patients with PCP	6 months	Treatment failure (inability to maintain a PaO2 despite increases in FiO2; deterioration of vital signs with a requirement for increased FiO2 after seven days); positive response: (resolution of baseline signs and symptoms and chest radiograph; decreased oxygen requirements after therapy) Secondary: Not reported	The response rate for patients treated with clindamycin-primaquine was higher than that for pentamidine only (64 vs 11%, respectively; P=0.03). Response rates were higher in patients treated with clindamycin-primaquine who had previously failed to respond to SMX-TMP (43%) compared to pentamidine (11%; P=0.26). Patients with HIV had a response rate of 71% with clindamycin-primaquine compared to 57% for those without HIV (P=1.00). Patients with HIV had a response rate of 0% with pentamidine compared to 20% for those without HIV (P=1.00). Secondary: Not reported
Smego et al.[81] (2001) Pentamidine, atovaquone, trimetrexate, eflornithine, clindamycin-primaquine, sulfamethoxazole-trimethoprim (SMX-TMP)	MA HIV-infected patients with confirmed PCP in whom initial anti-pneumocystis treatment failed and the patient required alternative drug therapy	N=497 Variable duration	Primary: Positive response to salvage therapy Secondary: Not reported	Primary: Efficacies of salvage regimens were as follows: clindamycin-primaquine (88% to 92%), atovaquone (80%), eflornithine hydrochloride (57%; P<0.01), SMX-TMP (53%; P<0.08), pentamidine (39%), and trimetrexate (30%). The combination of clindamycin plus primaquine appears to be the most effective alternative treatment for patients with PCP who are unresponsive to conventional anti-pneumocystis agents. Secondary: Not reported
Trichomoniasis				
O-Prasertsawat et al.[82] (1992)	DB, PG, RCT Women with vaginal	N=132 Follow-up 6 to 16 days	Primary: Clinical cure, adverse effects	Primary: Microbiologic cure was reported in 98.5 and 100% of patients receiving metronidazole and tinidazole, respectively (P=NS).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Metronidazole 1.6 g divided into two doses vs tinidazole 2 g single dose	trichomoniasis (Thailand)		Secondary: Not reported	The most frequently reported adverse events were bitter taste: 36.9% with tinidazole vs 23.9% with metronidazole, and nausea and vomiting (20.0 vs 17.9%, respectively). Secondary: Not reported
Gabriel et al.[83] (1982) Metronidazole 2 g as a single dose vs tinidazole 2 g as a single dose	PG, RCT, SB Women with vaginal trichomoniasis	N=82 2 weeks	Primary: Clinical cure (absence of *Trichomonas vaginalis* on vaginal smears and negative cultures), adverse events Secondary: Not reported	Primary: Clinical cure was reported in 97.5 and 95.3% of patients receiving metronidazole and tinidazole, respectively (P=NS). No adverse events were reported with either regimen. Secondary: Not reported
Aimakhu et al.[84] (1975) Metronidazole 200 mg TID for seven days vs tinidazole 2 g as a single dose	PG, RCT, SB Women with vaginal trichomoniasis	N=50 7 days	Primary: Microscopic cure Secondary: Not reported	Primary: Microscopic cure was reported in 100 and 96.0% of patients receiving metronidazole and tinidazole, respectively (P=NS). Secondary: Not reported
Forna et al.[85] (2003) Various antitrichomonal regimens, including oral and vaginal	MA Symptomatic or asymptomatic women, including adolescents, with confirmed	54 trials Duration varied	Primary: Parasitological cure, clinical cure (clearance of discharge, soreness, itching), side effects and	Primary: Two trials compared different doses of short treatment metronidazole. Doses of metronidazole 1 g or less were less effective than doses of 1.5 g or more in terms of failure to achieve parasitological cure (RR, 2.97; 95% CI, 1.92 to 4.59) with similar rates of side effects. Two trials compared a single 2 g oral dose of metronidazole with a five to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
products, single-dose vs multi-day regimens, different dose comparisons of same drug, active vs active and/or no treatment Only data relevant to metronidazole and/or tinidazole was included in the results.	*Trichomonas vaginalis* vaginitis		complications of treatment Secondary: Not reported	seven day course of metronidazole. Parasitological cure was achieved in 88 and 92% of women with short and long treatments, respectively. Side effects were mainly gastrointestinal (nausea, vomiting) and more frequent with the single dose (15 vs 7%). In one trial with 468 women enrolled, only 38% attended the follow-up visit. Two studies compared a standard one week course of metronidazole with short course tinidazole and ornidazole, respectively. Overall, short treatment was comparable to long treatment in terms of no parasitological cure (RR, 1.12; 95% CI, 0.58 to 2.16). Side effects, especially nausea/vomiting/dizziness were significantly more frequent with short treatment. Metronidazole was compared to tinidazole in eight studies. Except for one study, all compared short regimens of each drug. There were no parasitological failures in two trials; however, a MA of all eight studies results noted a statistically significant higher treatment failure rate (RR, 3.24; 95% CI, 1.66 to 6.32), higher clinical failure rate (RR, 3.81; 95% CI, 1.83 to 7.90), and higher side effect rate (RR, 1.65; 95% CI, 1.35 to 2.02) with metronidazole. The author states that these results should be interpreted with caution as blind assessment of outcomes was reported in only one of eight trials. There was no statistical difference in parasitological or clinical outcomes in this trial. The included trials showed that almost any nitroimidazole drug given as a single dose or over a longer period results in parasitological cure in 90% of cases. Oral single dose treatment with any nitroimidazole seems to be effective in achieving short term parasitological cure, but is associated with more frequent side effects than either longer oral or intravaginal treatment. Although rarely severe, side effects seem to be relatively common and dose related. It is not possible to conclude that tinidazole is more effective than metronidazole from the evidence reviewed. Outcome assessments were blinded in only one study that showed no difference between the two drugs.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Nitroimidazole drugs seem to be effective in achieving parasitological cure in short term follow-up. Partner treatment can be effective in decreasing longer term reinfection rates. Secondary: Not reported
Miscellaneous				
Nelson et al.[86] (2011) Metronidazole, vancomycin, fusidic acid, nitazoxanide, teicoplanin, rifampin, rifaximin, bacitracin, fidaxomicin	MA Patients with *Clostridium difficile*-associated diarrhea	N=1,152 (15 trials) Variable duration	Primary: Initial resolution of diarrhea; initial conversion of stool to *Clostridium difficile* cytotoxin or negative stool culture; recurrence of diarrhea; recurrence of *Clostridium difficile* cytotoxin or positive stool culture; patient response to cessation of prior antibiotic therapy; emergent surgery; death Secondary: Not reported	Primary: Only three of the 15 studies could be analyzed for direct comparison of metronidazole and vancomycin. There was no difference in symptomatic cure minus recurrences between the two medications (RR, 0.91; 95% CI, 0.81 to 1.03). Vancomycin was favored over bacitracin for symptomatic cure (RR, 0.58; 95% CI, 0.34 to 0.99) and bacteriologic initial response (RR, 0.52; 95% CI, 0.31 to 0.86). There was no difference in symptomatic recurrence. Teicoplanin was found to be more effective than vancomycin for: symptomatic cure of *Clostridium difficile* (RR, 1.21; 95% CI, 1.00 to 1.46); bacteriologic initial response (RR, 1.43; 95% CI, 1.14 to 1.81); bacteriologic cure (RR, 1.82; 95% CI, 1.19 to 2.78). There was no difference in symptomatic initial response, symptomatic recurrence, or bacteriologic recurrence. There was no difference between fusidic acid and vancomycin in symptomatic initial response, symptomatic cure, bacteriologic initial response, bacteriologic cure, symptomatic recurrence or bacteriologic recurrence. There was no difference between nitazoxanide and vancomycin in symptomatic initial response, recurrence of diarrhea within 31 days or symptomatic cure. There was no difference between rifaximin and vancomycin in symptomatic initial response or bacteriologic initial response. There was no difference between metronidazole and nitazoxanide in initial

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				resolution of diarrhea or recurrence of diarrhea at 31 days. There was no difference between metronidazole and metronidazole plus rifampin in initial resolution of diarrhea or recurrence of diarrhea within 40 days. Teicoplanin was more effective than metronidazole for bacteriologic initial cure (RR, 0.76; 95% CI, 0.6 to 0.98); bacteriologic cure (RR, 0.76; 95% CI, 0.58 to 1.00). There was no difference between teicoplanin and metronidazole in outcome of symptomatic cure, initial symptomatic response, or symptomatic recurrence. There was no difference between metronidazole and fusidic acid in symptomatic initial response, symptomatic cure, bacteriologic initial cure, bacteriologic cure or symptomatic response. Teicoplanin was more effective than fusidic acid for symptomatic cure (RR, 1.36; 95% CI, 1.02 to 1.83); bacteriologic initial cure (RR, 1.68; 95% CI, 1.19 to 2.37); bacteriologic cure (RR, 1.73; 95% CI, 1.19 to 2.51). There was no difference between teicoplanin and fusidic acid in symptomatic initial response or symptomatic recurrence. There was no difference between high-dose and low-dose vancomycin or teicoplanin therapy for symptomatic initial response. There was no difference between high-dose and low-dose vancomycin, fidaxomicin, or teicoplanin therapy for symptomatic recurrence. There was no difference between high-dose and low-dose vancomycin or teicoplanin therapy for symptomatic cure. There was no difference between high-dose and low-dose vancomycin or teicoplanin therapy for bacteriologic cure.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Zar et al.[87] (2007) Metronidazole 250 mg orally four times per day for 10 days vs vancomycin 125 mg orally four times per day for 10 days	DB, PC, RCT Patients with *Clostridium difficile*-associated diarrhea	N=172 21 days	Primary: Clinical cure Secondary: Not reported	Primary: Among the patients with mild *Clostridium difficile*-associated diarrhea, treatment with metronidazole or vancomycin resulted in clinical cure in 90 and 98% of the patients, respectively (P=0.36). Among the patients with severe *Clostridium difficile*-associated diarrhea, treatment with metronidazole or vancomycin resulted in clinical cure in 76 and 97% of the patients, respectively (P=0.02). Clinical symptoms recurred in 15% of the patients treated with metronidazole and 14% of those treated with vancomycin. Secondary: Not reported
McFarland et al.[88] (2002) Metronidazole ≤1 g to 2 g orally per day; taper or pulse vs vancomycin ≤1 g to ≥2 g orally per day; taper, pulse, or combination with another agent	DB, PC, RCT Patients 18 to 91 years of age with recurrent episodes of *Clostridium difficile* disease; ≥1 prior episode within one year	N=163 2 to 4 months	Primary: Incidence of another *Clostridium difficile* recurrence during study subsequent to the enrollment episode, or incidence of cure (i.e., absence of recurrence) two months after antibiotic treatment Secondary: Not reported	Primary: *Clostridium difficile* was cleared in 89% of the vancomycin group vs 59% of the metronidazole group (P<0.001). Tapered and pulsed dose courses of vancomycin resulted in fewer recurrences than metronidazole (P=0.01 and P=0.02, respectively). Overall failure rates did not differ significantly (P=0.77). Secondary: Not reported
Bricker et al.[89] (2005) Metronidazole or	MA Patients with diarrhea who	N=582 Precise duration	Primary: Initial resolution of diarrhea, initial conversion of stool	Primary: For initial symptomatic resolution, metronidazole, bacitracin, teicoplanin, fusidic acid, and rifaximin were as effective as vancomycin. Vancomycin was more effective than placebo (P=0.03) in a small study (N=21).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
bacitracin or fusidic acid* or teicoplanin* or rifaximin vs vancomycin vs placebo	recently received antibiotics for an infection other than *Clostridium difficile*	of therapy not specified	to *Clostridium difficile* cytotoxin and/or stool culture negative, recurrence of diarrhea, recurrence of fecal *Clostridium difficile* cytotoxin and/or positive stool culture, patient response to cessation of prior antibiotic therapy Secondary: Not reported	With regards to symptomatic cure, metronidazole, bacitracin and fusidic acid were found similar to vancomycin. Teicoplanin was slightly more effective than vancomycin (P=0.06). For initial bacteriologic resolution, vancomycin was more effective than placebo (P=0.03); teicoplanin was more effective than vancomycin (P=0.002); and metronidazole, fusidic acid, and rifaximin were as effective as vancomycin (P=0.008). In terms of bacteriologic cure, in comparison with vancomycin, teicoplanin was more effective (P=0.006), metronidazole was as effective (P=0.07), and fusidic acid was less effective (P=0.01). Patients were retreated in various ways, which made it difficult to compare the antibacterials for efficacy. There were a total of nine deaths, five of which were specified to be due to underlying illness and not related to treatment. Secondary: Not reported
Al-Nassir et al.[90] (2008) Metronidazole vs vancomycin	OS, PRO Patients with *Clostridium difficile*-associated diarrhea	N=82 13 days	Primary: Concentration of VRE overgrowth pre- and post-*Clostridium difficile*-associated diarrhea therapy Secondary: Rate of new VRE colonization	Primary: Vancomycin-treated patients were more likely to be in the intensive care unit during therapy and there was a non-significant trend towards more concurrent antibiotic use in the vancomycin treatment arm. For patients with VRE colonization prior to study, there was no significant difference in length of therapy for vancomycin or metronidazole (11.2 vs 12.1 days, respectively; P=0.088). There was no significant difference among the groups in concentrations of VRE prior to therapy between or at two weeks posttreatment (P>0.35). At 21 to 25 days posttreatment, there was a significant decrease in VRE in both groups (P<0.049). For patients who were not colonized with VRE prior to study, new colonization of VRE in stool cultures occurred in 14% of metronidazole-treated courses and 8% of vancomycin-treated courses (P=1.0). No occult

