Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Clinical Packet
November 9, 2016

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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).

Preferred with Clinical Criteria: Listed on the Agency's Preferred Drug Lists but will require a prior authorization. Clinical criteria must be met in order to be approved. For a non-preferred product to be approved, failure with a designated number of preferred agents and clinical criteria must be met.

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
- 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

Preferred Agents

- Requests for preferred agents in the HCV anti-infective class must meet certain clinical criteria, please see Form 415 Criteria instruction booklet.

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®, 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 allergy or contraindication to sofosbuvir.

- For Daklinza®, Harvoni®, Sovaldi®, Technivie®, Viekira Pak®, and Zepatier™ please see separate PA form for specific information.

- For Olysio® in combination with Sovaldi®, please see separate PA Form.

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 (PA)

- 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 9, 2016
9:00 a.m. – 12:00 noon

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1. Opening remarks……..…….....Chair
2. Approval of August 10, 2016 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……..….……...UMass Clinical Pharmacy Services
   - Anthelmintics - AHFS 080800
   - Aminoglycosides - AHFS 081202
   - Cephalosporins - AHFS 081206
   - Miscellaneous β-Lactam Antibiotics - AHFS 081207
   - Chloramphenicol - AHFS 081208
   - Macrolides - AHFS 081212
   - Penicillins - AHFS 081216
   - Quinolones - AHFS 081218
   - Sulfonamides - AHFS 081220
   - Tetracyclines - AHFS 081224
   - Antibacterials, Miscellaneous - AHFS 081228
6. New Drug Reviews…..…….…….UMass Clinical Pharmacy Services
   - Praluent® (Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) Inhibitors - AHFS 240624)
   - Epclusa® (HCV Antivirals - AHFS 081840)
   - Viekira XR® (HCV Antivirals - AHFS 081840)
7. Results of voting announced……...…….....…….Chair
8. New business
   - Election of Committee's Vice Chairperson
   - 2017 P&T Meeting Dates:
     i. February 8, 2017
     ii. May 10, 2017
     iii. August 9, 2017
     iv. November 8, 2017
9. Adjourn

Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Anthelmintics
AHFS Class 080800
November 9, 2016

I. Overview

The anthelmintics are approved for the treatment of cestode, nematode, and trematode infections.[1-6] Infections caused by helminths, or parasitic worms, are among the most prevalent infections in the world and are a leading cause of morbidity.[7] Helminths that parasitize humans are classified into cestodes (tapeworms), nematodes (roundworms), and trematodes (flukes).[7,8] Pinworm infections (*Enterobiasis vermicularis*) are the most common helminthic infections in the United States, followed by *Ascaris lumbricoides*.[9]

Helminths vary with respect to life cycle, bodily structure, localization within the host, epidemiology, and susceptibility to chemotherapy.[8] The population density of the worm burden is an important factor in determining the pathogenicity of the infection.[10] Most infected persons harbor few worms and are asymptomatic or exhibit minimal signs or symptoms of disease.[7] However, persons with large numbers of worms are at risk for severe disease. Children infected with helminths are at risk of malnutrition, impaired growth, and impaired intellectual development. The diagnosis of helminthic infections is based primarily on microscopic examination of stool, urine, blood, other body fluids, and/or tissues.

The anthelmintics act locally to expel worms from the gastrointestinal tract. They also act systemically to eradicate adult helminths or developmental forms that invade organs and tissues.[8] Most human infections, caused by either flukes or intestinal helminths, may be cured or controlled by the available anthelmintic agents. Systemic infections caused by tissue-dwelling helminths may only partially respond to currently available drugs. Acquired resistance to anthelmintics in humans has yet to become a major factor limiting clinical efficacy.

The anthelmintic agents differ with regards to their mechanism of action. Albendazole exhibits inhibitory effects on tubulin polymerization, which results in the loss of cytoplasmic microtubules. Ivermectin binds to glutamate-gated chloride ion channels leading to hyperpolarization of the nerve or muscle cell, which results in paralysis and death of the parasite. Mebendazole irreversibly blocks glucose uptake and other nutrients in susceptible adult intestine-dwelling helminths. Praziquantel induces a rapid contraction of schistosomes by affecting the permeability of the cell membrane, which causes vacuolization and disintegration of the schistosome tegument.[1-6]

The anthelmintics that are included in this review are listed in Table 1. This review encompasses all oral dosage forms and strengths. This class was last reviewed in August 2014.

Table 1. Anthelmintics Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Albendazole	tablet	Albenza®	none
Ivermectin	tablet	Stromectol®*	ivermectin
Mebendazole	chewable tablet	Emverm®	none
Praziquantel	tablet	Biltricide®	none

PDL=Preferred Drug List.

The anthelmintics have been shown to be active against the strains of organisms 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 anthelmintics that are noted in Table 4. 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 antiparasitic 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 Anthelmintics[1-6]

Organism	Albendazole	Ivermectin	Mebendazole	Praziquantel
Cestodes (Tapeworms)				
Echinococcus granulosus	✔			
Taenia solium	✔			
Nematodes (Roundworms)				
Ancylostoma duodenale			✔	
Ascaris lumbricoides			✔	
Enterobius vermicularis			✔	
Necator americanus			✔	
Onchocerca volvulus		✔		
Strongyloides stercoralis		✔		
Trichuris trichiura			✔	
Trematodes (Flukes)				
Clonorchis sinensis				✔
Opisthorchis viverrini				✔
Schistosoma haematobium				✔
Schistosoma japonicum				✔
Schistosoma mansoni				✔
Schistosoma mekongi				✔

II. Evidence-Based Medicine and Current Treatment Guidelines

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

Table 3. Treatment Guidelines Using the Anthelmintics

Clinical Guideline	Recommendation(s)
Infectious Diseases Society of America: **Clinical Practice Guidelines: Management of Encephalitis (2008)[11]** **(Was reviewed and deemed current as of July 2011)**	Empirical therapy • Acyclovir should be initiated in all patients with suspected encephalitis, pending results of diagnostic studies. • Other empirical antimicrobial agents should be initiated on the basis of specific epidemiologic or clinical factors, including appropriate therapy for presumed bacterial meningitis, if clinically indicated. • In patients with clinical clues suggestive of rickettsial or ehrlichial infection during the appropriate season, doxycycline should be added to empirical treatment regimens. Bacteria • *Bartonella bacilliformis:* chloramphenicol, ciprofloxacin, doxycycline, ampicillin, or sulfamethoxazole-trimethoprim is recommended. • *Bartonella henselae:* doxycycline or azithromycin, with or without rifampin, can be considered. • *Listeria monocytogenes:* ampicillin plus gentamicin is recommended; sulfamethoxazole-trimethoprim is an alternative in the penicillin-allergic patient. • *Mycoplasma pneumoniae:* antimicrobial therapy (azithromycin, doxycycline, or a fluoroquinolone) can be considered. • *Tropheryma whipplei:* ceftriaxone, followed by either sulfamethoxazole-trimethoprim or cefixime, is recommended. Helminths • *Baylisascaris procyonis:* albendazole plus diethylcarbamazine can be considered; adjunctive corticosteroids should also be considered. • *Gnathostoma* species: albendazole or ivermectin is recommended. • *Taenia solium:* need for treatment should be individualized; albendazole and

Clinical Guideline	Recommendation(s)
	corticosteroids are recommended; praziquantel can be considered as an alternative. <u>Rickettsioses and ehrlichiosis</u> • *Anaplasma phagocytophilum:* doxycycline is recommended. • *Ehrlichia chaffeensis:* doxycycline is recommended. • *Rickettsia rickettsii:* doxycycline is recommended; chloramphenicol can be considered an alternative in selected clinical scenarios, such as pregnancy. • *Coxiella burnetii:* doxycycline plus a fluoroquinolone plus rifampin is recommended. <u>Spirochetes</u> • *Borrelia burgdorferi:* ceftriaxone, cefotaxime, or penicillin G is recommended. • *Treponema pallidum:* penicillin G is recommended; ceftriaxone is an alternative. <u>Protozoa</u> • *Acanthamoeba:* sulfamethoxazole-trimethoprim plus rifampin plus ketoconazole or fluconazole plus sulfadiazine plus pyrimethamine can be considered. • *Balamuthia mandrillaris:* pentamidine, combined with a macrolide (azithromycin or clarithromycin), fluconazole, sulfadiazine, flucytosine, and a phenothiazine can be considered. • *Naegleria fowleri:* amphotericin B (intravenous and intrathecal) and rifampin, combined with other agents, can be considered. • *Plasmodium falciparum:* quinine, quinidine, or artemether is recommended; atovaquone-proguanil is an alternative; exchange transfusion is recommended for patients with 110% parasitemia or cerebral malaria; corticosteroids are not recommended. • *Toxoplasma gondii:* pyrimethamine plus either sulfadiazine or clindamycin is recommended; sulfamethoxazole-trimethoprim alone and pyrimethamine plus atovaquone, clarithromycin, azithromycin, or dapsone are alternatives. • *Trypanosoma brucei gambiense:* eflornithine is recommended; melarsoprol is an alternative. • *Trypanosoma brucei rhodesiense:* melarsoprol is recommended.
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	• Hematopoietic stem cell transplant candidates with pretransplant screening tests positive for *Strongyloides* species, or those with an unexplained eosinophilia and a travel or residence history indicative of exposure to *Strongyloides stercoralis*, should be empirically treated before transplantation. • The preferred prophylactic treatment is ivermectin 200 µg/kg/day orally for two consecutive days; this regimen is repeated after two weeks. • The alternative prophylactic treatment is albendazole 400 mg orally twice daily for seven days or thiabendazole 25 mg/kg orally twice daily for two days. • Some clinicians advocate preemptive treatment for patients from endemic areas who have no symptoms, no eosinophilia, and negative screening test results. • Indications for empiric treatment for strongyloidiasis before hematopoietic stem cell transplant are the same among children or adults, except for children weighing <15 kg, for whom the preferred drug is thiabendazole.

Clinical Guideline	Recommendation(s)
Infectious Diseases Canada/Centers for Disease Control and Prevention: **Guidelines for Preventing Infectious Complications Among Hematopoietic Stem Cell Transplantation Recipients: A Global Perspective (2009)**[12]	

III. Indications

The Food and Drug Administration (FDA)-approved indications for the anthelmintics 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 Anthelmintics[1-6]

Indication	Albendazole	Ivermectin	Mebendazole	Praziquantel
Cestodes (Tapeworms)				
Cystic hydatid disease of the liver, lung, and peritoneum	✔			
Parenchymal neurocysticercosis due to active lesions	✔			
Nematodes (Roundworms)				
Onchocerciasis		✔		
Strongyloidiasis of the intestinal tract		✔		
Ascariasis (*Ascaris lumbricoides*)			✔	
Hookworm (*Ancylostoma duodenale* and *Necator americanus*)			✔	
Pinworm (*Enterobiasis vermicularis*)			✔	
Whipworm (*Trichuriasis trichiura*)			✔	
Trematodes (Flukes)				
Clonorchiasis (liver flukes)				✔
Opisthorchiasis (liver flukes)				✔
Schistosomiasis, all species				✔

IV. Pharmacokinetics

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

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

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Albendazole	<5	70	Liver	Renal (<1)	8 to 12
Ivermectin	Well absorbed	>99	Liver	Renal (<1); Feces	18
Mebendazole	5 to 10	95	Liver	Renal (2); Feces (98)	1 to 12
Praziquantel	80	80	Liver	Renal (80)	0.8 to 3.0

V. Drug Interactions

Major drug interactions with the anthelmintics are listed in Table 6.

Table 6. Major Drug Interactions with the Anthelmintics[2]

Generic Name(s)	Interaction	Mechanism
Praziquantel	Carbamazepine	Concurrent use of carbamazepine and praziquantel may result in significantly decreased praziquantel plasma concentrations.
Praziquantel	Dexamethasone	Concurrent use of dexamethasone and praziquantel may result in significantly decreased praziquantel plasma concentrations.
Praziquantel	Phenobarbital	Concurrent use of phenobarbital and praziquantel may result in significantly decreased praziquantel plasma concentrations.
Praziquantel	Phenytoin	Concurrent use of phenytoin and praziquantel may result in significantly decreased praziquantel plasma concentrations.
Praziquantel	Rifampin	Rifampin may increase the hepatic metabolism of praziquantel, resulting in reduced plasma levels and possibly producing a loss in therapeutic effect.

VI. Adverse Drug Events

The most common adverse drug events reported with the anthelmintics are listed in Table 7. At recommended dosages, the anthelmintics are generally well tolerated. Some adverse effects may be secondary to the parasitic infection being treated and/or to dead and dying parasites rather than to the drug itself. Such effects may be more frequent and/or severe in patients with a heavy worm burden. Cutaneous and/or systemic reactions of varying severity (Mazzotti reaction) and ocular effects may occur in patients with onchocerciasis receiving macrofilaricidal drugs, such as ivermectin. Patients with onchocerciasis who are also heavily infected with *Loa loa* may develop serious or fatal neurologic events (e.g., encephalopathy and coma) either spontaneously or following rapid killing of microfilariae with macrofilaricidal agents.

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

Adverse Events	Albendazole	Ivermectin	Mebendazole	Praziquantel
Cardiovascular				
Arrhythmia	-	-	-	✔
Chest discomfort	-	<1	-	-
Dyspnea	-	<1	-	-
Facial edema	-	1	-	-
Hypotension	-	<1	-	-
Orthostatic hypotension	-	1	-	-
Peripheral edema	-	✔	-	-
Tachycardia	-	4	-	-
Central Nervous System				
Asthenia	-	<1	-	✔
Coma	-	✔	-	-
Confusion	-	✔	-	-
Dizziness	1	3	✔	✔
Drowsiness	-	✔	✔	-
Fatigue	-	<1	-	-
Fever	1	-	-	✔
Headache	1 to 11	<1	✔	✔
Increased intracranial pressure	0 to 2	-	-	-
Insomnia	-	-	-	-
Lethargy	-	✔	-	-
Malaise	-	-	-	✔
Meningeal signs	1	-	-	-

Adverse Events	Albendazole	Ivermectin	Mebendazole	Praziquantel
Mental status changes	-	✔	-	-
Seizures	-	✔	✔	✔
Somnolence	-	<1	-	✔
Stupor	-	✔	-	-
Tremor	-	✔	-	-
Vertigo	1	<1	-	✔
Dermatological				
Alopecia	<1 to 2	-	✔	-
Erythema multiforme	✔	-	-	-
Pruritus	-	3	✔	✔
Rash	<1	<1	✔	-
Stevens-Johnson syndrome	✔	✔	✔	-
Toxic epidermal necrolysis	-	✔	✔	-
Urticaria	<1	<1	✔	✔
Gastrointestinal				
Abdominal pain	0 to 6	<1	✔	✔
Anorexia	-	<1	-	✔
Constipation	-	<1	-	-
Diarrhea	-	2	✔	✔
Fecal incontinence	-	✔	-	-
Nausea	4 to 6	2	-	-
Vomiting	4 to 6	<1	✔	✔
Genitourinary				
Acute renal failure	✔	-	-	-
Glomerulonephritis	-	-	✔	-
Hematuria	-	-	✔	-
Urinary incontinence	-	✔	-	-
Hematologic				
Anemia	-	✔	-	-
Agranulocytosis	<1	-	✔	-
Aplastic anemia	✔	-	-	-
Bone marrow suppression	✔	-	-	-
Eosinophilia	-	3	✔	✔
Hemoglobin decreased	-	-	✔	-
Hemoglobin increased	-	1	-	-
Granulocytopenia	<1	-	-	-
Leukopenia	<1	✔	✔	-
Neutropenia	✔	-	✔	-
Pancytopenia	<1	-	-	-
Thrombocytopenia	<1	-	-	-
Hepatic				
Abnormal liver function tests	1 to 16	2	✔	-
Acute liver failure	✔	-	-	-
Hepatitis	✔	-	✔	-
Hyperbilirubinemia	-	✔	-	-
Musculoskeletal				
Back pain	-	✔	-	-
Myalgia	-	<1	-	✔
Neck pain	-	✔	-	-
Weakness	-	-	-	-
Special Senses				
Abnormal eye sensation	-	✔	-	-
Anterior uveitis	-	✔	-	-
Chorioretinitis	-	✔	-	-

Adverse Events	Albendazole	Ivermectin	Mebendazole	Praziquantel
Choroiditis	-	✔	-	-
Conjunctival hemorrhage	-	✔	-	-
Conjunctivitis	-	✔	-	-
Eyelid edema	-	✔	-	-
Keratitis	-	✔	-	-
Ocular limbitis	-	4 to 6	-	-
Ocular punctate opacity	-	✔	-	-
Red eye	-	✔	-	-
Other				
Angioedema	-	1	✔	-
Asthma exacerbation	-	✔	-	-
Hypersensitivity reaction	<1	-	✔	✔
Mazzotti-type reaction	-	>10	-	-

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

VII. Dosing and Administration

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

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

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Albendazole	Cystic hydatid disease of the liver, lung, and peritoneum: Tablet: <60 kg, 15 mg/kg/day given in divided doses twice daily with meals, with a maximum total daily dose of 800 mg (28-day cycle followed by a 14-day albendazole-free interval, for a total of three cycles); ≥60 kg, 400 mg twice daily with meals (28-day cycle followed by a 14-day albendazole-free interval, for a total of three cycles) Parenchymal neurocysticercosis due to active lesions: Tablet: <60 kg, 15 mg/kg/day given in divided doses twice daily with meals, with a maximum total daily dose of 800 mg, for eight to 30 days; ≥60 kg, 400 mg twice daily with meals for eight to 30 days	Cystic hydatid disease of the liver, lung, and peritoneum: Tablet: <60 kg, 15 mg/kg/day given in divided doses twice daily with meals, with a maximum total daily dose of 800 mg (28-day cycle followed by a 14-day albendazole-free interval, for a total of three cycles); ≥60 kg, 400 mg twice daily with meals (28-day cycle followed by a 14-day albendazole-free interval, for a total of three cycles) Parenchymal neurocysticercosis due to active lesions: Tablet: <60 kg, 15 mg/kg/day given in divided doses twice daily with meals, with a maximum total daily dose of 800 mg, for eight to 30 days; ≥60 kg, 400 mg twice daily with meals for eight to 30 days	Tablet: 200 mg
Ivermectin	Onchocerciasis: Tablet: A single oral dose designed to provide approximately 150 µg of ivermectin per kg of body weight; retreatment may be considered at intervals as short as three months Strongyloidiasis of the intestinal tract:	Onchocerciasis: Tablet: ≥15 kg, A single oral dose designed to provide approximately 150 µg of ivermectin per kg of body weight; retreatment may be considered at intervals as short as three months Strongyloidiasis of the intestinal tract:	Tablet: 3 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Tablet: A single oral dose designed to provide approximately 200 µg of ivermectin per kg of body weight; in general, additional doses are not necessary	Tablet: ≥15 kg, A single oral dose designed to provide approximately 200 µg of ivermectin per kg of body weight; in general, additional doses are not necessary	
Mebendazole	Hookworm: Tablet: 100 mg twice daily for three consecutive days; repeat in three weeks if necessary Pinworm: Tablet: 100 mg once; repeat in three weeks if necessary Roundworm: Tablet: 100 mg twice daily for three consecutive days; repeat in three weeks if necessary Whipworm: Tablet: 100 mg twice daily for three consecutive days; repeat in three weeks if necessary	Hookworm: ≥2 years of age: Tablet: 100 mg twice daily for three consecutive days; repeat in three weeks if necessary Pinworm: ≥2 years of age: Tablet: 100 mg once; repeat in three weeks if necessary Roundworm: ≥2 years of age: Tablet: 100 mg twice daily for three consecutive days; repeat in three weeks if necessary Whipworm: ≥2 years of age: Tablet: 100 mg twice daily for three consecutive days; repeat in three weeks if necessary	Chewable tablet: 100 mg
Praziquantel	Clonorchiasis, opisthorchiasis: Tablet: 25 mg/kg three times per day as a one day treatment Schistosomiasis, all species: Tablet: 20 mg/kg three times per day as a one day treatment	Clonorchiasis, opisthorchiasis: Tablet: ≥4 years of age, 25 mg/kg three times per day as a one day treatment Schistosomiasis, all specifies: Tablet: ≥4 years of age: 20 mg/kg three times per day as a one day treatment	Tablet: 600 mg

VIII. Effectiveness

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

Table 9. Comparative Clinical Trials with the Anthelmintics

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cestodes (Tapeworms)				
Chaurasia et al.[13] (2010) Albendazole 15 mg/kg/day for three days vs placebo	DB, PC, RCT Patients with new onset seizures and solitary cysticercus granuloma (neurocysticercosis)	N=67 6 months	Primary: Resolution of lesion on computed tomography scan, seizure control at six months Secondary: Not reported	Primary: Complete resolution of lesions in the albendazole group was 84.8% compared to 41.2% in the placebo group (P=0.001). Partial resolution of lesions occurred in 6% of albendazole patients compared to 11.8% of placebo patients (P=0.06). Seizures occurred in 9.1% of albendazole patients and 2.9% of placebo treated patients (P=0.239). Secondary: Not reported
Carpio et al.[14] (2008) Albendazole 400 mg every 12 hours (>50 kg) or 15 mg/kg/day (<50 kg) for eight days vs placebo All patients received prednisone; anticonvulsants were allowed for patients with	DB, PC, RCT Patients of any age or gender with new onset of symptoms associated with neurocysticercosis and active and/or transitional neurocysticercosis cysts (Ecuador)	N=178 1 year	Primary: Disappearance of active cysts by 12 months of follow-up Secondary: Disappearance of transitional or calcified cysts at one, six and 12 months, change in number of cysts in a specific phase, time to seizure recurrence, and adverse events	Primary: Active cysts were identified in 69% of the albendazole treatment group and 66% of the placebo group. By 12 months following treatment, 38% of those with 12 month scans were free of active cysts in the treatment group compared to 20% in the placebo group (P=0.048). Secondary: The difference in cyst disappearance by treatment was greatest at one month of follow-up, with 31% of those in the albendazole group being free of active cysts at month one of follow-up compared to 7% of those in the placebo group (P=0.001). Of those patients followed and scanned at six months, 35% were free of active cysts in the albendazole treatment arm compared to 12% in the placebo group (P=0.006). The mean number of active cysts decreased between baseline and month