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				VRE infections occurred in patients with newly positive VRE stool cultures.
Al-Nassir et al.[91] (2008) Metronidazole vs vancomycin	OS, PRO Patients with *Clostridium difficile*-associated diarrhea	N=52 9 months	Primary: Time to resolution of diarrhea; time to undetectable levels of *Clostridium difficile* in stool Secondary: Not reported	Primary: More vancomycin-treated patients had previous *Clostridium difficile*-associated diarrhea (38.9 vs 2.9%; P=0.002) compared to metronidazole treated patients. A total of 29% of metronidazole-treated patients had therapy changed to vancomycin after 3 to 10 days due to persistent symptoms. Patients with a change in therapy were not more likely to be infected with a resistant strain of *Clostridium difficile*. Patients with a change in therapy were more likely to be prescribed a proton-pump inhibitor or have continued use of other antibiotics during *Clostridium difficile* treatment. After five days, vancomycin- treated patients were more likely to have undetectable levels of *Clostridium difficile* (HR, 3.99; 95% CI, 1.41 to 11.3; P=0.009). After five days, vancomycin-treated patients were more likely to have resolution of diarrhea (HR, 4.17; 95% CI, 1.53 to 11.4; P=0.005). Secondary: Not reported
Ortiz et al.[92] (2001) Nitazoxanide 100 mg BID (ages 2 to 3 years) or 200 mg BID (ages 4 to 11 years) for three days vs metronidazole 125 mg BID (ages 2 to 5	PRO, RCT Children 2 to 11 years of age with acute diarrhea and cysts within seven days	N=110 7 days	Primary: Clinical response at seven days Secondary: Parasitological response	Primary: There was no difference in the proportion of children with a clinical “well” response at seven days between the nitazoxanide group (85%) and the metronidazole group (80%; P=0.6148). Secondary: There was no difference in the proportion of children with a parasitological response at seven days between the nitazoxanide group (71%) and the metronidazole group, (75%; P=0.8307). The adverse events were similar between both groups and were mild in nature. Most were thought to be due to giardiasis.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
years) or 250 mg BID (ages 6 to 11 years) for five days				
Musher et al.[93] (2009) Nitazoxanide 500 mg every 12 hours vs vancomycin 125 mg orally every six hours	DB, PRO, RCT Patients with *Clostridium difficile* (+) stool cultures with ≥3 loose stools/24 hours, and either: fever >35 C, abdominal pain, or leukocytosis	N=50 1 month	Primary: Clinical response at the end of treatment (10 to 13 days) Secondary: Time to resolution of symptoms; sustained response rate at 31 days	Primary: Response to treatment occurred in 74% of vancomycin-treated patients and 77% of nitazoxanide-treated patients (95% CI, -24 to 28). Those that completed therapy had response rates of 87% in the vancomycin group and 94% in the nitazoxanide group (95% CI, -18 to 30). Secondary: The time to resolution of all symptoms was similar in the two groups (P=0.55). Two patients treated with vancomycin and one patient treated with nitazoxanide had a relapse within 31 days. Sustained response rates in the intent-to-treat group were 67% in the vancomycin group and 73% in the nitazoxanide group, (95% CI, -22 to 32). Sustained response rates in patients that completed therapy were 78% in vancomycin-treated patients and 89% in nitazoxanide-treated patients (95% CI, -18 to 35).
Solomkin et al.[94] (2009) Metronidazole 500 mg IV BID plus ceftriaxone 2 g IV once daily for 3 to 14 days vs moxifloxacin 400 mg IV once daily for 3 to 14 days	DB, MC, RCT Patients ≥18 years of age with community-origin complicated intra-abdominal infections with an expected duration of treatment with IV antimicrobials of 3 to 14 days	N=364 Up to 28 days	Primary: Clinical success rate at the test of cure visit (10 to 14 days after the end of therapy) Secondary: Clinical and bacteriological success rates on days three and five during treatment and at the end of treatment; bacteriological	Primary: At the test of cure visit, cure rates were 90.2% for moxifloxacin and 96.5% for ceftriaxone/metronidazole (95% CI, −11.7 to −1.7). In the intent-to-treat population, the clinical cure rates were 87.2% for moxifloxacin and 91.2% for ceftriaxone/metronidazole (95% CI, −10.7 to 1.9). Moxifloxacin was found to be non-inferior to ceftriaxone/metronidazole in the per protocol and intent-to-treat populations. Secondary: During treatment, clinical improvement occurred in similar proportions of per protocol patients in the moxifloxacin group (31.0%) and the ceftriaxone/metronidazole group (28.1%). In the intent-to-treat population, clinical improvement occurred in 30.6% of patients receiving moxifloxacin and 27.1% of patients receiving ceftriaxone/metronidazole. In the per protocol population, clinical resolution at end of treatment

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			success rate at the test of cure visit; and clinical success rate at the test of cure visit in patients with bacteriologically proven complicated intra-abdominal infections	occurred in 92.5% of patients receiving moxifloxacin and in 97.1% of patients receiving ceftriaxone/metronidazole (95% CI, −9.8 to −0.2). In the intent-to-treat population, clinical resolution at end of treatment occurred in 91.1% of patients receiving moxifloxacin and in 94.5% of patients receiving ceftriaxone/metronidazole. Bacteriological success rates were comparable between treatment groups. The bacteriological success rates in the microbiologically valid population at test of cure support the clinical results of moxifloxacin vs ceftriaxone/metronidazole (89.4 vs 95.9%, respectively; 95% CI, −13.3 to −0.6). The overall incidence of treatment-emergent adverse events was similar between the two treatment groups (31.7% with moxifloxacin vs 24.3% with ceftriaxone/metronidazole; P=0.129).
Towfigh et al.[95] (2010) Metronidazole 1 to 2 g IV daily in divided doses plus ceftriaxone 2 g IV once daily for 4 to 14 days vs tigecycline 100 mg IV as an initial dose, followed by 50 mg IV every 12 hours for 4 to 14 days	MC, OL, RCT Patients ≥18 years of age with complicated intra-abdominal infections	N=473 Up to 35 days	Primary: Clinical response in the clinically evaluable population at the test of cure visit Secondary: Bacteriological efficacy and safety	Primary: In the clinically evaluable population, clinical cure was reported in 70% of patients receiving tigecycline and in 74% of patients in the metronidazole plus ceftriaxone group (-4.0; 95% CI, -13.1 to 5.1; P=0.009). Tigecycline was found to be non-inferior to metronidazole plus ceftriaxone. Secondary: Clinical cure rates for the microbiologically evaluable population were 66% with tigecycline and 70% with metronidazole plus ceftriaxone (-3.4; 95% CI, -14.5 to 7.8; P=0.020). Tigecycline was found to be non-inferior to metronidazole plus ceftriaxone. In the clinical modified intent-to-treat population, clinical cure was reported in 64% of patients receiving tigecycline and in 71% of patients receiving metronidazole plus ceftriaxone (-7.0; 95% CI, -15.8 to 1.08; P=0.038). Tigecycline was found to be non-inferior to metronidazole plus ceftriaxone. *Escherichia coli* and *Bacteroides fragilis* were the most commonly isolated bacteria. For the microbiologically evaluable population, clinical cure rates for the different pathogens were similar between the two treatment groups. At test of cure in the microbiologically evaluable

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				population, infections were cured in 68.0 and 67.0% of all monomicrobial and polymicrobial infections, respectively, in the tigecycline-treated patients, and 71.5 and 68.3% of all monomicrobial and polymicrobial infections, respectively, in the metronidazole plus ceftriaxone-treated patients. Adverse events were similar with tigecycline and metronidazole plus ceftriaxone. There were no significant differences in the incidence of patients reporting one or more serious adverse events among the treatment groups (P=1.000). The most frequently reported serious adverse events overall were abscess (6.6%), infection (1.5%), respiratory failure (1.5%), abdominal pain (1.3%) and ileus (1.3%).
Kow et al.[96] (1995) Metronidazole 500 mg IV plus cefotaxime 1 g on induction of anesthesia vs cefoxitin 2 g IV on induction of anesthesia vs cefoxitin 2 g IV on induction of anesthesia plus another 2 g at 6 and 12 hours postoperatively vs	MC, RCT Patients 16 years of age and older admitted to the hospital for all types of intra-abdominal surgery	N=1,010 4 to 6 weeks post-operation	Primary: Incidence of wound infections, length of hospital stay Secondary: Not reported	Primary: Wound infections were diagnosed in 5.7% of all patients. The incidence of wound infections was not significantly different between treatment groups (P>0.19). There was no significant difference in length of hospital stay between the treatment groups. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
cefotaxime 1 g plus metronidazole 500 mg IV on induction of anesthesia followed by cefotaxime 1 g at 6 and 12 hours postoperatively				
Lewis[97] (2002) Metronidazole 2 g orally vs neomycin 2 g orally vs amikacin 1 g IV vs metronidazole 1 g IV vs placebo	DB, PC, RCT Patients scheduled to undergo elective surgery of the colon	N=215 3 years	Primary: Wound infections Secondary: Not reported	Primary: Wound infections occurred in five patients in the combined group (oral and systemic antibiotics) but in 17 of the systemic antibiotic-only group (P<0.01; RR, 0.29; 95% CI, 0.11 to 0.75). Bacteria isolated from wound infections and wound fat were more frequent in the colon in the systemic group (P<0.001) and occurred in wound fat in the systemic group twice as often as in the combined group (P<0.001). The summary weighted risk difference in surgical site infections between groups and the summary risk ratios both favored combined prophylaxis (risk difference=0.56; 95% CI, 0.26 to 0.86; RR, 0.51; 95% CI, 0.24 to 0.78; P<0.001). Secondary: Not reported
Song et al.[98] (1998) Metronidazole plus cefuroxime	MA Surgical patients	147 trials 12 years	Primary: Rate of surgical wound infections Secondary: Not reported	Primary: There was no significant difference in the rate of surgical wound infections between many different regimens. However, certain regimens appeared to be inadequate (e.g., metronidazole alone, doxycycline alone, piperacillin alone, oral neomycin plus

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs gentamicin plus metronidazole vs first or second generation cephalosporin vs third generation cephalosporin vs other agents as monotherapy or combination therapy				erythromycin on the day before operation). A single dose administered immediately before the operation (or short-term use) was judged as effective as long-term postoperative antimicrobial prophylaxis (OR, 1.17; 95% CI, 0.90 to 1.53). There is no convincing evidence to suggest that the new-generation cephalosporins are more effective than first generation cephalosporins (OR, 1.07; 95% CI, 0.54 to 2.12). Secondary: Not reported
Lauritano et al.[99] (2009) Metronidazole 250 mg TID for seven days vs rifaximin 400 mg TID for seven days	PRO, RCT Patients with bloating, abdominal pain, flatulence or diarrhea for ≥6 months due to small intestine bacterial overgrowth	N=142 7 days	Primary: Glucose breath test normalization rate Secondary: Adverse events	Primary: Glucose breath test normalization rate was significantly higher in the rifaximin group compared to the metronidazole group (63.5 vs 43.7%, respectively; P<0.05). There were no significant differences in the per-protocol group. Secondary: The incidence of adverse events was significantly higher in the metronidazole group compared to the rifaximin group (22.5 vs 8.5%, respectively; OR, 1.59; 95% CI, 1.15 to 8.61). Five drop outs occurred in the metronidazole group due to adverse events compared to none in the rifaximin group.
Buranawarodomkul et al.[100] (1990)	OS, PRO Female patients 15	N=171 1 to 2 weeks	Primary: Cure (defined as absence of	Primary: After treatment, 8% of patients treated with metronidazole and 14% of patients treated with tinidazole had 3 or more symptoms. There was no

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Tinidazole 2 g as a single dose vs metronidazole 500 mg BID for seven days	to 45 years of age with non-specific vaginitis		symptoms and presence of <3 criteria) Secondary: Not reported	statistical significant difference between metronidazole and tinidazole in patients with less than three symptoms (P=0.1688). In both groups, leukorrhea, itching, offensive odor and pelvic discomfort were all significantly reduced from pre- to posttreatment for both metronidazole and tinidazole (P<0.01 for both). There was no difference in posttreatment reduction of leukorrhea, itching, offensive odor, pelvic discomfort or dysuria when metronidazole was compared to tinidazole (P>0.05). Dysuria was not significantly reduced in the metronidazole group from pre- (8%) to posttreatment (2%; P=0.086). There was a significant difference in the incidence of adverse events between metronidazole (22%) and tinidazole (8%; P=0.025). Secondary: Not reported

*Product not commercially available in the United States.
Drug regimen abbreviations: BID=twice daily, IV=intravenous, TID=three times daily
Study abbreviations: AC=active control, CI=confidence interval, DB=double-blind, HR=hazard ratio, MA=meta-analysis, MC=multicenter, NS=not significant, OL=open-label, OR=odds ratio, OS=observational, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, Retro=retrospective, RR=relative risk, SB=single-blind
Miscellaneous abbreviations: AIDS=acquired immunodeficiency virus, HIV=human immunodeficiency virus, PCP=*Pneumocystis carinii* pneumonia, SMX-TMP=sulfamethoxazole-trimethoprim, STD=sexually transmitted disease, VRE=vancomycin-resistant enterococci

Additional Evidence

Dose Simplification
A search of Medline and PubMed did not reveal data pertinent to this topic.

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 12. Relative Cost of the Antiprotozoals, Miscellaneous

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Atovaquone	suspension	Mepron®*	$$$$$	$$$$$
Metronidazole	capsule, extended-release tablet, injection, tablet	Flagyl®*, Flagyl ER®	$$$-$$$$	$
Nitazoxanide	suspension, tablet	Alinia®	$$$-$$$$	N/A
Pentamidine	inhalation, injection	NebuPent®, Pentam 300®	$$$	N/A
Tinidazole	tablet	Tindamax®*	$$$	$$

*Generic is available in at least one dosage form or strength.
N/A=Not available

X. Conclusions

The miscellaneous antiprotozoals are used to treat a variety of infectious diseases, including amebiasis, anaerobic bacterial infections, bacterial vaginosis, cryptosporidiosis, giardiasis, *Pneumocystis* pneumonia (PCP) and trichomoniasis.[1-11] Atovaquone, metronidazole, and tinidazole are available in a generic formulation.

Metronidazole, nitazoxanide and tinidazole are approved for the treatment of intestinal protozoa.[5-8,11] Guidelines recommend the use of metronidazole or tinidazole for the treatment of patients with amebiasis.[23,25] The majority of the clinical trials evaluating these agents were conducted in the 1970's and found that tinidazole was more effective than metronidazole.[29,32-34,41,36,37,39] However, metronidazole was only administered for two to five days. Current dosing and consensus guidelines recommend the use of metronidazole for 10 days for the treatment of

amebiasis. Nitazoxanide is recommended for the initial treatment of cryptosporidiosis in immunocompetent individuals, and it has been shown to be more effective than placebo in clinical trials.[23,56-59,61,] Guidelines recommend the use of nitazoxanide or tinidazole for the initial treatment of giardiasis.[23] Metronidazole is considered an alternative treatment option due to the high frequency of gastrointestinal adverse events. The majority of the clinical trials have compared metronidazole with tinidazole and found that tinidazole was more effective.[32,63,65-67,69] However, metronidazole was only administered as a single dose. Clinical trials that evaluated the use of metronidazole for five days demonstrated similar clinical response rates as nitazoxanide and tinidazole.[62,68]

Atovaquone is approved for the prevention and treatment of PCP in patients who are intolerant to sulfamethoxazole-trimethoprim.[4] Aerosolized pentamidine is approved for the prevention of PCP in high-risk, Human Immunodeficiency Virus (HIV)-infected patients, and intravenous pentamidine is approved for the treatment of PCP (all patient types).[9-10] Guidelines recommend the initial use of sulfamethoxazole-trimethoprim for both the prevention and treatment of PCP.[18] Atovaquone and pentamidine are recommended as one of several alternative treatment options in patients who cannot tolerate sulfamethoxazole-trimethoprim.[18] Clinical trials have found that sulfamethoxazole-trimethoprim is more effective for the prevention of PCP than atovaquone or aerosolized pentamidine.[75-78] One study directly compared atovaquone and aerosolized pentamidine for the prevention of PCP and found that both agents were equally effective.[74] Another study directly compared atovaquone with intravenous pentamidine for the treatment of PCP and found that both agents were similar in efficacy.[79]

Metronidazole and tinidazole are approved for the treatment of bacterial vaginosis and trichomoniasis. Guidelines recommend the use of metronidazole or clindamycin for the initial treatment of bacterial vaginosis, and clinical trials have demonstrated similar outcomes with these agents.[19-20,43,44-50] Studies directly comparing metronidazole and tinidazole have also demonstrated similar cure rates.[51,52,101] For the treatment of trichomoniasis, guidelines recommend the use of metronidazole or tinidazole, and both agents have demonstrated similar efficacy in clinical trials.[19-20,82-84]

Metronidazole is approved for the treatment of a variety of other anaerobic bacterial infections. Guidelines recommend the use of metronidazole (alone or in combination with other anti-aerobic agents) for the treatment of *Clostridium difficile*-associated diarrhea, intra-abdominal infections, pelvic inflammatory disease, skin and soft-tissue infections and for surgical prophylaxis.[21,25-28]

There is insufficient evidence to support that one brand miscellaneous antiprotozoal agent is safer or more efficacious than another within its given indication. These agents may be considered first-line therapy in special circumstances. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand miscellaneous antiprotozoals within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand miscellaneous antiprotozoal is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Urinary Anti-infectives
AHFS Class 083600
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I. Overview

The urinary anti-infectives are approved for the prophylaxis and treatment of urinary tract infections (UTIs), as well as for the relief of local symptoms associated with infections or caused by diagnostic procedures.[1-10] There are several single entity and combination products included in this review. Each of the agents has a unique mechanism of action and place in therapy.

Fosfomycin is a synthetic, broad spectrum antibacterial which inactivates the enzyme enolpyruvyl transferase, thereby inhibiting cell wall synthesis. It is available as a single-dose sachet, which must be dissolved in water before oral administration.[4,11,12]

Methenamine is hydrolyzed to formaldehyde in acidic urine, which is bactericidal against both gram-positive and gram-negative pathogens. It is approved for the prophylaxis of recurrent UTIs and should only be used after eradication of the infection by other appropriate antimicrobial agents. Methenamine may be used for prolonged periods of time because, unlike conventional antibiotics, acquired resistance does not appear to develop.[5] Methenamine is also available as fixed-dose combination products which contain several ingredients to enhance the anti-infective properties and relieve symptoms associated with UTIs. Methylene blue is a weak antiseptic, phenyl salicylate is a mild analgesic, and sodium phosphate helps to lower the pH in the urine. Hyoscyamine is a parasympatholytic, which relaxes smooth muscle.[1-3]

Nitrofurantoin is reduced to reactive intermediates by bacterial flavoproteins, which inhibits protein synthesis, aerobic energy metabolism, deoxyribonucleic acid synthesis, ribonucleic acid synthesis, and cell wall synthesis.[6-8] It is available in several formulations, including a monohydrate suspension, a macrocrystalline capsule, and a fixed-dose combination product. Nitrofurantoin macrocrystals are a larger crystal form of nitrofurantoin monohydrate, allowing for slower absorption and less excretion.[7] The fixed-dose combination product contains 25% macrocrystalline nitrofurantoin and 75% nitrofurantoin monohydrate. The monohydrate component forms a gel matrix upon exposure to gastric and intestinal fluids, which releases nitrofurantoin over time.[8]

Trimethoprim binds to and reversibly inhibits dihydrofolate reductase and blocks the production of tetrahydrofolic acid, which interferes with bacterial biosynthesis of nucleic acids and proteins. It is approved for the treatment of uncomplicated UTIs and may also be used for the treatment of acute otitis media.[9] Trimethoprim is also available in a fixed-dose combination with sulfamethoxazole, which is reviewed with the sulfonamides (American Hospital Formulary Service 081220) and is not included in this review.

The urinary anti-infectives that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. The majority of the products are available in a generic formulation. This class was last reviewed in May 2012.

Table 1. Urinary Anti-infectives Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Fosfomycin	packet	Monurol®	none
Methenamine	tablet	Hiprex®*	methenamine
Nitrofurantoin	suspension	Furadantin®*	nitrofurantoin
Nitrofurantoin macrocrystals	capsule	Macrodantin®*	nitrofurantoin macrocrystals
Trimethoprim	solution, tablet	Primsol®	trimethoprim
Combination Products			
Methenamine, methylene blue, phenyl salicylate, sodium phosphate, and	capsule, tablet	Urin D.S.®*, Urimar T®, Utica C®*	methenamine, methylene blue, phenyl salicylate, sodium phosphate, and

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
hyoscyamine			hyoscyamine
Methenamine and sodium phosphate	tablet	Uroqid-Acid No.2®	none
Methenamine, sodium phosphate, methylene blue, and hyoscyamine	tablet	N/A	methenamine, sodium phosphate, methylene blue, and hyoscyamine
Nitrofurantoin and nitrofurantoin macrocrystals	capsule	Macrobid®*	nitrofurantoin and nitrofurantoin macrocrystals

*Generic is available in at least one dosage form or strength.
N/A=Not available, PDL=Preferred Drug List

The urinary anti-infectives have been shown to be active against the strains of microorganisms indicated in Table 2. This activity has been demonstrated in clinical infections and is represented by the Food and Drug Administration (FDA)-approved indications for the urinary anti-infectives that are noted in Table 4. These agents may also have been found to show activity to other microorganisms in vitro; however, the clinical significance of this is unknown since their safety and efficacy in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled trials. Although empiric anti-infective therapy may be initiated before culture and susceptibility test results are known, once results become available, appropriate therapy should be selected. There is no information available regarding the microorganisms that are susceptible to the methenamine combination products.[1-3]

Table 2. Microorganisms Susceptible to the Urinary Anti-infectives[1-9]

Organism	Single Entity Agents					Combination Products*
	Fosfomycin	Methenamine	Nitrofurantoin	Nitrofurantoin Macrocrystals	Trimethoprim	Nitrofurantoin and Nitrofurantoin Macrocrystals
Gram-Positive Aerobes						
Enterococcus species		✔	✔	✔		
Enterococcus faecalis	✔					
Staphylococcus species		✔			✔	
Staphylococcus aureus			✔	✔		
Streptococcus pneumoniae					✔	
Staphylococcus saprophyticus					✔	✔
Gram-Negative Aerobes						
Enterobacter species			✔	✔	✔	
Escherichia coli	✔	✔	✔	✔	✔	✔
Haemophilus influenzae					✔	
Klebsiella species			✔	✔		
Klebsiella pneumoniae					✔	
Proteus mirabilis					✔	

*Clinical information was not identified for the combination products not listed in this table.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the urinary anti-infectives are summarized in Table 3.

Table 3. Treatment Guidelines Using the Urinary Anti-infectives

Clinical Guideline	Recommendation(s)
American Academy of Pediatrics/American Academy of Family Physicians: **Diagnosis and Management of Acute Otitis Media (2013)**[13]	Observation option • Observation without use of antibacterial agents in a child with unilateral acute otitis media is an option for selected children based on age, illness severity, and assurance of follow-up after joint decision-making with the parent(s)/caregiver. The "observation option" for acute otitis media refers to deferring antibacterial treatment of selected children for 48 to 72 hours and limiting management to symptomatic relief. This option should be limited to otherwise healthy children six months and older without severe symptoms at presentation. Antibacterial options - temperature <39°C without severe otalgia • For the initial treatment of otitis media, the recommended agent is amoxicillin 80 to 90 mg/kg/day. • For treatment failures at 48 to 72 hours after initial management with observation option, the recommended agent is amoxicillin 80 to 90 mg/kg/day. • For treatment failures at 48 to 72 hours after initial management with antibacterial agents, the recommended agent is amoxicillin-clavulanate. Antibacterial options - temperature ≥39°C and/or severe otalgia • For the initial treatment of otitis media, the recommended agent is amoxicillin-clavulanate. • For treatment failures at 48 to 72 hours after initial management with observation option, the recommended agent is amoxicillin-clavulanate. • For treatment failures at 48 to 72 hours after initial management with antibacterial agents, the recommended agent is ceftriaxone for three days.
Infectious Diseases Society of America/European Society for Microbiology and Infectious Diseases: **International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women (2010)**[14]	Acute uncomplicated bacterial cystitis • Nitrofurantoin monohydrate/macrocrystals (100 mg twice daily for five days) is an appropriate choice for therapy due to minimal resistance and propensity for collateral damage. • Sulfamethoxazole-trimethoprim (800-160 mg twice daily for three days) is an appropriate choice for therapy, given its efficacy as assessed in numerous clinical trials, if local resistance rates of uropathogens causing acute uncomplicated cystitis do not exceed 20% or if the infecting strain is known to be susceptible. • Fosfomycin (3 grams in a single dose) is an appropriate choice for therapy where it's available due to minimal resistance and propensity for collateral damage, but it appears to be less effective compared to standard short-course regimens. • Ofloxacin, ciprofloxacin and levofloxacin are highly efficacious in three-day regimens, but have a propensity for collateral damage and should be reserved for important uses other than acute cystitis and thus should be considered alternative antimicrobials for acute cystitis. • β-lactam agents, including amoxicillin-clavulanate, cefdinir, cefaclor, and cefpodoxime-proxetil, in three to seven day regimens are appropriate choices for therapy when other recommended agents cannot be used. Other β-lactams, such as cephalexin are less well studied, but may also be appropriate in certain settings. The β-lactams are generally less effective and have more adverse effects compared to other urinary tract infection antimicrobials. For these reasons, β-lactams should be used with caution for uncomplicated cystitis. • Amoxicillin or ampicillin should not be used for empirical treatment given the