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
newly occurring seizures.				one for the albendazole (mean number at baseline 3.88 and at one month 1.86) group but not for the placebo group (mean at baseline 2.67 and at one month 2.69). Those taking albendazole had a significant decrease in the number of active cysts between baseline and month one compared to those in the placebo group (P=0.001). There was no difference by treatment group in the change in the number of active cysts between month one and month six (P=0.797) or month six and month 12 of follow-up (P=0.938). The change in the number of transitional cysts and inactive calcifications between baseline and month one of follow-up did not differ by treatment group (transitional cysts; P=0.234, calcifications; P=0.456). The mean time seizure free was 8.86 months in the albendazole group vs 7.67 months in the placebo group (P=0.274). The three most common symptoms reported during treatment, and the first month following treatment, were headache, seizures, and stomach problems. During the eight days of treatment, three patients developed intracranial hypertension, all in the placebo group.
Bildik et al.[15] (2007) Albendazole 10 mg/kg twice daily prior to surgery (group I=one month; group II=two months; group III=three months) vs	RCT Patients with isolated hydatid cysts of the liver	N=84 3 months	Primary: Clinical signs of disease Secondary: Not reported	Primary: Thirty-five percent of the patients showed no clinical signs of the disease. Sixty-two percent had tenderness in the right hypochondrium, 34.5% had hepatomegaly, and 30.0% had palpable mass. Following treatment with albendazole, scoleces were alive in 47.6% of patients in group I, 33.3% of patients in group II, and 0.9% of patients in group III. In the control group, 80% of patients' scoleces were intact. When group III was compared to the control group, a significant difference was observed (P<0.05). There was a significant difference between the groups when groups I and II were compared to group III.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
no preoperative therapy				Secondary: Not reported
Wen et al.[16] (1994) Albendazole 15 to 20 mg/kg/day orally, for 30 days with intervals of 10 days between treatments for three to six courses (12 to 18 courses for multi-organ cystic echinococcosis and alveolar echinococcosis) vs albendazole and surgery vs surgery	OL Patients with cystic echinococcosis or alveolar echinococcosis in China	N=178 3 to 7 years	Primary: Endocyst collapse rate, proscolex viability, cyst wall pathology, clinical symptoms and signs Secondary: Side effects	Primary: Twenty-seven of 34 cysts (79.4%) in patients treated with albendazole and surgery showed increased necrotic changes and decreased viability of the cysts compared to the surgery group (P<0.001). However, 10 of 84 (11.9%) cysts in the surgery group showed spontaneous evidence of necrosis at surgery. Albendazole treatment alone was successful in 14 (24.1%) patients, resulted in improvement in 29 (50%) patients and had no effect in 15 (25.9%) patients. Seven of the alveolar echinococcosis patients treated with albendazole and surgery showed improvement, with hydatid masses diminished or disappeared, jaundice subsided, and appetite and energy regained. Of the remaining seven patients who continued to receive albendazole for six to 15 more courses, four stabilized, and three deteriorated of which two died. Of the five alveolar echinococcosis patients receiving albendazole alone, one improved, two stabilized, and two deteriorated of which one died. Secondary: Side effects were reported in 18.4% of patients receiving albendazole and were primarily gastrointestinal symptoms (diarrhea, nausea, abdominal pain and vomiting) and transient elevation of serum transaminase levels. Albendazole was withdrawn in one patient after one week of therapy due to intolerable itch.
Kaur et al.[17] (2009) Albendazole 15 mg/kg/day in three divided doses for seven days, plus prednisolone 2 mg/kg/day for	DB, PC, RCT Children one to 13 years of age with seizures due to neurocysticercosis	N=112 1 year	Primary: Recurrence of seizure and resolution of lesions on CT Secondary: Not reported	Primary: Resolution of lesions at one, three, and six months was higher in the praziquantel group (35, 60, and 72%, respectively) compared to those receiving placebo (25, 42, and 52%, respectively), but this did not reach statistical significance. Non-resolution and calcification at one, three, and six months were numerically lower in the praziquantel group compared to placebo; however, this was not significant.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
five days, plus praziquantel 75 mg/kg/day in three divided doses for one day vs albendazole 15 mg/kg/day in three divided doses for seven days, plus prednisolone 2 mg/kg/day for five days, plus placebo				Recurrence of seizures within six months of therapy was reported in three children in each treatment group. There were no signs of elevated intracranial pressure. Secondary: Not reported
Del Brutto et al.[18] (2006) Albendazole vs praziquantel vs placebo vs no therapy	MA Patients with neurocysticercosis	N=942 (11 trials) Variable duration	Primary: Resolution of cystic lesions, risk of seizure recurrence, frequency of seizures Secondary: Effect of corticosteroids on cysticidal drug efficacy, adverse events	Primary: Cysticidal drug therapy was associated with complete resolution of cystic lesions (44 vs 19%; P=0.025). Trials on enhancing lesions showed a trend toward lesion resolution favoring the use of cysticidal drugs (72 vs 63%; P=0.38) that became statistically significant when an outlier trial was excluded from the analysis (69 vs 55%; P=0.006). Risk for seizure recurrence was lower after cysticidal treatment in patients with enhancing lesions (14 vs 37%; P<0.001). The single trial evaluating the frequency of seizures in patients with cystic lesions showed a 67% reduction in the rate of generalized seizures with treatment (P=0.006). This MA did not further analyze and compare the efficacy or safety of albendazole to praziquantel. Secondary: Only one study compared the efficacy of cysticidal drugs alone or in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				combination with corticosteroids, showing that albendazole plus dexamethasone was not better than albendazole alone in terms of lesion resolution (74 vs 76%) or risk of seizure recurrence during follow-up (12 vs 14%). Data from the trials did not allow an evaluation of the exact number of patients developing adverse events, but these manifestations generally were mild and resolved with analgesics or other symptomatic medications in a few days. The occurrence of adverse events did not differ between albendazole or praziquantel, or whether the patient received routine corticosteroids.
Das et al.[19] (2007) Group A Albendazole 15 mg/kg/day for 14 days plus dexamethasone 2 mg every eight hours for 14 days, plus antiepileptic drugs vs Group B antiepileptic drugs plus placebo	RCT Patients with newly diagnosed neurocysticercosis with more than one lesion detected on contrast head computed tomography imaging	N=300 8 years	Primary: Recurrence of seizures, encephalopathy, need for subsequent hospital admission, death, resolution of lesions on follow-up computed tomography Secondary: Not reported	Primary: During the first year of treatment the incidences of seizure, encephalopathy, and readmission were greater for group A than group B (group A: 95% CI, 0.20 to 0.34; group B: 95% CI, 0.10 to 0.22; P=0.05). Two patients in group A died from intractable seizures and encephalopathy in the first three months of treatment. For every follow-up point after one year of treatment, the incidences of seizure and need for readmission were also marginally higher in group A, but the differences were not statistically significant. Over the entire study period, the proportion of patients with complete resolution of lesions was greater in group B than in group A (group A: 95% CI, 0.56 to 0.57; group B: 95% CI, 0.72 to 0.74; P=0.05), but the proportion of patients with calcification of lesions was greater in group A than in group B (group A: 95% CI, 0.33 to 0.34; group B: 95% CI, 0.22 to 0.23; P=0.05). Secondary: Not reported
Nematodes (Roundworms)				
Issaka-Tinorgah et al.[20] (1994) Ivermectin 150	PC, RCT, SB Patients over 18 years of age from a Ghana village	N=385 15 months	Primary: Emergence and migration of guinea worms, adverse events	Primary: There was no significant difference in the proportion of persons with emergent guinea worms between the two treatment groups. Overall, 54 of the 385 participants who were followed for 15 months developed a total of 69 emergent guinea worms.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
µg/kg as a single dose vs placebo	highly endemic for guinea worm infections		Secondary: Not reported	Migration of guinea worms in the tissues was not affected by ivermectin, with 80% of emergent guinea worms located below the knee. There was no difference in the patterns of adverse events between the ivermectin and placebo groups. Secondary: Not reported
Fobi et al.[21] (2005) Gardon et al.[22] (2002) Kamgno et al.[23] (2004) Ivermectin 150 µg/kg annually (reference group) vs ivermectin 150 µg/kg every three months vs ivermectin 400 µg/kg then 800 µg/kg annually vs ivermectin 400 then 800 µg/kg every three months	DB, RCT Men 18 to 60 years of age with *Onchocerca volvulus* infections (Cameroon)	N=657 3 years	Primary: Vital status of female worms[35], adverse events[36], ophthalmological exam[34], ocular and visual symptoms[34] Secondary [35]: Fertility of female worms, skin microfilariae, number of non-fertile female and male worms	Primary and Secondary: After three years, more female worms had died in the groups treated every three months than in the reference group (150 µg/kg dose: OR, 1.84; 95% CI, 1.23 to 2.75; P=0.003 and 400 to 800 µg/kg dose: OR, 2.17; 95% CI, 1.42 to 3.31; P<0.001). Female worms were also less fertile in these groups than in the reference group (OR, 0.24; 95% CI, 0.14 to 0.43; P<0.0001 and OR, 0.14; 95% CI, 0.06 to 0.29; P<0.0001, respectively). No difference was recorded between groups treated yearly (P=0.83 for the proportion of dead females). More than 90% of patients on yearly treatment had microfilariae in their skin snips (difference, 1.9%; 95% CI, 3.9 to 7.8; P=0.52), compared to 40 and 26%, respectively, in the groups treated every three months at 150 µg/kg and at high doses (difference, 13.8%; 95% CI, 2.5 to 25.1; P=0.0180). The mean numbers of skin microfilariae did not differ between the two groups treated yearly (P=0.45). High doses (400 to 800 µg/kg) administered annually produced little marginal parasitological benefit compared to 150 µg/kg. After the first dose, dosing every three months was associated with a reduced risk of reactions, especially edematous swellings, pruritus, and back pain. Edematous swellings and subjective ocular troubles were found to be associated with high doses of ivermectin. Transitory subjective visual problems were reported more frequently in the two groups receiving the high ivermectin doses than in the reference group (P<0.03 and P<0.001 for the ivermectin 800 µg/kg annual and every three

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Every patient was given a clearing dose of 150 µg/kg ivermectin prior to the start of the study.				month regimens, respectively). In the ophthalmological examinations, the only differences recorded between the groups were a lower prevalence and mean number of microfilariae in the anterior chamber in the groups treated every three months, and, at the first examination round, a higher prevalence of early lesions of the iris in the group treated at high doses annually. Results of the ophthalmological exam did not show the cause of the transitory ocular complaints, nor explain why they were more frequent in the groups treated with higher doses.
Awadzi et al.[24] (1999) Ivermectin 150 µg/kg as a single dose vs ivermectin 150 µg/kg or placebo, then 400 µg/kg vs ivermectin 150 µg/kg or placebo, then 600 µg/kg vs ivermectin 150 µg/kg or placebo, then 800 µg/kg vs ivermectin 800 µg/kg for two	DB, PC, RCT Males infected with *Onchocerca volvulus* (Ghana)	N=100 21 months	Primary: Nodule characteristics, adult worm viability, reproductive activity, skin and ocular microfilariae Secondary: Not reported	Primary: There were no significant trends among the dosage regimens regarding the number of live worms per nodule, the male: female ratio or in the number of nodules with live microfilariae (P>0.05). There was however a significant trend to a reduction in the number of nodules without male worms with increasing doses of ivermectin (P=0.02). There was no significant trend in mortality among female and male worms in the treated groups (P>0.05). Increasing doses of ivermectin had no marked effect on embryogenesis. There was a significant trend towards an increase in the number of female worms with nearly empty uteri (P=0.04), and a reduction in the proportion of female worms with young embryos (P=0.015) and coiled microfilariae (P=0.004) with increasing doses. There was no significant trend with dose in the proportion of worms with young oocytes only, with stretched microfilariae, or with degenerate stretched microfilariae. Between 95% and 100% of live male worms contained intact spermatozoa with no differences between groups. At days 30 and 180, the higher dose groups had a greater suppression of skin microfilariae (P<0.05) but the effect was minor (maximum differences were 1.6%) and transient. By one year, the mean skin microfilariae densities were again similar in all groups. The clearance of ocular microfilariae was also similar in all groups. There was no significant difference in ocular mf between the treatment groups. Overall, the treatment groups maintained at one year a 96% reduction on initial counts for both skin and ocular microfilariae. Total doses of ivermectin (≤1,600 µg/kg) were not more effective than 150

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
doses				µg/kg. They did not reproduce the marked inhibitory effects of the repeat standard-dose regimens on embryogenesis, or the modest effect on adult worm viability, at comparable total doses.
Olsen et al.[25] (2009) Albendazole: Albendazole 400 mg as a single dose Mebendazole 1: Mebendazole 100 mg twice daily for 3 days (study 1) Mebendazole 2: Mebendazole 100 mg twice daily for 5 days (study 2)	OL School-age children infected with *Trichuris trichiura*	Albendazole: N=70 14 days Mebendazole 1: N=34 3 days Mebendazole 2: N=35 7 days	Primary: Albendazole: Cure and egg reduction rates Mebendazole 1/2: Recovery of adult *Trichuris trichiura* worms Secondary: Not reported	Primary: Albendazole study: At day seven, the cure rate (negative for eggs in stool sample) was 8% and the geometric egg reduction rate was 89% (P<0.001). At day 14, all children were egg-positive and the egg count was 57% higher than baseline (P<0.001). Mebendazole 1 study: With the three day course of mebendazole, four adult worms were obtained at days three to five after the start of treatment from two of the 34 children delivering 24 hour stool samples. Mebendazole 2 study: With the five day course of mebendazole, 10 of 21 infected children expelled a total of 27 worms. Secondary: Not reported
Critchley et al.[26] (2005) Albendazole vs placebo, ivermectin, diethyl-carbamazine	MA Patients with lymphatic filariasis	N=6,997 (7 trials) Up to 2 years	Primary: Microfilariae prevalence, microfilariae density, antigenemia prevalence or density, adult worms Secondary: Acute filariasis, appearance or disappearance of hydrocele or	Primary and Secondary: A comparison of albendazole to placebo detected no effect on microfilariae prevalence after three to 12 months (N=920 participants, three trials). One trial (N=499) reported a significantly greater reduction in microfilariae density at six months in the albendazole group compared to placebo (34.7 vs 10.3% reduction, respectively; P<0.05). There were no statistically significant differences in the prevalence of circulating filarial antigen positivity from two trials after six to 12 months (N=1,090). One trial reported no statistically significant difference in the development of acute filariasis, leg lymphedema, and hydrocele, or improvement of hydrocele and leg lymphedema; however, the trials lacked power so clinically important differences cannot be ruled out. One trial reported no statistically significant difference in systemic adverse events between

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			change in size, adverse events	albendazole and placebo. Another trial reported statistically significant reductions in myalgias and cough for albendazole compared to placebo, but no statistically significant differences in headache, fever or mean treatment impact score. Albendazole performed slightly worse than ivermectin in two trials (N=436). Albendazole was slightly poorer in clearing microfilariae, but this only just reached statistical significance (RR, 0.84; 95% CI, 0.72 to 0.9; N=198). There was no statistically significant difference in the number of patients positive for circulating filarial antigen after 12 months for those treated with albendazole or ivermectin. Ivermectin produced higher reductions in microfilariae and antigen densities than albendazole (statistical tests were only applied in one comparison where P=0.02). One trial reported no statistically significant differences in the risk of developing hydrocele, or improvements in lymphedema or hydrocele, but sample sizes were small and CIs wide. There was no statistically significant difference in the number of systemic adverse events between albendazole and ivermectin. When albendazole was added to ivermectin, microfilariae prevalence and density were statistically significantly lower with the combination compared to ivermectin alone in two of three trials (N=649). There were no significant differences in the remainder of the primary and secondary end points. Compared to diethylcarbamazine, two small trials (N=56) found little difference in microfilariae prevalence over an extended follow-up. One larger trial (N=502) found a statistically significant effect for diethylcarbamazine at six months (RR, 1.74; 95% CI, 1.05 to 2.88), but not at three months. Microfilariae density appeared to fall faster with diethylcarbamazine compared to albendazole; however, there were no statistically significant differences in percentage reductions at any time points. Antigen density was reduced by 17% in the diethylcarbamazine group compared to 3.2% in the albendazole group (P<0.05). The mean score of adverse reaction intensity was lower for albendazole compared to diethylcarbamazine (P<0.05), but the validity and clinical significance of this scoring system was uncertain. There were no significant differences in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				the remainder of the primary and secondary end points. Two trials compared albendazole plus diethylcarbamazine with diethylcarbamazine alone and found no statistically significant difference in microfilariae prevalence, though one trial favored the combination at six months (RR, 0.62; 95% CI, 0.32 to 1.21; N=491). This trial also found a significant reduction in microfilariae density with the combination arm vs albendazole (80.4 vs 50.4%, respectively; P<0.05). There were no significant differences in the remainder of the primary and secondary end points.
Datry et al.[27] (1994) Albendazole 400 mg/day for three days vs ivermectin 150 to 200 µg/kg as a single dose	OL, RCT Patients with *Strongyloides stercoralis* of the intestinal tract (France)	N=60 90 days	Primary: Parasitological cure, adverse events Secondary: Not reported	Primary: Ivermectin was significantly more effective in producing parasitological cure than albendazole (83 vs 38%; P<0.01). Clinical and biological adverse reactions were negligible in both treatment groups. The 20 patients who failed therapy were given a second treatment course with ivermectin in a single dose or on two consecutive days. Sixteen patients were cured and the other four had only incomplete follow-up. Secondary: Not reported
Wen et al.[28] (2008) Ivermectin 0.1 mg/kg as a single dose (*Ascaris* infection) vs ivermectin 0.2 mg/kg as a single dose (*Trichuris* or *Enterobius*	DB, MC, PC, RCT Fecal egg-positive farmers and children over six years of age from rural areas with confirmed intestinal nematode infections	N=816 Single dose	Primary: Cure rates and egg reduction rates Secondary: Adverse events	Primary: The cure rates of ivermectin against *Ascaris* (100%) and *Trichuris* (66.7%) infections were similar to albendazole against *Ascaris* (99.0%; P=1.000) and *Trichuris* (67.7%; P=0.881). Ivermectin was less effective against hookworm (33.3%) and *Enterobius* (52.9%) than albendazole (69.6%; P<0.0001). The percentages of the worms expelled were 41.9, 48.6, 9.6, 0 and 0% in a total of 681worms released on days one through five after ivermectin treatment, respectively. The percentages of the worms expelled with albendazole were 0.1, 24.3, 52.6, 22.9 and 0.1% in a total of 744 worms released on days one

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
infection) vs albendazole 6.7 mg/kg as a single dose				through five post-treatment, respectively. Expulsion of worms reached a peak on day three after albendazole treatment. Secondary: For ivermectin, adverse events included dizziness, abdominal pain, and tiredness, which were mild and transient. For albendazole, a total of 2.21% of patients experienced adverse events, including dizziness, vomiting, and diarrhea. No significant difference between the two treatments in terms of adverse events was shown (P=0.806).
Suputtamongkol et al.[29] (2011) Ivermectin 200 µg/kg as a single dose vs ivermectin 200 mg/kg as a single dose given two weeks apart vs albendazole 400 mg twice daily for seven days	OL, PRO, RCT Patients ≥18 years of age with *Strongyloides stercoralis* larvae on microscopy (chronic strongyloidiasis)	N=90 19 to 36 weeks	Primary: Cure (clinical improvement and absence of larvae in stool at day 14 of treatment and through follow up), failure (presence of larvae two weeks after initiation of treatment or reappearance of larvae during follow-up) Secondary: Not reported	Primary: Parasite elimination occurred in 63.3% of albendazole patients, in 96.8% of patients receiving a single dose of ivermectin, and in 93.1% of patients receiving two doses of ivermectin (P=0.006). Patients receiving albendazole had 14.7 times (95% CI, 1.8 to 111.9) and 5.7 times (95% CI, 1.3 to 25.7) higher risk for reinfection/relapse of strongyloidiasis compared to patients receiving single-dose or double-dose ivermectin therapy, respectively. Overall, albendazole and ivermectin were well tolerated. Secondary: Not reported
Muchiri et al.[30] (2001) Albendazole 600 mg at 6 month	DB, RCT Children ages 4 to 19 years of age with *Ascaris*	N=1,186 1 year	Primary: Cure rate, egg reduction Secondary:	Primary: The cure rates for albendazole were 92.4% for hookworm infection, 83.5% for *Ascaris lumbricoides*, and 67.8% for *Trichuris trichiura*. Mebendazole given either two or three times in a year had cure rates of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
intervals vs mebendazole 600 mg at 4 or 6 month intervals	*lumbricoides*, *Trichuris trichiura* and/or hookworm infections in West Kenya		Not reported	50.0 and 55.0%, respectively, for hookworm, 79.6 and 97.5% for *Ascaris lumbricoides*, and 60.6 and 68.3% for *Trichuris trichiura* infection. Albendazole was significantly more effective than either regimen of mebendazole for treating hookworm infections (P<0.0001). Three doses of mebendazole were more effective against *Ascaris lumbricoides* than two doses of albendazole (P<0.0001). The cure rate for *Trichuris trichiura* by mebendazole given at four-month intervals was higher than the six-month regimen (P=0.035), but comparable to albendazole given at six-month intervals. The geometric mean intensity of hookworm eggs per gram of stool decreased by 96.7% after albendazole treatment compared to 66.3 and 85.1%, respectively, for second or third doses of mebendazole (P<0.05) over the same period. Reductions in eggs per gram for *Ascaris lumbricoides* and *Trichuris trichiura* were comparable for both drugs. Secondary: Not reported
Legesse et al.[31] (2002) Albendazole 400 mg as a single dose vs mebendazole 100 mg two times a day for 3 days	RCT Patients with single or mixed *Ascaris lumbricoides* and/or *Trichuris trichiura* infections	N=not specified 3 days	Primary: Cure rate, egg reduction, adverse effects Secondary: Not reported	Primary: Both drugs were found to be highly effective against *Ascaris lumbricoides* infection, with cure rates >96.0% and egg reduction rates >99.8%. The efficacy of the two drugs against *Trichuris trichiura* infection was low. Mebendazole exhibited a cure rate of 34.7% and egg reduction of 92.3%, as opposed to 13.9 and 63.4%, respectively, for albendazole. More complaints were reported by individuals treated with albendazole than with mebendazole. Secondary: Not reported
Legesse et al.[32] (2004) Albendazole 400 mg as a single dose	RCT Children 6 to 19 years of age with *Ascaris*	N=534 21 days	Primary: Cure and egg reduction rates Secondary:	Primary: The cure rate and egg reduction rates obtained with albendazole and mebendazole from the three brands were not significantly different in the treatment of ascariasis.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs mebendazole 100 mg two times a day for 3 days	*lumbricoides* and/or *Trichuris trichiura* infections (Ethiopia)		Not reported	Significant differences were found among the percentage cure and egg reduction rates of the four groups in the treatment of trichuriasis. The highest cure rate (89.8%) and egg reduction rate (99.1%) were observed with Janssen mebendazole (Vermox®), followed by Unibios (India) mebendazole (53.3 cure and 96.5% egg reduction rates), and then East African mebendazole (27.9 cure and 88.5% egg reduction rates) with P<0.05 between the three brands. The lowest cure (17.1%) and egg reduction (69.8%) rates were seen in the albendazole-treated group (P<0.05 compared to the mebendazole brands). Secondary: Not reported
Flohr et al.[33] (2007) Study 1 Mebendazole 500 mg once vs placebo Study 2 Mebendazole 500 mg daily for 3 days vs albendazole 400 mg once vs albendazole 400 mg daily for 3 days	RCT Study 1 6- to 11-year-old children attending school in Khanh Hoa province, central Vietnam Study 2 Adults 16 years of age and older living in one village in Khanh Hoa province, central Vietnam	N=271 (Study 1) N=209 (Study 2) 2 weeks	Primary: Hookworm intensity as measured by percent decline in arithmetic mean eggs per gram after treatment Secondary: Cure from hookworm infection	Primary: Study 1 Efficacy in terms of percentage reduction in arithmetic mean eggs per gram feces relative to placebo was not significantly different between the mebendazole treatment group and the placebo group (31%, 95% CI −9 to 56). Study 2 The estimated reduction in arithmetic mean eggs per gram of feces relative to placebo was 63% (95% CI, 30 to 81), 75% (95% CI, 47 to 88), and 88% (95% CI, 58 to 97) for triple dose mebendazole, single dose albendazole, and triple dose albendazole, respectively. Secondary: Study 1 There was no significant difference between treatments in the proportion of infected children cured at two weeks: 33% in the placebo group and 38% in the mebendazole group. Study 2 The cure rates were 26% for three dose mebendazole, 45% for single dose albendazole, 79% for three dose albendazole, and 35% for placebo. Only the triple dose albendazole course was significantly superior to placebo in terms of cure (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo				
Sacko et al.[34] (1999) Albendazole 400 mg as a single dose vs mebendazole 500 mg as a single dose vs pyrantel pamoate 12.5 mg/kg as a single dose vs placebo	PC, RCT, SB Patients 3 to 70 years of age with hookworm infections (Mali, West Africa)	N=145 10 days	Primary: Efficacy (evaluated by seven procedures which included cure rate) Secondary: Not reported	Primary: Cure rates were reported in 83.8% of patients receiving albendazole, 51.4% of patients receiving mebendazole, 37.8% of patients receiving pyrantel pamoate and 16.7% of patients receiving placebo. Using other efficacy measurements, albendazole was the most effective showing efficacies in the range of 92.1 to 99.5%, depending on the method of evaluation and the particular subset of the treatment group. Neither mebendazole nor pyrantel pamoate was as effective, with efficacies ranging from 60.9 to 89.9%, and 4.8 to 89.7%, respectively. Secondary: Not reported
Simonsen et al.[35] (2004) Ivermectin 150 to 200 µg/kg vs ivermectin 150 to 200 µg/kg and albendazole 400 mg	DB, RCT Children infected with *Wuchereria bancrofti* (Tanzania)	N=1,829 Duration not specified	Primary: Prevalence and intensities of *Wuchereria bancrofti* microfilariae and circulating filarial antigen Secondary: Not reported	Primary: The overall prevalence of *Wuchereria bancrofti* microfilariae and circulating filarial antigen was 17.3 and 43.7%, respectively. Both treatment regimens resulted in a considerable decrease in mean microfilariae intensities, with overall reductions being slightly but statistically significantly higher for the combination than for ivermectin alone. The difference in effect between the two regimens was most pronounced at six months, whereas it was minor at 12 months after treatment. The relative effect of treatment on mean circulating filarial antigen units was less pronounced than on microfilariae.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				For both treatment regimens, reductions in circulating filarial antigen intensity appeared to be higher in children who were both circulating filarial antigen and microfilariae positive before treatment, which may suggest that treatment mainly affected the survival and/or production of microfilariae, rather than the survival of adult worms. Adverse reactions were few and mild in both groups, and mainly reported from pretreatment microfilariae and circulating filarial antigen positive children. Secondary: Not reported
Awadzi et al.[36] (2003) Albendazole 400 mg plus placebo vs ivermectin 200 µg/kg as a single dose plus placebo vs albendazole 400 mg plus ivermectin 200 µg/kg as a single dose vs no treatment	DB, PC, RCT Male patients 19 to 54 years of age with moderate to heavy *Onchocerca volvulus* microfiladermia and palpable onchocercal nodules (Ghana)	N=42 1 year	Primary: Viability and reproductive activity of adult worms determined by histopathology and noted by two independent readers, macrofilaricidal efficacy (measured by reductions in microfilariae skin counts), pharmacokinetic parameters, adverse events Secondary: Not reported	Primary: No difference in the viability of the adult worms between the ivermectin groups was reported. The combination was not consistently more effective than ivermectin alone in the effects on reproductive activity. There was no difference between albendazole and no treatment in the effect on adult-worm reproductive activity. There was no difference between the ivermectin groups in the rate at which microfilariae were killed or in the macrofilaricidal efficacy. Both groups reduced microfilariae skin counts by 99% at day 30.The overall reduction of microfilariae skin counts with albendazole was 22% at day 30. There was no significant pharmacokinetic interaction when albendazole was administered with ivermectin. The co-administration of albendazole with ivermectin did not produce more severe adverse effects than ivermectin alone. Secondary: Not reported
Knopp et al.[37] (2010)	DB, PC, PRO, RCT	N=610	Primary: Cure rate	Primary: The highest cure rate was 55% in the mebendazole-ivermectin group,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Albendazole 400 mg as a single dose vs albendazole 400 mg plus ivermectin 200 µg/kg as a single dose vs mebendazole 500 mg as a single dose vs mebendazole 500 mg plus ivermectin 200 µg/kg as a single dose	Children in grades one through seven with *Trichuris trichiura* positive stool smears in Tanzania	Median 29 days	(percentage of children excreting eggs before treatment who became negative), egg reduction rate Secondary: Adverse events	followed by a 38% cure rate in the albendazole-ivermectin group. Mebendazole cured significantly more *Trichuris trichiura* compared to albendazole (OR, 2.05; 95% CI, 1.38 to 3.04). Ivermectin cured significantly more *Trichuris trichiura* compared to placebo (OR, 5.4; 95% CI, 3.55 to 8.22). The addition of Ivermectin increased cure rate from 14 to 47% compared to placebo. The highest egg reduction rate was seen in the mebendazole-ivermectin group (97%), which was significantly greater than in the albendazole-ivermectin group (91%). The lowest egg reduction rates were observed in the monotherapy groups. Albendazole treated groups had significantly greater reductions in hookworm infections compared to other groups. Secondary: Abdominal cramps were reported in 13% of children, headache, fatigue and nausea were reported in 5% of children and 3% of children experienced diarrhea and vertigo.
Belizario et al.[38] (2003) Albendazole 400 mg as a single dose vs ivermectin 200 µg/kg as a single dose vs diethylcarbamazin	PC, RCT, SB Children in an elementary school in the Philippines infected with *Ascaris lumbricoides* and/or *Trichuris trichiura*	N=784 1 year	Primary: Cure and infection rates, egg counts Secondary: Not reported	Primary: Albendazole, ivermectin, and the drug combinations gave significantly higher cure and egg reduction rates for ascariasis than diethylcarbamazine (P<0.001). Infection rates were significantly higher at day 180 with diethylcarbamazine (P<0.001); however, there were no significant differences between treatments on day 360. Albendazole, ivermectin, and albendazole plus ivermectin produced cure rates of 69.7, 78.4, and 78.1%, respectively. For trichuriasis, albendazole plus ivermectin produced significantly higher cure rates (P<0.001) and egg reduction rates (P<0.001) than other treatments. Albendazole plus ivermectin produced the lowest infection rates on days 180 and 360 (P<0.001). Albendazole, ivermectin, and albendazole plus ivermectin produced cure rates of 31.5, 35.1, and 65.1%, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
e 150 mg as a single dose vs albendazole 400 mg and diethylcarbamazine 150 mg as a single dose vs albendazole 400 mg and ivermectin 200 µg/kg as a single dose				Secondary: Not reported
Makunde et al.[39] (2004) <u>Co-infections:</u> Albendazole 400 mg and ivermectin 150 µg/kg as a single dose or placebo; 5 days later the treatment regimen was reversed <u>Single infections:</u> Albendazole 400 mg and ivermectin 150 µg/kg as a single dose or albendazole 400 mg as a single dose	RCT (Co-infections: DB, PC, XO; single infections: OL) Patients 15 to 55 years of age co-infected with *Onchocerca volvulus* and *Wuchereria bancrofti* or single infections with *Wuchereria bancrofti* (Tanzania)	N=40 1 year	Primary: Microfilariae intensity, microfilariae prevalence, adverse reactions Secondary: Not reported	Primary: The treatment of co-infections with albendazole and ivermectin resulted in a rapid reduction of microfilariae intensity that was sustained throughout the 12 months of follow-up. Microfilariae prevalence was reduced to 13 and 6% for *Onchocerca volvulus* and *Wuchereria bancrofti*, respectively, at 14 days posttreatment but increased throughout the rest of the follow-up ranging from 33 to 53% for *Onchocerca volvulus* and 40 to 67% for *Wuchereria bancrofti*. Treatment of single *Wuchereria bancrofti* infection with albendazole resulted in a sustained reduction of microfilariae intensity throughout the follow-up period, and the addition of ivermectin significantly improved efficacy at all time points ($P<0.05$). Treatment with albendazole alone resulted in a 15 to 38% reduction in mf prevalence, compared to reductions of 73 to 100% in the combination group. There was no significant difference between single and co-infected individuals in the geometric mean mf intensity of *Wuchereria bancrofti* during albendazole and ivermectin treatment.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The frequency of adverse events in co-infected individuals was 63 and 57% in the combination and placebo groups, respectively, and of mild or moderate intensity. The frequency of adverse events in patients with single infections was 50 and 38% in the combination and albendazole monotherapy groups, respectively, and was of similar intensity to those experienced by patients with co-infections. There were no differences in adverse events between treatment groups. Secondary: Not reported
Dembele et al.[40] (2010) Albendazole 400 mg plus ivermectin 150 µg/kg administered annually for two years (low dose) vs albendazole 800 mg plus ivermectin 400 µg/kg administered bi-annually for two years (high dose)	RCT Patients14 to 65 years of age with *Wuchereria bancrofti* microfilariae	N=42 24 months	Primary: Difference in *Wuchereria bancrofti* levels at 12 months Secondary: Circulating antigen levels, presence of eosinophilia	Primary: Microfilarial levels were significantly decreased in the high dose group at 12 months (P<0.001), 18 months (P<0.019), and 24 months (P<0.044) compared to standard dose groups. Complete clearance was significantly more common in the high dose group (zero patients with microfilariae at 12, 18, and 24 months) compared to standard dose group (12, six and five patients with microfilaria at 12, 18, and 24 months, respectively; P<0.001, P=0.02, and P=0.02, respectively). Secondary: Circulating antigen levels decreased over 24 months, with differences that were not significant between the treatment groups. Eosinophilia (>500 cells/mm^3) decreased in both groups, with the most significant change occurring after six months.
Bregani et al.[41] (2006) Ivermectin 200 µg/kg biweekly for three subsequent administrations vs	OL Patients 9 to 90 years of age with *Mansonella perstans* infections (Chad)	N=165 15 months	Primary: Microfilariae density, median eosinophil percentage, recovery (full recovery defined as the number of patients with	Primary: In the diethylcarbamazine group, microfilariae density significantly decreased (P<0.01), while median eosinophil percentage increased both after the first (P<0.01) and second course of treatment (P=NS). However, the second course of treatment further improved the full recovery (complete elimination of microfilariae) from 3.8 to 15.0%. In the mebendazole group, a significant decrease in microfilariae was observed (P<0.01), while median eosinophil percentage did not change

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
diethylcarbamazine 200 mg twice daily for 21 days, course repeated if full response not achieved vs mebendazole 100 mg twice daily for 28 days vs praziquantel 40 mg/kg as a single dose vs thiabendazole 50 mg/kg for children or 3 g for adults as a single dose or in double administration on the first and eighth days vs diethylcarbamazine 200 mg twice daily for 21 days plus mebendazole			complete clearance of blood microfilaria and partial recovery defined as number of patients with reduction of blood microfilaria without complete clearance), adverse events Secondary: Not reported	(P=NS). A full recovery and overall response were observed in 21.7% and 87.0% of patients, respectively. In the thiabendazole group, a statistically significant decrease in microfilariae was reached only after the second therapeutic step (-33.3%; P<0.04). Full response was achieved in one case (6.7% of patients), and an overall response of 73.0% was observed in the group who received two consecutive treatments. Thiabendazole was significantly less effective both on microfilariae reduction and on full response than diethylcarbamazine and mebendazole. In the diethylcarbamazine plus mebendazole treatment group, a highly significant fall in microfilariae was seen (P<0.01), while median eosinophil percentage values showed the same trend towards an increase as in the diethylcarbamazine group. No significant difference was observed in microfilariae reduction among the three treatment regimens using the combination of diethylcarbamazine and mebendazole. The combination of diethylcarbamazine and mebendazole produced full and overall recovery rates of 37 and 96%, respectively. There were no significant changes in microfilariae density in the groups receiving ivermectin, praziquantel or no treatment. Full and overall recovery was reported in 0 and 44.4% of patients, respectively, who received no treatment. All treatments were well tolerated and no adverse effects were observed. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
100 mg for 21 days or 100 mg twice daily for 14 or 21 days				
Tarr et al.[42] (2003) Ivermectin rectal enema 200 µg/kg/day for seven days (prepared from tablets) in combination with nasogastric albendazole and ivermectin for 14 days, an additional five days of oral ivermectin were given two weeks after hospital discharge	Case report 55-year-old female renal transplant recipient with *Strongyloides stercoralis* hyperinfection syndrome and progressive ileus unresponsive to nasogastric albendazole and ivermectin	N=1 19 months	Primary: Clinical symptoms, presence of larvae, adverse events Secondary: Not reported	Primary: The patient improved markedly within approximately 72 hours and recovered fully. Stool studies, done periodically and, in the absence of symptoms, were negative for *Strongyloides stercoralis.* The ivermectin enemas were well tolerated, diarrhea was not induced. Nausea, abdominal pain, and shortness of breath resolved, and oxygen requirements as well as amounts of larvae in nasogastric aspirate samples decreased. At 19 months, the patient had no gastrointestinal symptoms. Secondary: Not reported
Albonico et al.[43] (2003) Mebendazole 500 mg vs levamisole 40 mg or 80 mg vs mebendazole 500	PC, RCT Children with *Ascaris lumbricoides*, hookworm and/or *Trichuris trichiura* infections (Pemba Island, Zanzibar)	N=904 21 days	Primary: Egg counts, cure rates, reductions in prevalence and egg reduction rates Secondary: Not reported	Primary: Follow-up egg counts, cure rates, reductions in prevalence and egg reduction rates for the three nematode infections were statistically significantly better with all of the drug regimens compared with those of baseline, except for cure rates for hookworm infections with mebendazole and for *T trichiura* infections with levamisole (although in both cases the mean egg counts were reduced substantially). Compared with placebo, all drug treatments produced significantly higher cure rates and egg reduction rates, and lower prevalence at follow-up, except for the egg reduction rate for levamisole in *T trichiura* infections. Both drugs had very high efficacy (98.5% and 99.1% egg reduction rates for levamisole and mebendazole, respectively) against *A lumbricoides*. Mebendazole alone and in combination with levamisole had better

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg plus levamisole 40 mg vs placebo				efficacy than levamisole alone for *T trichiura* infection (81% and 85% vs 41.5% egg reduction rates, P<0.001). Levamisole treatment produced a marginally significant reduction in prevalence of hookworm infection, which was greater than the reduction seen with mebendazole (8.9% vs 3.6%, P<0.05); the combination had better efficacy in reducing prevalence than either drug alone (23.6%, P<0.001). The egg reduction rate for hookworm infection was 88.7% for the combined treatment, but significantly less for either drug alone (61.3% for levamisole and 52.1% for mebendazole, P<0.001). No difference in mebendazole efficacy was found in children who had been treated repeatedly compared with those who had not been treated previously. Secondary: Not reported
Cleary et al.[44] (2007) Mebendazole 100 mg as a single treatment every 3 months vs mebendazole 100 mg as a single treatment every 12 months	CC Persons living along Amazon tributaries in Northeastern Peru	N=126 (stool samples) 2 years	Primary: Cure rates Secondary: Not reported	Primary: At 12 months and 24 months, 91.0% and 92.5% of the treatment group, respectively, had negative stool samples for *A. lumbricoides*. Changes in growth were evaluated based upon the quantity of individuals who were less than the 3rd percentile value for weight. A 12% improvement in those subjects below the 3rd percentile was observed over the villagers living in remote locations (control villages). Secondary: Not reported
Trematodes (Flukes)				
Kjetland et al.[45] (2006) Praziquantel 40 mg/kg as a single dose or 60 mg/kg	OL Women 20 to 49 years of age infected with *Schistosoma*	N=527 12 months	Primary: Cure rate, ova, change in shape and size of lesions, detection of sexually	Primary: *Schistosoma haematobium* ova were found in 39% of women at baseline, which decreased to 7 and 5% at three and 12 months, respectively. At baseline, 46% of the women had "sandy patches" (areas of granulomatous lesions containing schistosome ova), 44% had

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
in two divided doses (five hours apart)	*haematobium* (Zimbabwe)		transmitted diseases Secondary: Not reported	neovascularization, and 23% had contact bleeding. Although urinary ova excretion decreased following treatment (OR, 10.3; 95% CI, 3.8 to 27.8; P<0.001), praziquantel treatment was not associated with a significant reduction in genital lesions or contact bleeding (P=0.31 to P=0.94). There was no influence of human immunodeficiency virus seropositivity on the effect of treatment. There was no significant association between the sexually transmitted diseases and sandy patches, neovascularization or contact bleeding. Secondary: Not reported
Li et al.[46] (2002) Praziquantel 40 mg/kg given at least three times over a five-year period	OL Patients nine to 65 years of age infected with *Schistosoma japonicum* were selected for the five-year longitudinal study, all egg-positive subjects were cured at the start of the study with praziquantel (China)	N=120 5 years	Primary: Prevalence, intensity of infection (defined as geometric mean eggs per gram), ultrasound changes Secondary: Not reported	Primary: Prevalence of schistosome infection fell by 43% and intensity of infection declined by 80% over the five-year study. However, transmission persisted at 13% per year for re-infection or new infection in the cohort. The prevalence of left-lobe enlargement and dilated portal vein fell significantly (P<0.01) to about half, although a few patients progressed during the study. At study endpoint, infection was nearly twice as common if the portal vein was dilated (23 vs 13%, respectively), but this association was not statistically significant (P>0.05). However, end point infection was even more strongly associated with left-lobe enlargement (57 vs 15%; P<0.01). The proportions of subjects with improved parenchymal and periportal fibrosis were much higher than the proportions of subjects that progressed (P<0.05). Reduction of prevalence and intensity of infection and improvement of subclinical morbidity were benefits of repeated treatments. Secondary: Not reported
Kabatereine et al.[47] (2003)	OL Patients five to 54	N=482 12 weeks	Primary: Cure rate, reduction in	Primary: The cure rate following the first and second treatments was 41.9 and 69.1%, respectively. The cure rate was higher in adults than in children,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Praziquantel 40 mg/kg as a single dose, repeated six weeks later	years of age infected with *Schistosoma mansoni* (Uganda)		intensity of infection, adverse reactions Secondary: Not reported	irrespective of intensity of infection. In addition, the cure rate declined markedly with increasing intensity of infection. The reduction in intensity of infection was marked, being 97.7 and 99.6% after the first and second treatments, respectively. A pre- and post-treatment symptom questionnaire revealed a broad range of side effects, including abdominal pain and diarrhea. However, no serious or long-lasting complications affecting compliance were observed. Secondary: Not reported
Raso et al.[48] (2004) Praziquantel 40 mg/kg as a single dose	OL Patients five days to 91 years of age infected with *Schistosoma mansoni* (Côte d'Ivoire)	N=200 6 weeks	Primary: Cure rate, egg reduction rate, adverse reaction Secondary: Not reported	Primary: The overall cure rate, assessed six weeks posttreatment, was 60.9%. The overall cure rates among individuals who had light, moderate, or heavy infections pretreatment were 70.3, 50.0, and 33.3%, respectively. The total egg count reduction was 61.4%. Among the 200 treated patients, 25 (12.5%) reported one or more side effects within 24 hours post-treatment. The most frequent side effects were abdominal pain, dizziness, and diarrhea. Secondary: Not reported
Picquet et al.[49] (1998) Praziquantel 40 mg/kg as a single dose repeated in 40 days	OL Adults and children infected with *Schistosoma mansoni* (Senegal)	N=113 153 days	Primary: Cure rate, egg counts, intensity reduction rate Secondary: Not reported	Primary: The overall cure rate after the first treatment was 42.5 and was 76.1% after the second treatment. The greatest increase in cure rate between the two treatments was in those individuals who were initially the most heavily infected (>1,000 eggs/gram of feces). The overall intensity reduction rate after the first and second treatments were 70.7 and 88.1%, respectively. There was no apparent difference in cure rate between younger (<20 years) and older individuals (>20 years). There was no evidence for the existence of a praziquantel tolerant strain of *Schistosoma mansoni*.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Degu et al.[50] (2002) Praziquantel 40 mg/kg as a single dose	OL All children 10 to 14 years of age attending the primary school in Gorgora, Amhara (Ethiopia)	N=325 6 weeks	Primary: Prevalence of *Schistosoma mansoni*, fecal eggs, egg reduction rate, evidence of resistance Secondary: Not reported	Primary: Of the 325 children examined, 50.8% had *Schistosoma mansoni* eggs in the first fecal sample. Six weeks after treatment, 94% of the children had no detectable *Schistosoma mansoni* eggs, and the average egg reduction rate was 97%. Sixty-seven of the children reported that they had previously been diagnosed with schistosomiasis and had been treated with praziquantel. Of these, 32 (47.8%) were found to be excreting eggs, a proportion not significantly different from the prevalence among children who did not report previous infection (52.2%). No evidence of praziquantel resistance was detected. Secondary: Not reported
Hou et al.[51] (2008) Praziquantel 60 mg/kg plus 6 mg/kg artemether (group A) vs praziquantel 60 mg/kg (group B) vs praziquantel 120 mg/kg plus 6 mg/kg artemether	DB, PC, RCT, Patients ten to 60 years of age weighing over 25 kg and diagnosed with acute *Schistosoma japonicum*	N=205 45 days	Primary: Human infection status Secondary: Hemoglobin and alanine aminotransferase levels over time	Primary: All groups had similarly high treatment efficacies ranging from 95.7% (group D) to 98.0% (group A). Comparisons of group A with group B and group C with group D for the determination of the additive effect of artemether showed that there were no significant difference in treatment efficacies in the regimens that included artemether (P=0.947). The two different dosages of praziquantel provided the same level of efficacy. Fever subsided in 3.9, 5.1, 6.4, and 5.2 days post-artemether treatment in groups A, B, C, and D, respectively (P=0.027). Combined artemether and praziquantel (60 mg/kg) treatment was the most effective for fever clearance. Patients in groups A , B, C, and D remained in hospital on average 6.4, 8.0, 9.4, and 8.9 days, respectively; the hospital stay of patients in group A was significantly shorter than in the other groups (P=0.023).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(group C) vs praziquantel 120 mg/kg (group D)				Secondary: Little change in hemoglobin levels of patients was observed over the course of the trial and there were no significant differences between the groups both pre- and post-treatment. In total, 34 cases had an elevated alanine aminotransferase level before treatment, of which 24 returned to normal at day 20 post-artemether treatment. There were no statistically significant differences between the groups, and the mean levels of alanine aminotransferase at 20 days post-artemether treatment dropped to normal levels.
Martins-Leite et al.[52] (2008) Praziquantel 50 mg/kg once and repeated after two months if necessary	OL Patients presenting with an infection with *Schistosoma mansoni* (Brazil)	N=91 1 year	Primary: Immune response and reversal of Symmers' fibrosis Secondary: Not reported	Primary: A significant reduction in the mean values for longitudinal and anteroposterior measurements of liver (left and right lobes), as well as the diameters of portal and splenic veins was observed. In contrast, the spleen measurements were augmented significantly. The numbers of individuals with non-detectable fibrosis and those with incipient fibrosis increased. One year after treatment with praziquantel, 29% of individuals reverted to a lower degree of fibrosis, 4% experienced an increase in fibrosis, and 67% did not experience any change. The proportion of individuals with pathology (grade 2 or 3) decreased from 24% prior to treatment to 4% after treatment ($P<0.001$). Nine (9.9%) participants remained positive for the presence of eggs of *Schistosoma mansoni*, and their infection levels ranged from four to 184 eggs/gram. When distributed according to the degree of hepatic fibrosis (classified into three groups as determined by posttreatment ultrasound measurements), no statistically significant differences in levels of cytokines could be detected. However, when the levels of these cytokines were categorized as low or high (on the basis of the median value of each cytokine titer for 91 patients) for individuals not presenting (group 0) or presenting (groups 1 and 2) with fibrosis, the proportion of subjects with a high level of IL-13 was significantly larger in the latter two groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Secondary: Not reported
Koukounari et al.[53] (2007) Praziquantel and albendazole Large-scale administration of the agents against soil-transmitted helminths by the national Burkinabe´ helminth control program.	EPI Burkinabe´ children six to 14 years of age	N=1,727 12 months	Primary: Parasitological and morbidity data Secondary: Not reported	Primary: During the 12 months between examinations, the overall prevalences of *Schistosoma haematobium, Schistosoma mansoni,* and hookworm infections decreased significantly (P<0.001). For both years examined, *Ascaris lumbricoides* infection was absent, and the prevalence of *Trichuris trichiura* infection was estimated to be 1.1% at baseline and totally absent one year later. A significant increase in mean hemoglobin concentration (P<0.001) and a significant decrease in the prevalence of anemia (P=0.021) were also observed. The unadjusted observed changes in both recent and chronic undernutrition from baseline to follow-up were not significant (P=0.135 and P=0.093, respectively). Secondary: Not reported
Miscellaneous Infections				
Namwanje et al.[54] (2011) <u>Schistosomiasis alone:</u> Albendazole 400 mg as a single dose + ivermectin 200 µg/kg as a single dose + praziquantel 40 mg/kg as a single dose vs	RCT Children five to 18 years of age with lymphatic filariasis alone; schistosomiasis alone; soil-transmitted helminthiasis alone; lymphatic filariasis + schistosomiasis and lymphatic filariasis + schistosomiasis +	N=235 5 weeks	Primary: Adverse drug events with triple therapy Secondary: Efficacy (mean percentage reduction in egg counts)	Primary: There were no significant differences in adverse drug events in the treatment group compared to the control group. A total of 22.2% of the test group (triple therapy) reported an adverse drug event compared to 66.7% of the control group. The most frequent adverse drug events reported were abdominal pain and headache. Secondary: The overall mean reduction in schistosomiasis eggs for the test group and control group was 99%. There was no significant difference among the treatment groups. The overall mean reduction in soil-transmitted helminthiasis eggs for the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
praziquantel 40 mg/kg as a single dose Schistosomiasis alone: Albendazole 400 mg as a single dose + ivermectin 200 µg/kg as a single dose + praziquantel 40 mg/kg as a single dose vs albendazole 400 mg as a single dose Lymphatic filariasis alone: Albendazole 400 mg as a single dose + ivermectin 200 µg/kg as a single dose + praziquantel 40 mg/kg as a single dose vs albendazole 400 mg as a single dose + ivermectin 200	soil-transmitted helminthiasis			test group was 94 and 93% for control group. There was no significant difference among the treatment groups. The overall mean reduction in lymphatic filariasis microfilariae was 92% in the test group and 99% in the control group. There was no significant difference among the treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
µg/kg as a single dose Lymphatic filariasis + schistosomiasis: Albendazole 400 mg as a single dose + ivermectin 200 µg/kg as a single dose + praziquantel 40 mg/kg as a single dose vs albendazole 400 mg as a single dose + ivermectin 200 µg/kg as a single dose followed by praziquantel 40 mg/kg as a single dose after one week Lymphatic filariasis + schistosomiasis + soil-transmitted helminthiasis: Albendazole 400 mg as a single dose + ivermectin 200 µg/kg as a single dose +				

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
praziquantel 40 mg/kg as a single dose vs albendazole 400 mg as a single dose + ivermectin 200 µg/kg as a single dose followed by praziquantel 40 mg/kg as a single dose after one week				

Study abbreviations: CC=case control, CI=confidence interval, DB=double-blind, EPI=epidemiologic study, MA=meta-analysis, MC=multicenter, OL=open-label, PC=placebo-controlled, PRO=prospective, OR=odds ratio, RCT=randomized-controlled trial, RR=relative risk, SB=single-blind, 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 10. Relative Cost of the Anthelmintics

Generic Name	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Albendazole	tablet	Albenza®	$$$$$	N/A
Ivermectin	tablet	Stromectol®*	$$	N/A
Mebendazole	chewable tablet	Emverm®	$$$$$	N/A
Praziquantel	tablet	Biltricide®	$$$	N/A

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

X. Conclusions

The anthelmintics are approved for the treatment of cestode, nematode, and trematode infections.[1-6] Infections caused by helminths, or parasitic worms, are among the most prevalent infections in the world and are a leading cause of morbidity.[7] Pinworm infections (*Enterobiasis vermicularis*) are the most common helminthic infections in the United States, followed by *Ascaris lumbricoides*.[9]

Albendazole is approved for the treatment of cestode infections, including cystic hydatid disease (liver, lung, and peritoneum) and parenchymal neurocysticercosis. Clinical trials have demonstrated successful treatment of cystic hydatid disease and parenchymal neurocysticercosis with this agent.[13-18]

Ivermectin is approved for the treatment of nematode infections, including onchocerciasis and strongyloidiasis of the intestinal tract. Clinical trials have demonstrated successful treatment of onchocerciasis and strongyloidiasis with this agent.[21-24,27,36]

Mebendazole is approved for the treatment of nematode infections, including ascariasis, hookworms, pinworms, and whipworms. Clinical trials have demonstrated successful treatment of helminthic infections with mebendazole.[30-32,34,43,44]

Praziquantel is approved for the treatment of trematode infections, including clonorchiasis, opisthorchiasis, and schistosomiasis. Several clinical trials have demonstrated successful treatment of schistosomiasis with praziquantel.[45-53]

Albendazole, ivermectin, mebendazole, and praziquantel are considered first-line therapy for some parasitic diseases that are not commonly seen in the United States. Therefore, patients with a diagnosis of one of these uncommon helminthic infections should be allowed approval for a brand anthelmintic through the medical justification portion of the prior authorization process.