Clinical Guideline	Recommendation(s)
	relatively poor efficacy and the very high prevalence of antimicrobial resistance to these agents worldwide. <u>Acute pyelonephritis</u> • Oral ciprofloxacin (500 mg twice daily) for seven days, with or without an initial 400 mg dose of intravenous ciprofloxacin, is an appropriate choice when resistance of community uropathogens to fluoroquinolones is not known to exceed 10%. A long-acting antimicrobial (i.e., ceftriaxone 1 gram or consolidated 24 hour dose of an aminoglycoside) may replace the initial one time intravenous ciprofloxacin, and is recommended if the fluoroquinolone resistance is thought to exceed 10%. • Once-daily fluoroquinolones (ciprofloxacin 100 mg extended-release for seven days, levofloxacin 750 mg for five days) is an appropriate choice when resistance to community uropathogens is not known to exceed 10%. If resistance is thought to exceed 10%, an initial intravenous dose of long-acting parenteral antimicrobial (ceftriaxone 1 gram or consolidated 24 hour dose of an aminoglycoside) is recommended. • Oral Sulfamethoxazole-trimethoprim (800-160 mg twice daily) for 14 days is an appropriate choice of therapy when the uropathogen is known to be susceptible. If susceptibility is unknown, an initial intravenous dose of long-acting parenteral antimicrobial (i.e., ceftriaxone 1 gram or consolidated 24 hour dose of an aminoglycoside) is recommended. • Oral β-lactams are less effective than other available agents for the treatment of pyelonephritis. If an oral β-lactam is used, an initial intravenous dose of long-acting parenteral antimicrobial (i.e., ceftriaxone 1 gram or consolidated 24 hour dose of an aminoglycoside) is recommended. • For patients requiring hospitalization, initial treatment with an intravenous antimicrobial regimen, such as a fluoroquinolone, an aminoglycoside with or without ampicillin, an extended-spectrum cephalosporin or extended-spectrum penicillin with or without an aminoglycoside, or a carbapenem is recommended. The choice between these agents should be based on local resistance data, and the regimen should be tailored on the basis of susceptibility results. Compared to

American College of Obstetricians and Gynecologists: **Treatment of Urinary Tract Infections in Nonpregnant Women (2008)**[15]	• For uncomplicated acute bacterial cystitis, recommended treatment regimens are as follows:
	  o Sulfamethoxazole-trimethoprim: one tablet (800-160 mg) twice daily for three days.
	  o Trimethoprim 100 mg twice daily for three days.
	  o Ciprofloxacin 250 mg twice daily for three days, levofloxacin 250 mg once daily for three days, norfloxacin 400 mg twice daily for three days, or gatifloxacin 200 mg, once daily for three days.
	  o Nitrofurantoin macrocrystals 50 to 100 mg four times daily for seven days, or nitrofurantoin monohydrate 100 mg twice daily for seven days.
	  o Fosfomycin tromethamine, 3 grams dose (powder) single dose.

Infectious Diseases Society of America: **Guidelines for the Diagnosis and Treatment of Asymptomatic Bacteriuria in Adults (2005)**[16] **(Reviewed and deemed current as of April**	• Pyuria is not an indication for antimicrobial treatment because treatment has not been shown to decrease the frequency of symptomatic infection or the risk of developing hypertension, chronic kidney disease, or genitourinary cancer; it also has not been shown to improve length of survival. • Treatment for asymptomatic bacteriuria in premenopausal, nonpregnant women is not recommended because treatment has not been shown to decrease the frequency of symptomatic infection or the risk of developing hypertension, chronic kidney disease, or genitourinary cancer, or to improve length of survival. • Treatment should be initiated in pregnant women with bacteriuria, as they are at increased risk of developing pyelonephritis and have a higher prevalence of

Clinical Guideline	Recommendation(s)
2013)	premature delivery and infants of low birth weight. Antibiotic treatment is recommended for three to seven days. • In the following special populations, treatment is not indicated for asymptomatic bacteriuria: catheterized patients, diabetic women, institutionalized and noninstitutionalized elderly patients, and persons with spinal cord injury. • To prevent bacteremia and sepsis, patients who have undergone traumatic genitourinary procedures associated with mucosal bleeding should be treated for asymptomatic bacteriuria. Antibiotic treatment should be initiated shortly before the procedure and continued only if the patient remains catheterized. • Treatment may be considered in asymptomatic catheterized women with persistent bacteriuria after 48 hours of catheter removal.
Infectious Diseases Society of America: **Diagnosis, Prevention, and Treatment of Catheter-Associated Urinary Tract Infection in Adults (2009)**[10] **(Reviewed and deemed current as of July 2013)**	• Methenamine salts should not be used to reduce catheter-associated bacteriuria or catheter-associated urinary tract infections in patients with long-term intermittent or long-term indwelling urethral or supra-pubic catheterization. • There is insufficient data to make recommendations regarding methenamine salts to decrease catheter-associated urinary tract infections in patients with condom catheters. • Methenamine salts may be used to reduce catheter-associated bacteriuria or catheter-associated urinary tract infections in gynecologic surgery patients catheterized for less than one week. • There is no data to recommend one methenamine salt over another. • Target urinary pH should be <6.0 when using methenamine salts.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the urinary anti-infectives are noted in Tables 4 and 5. While agents within this therapeutic class may have demonstrated positive activity via in vitro trials, the clinical significance of this activity remains unknown until fully demonstrated in well-controlled, peer-reviewed in vivo clinical trials. As such, this review and the recommendations provided are based exclusively upon the results of such clinical trials.

Table 4. FDA-Approved Indications for the Single Entity Urinary Anti-infectives[1-9]

Indications	Fosfomycin	Methenamine	Nitrofurantoin	Nitrofurantoin Macrocrystals	Trimethoprim
Prophylactic or suppressive treatment of frequently recurring urinary tract infections		✔			
Treatment of uncomplicated urinary tract infections	✔				
Treatment of urinary tract infections			✔	✔	✔

Table 5. FDA-Approved Indications for the Combination Urinary Anti-infectives[1-9]

Indications	Methenamine, Methylene Blue, Phenyl Salicylate, Sodium Phosphate and Hyoscyamine	Methenamine and Sodium Phosphate	Methenamine, Sodium Phosphate, Methylene Blue and Hyoscyamine	Nitrofurantoin and Nitrofurantoin Macrocrystals
Acute otitis media				✔
Prophylactic or suppressive treatment of frequently recurring urinary tract infections		✔		
Relief of local symptoms associated with urinary tract infections	✔		✔	
Relief of urinary tract symptoms caused by diagnostic procedures	✔		✔	
Treatment of symptoms of irritative voiding	✔			
Treatment of uncomplicated urinary tract infections			✔	
Treatment of urinary tract infections				✔

IV. Pharmacokinetics

The pharmacokinetic parameters of the urinary anti-infectives are listed in Table 6. Information regarding the pharmacokinetic parameters for the specific methenamine combination products is not available.[1-3]

Table 6. Pharmacokinetic Parameters of the Urinary Anti-infectives[1-9]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents					
Fosfomycin	34 to 58	0	none	Renal (38) Feces (18)	5.7
Methenamine	Not reported	Not reported	Liver (10 to 25)	Renal (90)	4.3
Nitrofurantoin	87 to 94	90	Not reported	Renal (34 to 40)	0.3 to 1
Nitrofurantoin macrocrystals	87 to 94	90	Not reported	Renal (20 to 25)	0.3 to 1
Trimethoprim	Not reported	44	Liver (10 to 20)	Renal (50 to 60) Feces (<4)	8 to 10
Combination Products					
Nitrofurantoin and nitrofurantoin macrocrystals	40	90	Not reported	Renal (20 to 25)	Not reported

V. Drug Interactions

Significant drug interactions with the urinary anti-infectives are listed in Table 7.

Table 7. Significant Drug Interactions with the Urinary Anti-infectives[1]

Generic Name(s)	Significance Level	Interaction	Mechanism
Trimethoprim	1	Dofetilide	Elevated dofetilide plasma concentrations may occur with increased risk of ventricular arrhythmias, including torsades de pointes.
Trimethoprim	1	Methotrexate	Trimethoprim may increase the risk of methotrexate-induced bone marrow suppression and megaloblastic anemia.
Methenamine	2	Sulfonamides	Methenamine is contraindicated for use with sulfonamides due to the potential for formation of insoluble precipitates in the urine.
Trimethoprim	2	Angiotensin converting enzyme inhibitors	Severe hyperkalemia has been reported with concurrent use of angiotensin converting enzyme inhibitors and trimethoprim.
Trimethoprim	2	Dapsone	Increased serum levels of dapsone and trimethoprim may occur, possibly increasing the pharmacologic and toxic effects of each drug.
Trimethoprim	2	Hydantoins	Serum hydantoin concentrations may be increased, producing an increase in the pharmacologic and toxic effects of hydantoins.

Significance level 1=major severity; significance level 2=moderate severity

VI. Adverse Drug Events

The most common adverse drug events reported with the urinary anti-infectives are listed in Tables 8 and 9.

Table 8. Adverse Drug Events (%) Reported with the Single Entity Urinary Anti-infectives[1-9]

Adverse Events	Fosfomycin	Methenamine	Nitrofurantoin	Nitrofurantoin Macrocrystals	Trimethoprim
Cardiovascular					
Chest pain	-	-	✔	✔	-
Electrocardiogram changes	-	-	✔	✔	-
Intracranial hypertension	-	-	✔	✔	-
Central Nervous System					
Aseptic meningitis	-	-	-	-	✔
Chills	-	-	✔	✔	-
Confusion	-	-	✔	✔	-
Depression	-	-	✔	✔	-
Dizziness	1 to 2	-	✔	✔	-
Drowsiness	-	-	✔	✔	-
Fatigue	<1	-	-	-	-
Fever	<1	-	✔	✔	✔
Headache	4 to 10	-	✔	✔	-
Insomnia	<1	-	-	-	-
Migraine	<1	-	-	-	-
Nervousness	<1	-	-	-	-
Nystagmus	-	-	✔	✔	-
Paresthesia	<1	-	-	-	-
Peripheral neuropathy	-	-	✔	✔	-
Psychotic reactions	-	-	✔	✔	-
Somnolence	<1	-	-	-	-
Vertigo	-	-	✔	✔	-
Dermatological					
Alopecia	-	-	✔	✔	-
Eczematous eruptions	-	-	✔	✔	-
Erythema multiforme	-	-	✔	✔	✔
Erythematous eruptions	-	-	✔	✔	-
Exfoliative dermatitis	-	-	✔	✔	✔
Maculopapular eruptions	-	-	✔	✔	-
Phototoxic eruptions	-	-	-	-	✔
Pruritus	<1	<4	✔	✔	✔

Adverse Events	Fosfomycin	Methenamine	Nitrofurantoin	Nitrofurantoin Macrocrystals	Trimethoprim
Rash	1.4	<3.5	-	-	3 to 6
Skin disorder	<1	-	-	-	-
Stevens-Johnson syndrome	-	-	✔	✔	✔
Toxic epidermal necrosis	-	-	-	-	✔
Urticaria	-	-	✔	✔	-
Gastrointestinal					
Abdominal pain	2.2	-	✔	✔	<1
Abnormal stools	<1	-	-	-	-
Anorexia	<1	-	✔	✔	-
Clostridium difficile associated diarrhea	-	-	✔	✔	-
Constipation	<1	-	✔	✔	-
Diarrhea	9 to 10	-	✔	✔	4.2
Dyspepsia	1 to 2	-	✔	✔	-
Epigastric distress	-	-	-	-	✔
Flatulence	<1	-	-	-	-
Nausea	4 to 5	<3.5	✔	✔	✔
Pseudomembranous colitis	-	-	✔	✔	-
Toxic megacolon	✔	-	-	-	-
Vomiting	<1	<3.5	✔	✔	✔
Xerostomia	<1	-	-	-	-
Genitourinary					
Albuminuria	-	✔	-	-	-
Dysuria	<1	<3.5	-	-	-
Hematuria	<1	<1	-	-	-
Menstrual disorder	<1	-	-	-	-
Urinary retention	-	-	-	-	-
Vaginitis	6 to 8	-	-	-	-
Hematologic					
Agranulocytosis	-	-	✔	✔	-
Aplastic anemia	-	-	✔	✔	-
Eosinophilia	-	-	✔	✔	✔
G6PD deficiency anemia	-	-	✔	✔	-
Granulocytopenia	-	-	✔	✔	-
Hemolytic anemia	-	-	✔	✔	-
Leukopenia	-	-	✔	✔	✔
Megaloblastic anemia	-	-	✔	✔	✔