Therefore, all brand anthelmintic products 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 anthelmintic 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.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Aminoglycosides
AHFS Class 081202
November 9, 2016

I. Overview

The parenteral aminoglycosides are used empirically as monotherapy or in combination with other antibacterial agents to treat serious infections, such as septicemia, respiratory tract infections, and complicated urinary tract infections.[1-3] Once susceptibility tests are available and a pathogen has been identified, the aminoglycosides are often discontinued so that treatment with a less toxic agent can be initiated.[3] Neomycin is administered orally as adjunctive therapy to suppress the normal bacterial flora of the bowel to prepare the gastrointestinal tract for surgery. It is also used as an adjunctive agent for the treatment of hepatic coma to reduce the ammonia-forming bacteria in the intestinal tract.[1-4] Tobramycin inhalation solution and inhalation powder are approved to improve respiratory symptoms in cystic fibrosis patients colonized with *Pseudomonas aeruginosa*.[5-8]

Currently, there are five inhaled tobramycin agents available on the market. TOBI® (tobramycin solution for inhalation) was the first available agent in 1997, followed by Bethkis® (tobramycin solution for inhalation) in early 2013, TOBI® Podhaler (tobramycin inhalation powder) in June 2013, generic tobramycin inhalation solution in November 2013, and lastly a new preparation, Kitabis® Pak (tobramycin solution for inhalation), in December 2014. All of these products have the same FDA-approved indication of management of cystic fibrosis adults and pediatric patients six years of age and older with *Pseudomonas aeruginosa*.[5-8] The most recently approved agent, Kitabis® Pak (tobramycin solution for inhalation), was FDA approved using the same clinical trial data as TOBI® (tobramycin solution for inhalation). This is the only agent that co-packages the generic tobramycin inhalation solution with a reusable nebulizer (PARI LC Plus™).[8] There are several minor differences between all of these agents, the most notable being that the TOBI® Podhaler (tobramycin inhalation powder) does not require a nebulizer and does not need to be stored in a refrigerator. In addition, the time to administer these agents does vary between products from two to seven minutes for the TOBI® Podhaler (tobramycin inhalation powder) and approximately 15 minutes for the remainder of the tobramycin agents.[2,5-8]

The antibacterial properties of aminoglycosides result from both the inhibition of bacterial protein synthesis and the creation of fissures in the outer membrane of the bacterial cell membrane. Irreversible binding to bacterial ribosomes and disruption of the cell membrane results in leakage of intracellular contents and accounts for most of the bactericidal activity.[3,9,10] The aminoglycosides display concentration-dependent bactericidal activity and a prolonged post-antibiotic effect. They act synergistically when administered with other antibacterial agents.[10] Resistance to the aminoglycosides has been reported infrequently. Amikacin has the broadest spectrum of activity and may be used to treat infections caused by gentamicin- and tobramycin-resistant organisms.[3,11]

The aminoglycosides that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All of the aminoglycosides are available in a generic formulation, with the exception of tobramycin inhalation powder. This class was last reviewed in August 2014. Kitabis® Pak was reviewed as a new drug in May 2016.

Table 1. Aminoglycosides Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Amikacin	injection	N/A	amikacin
Gentamicin	injection	N/A	gentamicin
Neomycin	tablet	N/A	neomycin
Paromomycin	capsule	N/A	paromomycin
Streptomycin	injection	N/A	streptomycin
Tobramycin	inhalation solution, inhalation powder, injection	Bethkis®, Kitabis®*, TOBI®*, TOBI Podhaler®	Bethkis®, Kitabis®, tobramycin

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

The aminoglycosides 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 aminoglycosides 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 Aminoglycosides[1-8]

Organism	Amikacin	Gentamicin	Neomycin	Paromomycin	Streptomycin	Tobramycin
Gram-Positive Bacteria						
Enterococcus faecalis					✔	
Staphylococcus species	✔	✔				
Staphylococcus aureus						✔
Streptococcus viridans					✔	
Gram-Negative Bacteria						
Acinetobacter species	✔					
Aerobacter aerogenes					✔	
Brucella species					✔	
Citrobacter species		✔				✔
Enterobacter species	✔	✔	✔			✔
Escherichia coli	✔	✔	✔		✔	✔
Francisella tularensis					✔	
Haemophilus ducreyi					✔	
Haemophilus influenzae					✔	
Klebsiella species	✔	✔	✔			✔
Klebsiella granulomatis					✔	
Klebsiella pneumoniae					✔	
Morganella morganii						✔
Proteus species	✔	✔			✔	✔
Providencia species	✔					✔
Pseudomonas species	✔					
Pseudomonas aeruginosa		✔				✔
Serratia species	✔	✔				✔
Yersinia pestis					✔	
Miscellaneous Organisms						
Entamoeba histolytica (protozoa)				✔		
Mycobacterium tuberculosis					✔	

II. Evidence-Based Medicine and Current Treatment Guidelines

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

Table 3. Treatment Guidelines Using the Aminoglycosides

Clinical Guideline	Recommendation(s)

European Society of Cardiology: **Guidelines for the Management of Infective Endocarditis (2015)**[12]	Main principles of prevention if infective endocarditis
	• The principle of antibiotic prophylaxis when performing procedures at risk of infective endocarditis (IE) in patients with predisposing cardiac conditions is maintained.
	• Antibiotic prophylaxis must be limited to patients with the highest risk of IE undergoing the highest risk dental procedures (dental procedures requiring manipulation of the gingival or periapical region of the teeth or perforation of the oral mucosa).
	  o Patients with a prosthetic valve, including transcatheter valve, or a prosthetic material used for cardiac valve repair.
	  o Patients with previous IE.
	  o Patients with congenital heart disease.
	• Good oral hygiene and regular dental review are more important than antibiotic prophylaxis to reduce the risk of IE.
	• Aseptic measures are mandatory during venous catheter manipulation and during any invasive procedures in order to reduce the rate of health care-associated IE.
	• Recommended prophylaxis for dental procedures at high-risk:
	  o Single-dose amoxicillin or penicillin 30 to 60 minutes before procedure.
	  o If allergy to penicillin or ampicillin, single-dose clindamycin 30 to 60 minutes before procedure.
	
	Antimicrobial therapy: principles
	• The treatment of infective endocarditis relies on the combination of prolonged antimicrobial therapy and - in about half of patients - surgical eradication of the infected tissues.
	• Prolonged therapy with a combination of bactericidal drugs is the basis of IE treatment. Drug treatment of prosthetic valve endocarditis (PVE) should last longer (at least six weeks) than that of native valve endocarditis (NVE) (two to six weeks).
	• In both NVE and PVE, the duration of treatment is based on the first day of effective antibiotic therapy, not on the day of surgery. A new full course of treatment should only start if valve cultures are positive, the choice of antibiotic being based on the susceptibility of the latest recovered bacterial isolate.
	• The indications and pattern of use of aminoglycosides have changed. They are no longer recommended in staphylococcal NVE because their clinical benefits have not been demonstrated but they can increase renal toxicity; and, when they are indicated in other conditions, aminoglycosides should be given in a single daily dose in order to reduce nephrotoxicity.
	• New antibiotic regimens have emerged in the treatment of staphylococcal IE, including daptomycin and the combination of high-doses of cotrimoxazole plus clindamycin, but additional investigations are necessary in large series before they can be recommended in all patients.
	
	Antimicrobial therapy: regimens
	• Antibiotic treatment of infective endocarditis due to oral streptococci and *Streptococcus* bovis group:
	  o Penicillin-susceptible strains:
	  ▪ Penicillin G, amoxicillin, or ceftriaxone for four weeks.
	  ▪ Penicillin G, amoxicillin, or ceftriaxone plus gentamicin or netilmicin for two weeks.

Clinical Guideline	Recommendation(s)
	▪ Vancomycin for four weeks (in beta-lactam allergic patients). o Penicillin-resistant strains: ▪ Penicillin G, amoxicillin, or ceftriaxone for four weeks plus gentamicin for two weeks. ▪ Vancomycin for four weeks plus gentamicin for two weeks (in beta-lactam allergic patients). • Antibiotic treatment of infective endocarditis due to *Staphylococcus* species: o Methicillin-susceptible strains (native valves): ▪ Flucloxacillin or oxacillin for four to six weeks. ▪ Cotrimoxazole intravenous for one week and oral for five weeks plus clindamycin for one week (for *Staphylococcus aureus*). o Penicillin-allergic patients or methicillin-resistant staphylococci (native valves): ▪ Vancomycin for four to six weeks. ▪ Alternative: Daptomycin for four to six weeks. ▪ Cotrimoxazole intravenous for one week and oral for five weeks plus clindamycin for one week (for *Staphylococcus aureus*). o Methicillin-susceptible strains (prosthetic valves): ▪ Flucloxacillin or oxacillin for at least six weeks, rifampin for at least six weeks, and gentamicin for two weeks. o Penicillin-allergic patients or methicillin-resistant staphylococci (prosthetic valves): ▪ Vancomycin for at least six weeks, rifampin for at least six weeks, and gentamicin for two weeks. • Antibiotic treatment of infective endocarditis due to *Enterococcus* species: o Beta-lactam and gentamicin susceptible strains: ▪ Amoxicillin for four to six weeks plus gentamicin for two to six weeks. ▪ Ampicillin plus gentamicin for six weeks. ▪ Vancomycin plus gentamicin for six weeks. • Antibiotic treatment of blood culture-negative infective endocarditis: o *Brucella* species: ▪ Doxycycline, cotrimoxazole, and rifampin for ≥3 months. o *Coxiella burnetii* (agent of Q fever): ▪ Doxycycline plus hydroxychloroquine for >18 months. o *Bartonella* species: ▪ Doxycycline orally for four weeks plus gentamicin for two weeks. o *Legionella* species: ▪ Levofloxacin intravenous for ≥6 weeks or clarithromycin intravenous for two weeks then orally for four weeks plus rifampin. o *Mycoplasma* species: ▪ Levofloxacin for ≥6 months. o *Tropheryma whipplei* (agent of Whipple's disease): ▪ Doxycycline plus hydroxychloroquine orally for ≥18 months. • Proposed antibiotic regimens for initial empirical treatment of infective endocarditis in acute severely ill patients (before pathogen identification): o Community-acquired native valves or late prosthetic valves (≥12 months post surgery) endocarditis: ▪ Ampicillin intravenous plus flucloxacillin or oxacillin intravenous plus gentamicin intravenous for once dose. ▪ Vancomycin intravenous plus gentamicin intravenous (for penicillin allergic patients).

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	○ Early PVE (<12 months post surgery) or nosocomial and non-nosocomial healthcare associated endocarditis: ▪ Vancomycin intravenous, gentamicin intravenous, and rifampin orally.
American College of Cardiology/American Heart Association: **2008 Focused Update Incorporated Into the American College of Cardiology/ American Heart Association 2006 Guidelines for the Management of Patients With Valvular Heart Disease (2008)[13]** American College of Cardiology/American Heart Association: **Guideline for the Management of Patients With Valvular Heart Disease (2014)[14] (although a more current guideline more detailed information was included as part of the 2008 Focused update; as such both are summarized together)**	<u>Rheumatic fever prophylaxis</u> • Primary prevention of rheumatic heart disease: ○ Penicillin G benzathine intramuscular once or penicillin V orally for 10 days. ○ Erythromycin estolate or erythromycin ethylsuccinate orally for 10 days, or azithromycin orally for five days in patients who are allergic to penicillin. • Secondary prevention of rheumatic fever: ○ Penicillin G benzathine intramuscular every four weeks, or penicillin V orally twice daily, or sulfadiazine orally once daily. ○ Erythromycin orally twice daily for patients who are allergic to penicillin. <u>Endocarditis prophylaxis</u> • Prophylaxis against infective endocarditis is reasonable for the following patients at highest risk for adverse outcomes from infective endocarditis who undergo dental procedures that involve manipulation of either gingival tissue or the periapical region of teeth or perforation of the oral mucosa: ○ Patients with prosthetic cardiac valve or prosthetic material used for cardiac valve repair. ○ Patients with previous infective endocarditis. ○ Patients with congenital heart disease. ○ Cardiac transplant recipients with valve regurgitation due to a structurally abnormal valve. • Prophylaxis against infective endocarditis is not recommended for non-dental procedures (such as transesophageal echocardiogram, esophagogastroduodenoscopy, or colonoscopy) in the absence of active infection. • Regimens for dental procedures (single dose 30 to 60 minutes before procedure): ○ Oral: amoxicillin. ○ Unable to take oral medications: ampicillin, cefazolin or ceftriaxone. ○ Allergic to penicillin or ampicillin (oral): cephalexin, clindamycin, or azithromycin. ○ Allergic to penicillins or ampicillin and unable to take oral medication: cefazolin, ceftriaxone, or clindamycin. • Therapy of native valve endocarditis caused by highly penicillin-susceptible viridans group streptococci and *Streptococcus bovis:* ○ Penicillin G or ceftriaxone for four weeks. ○ Ceftriaxone plus gentamicin for two weeks. ○ Vancomycin for four weeks in patients allergic to penicillin. • Therapy of native valve endocarditis caused by strains of viridans group streptococci and *Streptococcus bovis* relatively resistant to penicillin: ○ Penicillin G or ceftriaxone for four weeks plus gentamicin for two weeks. ○ Vancomycin for four weeks in patients allergic to penicillin. • Therapy for native valve or prosthetic valve enterococcal endocarditis caused by strains susceptible to penicillin, gentamicin, and vancomycin: ○ Ampicillin for four to six weeks or penicillin G plus gentamicin for four to six weeks. ○ Vancomycin plus gentamicin for six weeks in patients allergic to penicillin. • Therapy for endocarditis caused by staphylococci in the absence of prosthetic materials:

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	o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin for six weeks plus the optional addition of gentamicin for three to five days. ▪ Cefazolin for six weeks with the optional addition of gentamicin in patients allergic to penicillin. o Oxacillin-resistant strains: ▪ Vancomycin for six weeks. • Therapy for prosthetic valve endocarditis caused by staphylococci: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin, rifampin, and gentamicin for ≥6 weeks. o Oxacillin-resistant strains: ▪ Vancomycin, rifampin, and gentamicin for ≥6 weeks. • Therapy for both native and prosthetic valve endocarditis caused by *Haemophilus* species *(Haemophilus parainfluenzae, Haemophilus aphrophilus, Haemophilus paraphrophilus), Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* species microorganisms: o Ceftriaxone for four weeks. o Ampicillin-sulbactam for four weeks. o Ciprofloxacin for four weeks. • Therapy for culture-negative endocarditis including *Bartonella* endocarditis: o Native valve: ▪ Ampicillin-sulbactam plus gentamicin (or vancomycin for patients allergic to penicillin) plus ciprofloxacin for four to six weeks. o Prosthetic valve (early; ≤1 year): ▪ Vancomycin for six weeks, plus gentamicin for two weeks, plus cefepime for six weeks, plus rifampin for six weeks. o Prosthetic valve (late; >1 year): ▪ Suspected *Bartonella*, culture negative: • Ceftriaxone for six weeks plus gentamicin with/without doxycycline for six weeks. ▪ Documented *Bartonella*, culture positive: • Doxycycline for six weeks plus gentamicin for two weeks.
American Heart Association: **Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications (2015)**[15]	• Therapy for native valve endocarditis caused by viridans group streptococci and *Streptococcus gallolyticus* (Formerly Known as *Streptococcus bovis)*: o Highly penicillin-susceptible strains: ▪ Penicillin G or ceftriaxone for four weeks. ▪ Penicillin G or ceftriaxone plus gentamicin for two weeks (in patients with uncomplicated infective endocarditis, rapid response to therapy, and no underlying renal disease). ▪ Vancomycin for four weeks (recommended only for patients unable to tolerate penicillin or ceftriaxone therapy). o Relatively penicillin-resistant strains: ▪ Penicillin for four weeks plus gentamicin for the first two weeks. ▪ If the isolate is ceftriaxone susceptible, then ceftriaxone alone may be considered. ▪ Vancomycin for four weeks (recommended only for patients unable to tolerate beta-lactam therapy). • Therapy for native valve endocarditis caused by *A defectiva* and *Granulicatella* Species and viridans group streptococci: o For patients with infective endocarditis caused by *A defectiva*, *Granulicatella* species, and viridans group streptococci with a penicillin MIC ≥0.5 µg/mL, treat with a combination of ampicillin or penicillin

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	plus gentamicin as done for enterococcal infective endocarditis with infectious diseases consultation. o If vancomycin is used in patients intolerant of ampicillin or penicillin, then the addition of gentamicin is not needed. o Ceftriaxone combined with gentamicin may be a reasonable alternative treatment option for isolates that are susceptible to ceftriaxone. • Therapy for endocarditis of prosthetic valves or other prosthetic material caused by viridans group streptococci and *Streptococcus gallolyticus* (Formerly Known as *Streptococcus bovis)*: o Penicillin for six weeks plus gentamicin for the first two weeks. o Extend gentamicin to six weeks if the MIC is >0.12 µg/mL for the infecting strain. o Vancomycin can be used in patients intolerant of penicillin, ceftriaxone, or gentamicin. • Therapy for endocarditis of prosthetic valves or other prosthetic material caused by *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and Groups B, C, F, and G β-Hemolytic Streptococci: o Penicillin, cefazolin, or ceftriaxone for four weeks is reasonable for infective endocarditis caused by *S pneumoniae*; vancomycin can be useful for patients intolerant of β-lactam therapy. o Six weeks of therapy is reasonable for prosthetic valve endocarditis caused by *S pneumoniae*. o High-dose penicillin or a third-generation cephalosporin is reasonable in patients with infective endocarditis caused by penicillin-resistant *S pneumoniae* without meningitis; if meningitis is present, then high doses of cefotaxime (or ceftriaxone) are reasonable. o The addition of vancomycin and rifampin to cefotaxime (or ceftriaxone) may be considered in patients with infective endocarditis caused by *S pneumoniae* that are resistant to cefotaxime. o Because of the complexities of infective endocarditis caused by *S pneumoniae*, consultation with an infectious diseases specialist is recommended. o For infective endocarditis caused by *S pyogenes*, four to six weeks of therapy with aqueous crystalline penicillin G or ceftriaxone is reasonable; vancomycin is reasonable only in patients intolerant of β-lactam therapy. o For infective endocarditis caused by group B, C, or G streptococci, the addition of gentamicin to penicillin G or ceftriaxone for at least the first two weeks of a four to six week treatment course may be considered. o Consultation with an infectious diseases specialist to guide treatment is recommended in patients with infective endocarditis caused by β-hemolytic streptococci. • Therapy for endocarditis caused by staphylococci in the absence of prosthetic valves or other prosthetic material: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin for six weeks. ▪ For penicillin-allergic individuals: cefazolin for six weeks. o Oxacillin-resistant strains ▪ Vancomycin for six weeks. ▪ Daptomycin for six weeks. • Therapy for prosthetic valve endocarditis caused by staphylococci: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin plus rifampin (for at least six weeks) and gentamicin (for two weeks). o Oxacillin-resistant strains: ▪ Vancomycin plus rifampin (for at least six weeks) and

Clinical Guideline	Recommendation(s)
	gentamicin (for two weeks). • Therapy for native valve or prosthetic valve enterococcal endocarditis: o Strains susceptible to penicillin and gentamicin: ▪ Ampicillin or penicillin G plus gentamicin for four to six weeks. ▪ Double β-lactam ampicillin plus ceftriaxone for six. o Strains susceptible to penicillin and resistant to aminoglycosides or streptomycin-susceptible gentamicin-resistant in patients able to tolerate β-Lactam therapy: ▪ Ampicillin plus ceftriaxone for six weeks. ▪ Ampicillin or penicillin G plus streptomycin for four to six weeks. o Vancomycin and aminoglycoside-susceptible penicillin-resistant enterococcus species in patients unable to tolerate β-lactam : ▪ Unable to tolerate β-lactams: • Vancomycin plus gentamicin for six weeks (vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone therapy). ▪ Intrinsic penicillin resistance: • Vancomycin plus gentamicin for six weeks. o Strains Resistant to Penicillin, Aminoglycosides, and Vancomycin: ▪ Linezolid or daptomycin for at least six weeks. • Therapy for both native and prosthetic valve endocarditis caused by *Haemophilus* species *(Haemophilus parainfluenzae, Haemophilus aphrophilus, Haemophilus paraphrophilus), Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* species microorganisms: o Ceftriaxone (cefotaxime or another third- or fourth-generation cephalosporin may be substituted) or ampicillin or ciprofloxacin for four weeks. Fluoroquinolone therapy recommended only for patients unable to tolerate cephalosporin and ampicillin therapy; levofloxacin or moxifloxacin may be substituted. • Therapy for culture-negative endocarditis including *Bartonella* endocarditis: o For patients with acute (days) clinical presentations of native valve infection, coverage for *S aureus*, β-hemolytic streptococci, and aerobic Gram-negative bacilli is reasonable. o For patients with a subacute (weeks) presentation of native valve endocarditis, coverage of *S aureus*, viridans group streptococci, HACEK, and enterococci is reasonable. o For patients with culture-negative prosthetic valve endocarditis, coverage for staphylococci, enterococci, and aerobic Gram-negative bacilli is reasonable if onset of symptoms is within one year of prosthetic valve placement. o If symptom onset is >1 year after valve placement, then infective endocarditis is more likely to be caused by staphylococci, viridans group streptococci, and enterococci, and antibiotic therapy for these potential pathogens is reasonable.
Infectious Diseases Society of America: **Clinical Practice Guidelines: Management of Encephalitis (2008)**[16]	Empirical therapy • Acyclovir should be initiated in all patients with suspected encephalitis, pending results of diagnostic studies. • Other empirical antimicrobial agents should be initiated on the basis of specific epidemiologic or clinical factors, including appropriate therapy for presumed bacterial meningitis, if clinically indicated. • In patients with clinical clues suggestive of rickettsial or ehrlichial infection during the appropriate season, doxycycline should be added to empirical

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(Was reviewed and deemed current as of July 2011)	treatment regimens. Bacteria • *Bartonella bacilliformis:* chloramphenicol, ciprofloxacin, doxycycline, ampicillin, or sulfamethoxazole-trimethoprim is recommended. • *Bartonella henselae:* doxycycline or azithromycin, with or without rifampin, can be considered. • *Listeria monocytogenes:* ampicillin plus gentamicin is recommended; sulfamethoxazole-trimethoprim is an alternative in the penicillin-allergic patient. • *Mycoplasma pneumoniae:* antimicrobial therapy (azithromycin, doxycycline, or a fluoroquinolone) can be considered. • *Tropheryma whipplei:* ceftriaxone, followed by either sulfamethoxazole-trimethoprim or cefixime, is recommended. Helminths • *Baylisascaris procyonis:* albendazole plus diethylcarbamazine can be considered; adjunctive corticosteroids should also be considered. • *Gnathostoma* species: albendazole or ivermectin is recommended. • *Taenia solium:* need for treatment should be individualized; albendazole and corticosteroids are recommended; praziquantel can be considered as an alternative. Rickettsioses and ehrlichiosis • *Anaplasma phagocytophilum:* doxycycline is recommended. • *Ehrlichia chaffeensis:* doxycycline is recommended. • *Rickettsia rickettsii:* doxycycline is recommended; chloramphenicol can be considered an alternative in selected clinical scenarios, such as pregnancy. • *Coxiella burnetii:* doxycycline plus a fluoroquinolone plus rifampin is recommended. Spirochetes • *Borrelia burgdorferi:* ceftriaxone, cefotaxime, or penicillin G is recommended. • *Treponema pallidum:* penicillin G is recommended; ceftriaxone is an alternative. Protozoa • *Acanthamoeba:* sulfamethoxazole-trimethoprim plus rifampin plus ketoconazole or fluconazole plus sulfadiazine plus pyrimethamine can be considered. • *Balamuthia mandrillaris:* pentamidine, combined with a macrolide (azithromycin or clarithromycin), fluconazole, sulfadiazine, flucytosine, and a phenothiazine can be considered. • *Naegleria fowleri:* amphotericin B (intravenous and intrathecal) and rifampin, combined with other agents, can be considered. • *Plasmodium falciparum:* quinine, quinidine, or artemether is recommended; atovaquone-proguanil is an alternative; exchange transfusion is recommended for patients with 110% parasitemia or cerebral malaria; corticosteroids are not recommended. • *Toxoplasma gondii:* pyrimethamine plus either sulfadiazine or clindamycin is recommended; sulfamethoxazole-trimethoprim alone and pyrimethamine plus atovaquone, clarithromycin, azithromycin, or dapsone are alternatives. • *Trypanosoma brucei gambiense:* eflornithine is recommended; melarsoprol is an alternative. • *Trypanosoma brucei rhodesiense:* melarsoprol is recommended.
European Federation of Neurological Societies:	Empirical therapy • Ceftriaxone 2 g every 12 to 24 hours or cefotaxime 2 g every six to eight hours. • Alternative therapy: meropenem 2 g every eight hours or chloramphenicol 1 g

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Guideline on the Management of Community-acquired Bacterial Meningitis (2008)[17]	every six hours. • If penicillin or cephalosporin-resistant pneumococcus is suspected, use ceftriaxone or cefotaxime plus vancomycin 60 mg/kg every 24 hours after a loading dose of 15 mg/kg. • Ampicillin-amoxicillin 2 g every four hours if *Listeria* is suspected. <u>Pathogen specific therapy</u> • Penicillin-sensitive pneumococcal meningitis: o Benzyl penicillin 250,000 U/kg/day, ampicillin-amoxicillin 2 g every four hours, ceftriaxone 2 g every 12 hours or cefotaxime 2 g every six to eight hours. o Alternative therapy: meropenem 2 g every eight hours or vancomycin 60 mg/kg every 24 hours as a continuous infusion after a 15 mg/kg loading dose plus rifampicin 600 mg every 12 hours, or moxifloxacin 400 mg daily. • Pneumococcus with reduced susceptibility to penicillin or cephalosporins: o Ceftriaxone or cefotaxime plus vancomycin±rifampicin. o Alternative therapy: moxifloxacin, meropenem or linezolid 600 mg combined with rifampicin. • Meningococcal meningitis: o Benzyl penicillin, ceftriaxone, or cefotaxime. o Alternative therapy: meropenem, chloramphenicol, or moxifloxacin. • *Haemophilus influenzae* type B: o Ceftriaxone or cefotaxime. o Alternative therapy: chloramphenicol–ampicillin-amoxicillin. • Listerial meningitis: o Ampicillin or amoxicillin 2 g every four hours±gentamicin 1 to 2 mg every eight hours for the first seven to 10 days. o Alternative therapy: sulfamethoxazole-trimethoprim 10 to 20 mg/kg every six to 12 hours or meropenem. • *Staphylococcal* species: o Flucloxacillin 2 g every four hours or vancomycin if penicillin allergy is suspected. o Rifampicin should also be considered in addition to either agent. Linezolid should be considered for methicillin-resistant staphylococcal meningitis. • Gram-negative *Enterobacteriaceae*: o Ceftriaxone, cefotaxime or meropenem. • Pseudomonal meningitis: o Meropenem±gentamicin.
Infectious Diseases Society of America: **Practice Guidelines for the Management of Bacterial Meningitis (2004)**[18]	<u>Empiric therapy</u> • Empirical antimicrobial therapy is initiated either when the lumbar puncture is delayed or for patients with purulent meningitis and a negative cerebrospinal fluid gram stain result: o Age <1 month: ampicillin plus cefotaxime or ampicillin plus an aminoglycoside. o Age one to 23 months: vancomycin plus a third-generation cephalosporin. o Age two to 50 years: vancomycin plus a third-generation cephalosporin. o Age >50 years: vancomycin plus ampicillin plus a third-generation cephalosporin. o Basilar skull fracture: vancomycin plus a third-generation cephalosporin. o Penetrating head trauma: vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem.

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	o Post neurosurgery: vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem. o Cerebrospinal fluid shunt: vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem. <u>Specific therapy</u> • Recommendations for specific antimicrobial therapy in bacterial meningitis are based on isolated pathogens and susceptibility. • *Streptococcus pneumoniae* o Penicillin minimum inhibitory concentrations <0.1 µg/mL: standard therapy includes penicillin G or ampicillin; alternative therapies include ceftriaxone, cefotaxime, or chloramphenicol. o Penicillin minimum inhibitory concentrations 0.1 to 1.0 µg/mL: standard therapy includes ceftriaxone or cefotaxime; alternative therapies include cefepime or meropenem. o Penicillin minimum inhibitory concentrations ≥2 µg/mL: standard therapies include vancomycin plus ceftriaxone or cefotaxime; alternative therapies include gatifloxacin or moxifloxacin. o Cefotaxime or ceftriaxone minimum inhibitory concentrations ≥1.0 µg/mL: standard therapies include vancomycin plus ceftriaxone or cefotaxime (consider addition of rifampin if minimum inhibitory concentrations of ceftriaxone is >2 µg/mL); alternative therapies include gatifloxacin or moxifloxacin. • *Neisseria meningitides* o Penicillin minimum inhibitory concentrations <0.1 µg/mL: standard therapy includes penicillin G or ampicillin; alternative therapy includes ceftriaxone, cefotaxime or chloramphenicol. o Penicillin minimum inhibitory concentrations 0.1 to 1.0 µg/mL: standard therapy includes ceftriaxone or cefotaxime; alternative therapies include chloramphenicol, a fluoroquinolone or meropenem. • *Listeria monocytogenes* o Standard therapy includes ampicillin or penicillin G; alternative therapies include sulfamethoxazole-trimethoprim or meropenem. • *Streptococcus agalactiae* o Standard therapy includes ampicillin or penicillin G; alternative therapies include ceftriaxone or cefotaxime. • *Escherichia coli* and other Enterobacteriaceae o Standard therapy includes a third-generation cephalosporin; alternative therapies include aztreonam, fluoroquinolone, meropenem, sulfamethoxazole-trimethoprim or ampicillin. • *Pseudomonas aeruginosa* o Standard therapies include cefepime or ceftazidime; alternative therapies include aztreonam, ciprofloxacin, or meropenem (addition of an aminoglycoside should be considered). • *Haemophilus influenzae* β-lactamase negative strains o Standard therapy includes ampicillin; alternative therapies include ceftriaxone, cefotaxime, cefepime, chloramphenicol or a fluoroquinolone. • *Haemophilus influenzae* β-lactamase positive strains o Standard therapy includes a third-generation cephalosporin; alternative therapies include cefepime, chloramphenicol or a fluoroquinolone. • *Staphylococcus aureus* methicillin susceptible o Standard therapy includes nafcillin or ofloxacin; alternative therapies include vancomycin or meropenem. • *Staphylococcus aureus* methicillin resistant o Standard therapy includes vancomycin (consider addition of rifampin);

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	alternative therapies include sulfamethoxazole-trimethoprim or linezolid.
	• *Staphylococcus epidermidis*
	  o Standard therapy includes vancomycin (consider addition of rifampin); alternative therapy includes linezolid.
	• *Enterococcus* species ampicillin susceptible
	  o Standard therapy includes ampicillin plus gentamicin.
	• *Enterococcus* species ampicillin resistant
	  o Standard therapy includes vancomycin plus gentamicin.
	• *Enterococcus* species ampicillin and vancomycin resistant
	  o Standard therapy includes linezolid.

Infectious Diseases Society of America: **Practice Guidelines for the Diagnosis and Management of Skin and Soft-Tissue Infections (2014)**[19]	Impetigo and ecthyma
	• Gram stain and culture of the pus or exudates from skin lesions of impetigo and ecthyma are recommended to help identify whether *Staphylococcus aureus* and/or a β-hemolytic *Streptococcus* is the cause (strong, moderate), but treatment without these studies is reasonable in typical cases.
	• Bullous and nonbullous impetigo can be treated with oral or topical antimicrobials, but oral therapy is recommended for patients with numerous lesions or in outbreaks affecting several people to help decrease transmission of infection. Treatment for ecthyma should be an oral antimicrobial.
	  o Treatment of bullous and nonbullous impetigo should be with either mupirocin or retapamulin twice daily for five days.
	  o Oral therapy for ecthyma or impetigo should be a seven-day regimen with an agent active against *S. aureus* unless cultures yield streptococci alone (when oral penicillin is the recommended agent). Because *S. aureus* isolates from impetigo and ecthyma are usually methicillin susceptible, dicloxacillin or cephalexin is recommended. When methcillin-resistant *S. aureus* (MRSA) is suspected or confirmed, doxycycline, clindamycin, or sulfamethoxazole-trimethoprim is recommended.
	
	Purulent skin and soft-tissue infections (cutaneous abscesses, furuncles, carbuncles, and inflamed epidermoid cysts)
	• Gram stain and culture of pus from carbuncles and abscesses are recommended, but treatment without these studies is reasonable in typical cases. Gram stain and culture of pus from inflamed epidermoid cysts are not recommended.
	• Incision and drainage is the recommended treatment for inflamed epidermoid cysts, carbuncles, abscesses, and large furuncles.
	• The decision to administer antibiotics directed against *S. aureus* as an adjunct to incision and drainage should be made based upon presence or absence of systemic inflammatory response syndrome (SIRS), such as temperature >38°C or <36°C, tachypnea >24 breaths per minute, tachycardia >90 beats per minute, or white blood cell count >12 000 or <400 cells/µL. An antibiotic active against MRSA is recommended for patients with carbuncles or abscesses who have failed initial antibiotic treatment or have markedly impaired host defenses or in patients with SIRS and hypotension.
	
	Recurrent skin abscesses
	• A recurrent abscess at a site of previous infection should prompt a search for local causes such as a pilonidal cyst, hidradenitis suppurativa, or foreign material.
	• Recurrent abscesses should be drained and cultured early in the course of infection.
	• After obtaining cultures of recurrent abscess, treat with a five to ten day

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	course of an antibiotic active against the pathogen isolated. • Consider a five-day decolonization regimen twice daily of intranasal mupirocin, daily chlorhexidine washes, and daily decontamination of personal items such as towels, sheets, and clothes for recurrent *S. aureus* infection. • Adult patients should be evaluated for neutrophil disorders if recurrent abscesses began in early childhood. Erysipelas and cellulitis • Cultures of blood or cutaneous aspirates, biopsies, or swabs are not routinely recommended except in patients with malignancy on chemotherapy, neutropenia, severe cell-mediated immunodeficiency, immersion injuries, and animal bites. • Typical cases of cellulitis without systemic signs of infection should receive an antimicrobial agent that is active against streptococci. For cellulitis with systemic signs of infection (moderate nonpurulent), systemic antibiotics are indicated. Many clinicians could include coverage against methicillin-susceptible *S. aureus* (MSSA). For patients whose cellulitis is associated with penetrating trauma, evidence of MRSA infection elsewhere, nasal colonization with MRSA, injection drug use, or SIRS (severe nonpurulent), vancomycin or another antimicrobial effective against both MRSA and streptococci is recommended. In severely compromised patients, broad-spectrum antimicrobial coverage may be considered. Vancomycin plus either piperacillin-tazobactam or imipenem/meropenem is recommended as a reasonable empiric regimen for severe infections. • The recommended duration of antimicrobial therapy is five days, but treatment should be extended if the infection has not improved within this time period. Surgical site infections • Suture removal plus incision and drainage should be performed for surgical site infections. • Adjunctive systemic antimicrobial therapy is not routinely indicated, but in conjunction with incision and drainage may be beneficial for surgical site infections associated with a significant systemic response. • A brief course of systemic antimicrobial therapy is indicated in patients with surgical site infections following clean operations on the trunk, head and neck, or extremities that also have systemic signs of infection. • A first-generation cephalosporin or an antistaphylococcal penicillin for MSSA, or vancomycin, linezolid, daptomycin, telavancin, or ceftaroline where risk factors for MRSA are high (nasal colonization, prior MRSA infection, recent hospitalization, recent antibiotics), is recommended. • Agents active against gram-negative bacteria and anaerobes, such as a cephalosporin or fluoroquinolone in combination with metronidazole, are recommended for infections following operations on the axilla, gastrointestinal tract, perineum, or female genital tract. Necrotizing fasciitis • Empiric antibiotic treatment should be broad (e.g., vancomycin or linezolid plus piperacillin-tazobactam or a carbapenem; or plus ceftriaxone and metronidazole), as the etiology can be polymicrobial (mixed aerobic–anaerobic microbes) or monomicrobial (group A streptococci, community-acquired MRSA). • Penicillin plus clindamycin is recommended for treatment of documented group A streptococcal necrotizing fasciitis.

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	Pyomyositis
	• Cultures of blood and abscess material should be obtained.
	• Vancomycin is recommended for initial empirical therapy. An agent active against enteric gram-negative bacilli should be added for infection in immunocompromised patients or following open trauma to the muscles.
	• Cefazolin or antistaphylococcal penicillin (e.g., nafcillin or oxacillin) is recommended for treatment of pyomyositis caused by MSSA.
	• Antibiotics should be administered intravenously initially, but once the patient is clinically improved, oral antibiotics are appropriate for patients in whom bacteremia cleared promptly and there is no evidence of endocarditis or metastatic abscess. Two to three weeks of therapy is recommended.
	
	Clostridial gas gangrene or myonecrosis
	• Urgent surgical exploration of the suspected gas gangrene site and surgical debridement of involved tissue should be performed.
	• In the absence of a definitive etiologic diagnosis, broad-spectrum treatment with vancomycin plus either piperacillin-tazobactam, ampicillin-sulbactam, or a carbapenem antimicrobial is recommended. Definitive antimicrobial therapy with penicillin and clindamycin is recommended for treatment of clostridial myonecrosis.
	
	Animal bites
	• Preemptive early antimicrobial therapy for three to five days is recommended for patients who:
	  o are immunocompromised;
	  o are asplenic;
	  o have advanced liver disease;
	  o have preexisting or resultant edema of the affected area;
	  o have moderate to severe injuries, especially to the hand or face; or
	  o have injuries that may have penetrated the periosteum or joint capsule.
	• 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
	  o β-lactam-β-lactamase combinations, piperacillin-tazobactam, second-generation cephalosporins, and carbapenems.
	• Tetanus toxoid should be administered to patients without toxoid vaccination within 10 years. Tetanus, diphtheria, and tetanus (Tdap) is preferred over Tetanus and diphtheria (Td) if the former has not been previously given.
	
	Cutaneous anthrax
	• Oral penicillin V 500 mg four times daily for seven to 10 days is the recommended treatment for naturally acquired cutaneous anthrax.
	• Ciprofloxacin 500 mg by mouth twice daily or levofloxacin 500 mg intravenously/orally every 24 hours for 60 days is recommended for bioterrorism cases because of presumed aerosol exposure.
	
	Bacillary angiomatosis and cat scratch disease
	• Azithromycin is recommended for cat scratch disease (strong, moderate)

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	according to the following dosing protocol: o Patients >45 kg: 500 mg on day one followed by 250 mg for four additional days. o Patients <45 kg: 10 mg/kg on day one and 5 mg/kg for four more days. • Erythromycin 500 mg four times daily or doxycycline 100 mg bid for two weeks to two months is recommended for treatment of bacillary angiomatosis. Erysipeloid • Penicillin (500 mg four times daily) or amoxicillin (500 mg three times daily) for seven to 10 days is recommended for treatment of erysipeloid. Glanders • Ceftazidime, gentamicin, imipenem, doxycycline, or ciprofloxacin is recommended based on in vitro susceptibility. Bubonic plague • Bubonic plague should be diagnosed by Gram stain and culture of aspirated material from a suppurative lymph node. Streptomycin (15 mg/kg intramuscularly every 12 hours) or doxycycline (100 mg twice daily by mouth) is recommended for treatment of bubonic plague. Gentamicin could be substituted for streptomycin. Tularemia • Streptomycin (15 mg/kg every 12 hours intramuscularly) or gentamicin (1.5 mg/kg every eight hours intravenously) is recommended for treatment of severe cases of tularemia. • Tetracycline (500 mg four times daily) or doxycycline (100 mg twice daily by mouth) is recommended for treatment of mild cases of tularemia.
Centers for Disease Control and Prevention: **Sexually Transmitted Diseases Treatment Guidelines (2015)**[20]	Arthritis and arthritis-dermatitis syndrome • Recommended regimen: o Ceftriaxone 1 g intramuscularly or intravenously every 24 hours plus azithromycin 1 g orally in a single dose. • Alternative regimen: o Cefotaxime 1 g intravenously every eight hours or ceftizoxime 1 g intravenously every eight hours plus azithromycin 1 g orally in a single dose. Bacterial vaginosis • Recommended regimens: o Metronidazole 500 mg orally twice a day for seven days. o Metronidazole gel 0.75%, one full applicator (5 g) intravaginally, once a day for five days. o Clindamycin cream 2%, one full applicator (5 g) intravaginally at bedtime for seven days. • Alternative regimens: o Tinidazole 2 g orally once daily for two days. o Tinidazole 1 g 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. Cervicitis • Recommended regimens for presumptive treatment:

Clinical Guideline	Recommendation(s)
	o Azithromycin 1 g orally in a single dose. o Doxycycline 100 mg orally twice a day for seven days. Chancroid • Recommended regimens: o Azithromycin 1 g 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. Chlamydial infections • Recommended regimens: o Azithromycin 1 g 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. Chlamydial infections among children • 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 g orally in a single dose. • Recommended regimens for children ≥8 years of age: o Azithromycin 1 g orally in a single dose. o Doxycycline 100 mg orally twice a day for seven days. Disseminated gonococcal infection • Recommended regimen: o Ceftriaxone 1 g intramuscular or intravenous every 24 hours. • Alternative regimens: o Cefotaxime 1 g intravenous every eight hours. o Ceftizoxime 1 g intravenous every eight hours. Epididymitis • 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. Granuloma inguinale (Donovanosis) • Recommended regimen: o Azithromycin 1 g orally once per week or 500 mg daily for at least three weeks and until all lesions have completely healed. • Alternative regimens: o Doxycycline 100 mg orally twice a day 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.

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	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 g intramuscular in a single dose plus azithromycin 1 g orally 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 25 to 50 mg/kg intravenous or intramuscular in a single dose, not to exceed 125 mg. • Recommended regimen for children who weigh ≤45 kg and who have bacteremia or arthritis: o Ceftriaxone 50 mg/kg (maximum dose: 1 g) 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 g intravenous every 12 hours plus azithromycin 1 g orally in a single dose. <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 g 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:

Clinical Guideline	Recommendation(s)
	o Erythromycin base or ethylsuccinate 50 mg/kg/day orally divided into four doses daily for 14 days. • Alternative regimen: o Azithromycin suspension, 20 mg/kg/day orally, one dose daily for three days. Pelvic inflammatory disease • Recommended parenteral regimen A: o Cefotetan 2 g intravenous every 12 hours. o Cefoxitin 2 g 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 g 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 g intramuscular in a single dose and probenecid, 1 g 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. Proctitis, proctocolitis, and enteritis • Recommended regimen: o Ceftriaxone 250 mg intramuscular plus doxycycline 100 mg orally twice a day for seven days. Recurrent and persistent urethritis • Recommended regimens: o Metronidazole 2 g orally in a single dose. o Tinidazole 2 g orally in a single dose plus azithromycin 1 g orally in a single dose (if not used for initial episode). Primary and secondary syphilis • 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. Early latent syphilis • 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.

Clinical Guideline	Recommendation(s)
	Late latent syphilis or latent syphilis of unknown duration • 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. Tertiary syphilis • 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. Trichomoniasis • Recommended regimen: o Metronidazole 2 g orally in a single dose. o Tinidazole 2 g orally in a single dose. • Alternative regimen: o Metronidazole 500 mg orally twice a day for seven days. Neurosyphilis • 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. Uncomplicated gonococcal infections of the cervix, urethra, and rectum • 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 1g orally in a single dose or doxycycline 100 mg orally twice a day for seven days. Uncomplicated gonococcal infections of the pharynx • Recommended regimens: o Ceftriaxone 250 mg intermuscular in a single dose plus azithromycin 1g orally in a single dose or doxycycline 100 mg orally twice a day for seven 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**	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 g 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

Clinical Guideline	Recommendation(s)
Women (2010)[21] Reviewed and deemed current as of 07/2013	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 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 g 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 g 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 g 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 g 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.

American College of Obstetricians and Gynecologists: **Treatment of Urinary Tract Infections in Nonpregnant Women (2008)[22]**	• 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 g dose (powder) single dose.