Adverse Events	Fosfomycin	Methenamine	Nitrofurantoin	Nitrofurantoin Macrocrystals	Trimethoprim
Methemoglobinemia	-	-	-	-	✔
Neutropenia	-	-	-	-	✔
Thrombocytopenia	-	-	✔	✔	✔
Hepatic					
Cholestatic jaundice	-	-	✔	✔	✔
Hepatic necrosis	-	-	✔	✔	-
Hepatitis	-	-	✔	✔	-
Laboratory Test Abnormalities					
Alanine transaminase increased	<1	✔	✔	✔	✔
Aspartate aminotransferase increased	-	-	✔	✔	✔
Blood urea nitrogen increased	-	-	-	-	✔
Hemoglobin decreased	-	-	✔	✔	-
Hyperkalemia	-	-	-	-	✔
Hyperphosphatemia	-	-	✔	✔	-
Hyponatremia	-	-	-	-	✔
Serum creatinine increased	-	-	-	-	✔
Musculoskeletal					
Arthralgia	-	-	✔	✔	-
Asthenia	1	-	-	-	-
Back pain	3	-	-	-	-
Malaise	-	-	-	-	-
Myalgia	<1	-	✔	✔	-
Respiratory					
Asthma exacerbation	✔	-	-	-	-
Cough	-	-	✔	✔	-
Cyanosis	-	-	✔	✔	-
Dyspnea	-	-	✔	✔	-
Pharyngitis	2.5	-	-	-	-
Pleural effusion	-	-	✔	✔	-
Pulmonary fibrosis	-	-	✔	✔	-
Pulmonary infiltration	-	-	✔	✔	-
Rhinitis	4.5	-	-	-	-
Shortness of breath	-	-	-	-	-
Other					
Amblyopia	-	-	-	-	-
Anaphylaxis	✔	-	✔	✔	✔

Adverse Events	Fosfomycin	Methenamine	Nitrofurantoin	Nitrofurantoin Macrocrystals	Trimethoprim
Angioedema	✔	-	-	-	-
Aplastic anemia	✔	-	-	-	-
Blurred vision	-	-	-	-	-
Bone/joint pain	-	-	-	-	-
Cholestatic jaundice	✔	-	-	-	-
Dysmenorrhea	2.6	-	-	-	-
Ear disorder	<1	-	-	-	-
Flu syndrome	<1	-	-	-	-
Flushing	-	-	-	-	-
Hearing loss	✔	-	-	-	-
Hepatic necrosis	✔	-	-	-	-
Hypersensitivity reactions	-	-	✔	✔	-
Lymphadenopathy	<1	-	-	-	-
Numbness/tingling	-	-	-	-	-
Optic neuritis	✔	-	✔	✔	-
Pain	2.2	-	-	-	-
Pancreatitis	-	-	✔	✔	-
Sialadenitis	-	-	✔	✔	-
Weakness of extremities	1 to 2	-	-	-	-

✔ Percent not specified.
- Event not reported or incidence <1%.

Table 9. Adverse Drug Events (%) Reported with the Combination Urinary Anti-infectives[1-9]

Adverse Events	Methenamine, Methylene Blue, Phenyl Salicylate, Sodium Phosphate and Hyoscyamine	Methenamine and Sodium Phosphate	Methenamine, Sodium Phosphate, Methylene Blue and Hyoscyamine	Nitrofurantoin and Nitrofurantoin Macrocrystals
Cardiovascular				
Chest pain	-	-	-	✔
Electrocardiogram changes	-	-	-	✔
Intracranial hypertension	-	-	-	✔
Central Nervous System				
Chills	-	-	-	<1
Confusion	-	✔	-	✔
Depression	-	-	-	✔

Adverse Events	Methenamine, Methylene Blue, Phenyl Salicylate, Sodium Phosphate and Hyoscyamine	Methenamine and Sodium Phosphate	Methenamine, Sodium Phosphate, Methylene Blue and Hyoscyamine	Nitrofurantoin and Nitrofurantoin Macrocrystals
Dizziness	✔	✔	✔	<1
Drowsiness	-	-	-	<1
Fatigue	-	✔	-	-
Fever	-	-	-	<1
Headache	-	✔	-	6
Malaise	-	✔	-	-
Nystagmus	-	-	-	✔
Peripheral neuropathy	-	-	-	✔
Psychotic reactions	-	-	-	✔
Seizures	-	✔	-	-
Vertigo	-	-	-	✔
Dermatological				
Alopecia	-	-	-	<1
Eczematous eruptions	-	-	-	✔
Erythema multiforme	-	-	-	✔
Erythematous eruptions	-	-	-	✔
Exfoliative dermatitis	-	-	-	✔
Maculopapular eruptions	-	-	-	✔
Pruritus	-	-	-	<1
Rash	-	✔	-	-
Stevens-Johnson syndrome	-	-	-	✔
Urticaria	-	-	-	<1
Gastrointestinal				
Abdominal pain	-	-	-	<1
Anorexia	-	-	-	✔
Clostridium difficile associated diarrhea	-	-	-	✔
Constipation	-	-	-	<1
Diarrhea	-	✔	-	<1
Dyspepsia	-	-	-	<1
Flatulence	-	-	-	1.5
Nausea	✔	✔	✔	8
Pseudomembranous colitis	-	-	-	✔
Vomiting	✔	✔	✔	<1
Xerostomia	✔	-	✔	-

Adverse Events	Methenamine, Methylene Blue, Phenyl Salicylate, Sodium Phosphate and Hyoscyamine	Methenamine and Sodium Phosphate	Methenamine, Sodium Phosphate, Methylene Blue and Hyoscyamine	Nitrofurantoin and Nitrofurantoin Macrocrystals
Genitourinary				
Dysuria	✔	✔	✔	-
Hematuria	-	✔	-	-
Urinary retention	✔	-	✔	-
Vaginitis	-	-	-	-
Hematologic				
Agranulocytosis	-	-	-	✔
Aplastic anemia	-	-	-	✔
Eosinophilia	-	-	-	✔
G6PD deficiency anemia	-	-	-	✔
Granulocytopenia	-	-	-	✔
Hemolytic anemia	-	-	-	✔
Leukopenia	-	-	-	✔
Megaloblastic anemia	-	-	-	✔
Methemoglobinemia	-	-	-	✔
Thrombocytopenia	-	-	-	✔
Musculoskeletal				
Arthralgia	-	-	-	✔
Asthenia	-	-	-	✔
Malaise	-	-	-	<1
Muscle cramps	-	✔	-	-
Myalgia	-	-	-	✔
Respiratory				
Cough	-	-	-	✔
Cyanosis	-	-	-	✔
Dyspnea	✔	✔	✔	✔
Pleural effusion	-	-	-	✔
Pulmonary hypersensitivity reactions	-	-	-	<1
Pulmonary infiltration	-	-	-	✔
Shortness of breath	✔	-	✔	-
Other				
Alanine transaminase increased	-	-	-	✔
Amblyopia	-	-	-	<1
Anaphylaxis	-	-	-	✔

Adverse Events	Methenamine, Methylene Blue, Phenyl Salicylate, Sodium Phosphate and Hyoscyamine	Methenamine and Sodium Phosphate	Methenamine, Sodium Phosphate, Methylene Blue and Hyoscyamine	Nitrofurantoin and Nitrofurantoin Macrocrystals
Aspartate aminotransferase increased	-	-	-	✔
Blurred vision	✔	-	✔	-
Bone/joint pain	-	✔	-	-
Cholestatic jaundice	-	-	-	✔
Flushing	✔	-	✔	-
Hemoglobin decreased	-	-	-	✔
Hepatic necrosis	-	-	-	✔
Hepatitis	-	-	-	✔
Hyperphosphatemia	-	-	-	✔
Hypersensitivity reactions	-	-	-	✔
Numbness/tingling	-	✔	-	-
Optic neuritis	-	-	-	✔
Pain	-	✔	-	-
Pancreatitis	-	-	-	✔
Sialadenitis	-	-	-	✔
Swelling of feet/lower legs	-	✔	-	-
Tachycardia	✔	✔	✔	-
Weakness of extremities	-	✔	-	-
Weight gain	-	✔	-	-

✔ Percent not specified.
- Event not reported or incidence <1%.

VII. Dosing and Administration

The usual dosing regimens for the urinary anti-infectives are listed in Table 10.

Table 10. Usual Dosing Regimens for the Urinary Anti-infectives[1-9]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Fosfomycin	Treatment of uncomplicated urinary tract infections: Packet: one 3 g sachet mixed with water before ingesting	Safety and efficacy in children <12 years of age have not been established.	Packet: 3 g
Methenamine	Prophylactic or suppressive treatment of frequently recurring urinary tract infections: Tablet: 1 g twice daily	Prophylactic or suppressive treatment of frequently recurring urinary tract infections: Tablet: 6 to 12 years of age, 0.5 to 1 g twice daily; ≥12 years of age, 1 g twice daily	Tablet: 500 mg 1 g
Nitrofurantoin	Long-term suppressive therapy for urinary tract infections: Suspension: 50 to 100 mg at bedtime Treatment of urinary tract infections: Suspension: 50 to 100 mg four times daily for one week or for at least three days after sterility of the urine is obtained	Long-term suppressive therapy for urinary tract infections: Suspension: ≥1 month of age, 1 mg/kg per 24 hours given in a single dose or two divided doses Treatment of urinary tract infections: Suspension: ≥1 month of age, 5 to 7 mg/kg per 24 hours given in four divided doses for one week, or for at least three days after sterility of the urine is obtained	Suspension: 25 mg/5 mL
Nitrofurantoin macrocrystals	Long-term suppressive therapy for urinary tract infections: Capsule: 50 to 100 mg at bedtime Treatment of urinary tract infections: Capsule: 50 to 100 mg four times daily for one week or for at least three days after sterility of the urine is obtained.	Long-term suppressive therapy for urinary tract infections: Capsule: ≥1 month of age,1 mg/kg per 24 hours given in a single dose or two divided doses Treatment of urinary tract infections: Capsule: ≥1 month of age, 5 to 7 mg/kg per 24 hours given in four divided doses for one week, or for at least three days after sterility of the urine is obtained	Capsule: 25 mg 50 mg 100 mg
Trimethoprim	Treatment of urinary tract infections: Solution, tablet: 100 mg every 12 hours or 200 mg every 24 hours for 10 days	Acute otitis media: Solution, tablet: ≥6 months of age, 10 mg/kg per 24 hours, given in divided doses every 12 hours for 10 days	Solution: 50 mg/5 mL Tablet: 100 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Combination Products			
Methenamine, methylene blue, phenyl salicylate, sodium phosphate, and hyoscyamine	Relief of local symptoms associated with urinary tract infections, relief of urinary tract symptoms caused by diagnostic procedures, treatment of symptoms of irritative voiding: Tablet: one tablet four times daily	Safety and efficacy in children <6 years of age have not been established. For children ≥6 years of age, the dosage should be individualized by the physician.	Tablet: 81.6-10.8-36.2-40.8-0.12 mg 120-10.8-36.2-40.8-0.12 mg
Methenamine and sodium phosphate	Prophylactic or suppressive treatment of frequently recurring urinary tract infections s: Tablet: initial, two tablets four times daily; maintenance, two to four tablets daily in divided doses	Safety and efficacy in children have not been established.	Tablet: 500-500 mg
Methenamine, sodium phosphate, methylene blue, and hyoscyamine	Relief of local symptoms associated with urinary tract infections, relief of urinary tract symptoms caused by diagnostic procedures, treatment of uncomplicated urinary tract infections: Tablet: one tablet four times daily	Safety and efficacy in children <12 years of age have not been established. For children ≥12 years of age, the dosage should be individualized by the physician.	Tablet: 81.6-40.8-10.8-0.12 mg
Nitrofurantoin and nitrofurantoin macrocrystals	Treatment of urinary tract infections: Capsule: 100 mg every 12 hours for seven days	Treatment of urinary tract infections: Capsule: ≥12 years of age, 100 mg every 12 hours for seven days	Capsule: 100 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the urinary anti-infectives are summarized in Table 11.