Cystic Fibrosis	<u>Aerosolized antibiotics</u>

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Foundation: **Cystic Fibrosis Pulmonary Guidelines (2013)**[23]	• For patients with cystic fibrosis, six years of age and older, who have moderate to severe lung disease with *Pseudomonas aeruginosa* persistently present in cultures of the airways, the chronic use of inhaled tobramycin to improve lung function, improve quality of life, and reduce exacerbations is strongly recommended. • For patients with cystic fibrosis, six years of age or older, who have mild lung disease, and with *Pseudomonas aeruginosa* persistently present in cultures of the airways, chronic use of inhaled tobramycin to reduce exacerbations is recommended. • For patients with cystic fibrosis, six years of age and older, who have moderate to severe lung disease with *Pseudomonas aeruginosa* persistently present in cultures of the airways, the chronic use of inhaled aztreonam to improve lung function and quality of life is strongly recommended. • For patients with cystic fibrosis, six years of age or older, who have mild lung disease, and with *Pseudomonas aeruginosa* persistently present in cultures of the airways, chronic use of inhaled aztreonam to improve lung function and quality of life is recommended. • For patients with cystic fibrosis, six years of age or older, with *Pseudomonas aeruginosa* persistently present in cultures of the airways, there is insufficient evidence to recommend for or against routinely providing other chronically inhaled antibiotics (i.e., carbenicillin, ceftazidime, colistin, gentamicin) to improve lung function, improve quality of life, or reduce exacerbations. <u>Anti-inflammatory agents</u> • For patients with cystic fibrosis, six years of age or older, without asthma or allergic bronchopulmonary aspergillosis, routine use of inhaled corticosteroids to improve lung function, quality of life and reduce pulmonary exacerbations is not recommended. • For patients with cystic fibrosis, six years of age or older, without asthma or allergic bronchopulmonary aspergillosis, chronic use of oral corticosteroids to improve lung function, quality of life or reduce exacerbations is not recommended. • For patients with cystic fibrosis, between six and 17 years of age, with an forced expiratory volume in one second greater than or equal to 60% predicted, the chronic use of oral ibuprofen, at a peak plasma concentration of 50 to 100 µg/mL, to slow the loss of lung function is recommended. • For patients with cystic fibrosis, 18 years of age and older, the evidence is insufficient to recommend for or against the chronic use of oral ibuprofen to slow the loss of lung function or reduce exacerbations. • For patients with cystic fibrosis, six years of age or older, there is insufficient evidence to recommend for or against routinely providing the chronic use of leukotriene modifiers to improve lung function, quality of life, or reduce exacerbations. <u>Antipseudomonal antibiotics</u> • For patients with cystic fibrosis, six years of age and older, with *Pseudomonas aeruginosa* persistently present in cultures of the airways, there is insufficient evidence to recommend for or against routinely providing the chronic use of oral antipseudomonal antibiotics to improve lung function, quality of life, or reduce exacerbations. <u>Antistaphylococcal antibiotics</u> • For patients with cystic fibrosis, six years of age or older, with *Staphylococcus aureus* persistently present in cultures of the airways, there is insufficient evidence to recommend for or against the chronic use of oral antistaphylococcal

Clinical Guideline	Recommendation(s)
	antibiotics to improve lung function and quality of life or reduce exacerbations. • For patients with cystic fibrosis, prophylactic use of oral antistaphylococcal antibiotics to improve lung function and quality of life or to reduce exacerbations is not recommended. <u>Bronchodilators</u> • For patients with cystic fibrosis, six years of age or older, there is insufficient evidence to recommend for or against chronic use of inhaled β_2-adrenergic receptor agonists to improve lung function and quality of life or reduce exacerbations. • For patients with cystic fibrosis, six years of age or older, there is insufficient evidence to recommend for or against routinely providing the chronic use of inhaled anticholinergic bronchodilators to improve lung function and quality of life or reduce exacerbations. • For patients with cystic fibrosis, six years of age or older, there is insufficient evidence to recommend for or against routinely providing chronic use of inhaled or oral N-acetylcysteine or inhaled glutathione to improve lung function, quality of life or reduce exacerbations. <u>Hypertonic saline</u> • For patients with cystic fibrosis, six years of age or older, chronic use of inhaled hypertonic saline to improve lung function, improve quality of life, and to reduce exacerbations is recommended. <u>Ivacaftor</u> • For patients with cystic fibrosis, six years of age or older, with at least one G551D CFTR mutation, the chronic use of ivacaftor to improve lung function, quality of life, and to reduce exacerbations is strongly recommended. <u>Macrolide antibiotics</u> • For patients with cystic fibrosis, six years of age or older, and with *Pseudomonas aeruginosa* persistently present in cultures of the airways, chronic use of azithromycin to improve lung function and to reduce exacerbations is recommended. • For patients with cystic fibrosis, six years of age or older, without *Pseudomonas aeruginosa* persistently present in cultures of the airways, chronic use of azithromycin to reduce exacerbations is recommended. <u>Recombinant human DNase</u> • For patients with cystic fibrosis, six years of age or older, with moderate to severe lung disease, chronic use of dornase alfa to improve lung function, improve quality of life, and reduce exacerbations is strongly recommended. • For patients with cystic fibrosis, six years of age or older, and asymptomatic or with mild lung disease, chronic use of dornase alfa to improve lung function and reduce exacerbations is recommended.
Infectious Diseases Society of America: **Management of Community-Acquired Pneumonia in Infants and Children Older Than 3 Months of Age (2011)**[24] Reviewed and deemed	<u>Outpatient treatment</u> • Antimicrobial therapy is not routinely required for preschool-aged children with community-acquired pneumonia, because viral pathogens are responsible for the great majority of clinical disease. • Amoxicillin should be used as first-line therapy for previously healthy, appropriately immunized infants and preschool children with mild to moderate community-acquired pneumonia suspected to be of bacterial origin. Amoxicillin provides appropriate coverage for *Streptococcus pneumoniae*. • For patients allergic to amoxicillin, the following agents are considered alternative treatment options:

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current as of 04/2013	○ Second- or third-generation cephalosporin (cefpodoxime, cefuroxime, cefprozil). ○ Levofloxacin (oral therapy). ○ Linezolid (oral therapy). • Macrolide antibiotics should be prescribed for treatment of children (primarily school-aged children and adolescents) evaluated in an outpatient setting with findings compatible with community-acquired pneumonia caused by atypical pathogens. <u>Inpatient treatment</u> • Ampicillin or penicillin G should be administered to the fully immunized infant or school-aged child admitted to a hospital ward with community-acquired pneumonia when local epidemiologic data document lack of substantial high-level penicillin resistance for invasive *Streptococcus pneumoniae*. • Empiric therapy with a third-generation parenteral cephalosporin (ceftriaxone or cefotaxime) should be prescribed for hospitalized infants and children who are not fully immunized, in regions where local epidemiology of invasive pneumococcal strains documents high-level penicillin resistance, or for infants and children with life-threatening infection, including those with empyema. • Non–β-lactam agents, such as vancomycin, have not been shown to be more effective than third-generation cephalosporins in the treatment of pneumococcal pneumonia for the degree of resistance noted currently in North America. • Empiric combination therapy with a macrolide (oral or parenteral), in addition to a β-lactam antibiotic, should be prescribed for the hospitalized child for whom *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* are significant considerations. • Vancomycin or clindamycin (based on local susceptibility data) should be provided in addition to β-lactam therapy if clinical, laboratory, or imaging characteristics are consistent with infection caused by *Staphylococcus aureus*.
Infectious Diseases Society of America/American Thoracic Society: **Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults (2007)**[25]	<u>Empirical antimicrobial therapy</u> • Recommendations are generally for a class of antibiotics rather than for a specific drug, unless outcome data clearly favor one drug. • Because overall efficacy remains good for many classes of agents, the more potent drugs are given preference because of their benefit in decreasing the risk of selection for antibiotic resistance. • Outpatient treatment ○ Previously healthy and no risk factors for drug-resistant *Streptococcus pneumoniae* infection: ▪ Macrolide (azithromycin, clarithromycin, or erythromycin). ▪ Doxycycline. ○ Presence of comorbidities, such as chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressing conditions or use of immunosuppressing drugs; use of antimicrobials within the previous three months (in which case an alternative from a different class should be selected); or other risks for drug-resistant Streptococcus pneumoniae infection: ▪ Respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin). ▪ β-lactam plus a macrolide (high-dose amoxicillin or amoxicillin-clavulanate is preferred; alternatives include ceftriaxone, cefpodoxime, and cefuroxime; doxycycline is an alternative to the macrolide). ○ In regions with a high rate of infection with high-level macrolide-resistant *Streptococcus pneumoniae*, consider the use of alternative agents listed above for any patient, including those without comorbidities.

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	• Inpatient, non-intensive care unit treatment
	  o Respiratory fluoroquinolone.
	  o β-lactam plus a macrolide (preferred β-lactam agents include cefotaxime, ceftriaxone, and ampicillin; ertapenem for selected patients; with doxycycline as an alternative to the macrolide. A respiratory fluoroquinolone should be used for penicillin-allergic patients).
	• Inpatient, intensive care unit treatment
	  o β-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) plus either azithromycin or a fluoroquinolone (for penicillin-allergic patients, a respiratory fluoroquinolone and aztreonam are recommended).
	  o For *Pseudomonas* infection, use an antipneumococcal, antipseudomonal β-lactam (piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin; OR
	  o Antipneumococcal, antipseudomonal β-lactam (listed above) plus an aminoglycoside and azithromycin; OR
	  o Antipneumococcal, antipseudomonal β-lactam (listed above) plus an aminoglycoside and an antipneumococcal fluoroquinolone (for penicillin-allergic patients, substitute aztreonam for the above β-lactam).
	  o For community-acquired methicillin-resistant *Staphylococcus aureus* infection, add vancomycin or linezolid.

American Thoracic Society/Infectious Diseases Society of America: **Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia (2005)**[26]	• Select an initial empiric therapy based on the absence or presence of risk factors for multidrug-resistant pathogens. These risk factors include prolonged duration of hospitalization (five days or more), admission from a healthcare-related facility, and recent prolonged antibiotic therapy.
	• Patients with healthcare-related pneumonia should be treated for potentially drug-resistant organisms, regardless of when during the hospital stay the pneumonia begins.
	• In selecting empiric therapy for patients who have recently received an antibiotic, an effort should be made to use an agent from a different antibiotic class, because recent therapy increases the probability of inappropriate therapy and can predispose to resistance to that same class of antibiotics.
	• Initial empiric antibiotic therapy for hospital-acquired pneumonia or ventilator-associated pneumonia in patients with no known risk factors for multidrug-resistant pathogens, early onset, and any disease severity:
	  o Ceftriaxone; OR
	  o Levofloxacin, moxifloxacin, ciprofloxacin; OR
	  o Ampicillin-sulbactam; OR
	  o Ertapenem.
	• Initial empiric antibiotic therapy for hospital-acquired pneumonia, ventilator-associated pneumonia, and healthcare-associated pneumonia in patients with late-onset disease or risk factors for multidrug-resistant pathogens and all disease severity–combination antibiotic therapy is recommended as follows:
	  o Antipseudomonal cephalosporin (cefepime, ceftazidime) or antipseudomonal carbapenem (imipenem or meropenem) or β-lactam-β-lactamase inhibitor (piperacillin-tazobactam) plus antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) or aminoglycoside (amikacin, gentamicin, or tobramycin) plus linezolid or vancomycin if methicillin-resistant *Staphylococcus aureus* risk factors are present or there is a high incidence locally.

World Health Organization: **Treatment of Tuberculosis (2010)**[27]	<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 for three times weekly. • Fixed-dose combination products are recommended to help prevent drug resistance. Prescription errors are likely to be less frequent because dosage

Clinical Guideline	Recommendation(s)
	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. New patients • The two-month rifampicin regimen (two isoniazid, rifampicin, pyrazinamide and ethambutol/six isoniazid and ethambutol) is associated with more relapses and deaths than the six-month rifampicin regimen (two isoniazid, rifampicin, pyrazinamide and ethambutol/four 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 isoniazid, rifampicin, pyrazinamide and ethambutol /six 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 isoniazid, rifampicin, pyrazinamide and ethambutol/four (isoniazid and rifampicin) three] provided that each dose is directly observed. • Three times weekly dosing throughout therapy [two (isoniazid, rifampicin, pyrazinamide and ethambutol) three/four (isoniazid and rifampicin) three] 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. Standard regimens for previously treated patients • 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 isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin/one isoniazid, rifampicin, pyrazinamide and ethambutol/five 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.
American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: **Practice Guidelines for the Treatment of Tuberculosis (2003)**[28]	• 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.

Clinical Guideline	Recommendation(s)
	• In most circumstances, the treatment regimen for all adults with previously untreated tuberculosis should consist of a two-month initial phase of isoniazid, 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.
Infectious Diseases Society of America: **Diagnosis and Management of Complicated Intra-abdominal Infection in Adults and Children (2010)**[29]	<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

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	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 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. <u>Health care-associated infection:</u> • 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. <u>Cholecystitis and cholangitis:</u> • 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: **Management of Patients with**	<u>Skin and soft-tissue infections</u> • For a cutaneous abscess, incision and drainage is the primary treatment. For simple abscesses or boils, incision and drainage alone is likely to be adequate. • Antibiotic therapy is recommended for abscesses associated with the following

Clinical Guideline	Recommendation(s)
Infections Caused by Methicillin-Resistant *Staphylococcus Aureus* (2011)[30]	conditions: severe or extensive disease (e.g., involving multiple sites of infection) or rapid progression in presence of associated cellulitis, signs and symptoms of systemic illness, associated comorbidities or immunosuppression, extremes of age, abscess in an area difficult to drain (e.g., face, hand, and genitalia), associated septic phlebitis, and lack of response to incision and drainage alone. • For outpatients with purulent cellulitis, empirical therapy for community-acquired methicillin-resistant *Staphylococcus aureus* is recommended pending culture results. Empirical therapy for infection due to beta-hemolytic streptococci is likely to be unnecessary. • For outpatients with non-purulent cellulitis, empirical therapy for infection due to beta-hemolytic streptococci is recommended. Empirical coverage for community-acquired methicillin-resistant *Staphylococcus aureus* is recommended in patients who do not respond to beta-lactam therapy and may be considered in those with systemic toxicity. • For empirical coverage of community-acquired methicillin-resistant *Staphylococcus aureus* in outpatients with skin and soft-tissue infections, oral antibiotic options include the following: clindamycin, sulfamethoxazole-trimethoprim, a tetracycline (doxycycline or minocycline), and linezolid. If coverage for both beta-hemolytic streptococci and community-acquired methicillin-resistant *Staphylococcus aureus* is desired, options include the following: clindamycin alone or sulfamethoxazole-trimethoprim or a tetracycline in combination with a beta-lactam (e.g., amoxicillin) or linezolid alone. • The use of rifampin as a single agent or as adjunctive therapy for the treatment of skin and soft-tissue infections is not recommended. • For hospitalized patients with complicated skin and soft-tissue infections, in addition to surgical debridement and broad-spectrum antibiotics, empirical therapy for methicillin-resistant *Staphylococcus aureus* should be considered pending culture data. Options include the following: vancomycin intravenous, linezolid oral or intravenous, daptomycin intravenous, telavancin intravenous, and clindamycin intravenous or oral. A beta-lactam antibiotic (e.g., cefazolin) may be considered in hospitalized patients with non-purulent cellulitis with modification to methicillin-resistant *Staphylococcus aureus*-active therapy if there is no clinical response. • For children with minor skin infections (such as impetigo) and secondarily infected skin lesions (such as eczema, ulcers, or lacerations), mupirocin 2% topical ointment can be used. • Tetracyclines should not be used in children <8 years of age. • In hospitalized children with skin and soft-tissue infections, vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, empirical therapy with clindamycin intravenous is an option if the clindamycin resistance rate is low (<10%) with transition to oral therapy if the strain is susceptible. Linezolid oral or intravenous is an alternative. <u>Methicillin-resistant Staphylococcus aureus and infective endocarditis (native valve)</u> • For adults with uncomplicated bacteremia, vancomycin or daptomycin intravenous for at least two weeks is recommended. For complicated bacteremia, four to six weeks of therapy is recommended, depending on the extent of infection. • For adults with infective endocarditis, intravenous vancomycin or daptomycin for six weeks is recommended. • Addition of gentamicin to vancomycin is not recommended for bacteremia or native valve infective endocarditis. <u>Methicillin-resistant *Staphylococcus aureus* bacteremia and infective endocarditis (prosthetic valve)</u>

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	• Intravenous vancomycin plus rifampin oral or intravenous for at least six weeks plus gentamicin intravenous for two weeks.
	• In children, vancomycin intravenous is recommended for the treatment of bacteremia and infective endocarditis. Duration of therapy may range from two to six weeks depending on source, presence of endovascular infection, and metastatic foci of infection.
	• Data regarding the safety and efficacy of alternative agents in children are limited, although daptomycin intravenous may be an option. Clindamycin or linezolid should not be used if there is concern for infective endocarditis or endovascular source of infection, but may be considered in children whose bacteremia rapidly clears and is not related to an endovascular focus.
	• Data are insufficient to support the routine use of combination therapy with rifampin or gentamicin in children with bacteremia or infective endocarditis.
	
	<u>Management of methicillin-resistant *Staphylococcus aureus* pneumonia</u>
	• For hospitalized patients with severe community-acquired pneumonia, empirical therapy for methicillin-resistant *Staphylococcus aureus* is recommended pending sputum and/or blood culture results.
	• For health care–associated methicillin-resistant *Staphylococcus aureus* or community-acquired methicillin-resistant *Staphylococcus aureus* pneumonia, intravenous vancomycin or linezolid oral or intravenous or clindamycin oral or intravenous, if the strain is susceptible, is recommended for seven to 21 days, depending on the extent of infection.
	• In children, intravenous vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, clindamycin intravenous can be used as empirical therapy if the clindamycin resistance rate is low (<10%) with transition to oral therapy if the strain is susceptible. Linezolid oral or intravenous is an alternative.
	
	<u>Management of methicillin-resistant *Staphylococcus aureus* bone and joint infections</u>
	• Antibiotics available for parenteral administration include intravenous vancomycin and daptomycin.
	• Some antibiotic options with parenteral and oral routes of administration include the following: sulfamethoxazole-trimethoprim in combination with rifampin, linezolid, and clindamycin. Some experts recommend the addition of rifampin. For patients with concurrent bacteremia, rifampin should be added after clearance of bacteremia.
	• A minimum eight-week course is recommended. Some experts suggest an additional one to three months (and possibly longer for chronic infection or if debridement is not performed) of oral rifampin-based combination therapy with sulfamethoxazole-trimethoprim, doxycycline-minocycline, clindamycin, or a fluoroquinolone, chosen on the basis of susceptibilities.
	• For septic arthritis, refer to antibiotic choices for osteomyelitis. A three to four-week course of therapy is suggested.
	
	<u>Management of methicillin-resistant *Staphylococcus aureus* infections of the central nervous system</u>
	• Meningitis
	  o Intravenous vancomycin for two weeks is recommended. Some experts recommend the addition of rifampin.
	  o Alternatives include the following: linezolid or sulfamethoxazole-trimethoprim.
	  o For central nervous system shunt infection, shunt removal is recommended, and it should not be replaced until cerebrospinal fluid cultures are repeatedly negative.

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	• Brain abscess, subdural empyema, spinal epidural abscess
	  o Intravenous vancomycin for four to six weeks is recommended. Some experts recommend the addition of rifampin.
	  o Alternatives include the following: linezolid and sulfamethoxazole-trimethoprim.
	• Septic thrombosis of cavernous or dural venous sinus
	  o Intravenous vancomycin for four to six weeks is recommended. Some experts recommend the addition of rifampin.
	  o Alternatives include the following: linezolid and sulfamethoxazole-trimethoprim.
	  o Intravenous vancomycin is recommended in children.

Infectious Diseases Society of America: **Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer (2010)**[31]
 	
Reviewed and deemed current as of 04/2013
	<u>Initial antibiotic therapy</u>
	• Oral route:
	  o For low-risk adults only; use ciprofloxacin plus amoxicillin-clavulanate.
	• Monotherapy with vancomycin not indicated:
	  o Choose therapy with one of the following agents: cefepime or ceftazidime, or imipenem or meropenem.
	• Two drugs without vancomycin:
	  o Choose an aminoglycoside plus antipseudomonal penicillin, cephalosporin (cefepime or ceftazidime), or carbapenem.
	• Vancomycin plus one or two antibiotics:
	  o Choose cefepime or ceftazidime plus vancomycin, with or without an aminoglycoside; carbapenem plus vancomycin, with or without an aminoglycoside; or antipseudomonal penicillin plus an aminoglycoside and vancomycin.
	
	<u>Modification of therapy during the first week of treatment</u>
	• Patient becomes afebrile in three to five days:
	  o Adjust therapy to the most appropriate drug(s). If no etiologic agent is identified and if the patient is at low risk initially, and oral antibiotic treatment was begun with no subsequent complications, continue use of the same drugs.
	  o If the patient was at low risk initially and therapy with intravenous drugs was begun with no subsequent complications, the regimen may be changed after 48 hours to oral ciprofloxacin plus amoxicillin-clavulanate for adults or cefixime for children.
	  o If the patient is at high risk initially with no subsequent complications, continue use of the same intravenous drugs.
	• Persistent fever throughout the first three to five days:
	  o Reassess therapy on day three. If there is no clinical worsening, continue use of the same antibiotics; stop vancomycin use if cultures do not yield organisms.
	  o If there is progressive disease, change antibiotics.
	  o If the patient is febrile after five days, consider adding an antifungal drug.
	
	<u>Antibiotic prophylaxis for afebrile neutropenic patients</u>
	• Use of antibiotic prophylaxis is not routine because of emerging antibiotic resistance, except for the use of sulfamethoxazole-trimethoprim to prevent *Pneumocystis carinii* pneumonitis.

National Comprehensive Cancer Network: **Prevention and Treatment of Cancer-Related**	<u>Low infection risk prophylaxis</u> • Antimicrobial prophylaxis is not recommended in patients with low infection risk. <u>Intermediate infection risk prophylaxis</u>

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Infections (2016)[32]	• Consider using fluoroquinolone prophylaxis.
	
	High infection risk prophylaxis
	• Consider using fluoroquinolone prophylaxis.
	• Additional prophylaxis may be necessary.
	
	Pneumocystis jirovecii prophylaxis
	• Sulfamethoxazole-trimethoprim is the preferred treatment. Sulfamethoxazole-trimethoprim has the additional benefit of activity against other pathogens including Nocardia, Toxoplasma, and Listeria.
	• Atovaquone, dapsone, and pentamidine are potential alternatives as prophylaxis for patients intolerant to sulfamethoxazole-trimethoprim.
	• Consider sulfamethoxazole-trimethoprim desensitization or atovaquone, dapsone, or pentamidine when *Pneumocystis* prophylaxis is required in patients who are sulfamethoxazole-trimethoprim intolerant. For patients receiving dapsone, consider assessing G6PD levels.
	
	Pneumococcal infection prophylaxis
	• Prophylaxis for pneumococcal infection should begin three months after patients undergo hematopoietic stem cell transplantation with penicillin, and prophylaxis should continue for at least one year after the transplant.
	• In regions that have pneumococcal isolates with intermediate or high-level resistance to penicillin, sulfamethoxazole-trimethoprim will likely be adequate for pneumococcal prophylaxis.
	
	Initial empiric antibiotic therapy
	• Patients with neutropenia should begin empiric treatment with broad spectrum antibiotics at the first sign of infection.
	• Intravenous antibiotic monotherapy for uncomplicated infections (choose one):
	  o Cefepime.
	  o Imipenem-cilastatin.
	  o Meropenem.
	  o Piperacillin-tazobactam.
	  o Ceftazidime.
	• Oral antibiotic combination therapy for low-risk patients with uncomplicated infections:
	  o Ciprofloxacin plus amoxicillin-clavulanate.
	  o Moxifloxacin.
	  o Oral antibiotic regimen recommended should not be used if quinolone prophylaxis was used.
	• Complicated infections (choose based on local antibiotic susceptibility patterns):
	  o Intravenous antibiotic monotherapy is preferred.
	  o Intravenous combination therapy could be considered especially in cases of resistance.
	
	Antibacterial agents: empiric gram-positive activity
	• Vancomycin
	  o Gram-positive organisms with the exception of vancomycin-resistant enterococci (VRE) and a number of rare organisms.
	  o Should not be considered as routine therapy for neutropenia and fever unless certain risk factors present.
	  o Dosing individualized with monitoring of levels; loading dose may be considered.
	• Daptomycin
	  o Has in vitro activity against VRE but is not food and drug

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	administration (FDA)-approved for this indication. o Weekly creatine phosphokinase (CPK) to monitor for rhabdomyolysis. o Not indicated for pneumonia due to inactivation by pulmonary surfactant. • Linezolid o Gram-positive organisms including VRE. o Hematologic toxicity (typically with prolonged cases over two weeks) may occur. o Not routinely use in fever and neutropenia, although may impair neutrophil and platelet recovery for extended use. o Treatment option for VRE and MRSA. o Peripheral/optic neuropathy with long-term use. <u>Antibacterial agents: anti-pseudomonal</u> • Cefepime o Broad-spectrum activity against most gram-positive and negative organisms (not active against most anaerobes and *Enterococcus* species). o Use for suspected/proven central nervous system (CNS) infection with susceptible organism. o Empiric therapy for neutropenic fever. • Ceftazidime o Relatively poor gram-positive activity (not active against most anaerobes and *Enterococcus* species). o Use for suspected/proven CNS infection with susceptible organism. o Empiric therapy for neutropenic fever (resistance among gram-negative rods at some centers). • Imipenem-cilastatin/ meropenem/ doripenem o Broad spectrum activity against most gram-positive, gram-negative, and anaerobic organisms. o Preferred against extended spectrum beta-lactamase and serious *Enterobacter* infections. o Carbapenem-resistant gram-negative rod infections are an increasing problem at a number of centers. o Use for suspected intra-abdominal source. o Meropenem is preferred over imipenem for suspected/proven CNS infection. o Effective in nosocomial pneumonia and intra-abdominal infections. • Piperacillin-tazobactam o Broad spectrum activity against most gram-positive, gram-negative, and anaerobic organisms. o Use for suspected intra-abdominal source. <u>Antibacterial agents: other</u> • Aminoglycosides o Activity primarily against gram-negative organisms. o Often used as empiric therapy in seriously ill or hemodynamically unstable patients. • Ciprofloxacin in combination with amoxicillin-clavulanate o Good activity against gram-negative and atypical organisms. Less active than “respiratory” fluoroquinolones against gram-positive organisms. o Ciprofloxacin alone has no activity against anaerobes. o Avoid for empiric therapy if patient recently treated with fluoroquinolone prophylaxis. • Levofloxacin/ moxifloxacin o Good activity against gram-negative and atypical organisms.

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	○ Levofloxacin has no activity against anaerobes. Moxifloxacin has limited activity against Pseudomonas. ○ Prophylaxis may increase bacterial resistance and superinfection. • Metronidazole ○ Good activity against anaerobic organisms. • Sulfamethoxazole-trimethoprim ○ Highly effective as prophylaxis against *Pneumocystis jiroveci* in high-risk patients. ○ Monitor for myelosuppression, hepatotoxicity, and hyperkalemia.
Working Group on Civilian Biodefense: **Plague as a Biological Weapon: Medical and Public Health Management Consensus Statement (2000)**[33]	• For adults with pneumonic plague in the contained casualty settings, the preferred choice is streptomycin or gentamicin and alternative choices include doxycycline, ciprofloxacin, or chloramphenicol. • For children with pneumonic plague in the contained casualty settings, the preferred choice is streptomycin or gentamicin and alternative choices include doxycycline, ciprofloxacin, or chloramphenicol. • For pregnant women with pneumonic plague in the contained casualty settings, the preferred choice is gentamicin and an alternative choice is doxycycline. • For adults with pneumonic plague in the mass casualty setting and postexposure prophylaxis, the preferred choice is doxycycline, or ciprofloxacin and the alternative choice is chloramphenicol. • For children with pneumonic plague in the mass casualty setting and postexposure prophylaxis, the preferred choice is doxycycline or ciprofloxacin and an alternative choice is chloramphenicol. • For pregnant women with pneumonic plague in the mass casualty setting and postexposure prophylaxis, the preferred choice is doxycycline or ciprofloxacin and an alternative choice is chloramphenicol.
American Society of Health-System Pharmacists/ Infectious Diseases Society of America/ Surgical Infection Society/ Society for Healthcare Epidemiology of America: **Clinical practice guidelines for antimicrobial prophylaxis in surgery (2013)**[34]	Common principles • The optimal time for administration of preoperative doses is within 60 minutes before surgical incision. Some agents, such as fluoroquinolones and vancomycin, require administration over one to two hours; therefore, the administration of these agents should begin within 120 minutes before surgical incision. • The selection of an appropriate antimicrobial agent for a specific patient should take into account the characteristics of the ideal agent, the comparative efficacy of the antimicrobial agent for the procedure, the safety profile, and the patient's medication allergies. • For most procedures, cefazolin is the drug of choice for prophylaxis because it is the most widely studied antimicrobial agent, with proven efficacy. It has a desirable duration of action, spectrum of activity against organisms commonly encountered in surgery, reasonable safety, and low cost. • There is little evidence to suggest that broad-spectrum antimicrobial agents (i.e., agents with broad in vitro antibacterial activity) result in lower rates of postoperative SSI compared with older antimicrobial agents with a narrower spectrum of activity. However, comparative studies are limited by small sample sizes, resulting in difficulty detecting a significant difference between antimicrobial agents. Cardiac procedures • For patients undergoing cardiac procedures, the recommended regimen is a single preincision dose of cefazolin or cefuroxime with appropriate intraoperative redosing. • For patients with serious allergy or adverse reaction to β-lactams, vancomycin or clindamycin may be an acceptable alternative. • Vancomycin should be used for prophylaxis in patients known to be colonized with MRSA. • Mupirocin should be given intranasally to all patients with documented *S. aureus*

Clinical Guideline	Recommendation(s)
	colonization. Thoracic procedures • In patients undergoing thoracic procedures, a single dose of cefazolin or ampicillin–sulbactam is recommended. • For patients with serious allergy or adverse reaction to β-lactams, vancomycin or clindamycin may be an acceptable alternative. • Vancomycin should be used for prophylaxis in patients known to be colonized with MRSA. Gastroduodenal procedures • Antimicrobial prophylaxis in gastroduodenal procedures should be considered for patients at highest risk for postoperative infections, including risk factors such as increased gastric pH (e.g., patients receiving acid-suppression therapy), gastroduodenal perforation, decreased gastric motility, gastric outlet obstruction, gastric bleeding, morbid obesity, ASA classification of ≥3, and cancer. • A single dose of cefazolin is recommended in procedures during which the lumen of the intestinal tract is entered. A single dose of cefazolin is recommended in clean procedures, such as highly selective vagotomy, and antireflux procedures only in patients at high risk of postoperative infection due to the presence of the above risk factors. • Alternative regimens for patients with β -lactam allergy include clindamycin or vancomycin plus gentamicin, aztreonam, or a fluoroquinolone. • Higher doses of antimicrobials are uniformly recommended in morbidly obese patients undergoing bariatric procedures. Higher doses of antimicrobials should be considered in significantly overweight patients undergoing gastroduodenal and endoscopic procedures. Biliary tract procedures • A single dose of cefazolin should be administered in patients undergoing open biliary tract procedures. • Alternatives include ampicillin–sulbactam and other cephalosporins (cefotetan, cefoxitin, and ceftriaxone). Alternative regimens for patients with β -lactam allergy include clindamycin or vancomycin plus gentamicin, aztreonam, or a fluoroquinolone; or metronidazole plus gentamicin or a fluoroquinolone. Appendectomy procedures • For uncomplicated appendicitis, the recommended regimen is a single dose of a cephalosporin with anaerobic activity (cefoxitin or cefotetan) or a single dose of a first-generation cephalosporin (cefazolin) plus metronidazole. • For β -lactam-allergic patients, alternative regimens include clindamycin plus gentamicin, aztreonam, or a fluoroquinolone; and metronidazole plus gentamicin or a fluoroquinolone (ciprofloxacin or levofloxacin). Small intestine procedures • For small bowel surgery without obstruction, the recommended regimen is a first generation cephalosporin (cefazolin). For small bowel surgery with intestinal obstruction, the recommended regimen is a cephalosporin with anaerobic activity (cefoxitin or cefotetan) or the combination of a first-generation cephalosporin (cefazolin) plus metronidazole. • For β -lactam-allergic patients, alternative regimens include clindamycin plus gentamicin, aztreonam, or a fluoroquinolone; and metronidazole plus gentamicin or a fluoroquinolone (ciprofloxacin or levofloxacin). Hernia repair procedures

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	• For hernioplasty and herniorrhaphy, the recommended regimen is a single dose of a first-generation cephalosporin (cefazolin). For patients known to be colonized with MRSA, it is reasonable to add a single preoperative dose of vancomycin to the recommended agent. For β –lactam-allergic patients, alternative regimens include clindamycin and vancomycin.
	
	Colorectal procedures
	• A single dose of second-generation cephalosporin with both aerobic and anaerobic activities (cefoxitin or cefotetan) or cefazolin plus metronidazole is recommended for colon procedures.
	• In institutions where there is increasing resistance to first- and second-generation cephalosporins among gram-negative isolates from SSIs, a single dose of ceftriaxone plus metronidazole is recommended over routine use of carbapenems. An alternative regimen is ampicillin–sulbactam.
	• In most patients, mechanical bowel preparation combined with a combination of oral neomycin sulfate plus oral erythromycin base or oral neomycin sulfate plus oral metronidazole should be given in addition to intravenous prophylaxis. The oral antimicrobial should be given as three doses over approximately 10 hours the afternoon and evening before the operation and after the mechanical bowel preparation.
	• Alternative regimens for patients with β–lactam allergies include (1) clindamycin plus an aminoglycoside, aztreonam, or a fluoroquinolone and (2) metronidazole plus an aminoglycoside or a fluoroquinolone. Metronidazole plus aztreonam is not recommended as an alternative because this combination has no aerobic gram-positive activity.
	
	Head and neck procedures
	• Clean procedures:
	  o Antimicrobial prophylaxis is not required.
	• Clean-contaminated procedures:
	  o Antimicrobial prophylaxis has not been shown to benefit patients undergoing tonsillectomy or functional endoscopic sinus procedures.
	  o The preferred regimens for patients undergoing other clean-contaminated head and neck procedures are (1) cefazolin or cefuroxime plus metronidazole and (2) ampicillin–sulbactam.
	  o Clindamycin is a reasonable alternative in patients with a documented β-lactam allergy. The addition of an aminoglycoside to clindamycin may be appropriate when there is an increased likelihood of gram-negative contamination of the surgical site.
	
	Neurosurgery procedures
	• A single dose of cefazolin is recommended for patients undergoing clean neurosurgical procedures, CSF-shunting procedures, or intrathecal pump placement. Clindamycin or vancomycin should be reserved as an alternative agent for patients with a documented β-lactam allergy (vancomycin for MRSA-colonized patients).
	
	Cesarean delivery procedures
	• The recommended regimen for all women undergoing cesarean delivery is a single dose of cefazolin administered before surgical incision. For patients with β-lactam allergies, an alternative regimen is clindamycin plus gentamicin.
	
	Hysterectomy procedures
	• The recommended regimen for women undergoing vaginal or abdominal hysterectomy, using an open or laparoscopic approach, is a single dose of cefazolin.

Clinical Guideline	Recommendation(s)
	• Cefoxitin, cefotetan, or ampicillin–sulbactam may also be used. Alternative agents for patients with a b-lactam allergy include (1) either clindamycin or vancomycin plus an aminoglycoside, aztreonam, or a fluoroquinolone and (2) metronidazole plus an aminoglycoside or a fluoroquinolone. Ophthalmic procedures • Due to the lack of robust data from trials, specific recommendations cannot be made regarding choice, route, or duration of prophylaxis. • As a general principle, the antimicrobial prophylaxis regimens used in ophthalmic procedures should provide coverage against common ocular pathogens, including *Staphylococcus* species and gram-negative organisms, particularly *Pseudomonas* species. Orthopedic procedures • Antimicrobial prophylaxis is not recommended for patients undergoing clean orthopedic procedures, including knee, hand, and foot procedures, arthroscopy, and other procedures without instrumentation or implantation of foreign materials. • Antimicrobial prophylaxis is recommended for orthopedic spinal procedures with and without instrumentation. The recommended regimen is cefazolin. • The recommended regimen in hip fracture repair or other orthopedic procedures involving internal fixation is cefazolin. Clindamycin and vancomycin should be reserved as alternative agents. • The recommended regimen for patients undergoing total hip, elbow, knee, ankle, or shoulder replacement is cefazolin. Clindamycin and vancomycin should be reserved as alternative agents. Urologic procedures • No antimicrobial prophylaxis is recommended for clean urologic procedures in patients without risk factors for postoperative infections. • Patients with preoperative bacteriuria or urinary tract infection should be treated before the procedure, when possible, to reduce the risk of postoperative infection. • For patients undergoing lower urinary tract instrumentation with risk factors for infection, the use of a fluoroquinolone or trimethoprim– sulfamethoxazole (oral or intravenous) or cefazolin (intravenous or intramuscular) is recommended. Vascular procedures • The recommended regimen for patients undergoing vascular procedures associated with a higher risk of infection, including implantation of prosthetic material, is cefazolin. Heart, lung, heart-lung, liver, pancreas, and kidney transplantation • Antimicrobial prophylaxis is indicated for all patients undergoing heart transplantation. The recommended regimen is a single dose of cefazolin. Alternatives include vancomycin or clindamycin with or without gentamicin, aztreonam, or a single fluoroquinolone dose. • Adult patients undergoing lung transplantation should receive antimicrobial prophylaxis, because of the high risk of infection. Patients with negative pretransplantation cultures should receive antimicrobial prophylaxis as appropriate for other types of cardiothoracic procedures. The recommended regimen is a single dose of cefazolin. • The recommended agents for patients undergoing liver transplantation are (1) piperacillin–tazobactam and (2) cefotaxime plus ampicillin. The duration of prophylaxis should be restricted to 24 hours or less. • The recommended regimen for patients undergoing pancreas or SPK

Clinical Guideline	Recommendation(s)
	transplantation is cefazolin. • The recommended agent for patients undergoing kidney transplantation is cefazolin. Plastic surgery and breast procedures • Antimicrobial prophylaxis is not recommended for most clean procedures in patients without additional postoperative infection risk factors. • Although no studies have demonstrated antimicrobial efficacy in these procedures, expert opinion recommends that patients with risk factors undergoing clean plastic procedures receive antimicrobial prophylaxis. The recommendation for clean-contaminated procedures, breast cancer procedures, and clean procedures with other risk factors is a single dose of cefazolin or ampicillin–sulbactam.
American College of Gastroenterology: **Practice Guidelines: Hepatic Encephalopathy (2001)**[35]	Bowel cleansing • Bowel cleansing is a standard therapeutic measure in hepatic encephalopathy. • 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. Nonabsorbable disaccharides • 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). Antibiotics • 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 g/day) should be given for one to two weeks. • For chronic encephalopathy, neomycin (1 to 2 g/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 aminoglycosides 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 Aminoglycosides[1-8]

Indication	Amikacin	Gentamicin	Neomycin	Paromomycin	Streptomycin	Tobramycin
Central Nervous System Infections						
Adjunctive therapy in hepatic coma			✔	✔		
Central nervous system infections	✔	✔			✔	✔ *
Dermatological Infections						
Burns	✔	✔				
Skin and skin-structure infections	✔	✔				✔ *
Gastrointestinal Infections						
Acute and chronic intestinal amebiasis				✔		
Gastrointestinal tract infections		✔				
Suppression of the normal bacterial flora of the bowel			✔			
Genitourinary Infections						
Chancroid					✔	
Granuloma inguinale					✔	
Urinary tract infections	✔	✔			✔	✔ *
Respiratory Infections						
Management of cystic fibrosis patients with *Pseudomonas aeruginosa*						✔ †
Pneumonia					✔	
Respiratory tract infections	✔	✔			✔	✔ *
Tuberculosis					✔	
Miscellaneous Infections						
Bacteremia					✔	
Bone and/or joint infections	✔	✔				✔ *
Brucellosis					✔	
Endocarditis					✔	
Intra-abdominal infections	✔					✔ *
Plague					✔	
Postoperative infections	✔					
Septicemia	✔	✔				✔ *
Serious infections caused by susceptible microorganisms	✔	✔			✔	
Tularemia					✔	

*Injection formulation.
†Inhalation formulation.

IV. Pharmacokinetics

The pharmacokinetic parameters for the aminoglycosides are summarized in Table 5.

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

Generic Name(s)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Amikacin	4 to 11	Not significant	Renal (90 to 98)	2
Gentamicin	0 to 30	Not reported	Renal (65 to 100)	1.5 to 4.0
Neomycin	0 to 88	Not reported	Renal (30 to 50) Feces (97)	3
Paromomycin	Not reported	Not reported	Feces (100)	Not reported
Streptomycin	34 to 35	Not significant	Renal (65)	2.5
Tobramycin	0 to 30	Not reported	Renal (60 to 85)	1.6 to 3.0

V. Drug Interactions

Major drug interactions with the aminoglycosides are listed in Table 6.

Table 6. Major Drug Interactions with the Aminoglycosides[2]

Generic Name(s)	Interaction	Mechanism
Aminoglycosides (amikacin, gentamicin, neomycin, streptomycin, tobramycin)	Nondepolarizing muscle relaxants	Aminoglycosides may increase the neuromuscular blocking effects of non-depolarizing muscle relaxants. Prolonged respiratory depression and apnea may occur.
Aminoglycosides (amikacin, gentamicin, streptomycin, tobramycin)	Succinylcholine	Neuromuscular blocking effects of succinylcholine may be increased by aminoglycosides. Prolonged respiratory depression with extended periods of apnea may occur.
Aminoglycosides (amikacin, gentamicin, neomycin, streptomycin, tobramycin)	Furosemide	Concurrent use of aminoglycosides and furosemide may result in increased amikacin plasma and tissue concentrations and additive ototoxicity and/or nephrotoxicity.
Aminoglycosides (amikacin, gentamicin, tobramycin)	Vancomycin	Concurrent use of aminoglycosides and vancomycin may result in additive ototoxicity and/or nephrotoxicity.
Aminoglycosides (amikacin, gentamicin, neomycin, paromomycin, streptomycin, tobramycin)	Colistimethate	Concurrent use of colistimethate sodium and aminoglycosides may result in respiratory depression.
Aminoglycosides (amikacin, gentamicin, neomycin, streptomycin, tobramycin)	Ethacrynic acid	Concurrent use of aminoglycosides and ethacrynic acid may result in increased amikacin plasma and tissue concentrations and additive ototoxicity.
Aminoglycosides (amikacin, gentamicin, neomycin, streptomycin, tobramycin)	Cidofovir	Concurrent use of aminoglycosides and cidofovir may result in nephrotoxicity.
Aminoglycosides (neomycin)	Sorafenib	Concurrent use of neomycin and sorafenib may result in decreased sorafenib exposure.
Aminoglycosides (tobramycin)	Mannitol	Concurrent use of mannitol and tobramycin may result in increased tobramycin plasma and tissue concentrations and additive ototoxicity and/or nephrotoxicity.

VI. Adverse Drug Events

The most common adverse drug events reported with the aminoglycosides are listed in Table 7. The boxed warnings for the aminoglycosides are listed in Tables 8 and 9. Ototoxicity and nephrotoxicity are the most serious adverse effects with the aminoglycosides and are most frequently reported in geriatric or dehydrated patients, patients with renal impairment, patients who are receiving high doses or for long periods, those who are also receiving or have received other ototoxic and/or nephrotoxic drugs, and in patients with preexisting tinnitus, vertigo, or hearing loss.

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

Adverse Events	Amikacin	Gentamicin	Neomycin	Paromomycin	Streptomycin	Tobramycin Inhalation	Tobramycin Injection
Cardiovascular							
Chest pain	-	-	-	-	-	26*	-
Edema	-	-	-	-	-	-	-
Hypertension	-	✔	-	-	-	-	-
Hypotension	✔	✔	-	-	-	-	-
Central Nervous System							
Acute organic brain syndrome	-	✔	-	-	-	-	-
Confusion	-	✔	-	-	-	-	✔
Convulsions	-	✔	-	-	-	-	-
Depression	-	✔	-	-	-	-	-
Disorientation	-	-	-	-	-	-	✔
Dizziness	-	✔	-	-	-	6*	✔
Drowsiness	-	-	-	-	-	-	-
Encephalopathy	-	✔	-	-	-	-	-
Fever	✔	✔	-	-	✔	33*	✔
Headache	✔	✔	-	-	-	11 to 27	✔
Lethargy	-	✔	-	-	-	6*	✔
Malaise	-	-	-	-	-	6*	-
Myasthenia gravis-like syndrome	-	✔	-	-	-	-	-
Neuromuscular blockade	✔	-	✔	-	-	-	-
Neurotoxicity	✔	✔	✔	-	✔	-	✔
Paresthesia	✔	✔	-	-	✔	-	-
Peripheral neuropathy	-	✔	-	-	-	-	-
Pseudotumor cerebri	-	✔	-	-	-	-	-
Pyrexia	-	-	-	-	-	16†	-
Vertigo	-	✔	-	-	✔	-	✔
Dermatological							
Alopecia	-	✔	-	-	-	-	-
Burning	-	✔	-	-	-	-	-

Adverse Events	Amikacin	Gentamicin	Neomycin	Paromomycin	Streptomycin	Tobramycin Inhalation	Tobramycin Injection
Erythema	-	-	-	-	-	-	-
Exfoliative dermatitis	-	-	-	-	✔	-	✔
Itching	-	✔	-	-	-	-	✔
Photosensitivity	-	-	-	-	-	-	-
Rash	✔	✔	-	-	✔	2 to 5	✔
Redness	-	-	-	-	-	-	-
Skin tingling	-	✔	-	-	-	-	-
Stinging	-	-	-	-	-	-	-
Urticaria	-	✔	-	-	✔	-	✔
Gastrointestinal							
Abdominal cramps	-	-	-	✔	-	-	-
Abdominal pain	-	-	-	-	-	13*	-
Anorexia	-	-	-	-	-	19*	-
Appetite decreased	-	✔	-	-	-	-	-
Diarrhea	-	-	-	✔	-	2 to 6*	✔
Dysgeusia	-	-	-	-	-	4†	-
Enterocolitis	-	-	-	-	-	-	-
Hemoptysis	-	-	-	-	-	13 to 19	-
Malabsorption syndrome	-	-	✔	-	-	-	-
Nausea	✔	✔	✔	✔	✔	8 to 11	✔
Salivation increased	-	✔	-	-	-	-	-
Sputum discoloration	-	-	-	-	-	21*	-
Sputum increased	-	-	-	-	-	38*	-
Stomatitis	-	✔	-	-	-	-	-
Taste perversion	-	-	-	-	-	7*	-
Vomiting	✔	✔	✔	-	✔	6 to 14	✔
Weight loss	-	✔	-	-	-	10*	-
Genitourinary							
Azotemia	✔	-	-	-	✔	-	-
Cylindruria	✔	✔	-	-	-	-	✔
Hematuria	✔	-	-	-	-	-	-
Nephrotoxicity	-	-	✔	-	-	-	-
Oliguria	✔	✔	-	-	-	-	✔
Proteinuria	✔	✔	-	-	-	-	✔
Pyuria	✔	-	-	-	-	-	-
Hematologic							
Agranulocytosis	-	✔	-	-	-	-	-

Adverse Events	Amikacin	Gentamicin	Neomycin	Paromomycin	Streptomycin	Tobramycin Inhalation	Tobramycin Injection
Anemia	✔	✔	-	-	-	-	✔
Eosinophilia	✔	✔	-	-	✔	2*	✔
Granulocytopenia	-	✔	-	-	-	-	✔
Hemolytic anemia	-	-	-	-	✔	-	-
Leukocytosis	-	-	-	-	-	-	✔
Leukopenia	-	✔	-	-	✔	-	✔
Pancytopenia	-	-	-	-	✔	-	-
Red blood cell sedimentation rate increased	-	-	-	-	-	8*	-
Reticulocytes decreased	-	✔	-	-	-	-	-
Reticulocytes increased	-	✔	-	-	-	-	-
Thrombocytopenia	-	✔	-	-	✔	-	✔
Laboratory Test Abnormalities							
Aspartate aminotransferase increased	-	✔	-	-	-	-	✔
Alanine transaminase increased	-	✔	-	-	-	-	✔
Bilirubin increased	-	✔	-	-	-	-	✔
Blood glucose increased	-	-	-	-	-	3†	-
Blood urea nitrogen increased	-	✔	-	-	-	-	✔
Calcium decreased	-	✔	-	-	-	-	✔
Immunoglobulins increased	-	-	-	-	-	2*	-
Lactate dehydrogenase increased	-	✔	-	-	-	-	✔
Magnesium decreased	-	✔	-	-	-	-	✔
Potassium decreased	-	✔	-	-	-	-	✔
Pulmonary function test decreased	-	-	-	-	-	7†	-
Serum creatinine increased	✔	✔	-	-	-	3*	✔
Sodium decreased	-	✔	-	-	-	-	✔
Musculoskeletal							
Arthralgia	✔	-	-	-	-	-	-
Asthenia	-	-	-	-	-	36*	-
Back pain	-	-	-	-	-	7*	-
Joint pain	-	✔	-	-	-	-	-
Muscle cramps	-	-	-	-	-	-	-
Muscle twitching	-	✔	-	-	-	-	-
Musculoskeletal chest pain	-	-	-	-	-	5†	-
Tremor	✔	-	-	-	-	-	-
Weakness	-	-	-	-	✔	-	-

Adverse Events	Amikacin	Gentamicin	Neomycin	Paromomycin	Streptomycin	Tobramycin Inhalation	Tobramycin Injection
Respiratory							
Apnea	-	-	-	-	-	-	✔
Asthma	-	-	-	-	-	16*	-
Bronchitis	-	-	-	-	-	3*	-
Chest discomfort	-	-	-	-	-	7†	-
Cough	-	-	-	-	-	48†	-
Cough increased	-	-	-	-	-	46*	-
Dyspnea	-	-	-	-	-	16 to 34	-
Hyperventilation	-	-	-	-	-	5*	-
Forced expiratory volume decreased	-	-	-	-	-	4 to 31	-
Lower respiratory tract infection	-	-	-	-	-	6*	-
Lung disorder	-	-	-	-	-	16 to 34	-
Nasal congestion	-	-	-	-	-	8†	-
Productive cough	-	-	-	-	-	18†	-
Pulmonary fibrosis	-	✔	-	-	-	-	-
Rales	-	-	-	-	-	7 to 19	-
Respiratory depression	-	✔	-	-	-	-	-
Rhinitis	-	-	-	-	-	35*	-
Sinusitis	-	-	-	-	-	8*	-
Throat irritation	-	-	-	-	-	5†	-
Wheezing	-	-	-	-	-	5 to 7	-
Special Senses							
Amblyopia	-	-	-	-	✔	-	-
Dysphonia	-	-	-	-	-	6 to 14	-
Ear pain	-	-	-	-	-	7*	-
Hearing loss	-	✔	-	-	✔	✔	✔
Ototoxicity	✔	✔	✔	-	✔	-	✔
Tinnitus	-	✔	-	-	-	3*	✔
Visual disturbances	-	✔	-	-	-	-	-
Other							
Anaphylaxis/anaphylactoid reaction	-	✔	-	-	✔	-	-
Angioneurotic edema	-	-	-	-	✔	-	-
Ear and labyrinth disorders	-	-	-	-	-	10†	-
Epistaxis	-	-	-	-	-	3 to 7	-
Hepatomegaly/splenomegaly	-	✔	-	-	-	-	-
Laryngeal edema	-	✔	-	-	-	-	-
Oropharyngeal pain	-	-	-	-	-	14†	-

Adverse Events	Amikacin	Gentamicin	Neomycin	Paromomycin	Streptomycin	Tobramycin Inhalation	Tobramycin Injection
Pain	-	-	-	-	-	8*	-
Pain at injection site	-	✔	-	-	-	-	✔
Pharyngitis	-	-	-	-	-	38*	-
Pharyngolaryngeal pain	-	-	-	-	-	3*	-
Purpura	-	✔	-	-	-	-	-
Tonsillitis	-	-	-	-	-	2*	-
Upper respiratory tract infection	-	-	-	-	-	7†	-
Voice alterations	-	-	-	-	-	13*	-

✔ Percent not specified.
- Event not reported or incidence <1%.
* Inhalation solution only.
† Inhalation powder only.