Table 11. Comparative Clinical Trials with the Urinary Anti-infectives

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Urinary Tract Infections (Complicated)				
Senol et al.[17] (2010) Fosfomycin 3 g every other night for three doses vs meropenem 1 g IV every eight hours or imipenem-cilastatin 500 mg IV every six hours for 14 days	OBS, PRO Adults with extended-spectrum beta-lactamase-producing *E Coli*-related complicated lower urinary tract infections	N=47 31 days	Primary: Clinical success (resolution of symptoms); microbiologic success (sterile cultures seven to nine days after treatment); relapse (isolation of extended-spectrum beta-lactamase - producing *E Coli* in the control urine cultures); reinfection (isolation of any pathogen in the control urine cultures performed 28 to 31 days after the start of therapy) Secondary: Not reported	Primary: Clinical and microbiological success in the fosfomycin and carbapenem group were similar (19/20 vs 21/27 and 16/20 vs 16/27, respectively; P>0.05). Relapse rates were similar between the fosfomycin and carbapenem group (1/16 vs 1/16, respectively; P>0.05). Reinfection rates were similar between the fosfomycin and carbapenem group (1/16 vs 1/16, respectively; P>0.05). In a subgroup of patients with indwelling catheters, the microbiologic success (87.5 vs 50%; P>0.079) and clinical success (100 vs 79%; P>0.05) was higher in the carbapenem group compared to the fosfomycin group; however, the differences did not reach statistical significance. Secondary: Not reported
Urinary Tract Infections (Recurrent)				
Cronberg et al.[18] (1987) Methenamine	DB, RCT, XO Women 40 to 80 years of age with	N=21 1 to 2 years	Primary: Effectiveness of methenamine hippurate, with and	Primary: In 27 patient years (14 patients completed one year and 13 patients completed both years), 52 attacks of cystitis due to reinfection occurred, which included 11 in patients receiving methenamine and 41 in patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
hippurate 1 g BID vs placebo Treatments were interchanged every six months for two years.	recurrent acute cystitis		without extra fluid intake, in preventing acute cystitis Secondary: Not reported	taking placebo. Methenamine hippurate reduced the incidence of acute cystitis by 73%. There were 2.1 infection per patient/year with placebo vs 0.8 with methenamine hippurate (P<0.01). There was no difference between patients taking extra fluid and normal fluid (28 vs 24 attacks, respectively) and extra fluid did not reduce the efficacy of methenamine (6 vs 5 attacks). Secondary: Not reported
Peterson et al.[19] (1986) Methenamine hippurate 0.5 g BID	PRO Females five to 12 years of age with recurrent urinary tract infections	N=20 12 months	Primary: Number of infections per patient per year Secondary: Not reported	Primary: Number of infections per patient per year was 3.1 before treatment with methenamine hippurate and 0.7 during treatment (P<0.001). After prophylaxis was stopped, the number of infections per patient per year increased to 1.4 (P<0.05, as compared to incidence of infection during treatment). There were several complaints regarding taste; however, no side effects were observed overall. Secondary: Not reported
Banovac et al.[20] (1978) Methenamine 1 g BID vs no antimicrobial therapy	OL, PRO Hospitalized patients with spinal cord injury and neurogenic bladder dysfunction treated with intermittent catheterization	N=56 Variable duration	Primary: Frequency of urinary tract infections based on weekly urinalysis and urine culture Secondary: Not reported	Primary: Patients treated with methenamine had 23.4% positive urine cultures compared to 57.5% in the untreated control group (P<0.001). Secondary: Not reported
Lee et al.[21] (2007)	MA	N=2,032 (13 RCT)	Primary: Symptomatic	Primary: Six studies (654 patients) reported symptomatic urinary tract infection

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Methenamine vs placebo or no treatment	At-risk populations for urinary tract infection including, renal tract calculi, women following gynecological operations, men undergoing prostate operations, pregnant women, premenopausal women, postmenopausal women, spinally injured males, recurrent urinary tract infections	5 days to 6 months	urinary tract infection and positive urine culture, quantitative urine culture, adverse reactions Secondary: Not reported	and eight studies (796 patients) reported bacteriuria. Overall, study quality was mixed. The overall pooled estimates for the major outcome measures were not interpretable because of underlying heterogeneity. The evaluation of symptomatic bacteria involved six studies (RR, 0.53; 95% CI, 0.24 to 1.18). The tests of heterogeneity was significant (P=0.003). The sensitivity analysis did not reveal any difference in overall effect when missing urine tests were assumed to be positive (RR, 0.53; 95% CI, 0.24 to 1.17) The evaluation of bacteruria analysis involved eight studies (RR, 0.67; 95% CI, 0.45 to 0.99). The Q test was significant using a random effects model indicating heterogeneity (P=0.0002). Subgroup analyses suggested that methenamine hippurate may have some benefit in patients without renal tract abnormalities (symptomatic urinary tract infection: RR, 0.24; 95% CI, 0.07 to 0.89; bacteriuria: RR, 0.56; 95% CI, 0.37 to 0.83), but not in patients with known renal tract abnormalities (symptomatic urinary tract infection: RR, 1.54; 95% CI, 0.38 to 6.20; bacteriuria: RR, 1.29; 95% CI, 0.54 to 3.07). For short-term treatment duration (one week or less) there was a significant reduction in symptomatic urinary tract infection in those without renal tract abnormalities (RR, 0.14; 95% CI, 0.05 to 0.38). The rate of adverse events was low. Nausea was the most common symptom and was noted in 12 patients from a total of six studies. Secondary: Not reported
Bourque et al.[22] (1956) Methenamine mandelate 1 g TID to QID	CS, OS Patients admitted to the hospital for urological study	N=100 Duration not specified	Primary Effectiveness based on nature of the condition, on the infecting organism, and in relation to	Primary Seventy-one cases were chronic infections and 29 were common, acute urinary infections. Of the chronic cases, 41% had complete urine sterilization, 21% had partial sterilization, and 38% showed no bacteriological change. Of the acute cases, 59% had complete sterilization, 24% had partial sterilization, and 17% showed no bacteriological change.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs no antimicrobial therapy			duration, urinary pH, and side effects Secondary: Not reported	The efficacy result was lowest at 33% for cases infected by streptococci. Efficacy rates ranged between 50 and 100% for all other infecting organisms. The shortest period in which urine was completely sterilized was three days, and the longest was 28 days. Methenamine mandelate demonstrated 80% effectiveness in acidic urine. There were two reports of burning on micturition and two reports of gastric distress. Secondary: Not reported
Kevorkian et al.[23] (1984) Methenamine mandelate vs placebo	PC Patients with neurogenic bladder dysfunction in a program of intermittent catheterization and bladder retraining	N=39 Duration not specified	Primary Development of infection during trial Secondary: Not reported	Primary Fifty-three percent of patients receiving methenamine mandelate (9/17) became infected compared to 86% in the placebo group (19/22; P<0.02). Secondary: Not reported
Vainrub et al.[24] (1977) Methenamine mandelate 1 g and ascorbic acid 1 g every six hours vs no antimicrobial therapy	PRO Paraplegic or quadriplegic inpatient men on the spinal cord unit with previously documented episodes of urinary infection who currently had an indwelling catheter or had one at some point in the past	N=32 5 days	Primary CFU per milliliter, leukocytes per milliliter, and pH for patients who had indwelling Foley or suprapubic catheters, and for those who were on a program of intermittent straight catheterization	Primary There was no significant difference between before and during treatment results for CFU and leukocyte per milliliter (P>0.7) or pH (P>0.3). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: Not reported	
Olsen et al.[25] (1983) Methenamine hippurate 1 g BID for six days vs cefotaxime 750 mg at the start of the operation, then BID for five days	RCT Men 52 to 90 years of age with urinary tract infection and benign prostatic hyperplasia undergoing transurethral prostatic resection	N=42 6 days	Primary: Clinical and bacteriological efficacy Secondary: Not reported	Primary: Postoperative temperature elevation (greater than 38ºC) occurred in one of the 22 patients in the cefotaxime group (4.5%), and in nine of the 20 in the methenamine hippurate group (45%; P<0.05). Fifty-nine percent of patients in the cefotaxime group responded to treatment (13/22 patients) compared to 5% in the methenamine hippurate group (1/20 patients; P<0.005). Secondary: Not reported
Brumfitt et al.[26] (1991) Methenamine hippurate 1 g BID vs nitrofurantoin 50 mg BID	RCT Female patients suffering from recurrent urinary infections	N=99 Up to 1 year	Primary: Number of patients experiencing no symptomatic episodes by monthly microbiological and clinical response Secondary: Not reported	Primary: Fifty-eight percent of patients receiving nitrofurantoin remained free of symptoms compared to 27% of patients receiving methenamine hippurate. Ninety-one percent of nitrofurantoin-treated patients remained abacteriuric while on therapy vs 67% of methenamine-treated patients. Twenty-eight percent of patients discontinued nitrofurantoin therapy compared to 3.5% of patients receiving methenamine. Nausea was the most frequently occurring adverse event in the nitrofurantoin group compared to the methenamine group. Secondary: Not reported
Kasanen et al.[27] (1982) Methenamine hippurate	PC, RCT Patients with recurrent urinary tract infections	N=290 1 year	Primary: Recurrence of urinary tract infections	Primary: Urinary tract infections recurred in 63.2% of patients given placebo compared to 34.2% of patients receiving methenamine hippurate, 25.0% of patients receiving nitrofurantoin, and 10.4% of patients treated with trimethoprim.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs nitrofurantoin vs trimethoprim vs placebo			Secondary: Not reported	Adverse events were mild and occurred most commonly in patients receiving nitrofurantoin (13.9 vs 2.9% with placebo, 4.1% with methenamine hippurate, and 3.9% with trimethoprim. Patients who withdrew were in the nitrofurantoin group (1.4%) or methenamine hippurate group (2.7%). Secondary: Not reported
Kuhlemeier et al.[28] (1985) Methenamine hippurate 1 g BID vs nitrofurantoin macrocrystals 50 mg TID vs SMX-TMP 400-80 mg BID vs nalidixic acid 500 mg QID vs ascorbic acid 1 g	MC Male hospitalized patients, free of indwelling catheters, with spinal cord injury who had experienced at least one bout of bacteriuria	N=161 Duration not specified	Primary: Prevention of future bacteriuria Secondary: Not reported	Primary: There was no statistically significant difference between all agents in preventing bacteriuria (P>0.05). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
QID				
Pfau et al.[29] (1992) Nitrofurantoin macrocrystals 50 mg single-dose vs cephalexin 250 mg single-dose	PRO Pregnant women with a history of urinary tract infections (and, in some instances, pyelonephritis) for postcoital prophylaxis	N=33 5 to 11 months	Primary: Incidence of urinary tract infections Secondary: Not reported	Primary: Urinary tract infections (130) occurred before prophylaxis (mean duration of observation: seven months) compared to only a single urinary tract infection occurring during pregnancy post-prophylaxis. Both nitrofurantoin macrocrystals and cephalexin reached high bacterial concentrations in the urinary tract and induced minimal to zero resistance in the introital gram-negative bacterial flora. Secondary: Not reported
Raz et al.[30] (1991) Nitrofurantoin 50 mg QD for six months vs norfloxacin 200 mg QD for six months	PRO Women ≥16 years of age with a history of at least three documented episodes of urinary tract infection during the last six months	N=102 6 months	Primary: Clinical bacteriological infections (defined as the isolation of an organism in quantitative counts of $>10^5$ CFU/mL; presence of dysuria, frequency or urgency, and/or suprapubic tenderness), drug-related side effects Secondary: Not reported	Primary: Urine samples were sterile in 70.7% of patients treated with nitrofurantoin and 92.4% of patients treated with norfloxacin (P<0.005); 65% of patients receiving nitrofurantoin remained free of symptoms compared to 81% of women receiving norfloxacin (P=0.05). The incidence of urinary tract infections after initiation of prophylaxis decreased from three episodes per six months before nitrofurantoin treatment to 0.03 episodes per six months after prophylaxis; and the incidence of urinary tract infections decreased from 3.1 episodes per six months before norfloxacin treatment to 0.02 episodes per six months after prophylaxis (P<0.005). Side effects occurred in 15% of women receiving norfloxacin and 17% of women given nitrofurantoin, with more severe effects reported with nitrofurantoin treatment (four patients discontinued treatment). Secondary: Not reported
Brumfitt et al.[31] (1985) Nitrofurantoin macrocrystals 100 mg QD for 12	RCT Patients with history of at least three urinary tract infections within the	N=72 12 months	Primary: Symptomatic attacks, bacteriuria Secondary: Not reported	Primary: Mean interval between symptomatic attacks from the pretreatment period was increased threefold while on either nitrofurantoin macrocrystals or trimethoprim treatment. Fifty-nine percent of patients receiving nitrofurantoin macrocrystals

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
months vs trimethoprim 100 mg QD for 12 months	previous 12 months			remained abacteriuric and asymptomatic throughout treatment vs 24% receiving trimethoprim (P<0.05). Treatment with nitrofurantoin macrocrystals was more effective at preventing bacteriuria compared to trimethoprim (P<0.05). Resistance was noted at a rate of approximately 5% per month in patients given trimethoprim, whereas no resistance occurred in patients given nitrofurantoin macrocrystals. Patients receiving nitrofurantoin macrocrystals reported more side effects compared to those receiving trimethoprim (40.0 vs 18.4%, respectively; P<0.05). Secondary: Not reported
Bendstrup et al.[32] (1990) Nitrofurantoin 1 to 1.5 mg/kg QD vs trimethoprim 2 to 3 mg/kg QD	DB, MC, RCT Children one to 14 years of age with recurrent urinary tract infections and urinary tract abnormalities	N=130 5 to 6.5 months	Primary: Urinary tract infections-free periods demonstrated by actuarial percentage recurrence-free curves Secondary: Not reported	Primary: In patients with abnormal urography and/or reflux, nitrofurantoin was associated with greater prophylaxis efficiency (P=0.0025); but there was no difference between nitrofurantoin and trimethoprim for prophylaxis in patients without urinary abnormalities. Following prophylaxis, there was no difference in actuarial percentage recurrence-free curves between the two groups (P=0.92). Patients receiving trimethoprim for prophylaxis were found to have 76% trimethoprim-resistant bacteria during prophylaxis, as compared to 8% before (P<0.0001) and 17% after prophylaxis (P<0.0001). Nitrofurantoin did not alter the pattern of resistance or bacteriological constellation. Side effects were reported in 37% of patients receiving nitrofurantoin vs 21% receiving trimethoprim (P=0.05); nitrofurantoin-treated patients most commonly reported gastrointestinal symptoms. Secondary: Not reported
Stamm et al.[33] (1980)	DB, PC	N=60	Primary: Infections per	Primary: Infections per patient-year were comparable in patients receiving

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Nitrofurantoin macrocrystals 100 mg QD vs trimethoprim 100 mg QD vs SMX-TMP 200-40 mg QD vs placebo	Women with history of urinary tract infection in preceding year	6 months	patient year Secondary: Not reported	nitrofurantoin macrocrystals (0.14), trimethoprim (0), or SMX-TMP (0.15), and occurred more frequently in the placebo group (2.8; P<0.001 for placebo vs each treatment regimen). Infections were more likely to develop following prophylaxis in women who had had three or more infections in the year prior to prophylaxis (P<0.005). Infections with pathogens other than *E coli* occurred more frequently following prophylaxis (P<0.05). Secondary: Not reported
Goettsch et al.[34] (2004) Nitrofurantoin vs trimethoprim vs norfloxacin	RETRO Women 15 to 65 years of age who received a first course (three, five, or seven days) of trimethoprim, nitrofurantoin or norfloxacin	N=16,703 Up to 31 days after the end of the initial treatment	Primary: Failure of initial treatment (defined by the need for additional treatment) Secondary: Not reported	Primary: Over 14% of total patients required a new prescription within 31 days after the end of initial treatment. Treatment failures were seen in 18.9% in patients who received a three-day course of nitrofurantoin and 15.6% in patients who received a three-day course of trimethoprim. Five days of treatment with nitrofurantoin macrocrystals, trimethoprim, or norfloxacin resulted in failure rates of 13.1, 13.2, and 12.3%, respectively. Norfloxacin for seven days demonstrated an 8.5% failure rate. Secondary: Not reported
Rajkumar et al.[35] (1988) Trimethoprim 10	PRO Children with repeated colony	N=112 10 days	Primary: Cure (absence of significant bacterial growth at	Primary: The cure rate was 100% for patients treated with trimethoprim compared to 100% for the SMX-TMP group (P>0.05), 93% for the sulfamethoxazole group (P<0.05), and 63% for the ampicillin group

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/kg QD for 10 days vs SMX-TMP 40-8 mg/kg QD for 10 days vs sulfamethoxazole 150 mg/kg QD for 10 days vs ampicillin 100 mg/kg QD for 10 days	counts of greater than 100,000 CFU/mL of the same organism grown in two to three consecutive clean catch specimens		end of treatment), failure (persistence of pathogens during therapy), relapse (regrowth of same organism within 28 days), recurrence (positive growth 28 days after therapy onset), side effects Secondary: Not reported	(P<0.01). The trimethoprim and SMX-TMP groups had no failures whereas the sulfamethoxazole and ampicillin groups had a 7% (P<0.05) and 37% (P<0.01) rate of failure, respectively. Relapses occurred in 4% of the trimethoprim-treated patients whereas the SMX-TMP group had a 7% relapse rate (P>0.05); sulfamethoxazole and ampicillin groups were not associated with any relapses. The trimethoprim group had 7% recurrence compared to 6% with SMX-TMP, 4% with sulfamethoxazole and 7% with ampicillin (P>0.05). GI side effects and skin rashes were not encountered in the trimethoprim group; white blood cell depression was the lowest in the trimethoprim group. Secondary: Not reported
Brumfitt et al.[36] (1972) Trimethoprim 200 mg BID for seven days vs SMX-TMP 800-160 mg BID for seven days vs ampicillin 1 g BID for seven days	PRO Pregnant patients with bacteriuria, hospitalized patients, and patients in general practice	N=96 6 weeks	Primary: Cure rates Secondary: Not reported	Primary: In pregnancy, the cure rates were equal (85%) with trimethoprim and SMX-TMP, 65% with ampicillin, and 78% with cephalexin (P value NS). In hospitalized patients, there was no significant difference in cure rates between the various treatment groups, which were 73% with trimethoprim, 84% with SMX-TMP, 67% with ampicillin, and 62% with cephalexin. In general practice, trimethoprim was associated with a 96% cure rate compared to 81% in the SMX-TMP group, 89% in the ampicillin group, and 62% in the cephalexin group. Results for cephalexin were significantly lower than the other groups (P<0.02). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs cephalexin 1 g BID for seven days				
Urinary Tract Infections (Uncomplicated)				
Estebanez et al.[37] (2009) Fosfomycin 3 g as a single dose vs amoxicillin-clavulanate 500 mg TID for seven days	PRO Pregnant women with asymptomatic	N=109 End of pregnancy	Primary: Microbiologic cure (defined by sterilized urine culture) Secondary: Rate of reinfection, recurrence, persistence, adverse events, and compliance	Primary: Microbiologic cure occurred in 80.37% of the amoxicillin-clavulanate group and 83.01% in the fosfomycin group (RR, 1.195; 95% CI, 0.451 to 3.165; P=0.72). Secondary: There was one reinfection in the fosfomycin group and eight in the amoxicillin-clavulanate group (RR, 0.13; 95% CI, 0.02 to 0.81; P=0.045). There was one recurrence in each group (RR, 1.06; 95% CI, 0.11 to 10.12; P=0.96). Five patients had persistent infections in the fosfomycin group vs two in the amoxicillin-clavulanate group (RR, 2.64; 95% CI, 0.59 to 11.79; P=0.39). One patient in the fosfomycin group and 11 patients in the amoxicillin-clavulanate group experienced adverse events (RR, 0.10; 95% CI, 0.01 to 0.72; P=0.008). There were five cases of non-compliance with amoxicillin-clavulanate and none with fosfomycin (RR, 0.00; 95% CI, 0.00 to 0.81; P=0.076).
Usta et al.[38] (2011) Fosfomycin 3 g as a single dose vs cefuroxime 500 mg	RCT Pregnant women ≥12 weeks gestation with uncomplicated lower urinary tract infections (bacteriuria and/or pyuria and positive	N=90 2 weeks	Primary: Clinical success (defined as resolution of symptoms); microbiologic cure Secondary: Not reported	Primary: There was no significant difference in clinical success rates between the treatment groups after two weeks. Clinical success rates were 78.6, 77.8, and 86.2% for the fosfomycin, amoxicillin-clavulanate and cefuroxime groups, respectively (P=NS). Microbiologic cure rates were 82.1, 81.5 and 89.7% in the fosfomycin, amoxicillin-clavulanate and cefuroxime groups, respectively (P>0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
BID for five days vs amoxicillin-clavulanate 625 mg BID for five days	urine culture)			Compliance was significantly higher in the fosfomycin group (100%) compared to the amoxicillin-clavulanate (77.8%) or cefuroxime (82.8%) (P<0.05). The most common adverse event was diarrhea with an incidence of 10.7% in the fosfomycin group, 11.1% in the amoxicillin-clavulanate group and 6.9% in the cefuroxime group. There was no significant difference between the groups with respect to adverse events. Secondary: Not reported
Elhanan et al.[39] (1994) Fosfomycin 3 g as a single-dose vs cephalexin 500 mg QID for five days	RCT Women ≥16 years of age with acute uncomplicated cystitis (symptoms of dysuria, frequency/urgency of urination, absence of fever/flank pain, pyuria, $\geq 10^5$ CFU/mL of an organism sensitive to both antibiotics)	N=112 5 days to 1 month	Primary: Clinical cure, microbiological cure Secondary: Not reported	Primary: At the five day follow-up, 91% of patients receiving fosfomycin and 91% of patients receiving cephalexin were considered clinically cured (P=NS); at one month, 86 and 78% were considered cured, respectively (P=NS). In terms of microbiological cure, 91% of fosfomycin-treated patients compared to 83% of cephalexin-treated patients were cured at five days; 81% of fosfomycin-treated patients compared to 68% of cephalexin-treated patients were cured at one month. Secondary: Not reported
Stein et al.[40] (1999) Fosfomycin 3 g as a single-dose vs nitrofurantoin monohydrate-macrocrystals 100 mg capsules BID	DB, RCT Females ≥12 years of age with symptoms of acute uncomplicated urinary tract infection	N=749 6 weeks	Primary: Bacteriologic response (cure, failure, relapse, or reinfection), clinical response (cure, improvement, or failure) at each visit Secondary:	Primary: The bacteriologic cure rate at visit two (five to 11 days after initial treatment dose) was 78.1% with fosfomycin and 86.3% with nitrofurantoin (P=0.02); at visit three (five to 11 days after last day of medication) the cure rate was 86.9% with fosfomycin and 80.9% with nitrofurantoin (P=0.17); at visit four (four to six weeks after last day of medication) the cure rate was 96% with fosfomycin and 91.1% with nitrofurantoin (P=0.18). There were no statistically significant differences between fosfomycin and nitrofurantoin in terms of clinical outcomes at any visit (P=0.3 to 0.91).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
for seven days			Not reported	Most commonly occurring adverse drug reactions in the fosfomycin group were diarrhea (2.4%), vaginitis (1.8%), and nausea (0.8%). The most common adverse drug reactions with nitrofurantoin were nausea (1.6%), vaginitis (1.6%), dizziness (0.8%), and diarrhea (0.8%). Seven patients in the fosfomycin group discontinued therapy (1.9%) vs 16 patients receiving nitrofurantoin (4.3%). Secondary: Not reported
Van Pienbrook et al.[41] (1993) Fosfomycin 3 g as a single-dose vs nitrofurantoin 50 mg QID for seven days	DB, MC, RCT Patients with acute, uncomplicated cystitis (acute dysuria, stranguria, and/or urinary frequency)	N=231 42 days	Primary: Clinical cure rates (resolution of symptoms based on patient's judgment), bacteriological cure rates at four, nine, and 42 days after treatment start Secondary: Not reported	Primary: No difference in clinical cure rates was seen between fosfomycin-treated patients and nitrofurantoin-treated patients at day four (94 vs 95%, respectively), day nine (95 vs 94%, respectively), or at day 42 (82 vs 80%, respectively; P>0.05 for all). Bacteriological assessments, based on difference in dipslide results at follow-up visits were NS. By day four, 43% of patients receiving fosfomycin reported side effect(s) vs 25% of patients given nitrofurantoin (P=0.00); most common adverse events were gastrointestinal complaints and were generally mild. At day nine, there was no difference in the incidence of side effects between fosfomycin and nitrofurantoin groups (20 vs 16%, respectively; P=NS). Secondary: Not reported
Ferraro et al.[42] (1990) Fosfomycin 3 g as a single-dose vs norfloxacin 400 mg	OL, RCT Elderly patients with uncomplicated lower urinary tract infection	N=60 Up to 25 to 35 days	Primary: Clinical resolution rate, bacteriological resolution rate Secondary: Not reported	Primary: Clinical and bacteriological resolution rates were 76.6% for patients treated with fosfomycin and 73.3% for patients treated with norfloxacin (P>0.05). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
BID for seven days				
Naber et al.[43] (1992) Fosfomycin 3 g as a single-dose vs SMX-TMP 1.92 g single-dose vs ofloxacin 200 mg single-dose	MC, RCT, SB Urine cultures of women with acute uncomplicated cystitis	N=349 7 days	Primary: Eradication of baseline pathogens based on urine culture Secondary: Not reported	Primary: At one week, baseline pathogens were eradicated in 87.1% of fosfomycin-treated patients, 88.9% of SMX-TMP-treated patients, and 86.4% of ofloxacin-treated patients. Secondary: Not reported
Naber et al.[44] (1990) Fosfomycin 3 g as a single-dose vs SMX-TMP 1.92 g single-dose vs ofloxacin 200 mg single-dose	RCT, SB Female patients with acute uncomplicated urinary tract infection	N=562 4 weeks	Primary: Clinical improvement based on amount of baseline bacteriuria Secondary: Not reported	Primary: Clinical improvement for patients with significant bacteriuria was seen in 94.7% of patients receiving fosfomycin, 94% of patients receiving SMX-TMP, and 95.4% of patients given ofloxacin at up to one week. Clinical improvement was seen in 81.9% of patients receiving fosfomycin, 79.4% of patients receiving SMX-TMP, and 80.8% of patients given ofloxacin at up to four weeks. Clinical improvement for patients with low count bacteriuria was demonstrated in 95.2% of patients receiving fosfomycin, 96.4% of patients receiving SMX-TMP, and 93.7% of patients given ofloxacin. In patients with no bacteriuria, clinical improvement was possible in 81.8% of patients given fosfomycin, 100% of patients taking SMX-TMP, and 100% of patients taking ofloxacin. Secondary: Not reported
Davis et al.[45] (1990)	DB, DD, RCT	N=55	Primary: Bacteriological	Primary: Patients receiving fosfomycin demonstrated 77.3% eradication of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Fosfomycin 3 g as a single-dose vs trimethoprim 200 mg single-dose	Non-pregnant adult women with symptoms of urinary tract infection (frequency, dysuria)	6 weeks	eradication, recurrence, reinfection, persistence of infection Secondary: Not reported	infection compared to 54.5% of patients treated with trimethoprim. Nine percent of fosfomycin-treated patients vs 4.5% of nitrofurantoin-treated patients had recurrence. Nine percent of fosfomycin-treated patients vs 4.5% of nitrofurantoin-treated patients had reinfection. Persistence was noted in 5% of fosfomycin-treated patients compared to 36% of trimethoprim-treated patients. Secondary: Not reported
Iravani et al.[46] (1999) Nitrofurantoin monohydrate-macrocrystals 100 mg BID for seven days vs SMX-TMP 800-160 mg tablets BID for seven days vs ciprofloxacin 100 mg tablets BID for three days	DB, MC, PRO, RCT Women ≥18 years of age with primary diagnosis of acute, symptomatic, uncomplicated urinary tract infection; confirmed by a positive urine culture within 48 hours of study onset, signs and symptoms of dysuria, pyuria, and urinary frequency for <10 days	N=713 Up to 6 weeks	Primary: Pathogen eradication after four to 10 days of therapy, clinical response rate (resolution of symptoms), relapse rate, adverse events Secondary: Not reported	Primary: Bacterial eradication was similar in the three treatment groups (ciprofloxacin, 88%; SMX-TMP, 93%; and nitrofurantoin, 86%). At the four to six week follow-up, ciprofloxacin had statistically higher eradication rates (91%) compared to SMX-TMP (79%; 95% CI, –20.6 to –3.9) and nitrofurantoin (82%; 95% CI, –17.1 to –0.9). Clinical resolution four to 10 days after therapy initiation and at the four to six week follow-up was similar among the three treatment groups. The frequency of adverse effects was not statistically different among the three treatment groups (P=0.093). However, ciprofloxacin caused fewer incidences of nausea compared to either of the other medications (P<0.001). Secondary: Not reported
Hooten et al.[47] (1995) Nitrofurantoin	PRO, RCT Women with acute uncomplicated	N=149 6 weeks	Primary: Cure, persistence of bacteriuria	Primary: At six weeks, the cure rate was 82% in patients treated with SMX-TMP, 61% in patients treated with nitrofurantoin (P=0.04 vs SMX-TMP), 67% in patients given amoxicillin (P=0.11 vs SMX-TMP), and 66% in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
macrocrystals 100 mg QID for three days vs SMX-TMP 800-160 mg BID for three days vs amoxicillin 500 mg TID for three days vs cefadroxil 500 mg BID for three days	cystitis		Secondary: Not reported	patients treated with cefadroxil (P=0.11 vs SMX-TMP). Persistence of significant bacteriuria was seen with 3% of patients receiving SMX-TMP, 16% of patients receiving nitrofurantoin (P=0.05 vs SMX-TMP), 14% of patients given amoxicillin (P=0.11 vs SMX-TMP), and 0% in patients receiving cefadroxil. Adverse events were seen in 43% of patients receiving nitrofurantoin, 35% of patients receiving SMX-TMP, 25% of patients given amoxicillin, and 30% in patients receiving cefadroxil. Secondary: Not reported
Gupta et al.[48] (2007) Nitrofurantoin monohydrate-macrocrystals 100 mg BID for five days vs SMX-TMP 800-160 mg tablets BID for three days	OL, RCT Women 18 to 45 years of age who were not pregnant, who were in good general health, and who had symptoms of acute cystitis (dysuria, frequency, and/or urgency) and a urine culture with at least 102 CFU/mL of a uropathogen	N=338 35 days	Primary: Clinical cure rate at the end of the entire study period (30 days after therapy) Secondary: Clinical and microbiological cure rates at the early follow-up visit (five to nine days after therapy)	Primary: Clinical cure was achieved in 79% of the SMX-TMP group and in 84% of the nitrofurantoin group (95% CI, -13% to 4%; P=0.25). Secondary: Clinical and microbiological cure rates at the first follow-up visit were similar in the SMX-TMP group and the nitrofurantoin group. Among women treated with SMX-TMP, there was a statistically significant decrease in clinical cure in women who had SMX-TMP–non-susceptible uropathogen compared to women who had a susceptible isolate. Overall, 84% of SMX-TMP–treated women with a SMX-TMP–susceptible uropathogen had a clinical cure compared to 41% with a SMX-TMP–non-susceptible uropathogen (P<0.001). Microbiological cure was achieved in 97% of SMX-TMP–treated women with a SMX-TMP–susceptible isolate vs 65% of women with a SMX-TMP–non-susceptible isolate (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Kasanen et al.[49] (1981) Trimethoprim 160 mg BID for seven days vs cephalexin 500 mg BID for seven days	MC, RCT Patients with acute urinary tract infections	N=241 6 weeks	Primary: Resolution of urinary tract infections, recurrence of urinary tract infection Secondary: Not reported	Primary: Three days after discontinuation of treatment, 98.3% of patients receiving trimethoprim demonstrated resolution of urinary tract infection compared to 82.1% of patients given cephalexin. Urinary tract infection recurred in 15.2% of trimethoprim-treated patients and 30.9% of cephalexin-treated patients after 6 weeks (P<0.025). Secondary: Not reported
Newsom et al.[50] (1986) Trimethoprim 200 mg BID for five days vs ciprofloxacin 100 mg BID for five days	PRO Elderly patients with urinary tract infections	N=40 5 days	Primary: Clinical and microbiological outcome at day five Secondary: Not reported	Primary: During ciprofloxacin therapy all patients had sterile urine and five days later only one patient had reinfection with *E coli*. In the trimethoprim group, the urine did not clear and only in one patient and was found to be a resistant organism. Secondary: Not reported
Treatment of *Pneumocystis jiroveci* Pneumonia				
Medina et al.[51] (1990) Dapsone 100 mg QD plus trimethoprim 20 mg/kg QD vs sulfamethoxazole 100 mg/kg QD plus trimethoprim 20	MA Patients with acquired immunodeficiency syndrome and mild-to-moderately-severe new onset *Pneumocystis jiroveci* pneumonia, and whose room air PAO_2-PaO_2 was 60 mm Hg or greater	33 trials Mean 21 days	Primary: Therapeutic failure, discontinuation of therapy due to treatment-related adverse effects Secondary: Not reported	Primary: Treatment failure was observed in three patients treated with SMX-TMP and two patients on dapsone-based regimen (P>0.3). More patients in the SMX-TMP group (57%) required a change of therapy due to intolerable adverse effects compared to the dapsone-based regimen group (30%; P<0.025). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/kg QD				
Miscellaneous				
Falagas et al.[52] (2010) Fosfomycin vs other antibiotics	MA Patients with microbiologically confirmed cystitis or suspicion of cystitis	N=1,657 (27 trials) 1 day to 18 months posttreatment	Primary: Clinical success (defined as complete cure and/or non-complete [improvement] resolution of symptoms Secondary: Microbiologic success (defined as eradication); microbiologic relapse; microbiologic reinfection; adverse events	<u>Non-pregnant females</u> Primary: There was no difference in clinical success among patients treated with fosfomycin compared to other treatments (RR, 1.00; 95% CI, 0.96 to 1.03). Secondary: There was no difference in microbiological success, microbiologic relapse or microbiologic reinfection among patients treated with fosfomycin compared to other treatments. There was no difference in adverse events or study withdrawal rates. <u>Non-pregnant females and males</u> Primary: There was no difference in clinical success among patients treated with fosfomycin compared to other treatments (RR, 0.98; 95% CI, 0.87 to 1.11). Secondary: There was no difference in microbiological success rates among the treatment groups (RR, 1.01; 95% CI, 0.88 to 1.17). There was no difference in adverse events or study withdrawal rates. <u>Pregnant females</u> Primary: There was insufficient data to analyze the primary outcome. Secondary: There was no difference in microbiological success rates among the treatment groups (RR, 1.00; 95% CI, 0.96 to 1.05). Pregnant women had fewer adverse events in the fosfomycin group vs all comparators (RR, 0.35; 95% CI, 0.12 to 0.97).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				<u>Pediatric patients</u> Primary: There was insufficient data to analyze the primary outcome. Secondary: There was no difference in microbiological success rates among the treatment groups (RR, 0.98; 95% CI, 0.92 to 1.05). There was no difference in adverse events or study withdrawal rates. <u>Other considerations</u> There was no difference in microbiological success between single-dose fosfomycin and single-dose comparator regimens. There was no difference in microbiological success between single-dose fosfomycin and longer comparator regimens.

Drug regimen abbreviations: BID=twice daily, IV=intravenous, QD=once daily, QID=four times daily, TID=three times daily
Study abbreviations: CI=confidence interval, CS=case studies, DB=double-blind, DD=double-dummy, MA=meta-analysis, MC=multicenter, NS=not significant, OBS=observational, OL=open-label, OS=observational study, PC=placebo-controlled, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, SB=single blind, XO=cross-over
Miscellaneous abbreviations: *C difficile=Clostridium difficile,* CFU=colony-forming units, SMX-TMP=sulfamethoxazole and trimethoprim

Additional Evidence

Dose Simplification
Trimethoprim administered as a single dose, or over the course of seven days, was evaluated in female patients with symptoms of lower urinary tract infection and positive bacteriuria.[53] Short-term efficacy was 82% for single-dose therapy and 94% for the seven-day regimen (P<0.001). Accumulated efficacy was 71% for single-dose and 87% for seven-day therapy (P<0.001). Adverse events were noted less frequently with single-dose therapy; however, this was not significant. van Merode et al. evaluated microbiological and clinical cure rates with trimethoprim administered over three days or five days in women with urinary tract infections. There was no significant difference in bacteriological cure rates between the three-day and five-day treatment regimens. After completing the three-day regimen, 44% of women considered themselves "not recovered" due to persistence of symptoms compared to 35% of women receiving the five-day treatment (P>0.05).[54]

Stable Therapy
A search of Medline and PubMed did not reveal data pertinent to this topic.

Impact on Physician Visits
A search of Medline and PubMed did not reveal data pertinent to this topic.

IX. Cost

A "relative cost index" is provided below as a comparison of the average cost per prescription for medications within this American Hospital Formulary Service (AHFS) drug class. To differentiate the average cost per prescription from one product to another, a specific number of '$' signs from one to five is assigned to each medication. Assignment of relative cost values is based upon current Alabama Medicaid prescription claims history and the average cost per prescription as paid at the retail pharmacy level. For brand or generic products with little or no recent utilization data, the average cost per prescription is calculated by using the Alabama Medicaid average acquisition cost (AAC) and the standard daily dosing per product labeling. Please note that the relative cost index does not factor in additional cost offsets available to the Alabama Medicaid program via pharmaceutical manufacturer rebating.

The relative cost index scale for this class is as follows:

Relative Cost Index Scale	
$	$0-$30 per Rx
$$	$31-$50 per Rx
$$$	$51-$100 per Rx
$$$$	$101-$200 per Rx
$$$$$	Over $200 per Rx

Rx=prescription

Table 12. Relative Cost of the Urinary Anti-infectives

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Fosfomycin	packet	Monurol®	$$$$	N/A
Methenamine	tablet	Hiprex®*	$$$$	$$$
Nitrofurantoin	suspension	Furadantin®*	$$$$	$$$$$
Nitrofurantoin macrocrystals	capsule	Macrodantin®*	$$$$	$$
Trimethoprim	solution, tablet	Primsol®	$$$	$
Combination Products				
Methenamine, methylene blue, phenyl salicylate, sodium phosphate, and hyoscyamine	capsule, tablet	Urin D.S.®*, Urimar T®, Utica C®*	$$$$	$
Methenamine and sodium phosphate	tablet	Uroqid-Acid No.2®	$$	N/A
Methenamine, sodium	tablet	N/A	N/A	$$

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
phosphate, methylene blue, and hyoscyamine				
Nitrofurantoin and nitrofurantoin macrocrystals	capsule	Macrobid®*	$$$	$$

*Generic is available in at least one dosage form or strength.
N/A=Not available.

X. Conclusions

The urinary anti-infectives are approved for the prophylaxis and treatment of urinary tract infections (UTIs), as well as for the relief of local symptoms associated with infections or caused by diagnostic procedures. Trimethoprim solution is also approved for the treatment of otitis media. There are several single entity and combination products available; each of the agents has a unique mechanism of action and place in therapy. The majority of the products are available in a generic formulation.[1-9]

For the treatment of uncomplicated UTIs, guidelines recommend trimethoprim (with or without sulfamethoxazole), nitrofurantoin, fosfomycin, or a quinolone as initial therapy.[14,15] Methenamine can be used for the treatment of catheter-associated bacteriuria and UTIs in gynecologic surgery patients who are catheterized for less than one week. However, it should not be used to reduce the risk of bacteriuria or UTIs in patients with long-term intermittent or long-term indwelling catheters.[10]

Clinical trials have demonstrated comparable efficacy among the urinary anti-infectives for the prophylaxis and treatment of UTIs.[28,32,33,40,41,45] Relatively few studies have demonstrated greater efficacy with one agent over another.[26,27,31] The urinary anti-infectives have also been shown to be comparable in efficacy to anti-infective agents in other classes.[17,35-39,42-44,46,48,52] There were no studies found that evaluated the efficacy and safety of the methenamine combination products.

There is insufficient evidence to support that one brand urinary anti-infective is safer or more efficacious than another. Formulations without a generic alternative should be managed through the medical justification portion of the prior authorization process.

Therefore, all brand urinary anti-infectives within the class reviewed are comparable to each other and to the generic products in the class (if applicable) and offer no significant clinical advantage over other alternatives in general use.

XI. Recommendations

No brand urinary anti-infective is recommended for preferred status. Alabama Medicaid should accept cost proposals from manufacturers to determine the most cost effective products and possibly designate one or more preferred brands.

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