Table 8. Boxed Warning for Parenteral Aminoglycosides[1]

WARNING
Patients treated with parenteral aminoglycosides should be under close clinical observation because of the potential ototoxicity and nephrotoxicity associated with their use. Safety for treatment periods which are longer than 14 days has not been established. **Ototoxicity:** Neurotoxicity, manifested as vestibular and permanent bilateral auditory ototoxicity, can occur in patients with preexisting renal damage and in patients with normal renal function treated at higher doses and/or periods longer than those recommended. The risk of aminoglycoside-induced ototoxicity is greater in patients with renal damage. High frequency deafness usually occurs first and can be detected only by audiometric testing. Vertigo may occur and may be evidence of vestibular injury. Other manifestations of neurotoxicity may include numbness, skin tingling, muscle twitching, and convulsions. The risk of hearing loss due to aminoglycosides increases with the degree of exposure to either high peak or high trough serum concentrations. Patients developing cochlear damage may not have symptoms during therapy to warn them of developing eighth-nerve toxicity, and total or partial irreversible bilateral deafness may occur after the drug has been discontinued. Aminoglycoside-induced ototoxicity is usually irreversible. **Nephrotoxicity:** Aminoglycosides are potentially nephrotoxic. The risk of nephrotoxicity is greater in patients with impaired renal function and in those who receive high doses or prolonged therapy. **Neuromuscular blockade:** Neuromuscular blockade and respiratory paralysis have been reported following parenteral injection, topical instillation (as in orthopedic and abdominal irrigation or in local treatment of empyema), and following oral use of aminoglycosides. The possibility of these phenomena should be considered if aminoglycosides are administered by any route, especially in patients receiving anesthetics, neuromuscular blocking agents such as tubocurarine, succinylcholine, decamethonium, or in patients receiving massive transfusions of citrate-anticoagulated blood. If blockage occurs, calcium salts may reverse these phenomena, but mechanical respiratory assistance may be necessary. **Monitoring:** Renal and eighth-nerve function should be closely monitored especially in patients with known or suspected renal impairment at the onset of therapy and also in those whose renal function is initially normal but who develop signs of renal dysfunction during therapy. Serum concentrations of amikacin should be monitored when feasible to assure adequate levels and to avoid potentially toxic levels and prolonged peak concentrations above 35 µg/mL. Urine should be examined for decreased specific gravity, increased excretion of proteins, and the presence of cells or casts. Blood urea nitrogen, serum creatinine, or creatinine clearance should be measured periodically. Serial audiograms should be obtained where feasible in patients old enough to be tested, particularly high-risk patients. Evidence of ototoxicity (dizziness, vertigo, tinnitus, roaring in the ears, and hearing loss) or nephrotoxicity requires discontinuation of the drug or dosage adjustment. **Concurrent therapy:** Concurrent and/or sequential systemic, oral, or topical use of other neurotoxic or nephrotoxic products, particularly bacitracin, cisplatin, amphotericin B, cephaloridine, paromomycin, viomycin, polymyxin B, colistin, vancomycin, or other aminoglycosides should be avoided. Other factors that may increase risk of toxicity are advanced age and dehydration. The concurrent use of amikacin with potent diuretics (ethacrynic acid, or furosemide) should be avoided because diuretics by themselves may cause ototoxicity. In addition, when administered intravenously, diuretics may enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue. **Pregnancy:** Aminoglycosides can cause fetal harm when administered to a pregnant woman.

Table 9. Boxed Warning for Neomycin[1]

WARNING
Toxicity: Systemic absorption of neomycin occurs following oral administration, and toxic reactions may occur. Patients treated with neomycin should be under close clinical observation because of the potential toxicity associated with the use of neomycin. Neurotoxicity (including ototoxicity) and nephrotoxicity following the oral use of neomycin sulfate have been reported, even when used in recommended doses. The

WARNING

potential for nephrotoxicity, permanent bilateral auditory ototoxicity, and sometimes vestibular toxicity, is present in patients with healthy renal function when treated with higher doses of neomycin or for longer periods than recommended. Serial, vestibular and audiometric tests, as well as tests of renal function, should be performed (especially in high-risk patients). The risk of nephrotoxicity and ototoxicity is greater in patients with impaired renal function. Ototoxicity is often delayed in onset, and patients developing cochlear damage will not have symptoms during therapy to warn them of developing eighth nerve destruction, and total or partial deafness may occur long after neomycin has been discontinued.

Other factors which increase the risk of toxicity are advanced age and dehydration.

Neuromuscular blockage: Neuromuscular blockage and respiratory paralysis have been reported following the oral use of neomycin. The possibility of the occurrence of neuromuscular blockage and respiratory paralysis should be considered if neomycin is administered, especially to patients receiving anesthetics; neuromuscular-blocking agents such as tubocurarine, succinylcholine, decamethonium; or massive transfusions of citrate anticoagulated blood. If blockage occurs, calcium salts may reverse these phenomena, but mechanical respiratory assistance may be necessary.

Concurrent therapy: Concurrent or sequential systemic, oral or topical use of other aminoglycosides, including paromomycin and other potentially nephrotoxic or neurotoxic drugs such as bacitracin, cisplatin, vancomycin, amphotericin B, polymyxin B, colistin and viomycin, should be avoided because the toxicity may be additive.

The concurrent use of neomycin with potent diuretics such as ethacrynic acid or furosemide should be avoided, since certain diuretics by themselves may cause ototoxicity. In addition, when administered intravenous, diuretics may enhance neomycin toxicity by altering the antibiotic concentration in serum and tissue.

VII. Dosing and Administration

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

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

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Amikacin	Unspecified infections: Injection: 15 mg/kg/day IM or IV, divided into two or three equal doses, administered at equally divided intervals; maximum, 15 mg/kg/day or 1.5 g/day (for heavier patients) Urinary tract infections (Uncomplicated): Injection: 250 mg IM or IV twice daily may be used	Unspecified infections: Injection: Newborns, 10 mg/kg loading dose, followed by 7.5 mg/kg every 12 hours; total daily dose should not exceed 15 mg/kg/day; children and older infants, 15 mg/kg/day IM or IV, divided into two or three equal doses, administered at equally divided intervals; maximum, 15 mg/kg/day or 1.5 g/day (for heavier patients)	Injection: 500 mg/2 mL 1,000 mg/4 mL
Gentamicin	Life-threatening infections: Injection: Up to 5 mg/kg/day IV or IM may be administered in three or four equal doses; the dose should be reduced to 3 mg/kg/day as soon as clinically indicated Serious infections: Injection: 3 mg/kg/day IV or IM in three equal doses every eight hours	Unspecified infections: Injection: Children, 6 to 7.5 mg/kg/day IV or IM (2 to 2.5 mg/kg every eight hours); infants and neonates, 7.5 mg/kg/day IV or IM (2.5 mg/kg every eight hours); premature or full-term neonates one week of age or younger, 5 mg/kg/day	Injection: 20 mg/2 mL 40 mg/mL

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		IV or IM (2.5 mg/kg every 12 hours)	
Neomycin	Adjunctive therapy in hepatic coma: Tablet: 4 to 12 g/day in divided doses for five to six days; treatment for periods longer than two weeks is not recommended Suppression of the normal bacterial flora of the bowel: Tablet: Initial, 1 g orally 19, 18, and nine hours prior to surgery with oral erythromycin as an adjunct to mechanical cleansing of bowel	Safety and efficacy in children have not been established.	Tablet: 500 mg
Paromomycin	Adjunctive therapy in hepatic coma: Capsule: 4 g daily in divided doses, for five to six days Acute and chronic intestinal amebiasis: Capsule: 25 to 35 mg/kg daily, in three doses with meals, for five to ten days	Acute and chronic intestinal amebiasis: Capsule: 25 to 35 mg/kg daily, in three doses with meals, for five to ten days	Capsule: 250 mg
Streptomycin	Endocarditis (Streptococcal infections): Injection: 1 g twice daily IM for the first week, and 500 mg twice daily IM for the second week in combination with penicillin Endocarditis (Enterococcal infections): Injection: 1 g twice daily IM for two weeks and 500 mg twice daily IM for an additional four weeks in combination with penicillin Plague: Injection: 2 g/day IM in two divided doses for a minimum of 10 days Tuberculosis: Injection: 15 mg/kg IM once daily, 25 to 30 mg/kg IM twice weekly, or 25 to 30 mg/kg IM three times weekly Tularemia: Injection: 1 to 2 g daily IM in two divided doses for seven to 14 days until the patient is afebrile for five to seven days Unspecified infections: Injection: 1 to 2 g IM in divided doses every six to 12 hours for moderate to severe infections; maximum, 2 g/day	Unspecified infections: Injection: 20 to 40 mg/kg/day in divided doses every six to 12 hours Tuberculosis: Injection: 20 to 40 mg/kg IM once daily, 25 to 30 mg/kg IM twice weekly, or 25 to 30 mg/kg IM three times weekly	Injection: 1 g
Tobramycin	Management of cystic fibrosis patients with *Pseudomonas aeruginosa*: Inhalation solution: 300 mg	Management of cystic fibrosis patients with *Pseudomonas aeruginosa* in patients ≥6 years	Inhalation solution: 300 mg/4 mL

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	administered twice daily for 28 days; after 28 days of therapy, patients should stop tobramycin therapy for the next 28 days, and then resume therapy for the next "28 days on/28 days off" cycle Inhalation powder: Four 28 mg capsules twice daily for 28 days; after 28 days of therapy, patients should stop tobramycin therapy for the next 28 days, and then resume therapy for the next "28 days on/28 days off" cycle Life-threatening infections: Injection: Up to 5 mg/kg/day IV or IM may be administered in three or four equal doses; the dosage should be reduced to 3 mg/kg/day as soon as clinically indicated Serious infections: Injection: 3 mg/kg/day IV or IM divided in three equal doses every eight hours	of age: Inhalation solution: 300 mg administered twice daily for 28 days; after 28 days of therapy, patients should stop tobramycin therapy for the next 28 days, and then resume therapy for the next "28 days on/28 days off" cycle Inhalation powder: Four 28 mg capsules twice daily for 28 days. After 28 days of therapy, patients should stop tobramycin therapy for the next 28 days, and then resume therapy for the next "28 days on/28 days off" cycle Septicemia in patients ≤1 week of age: Injection: Up to 4 mg/kg/day IV or IM may be administered in two equal doses every 12 hours Septicemia in patients >1 week of age: Injection: 6 to 7.5 mg/kg/day IV or IM in three or four equally divided doses (2 to 2.5 mg/kg every eight hours or 1.5 to 1.89 mg/kg every six hours)	300 mg/5 mL Inhalation powder: 28 mg Injection: 10 mg/mL 40 mg/mL 1.2 g

Abbreviations: IM=intramuscular, IV=intravenous

VIII. Effectiveness

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

Table 11. Comparative Clinical Trials with the Aminoglycosides

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cystic Fibrosis				
Ramsey et al.[36] (1999) Tobramycin inhalation solution 300 mg BID for three cycles (each cycle consisting of 28 days during which the medication was administered and 28 days during which it was not administered) vs placebo	DB, MC, PC Patients at least six years of age with cystic fibrosis, a respiratory tract culture positive for *Pseudomonas aeruginosa*, ability to perform pulmonary function tests, and FEV_1 25 to 75% of predicted value	N=520 24 weeks	Primary: FEV_1 and the density of *Pseudomonas aeruginosa* in sputum at 20 weeks Secondary: Hospitalization and treatment with IV antipseudomonal antibiotics	Primary: At the end of 20 weeks, patients treated with tobramycin inhalation solution had an average 10% increase in FEV_1, as compared to 2% decline for the patients receiving placebo (P<0.001). At the end of 20 weeks, patients treated with tobramycin inhalation solution had an average reduction of 0.8 log_{10} colony forming unit per gram of sputum, as compared to the value at 0 weeks, whereas the density in the placebo group had increased by 0.3 log_{10} colony forming unit per gram (P<0.001). Secondary: Patients receiving tobramycin were 26% less likely to be hospitalized and 36% less likely to require IV antipseudomonal antibiotics.
Murphy et al.[37] (2004) Tobramycin inhalation solution 300 mg BID for seven cycles (each cycle consisting of 28 days during which the medication was administered and 28	MC, OL, PG, RCT Patients six to 10 years of age with cystic fibrosis and chronic *Pseudomonas aeruginosa*, FEV_1 $\geq$70% and $\leq$110% of predicted value; patients 11 to 15 years of age with	N=184 56 weeks	Primary: Rate of lung function decline, FEV_1, rates of hospitalization, and concomitant antibiotic use Secondary: Not reported	Primary: Patients treated with tobramycin inhalation solution trended toward improvement in percent predicted FEV_1 over control group at weeks 20 and 32, but the improvement was not statistically significant. Significantly fewer tobramycin inhalation solution patients were hospitalized for worsening of respiratory symptoms (11.0 vs 25.6%; P<0.011), and fewer tobramycin inhalation solution patients were hospitalized overall (16.5 vs 27.8%; P<0.065). Fewer tobramycin inhalation solution patients received antibiotics other than the study drug (78.0 vs 95.6%), and significantly fewer patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
days during which it was not administered) vs placebo	cystic fibrosis and FEV_1 >70% and <90% of predicted value			received oral antibiotics (76.9 vs 91.1%; P<0.009). Secondary: Not reported
Quittner et al.[38] (2002) Tobramycin inhalation solution 300 mg BID for 28 days for three cycles vs placebo	RETRO Patients greater than six years of age with cystic fibrosis who were infected with *Pseudomonas aeruginosa* and had an FEV_1 25 to 75% of predicted values	N=520 24 weeks	Primary: Improvement in quality of life Secondary: Not reported	Primary: Patients treated with tobramycin inhalation solution were more likely to report improvement in quality of life than those receiving placebo (P<0.005). Secondary: Not reported
Moss et al.[39] (2002) Tobramycin inhalation solution 300 mg BID for 28 days for three cycles vs placebo	OL Patients 13 to 17 years of age with cystic fibrosis who were infected with *Pseudomonas aeruginosa* and had an FEV_1 ≥25 and ≤75% of predicted values	N=128 2 years	Primary: Pulmonary function, *Pseudomonas aeruginosa* colony-forming unit density, incidence of hospitalization and IV antibiotic use, weight gain Secondary: Not reported	Primary: Patients originally randomized to tobramycin inhalation solution and placebo treatments exhibited improvements in FEV_1 percent predicted of 13.5 and 9.4%, respectively. Improvement in pulmonary function was significantly correlated with reduction in *Pseudomonas aeruginosa* colony forming unit density (P=0.0001). The average number of hospitalizations and IV antibiotic courses did not increase over time. Secondary: Not reported
Bowman[40] (2002) Tobramycin	OL Patients at least six years of age with	N=396 48 weeks	Primary: Pulmonary function and antibiotic use	Primary: At the start of the OL study period, the patients who had been receiving tobramycin inhalation solution continued to show mean FEV_1 values that remained above their baseline values. The patients who were crossed over

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
inhalation solution 300 mg BID for nine cycles (each cycle consisting of 28 days during which the study drug was administered and 28 days during which it was not administered)	cystic fibrosis who were infected with *Pseudomonas aeruginosa* and had an FEV_1 ≥25 and ≤75% of predicted values		Secondary: Not reported	from placebo to OL tobramycin inhalation solution had a marked improvement in their pulmonary function. However, mean FEV_1 in the placebo group did not reach the levels seen in patients who had received with tobramycin inhalation solution in the initial, DB phase. By the end of the 12th treatment cycle, the mean FEV_1 in the tobramycin inhalation solution-only group was 4.7% above the baseline value at the start of the study. Mean FEV_1 at endpoint in patients in the placebo-tobramycin inhalation solution XO group was slightly less than the baseline level, but was still greater than it had been at the end of the placebo phase (week 24). In addition to improvement in the FEV_1, patients who were treated with tobramycin inhalation solution had a significant reduction in the number of courses of IV anti-pseudomonal antibiotic use per year. The patients receiving placebo required 1.9 courses of anti-pseudomonal antibiotics per patient per year, while the patients receiving tobramycin inhalation solution (both the randomized and the OL portions of the trial, regardless of initial study group assignment) required approximately 1.25 courses per patient per year. A subgroup analysis was performed evaluating the change in FEV_1 for patients aged 13 to 17 years. The adolescent patients treated with tobramycin inhalation solution from the beginning had a marked improvement of approximately 15% in their FEV_1 over the first three cycles of treatment. This contrasts with an approximately 8% decline in FEV_1 for the adolescent patients treated with placebo. The patients who continued tobramycin inhalation solution maintained their level of improvement over the next nine cycles, ending with an FEV_1 that was still an average of 14.3% above their week 0 baseline after 12 cycles of tobramycin inhalation solution. The group of adolescent patients who crossed over from the conventional therapy with placebo aerosol to receive tobramycin inhalation solution in the OL phase showed a marked improvement during subsequent cycles. This degree of improvement was similar to that seen in the group who started on tobramycin inhalation solution in the DB study. The mean FEV_1

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				values of this XO group after nine cycles (72 weeks) of tobramycin inhalation solution were maintained at levels above those at the start of the OL part of the study. Secondary: Not reported
Briesacher et al.[41] (2011) Tobramycin inhalation solution	RETRO Patients with cystic fibrosis with at least one claim for tobramycin inhalation solution	N=804 Variable duration	Primary: Adherence and hospitalization Secondary: Not reported	Primary: Chronic use of tobramycin inhalation solution was low in patients with *Pseudomonas aeruginosa* as only 6% were dispensed four or more cycles per year. Tobramycin inhalation solution usage was similar for patients with and without the diagnosis of *Pseudomonas aeruginosa*. In comparison to patients with high utilization of tobramycin inhalation solution, those using less than four cycles a year were more likely to be hospitalized. High use of tobramycin inhalation solution was associated with a decreased risk of hospitalization relative to low use (AOR, 0.40; 95% CI, 0.19 to 0.84). A higher than average comorbidity risk (AOR, 7.53; 95% CI, 5.20 to 10.90), a coded diagnosis of *Pseudomonas aeruginosa* (AOR, 3.0; 95% CI, 2.13 to 4.32), and a coded diagnosis of failure to thrive/growth failure (AOR, 2.8; 95% CI, 1.09 to 7.14) were all independently associated with an increased risk of hospitalization. Secondary: Not reported
O'Sullivan et al.[42] (2011) Tobramycin inhalation solution	RETRO Patients at least six years of age with cystic fibrosis and pulmonary infections	N=1,064 1 year	Primary: Health care utilization Secondary: Not reported	Primary: A higher percentage of children had at least one cystic fibrosis-related office visit (P=0.0046), cystic fibrosis-related outpatient hospital visit (P<0.0001), outpatient hospital visit for any reason (P=0.0016), and cystic fibrosis-related emergency room visit (P=0.0159) compared to adults. Adults with cystic fibrosis averaged about 12 office visits per year for any diagnosis, compared to about 10 visits per year among children (P=0.0067). Children had more cystic fibrosis-related outpatient hospital visits

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(P=0.004) as well as prescriptions for than tobramycin inhalation solution (P=0.0007) and dornase alfa (P<0.0001) compared to adult patients. Adults had more frequent inpatient stays for any diagnosis (P=0.0021) and numbers of prescriptions for antibiotics other than tobramycin inhalation solution and azithromycin compared to children (P=0.0009). Adults had an average of 43 prescriptions per year compared to 39 prescriptions per year for children (P=0.03). Secondary: Not reported
Ratjen et al.[43] (2010) Tobramycin inhalation solution for an additional 28 days vs discontinuation of tobramycin	MC, OL, RCT Patients at least six months with cystic fibrosis and early *Pseudomonas aeruginosa* infection who had already received 28 days of treatment with tobramycin inhalation solution	N=123 56 days	Primary: Median time to recurrence of any strain of *Pseudomonas aeruginosa* Secondary: Proportion of patients free of *Pseudomonas aeruginosa* one month after the end of treatment; time to recurrence of any strain of *Pseudomonas aeruginosa*; number of patients with the same genotype of *Pseudomonas aeruginosa* at baseline and recurrence or a	Primary: The median time to recurrence of *Pseudomonas aeruginosa* was 26.12 and 25.82 months following than tobramycin inhalation solution for 28 and 56 days, respectively (P=0.593). At the time of each patient's final study visit, 66% of patients remained free of *Pseudomonas aeruginosa* in the 28-day than tobramycin inhalation solution group and 69% remained free of *Pseudomonas aeruginosa* in the 56-day than tobramycin inhalation solution group. Secondary: The proportion of patients free of *Pseudomonas aeruginosa* at day 28 and one month after the end of treatment was comparable in both groups. The proportion of patients free of *Pseudomonas aeruginosa* one month after the end of treatment was similar in sputum producers and non-sputum producers. Paired samples (baseline and recurrence) were available in 21 patients, of which 12 had the same genotype at baseline and at recurrence. For the remaining patients (n=9), paired samples were of a different genotype. Two patients (5.3%) in the 56-day than tobramycin inhalation solution group were hospitalized on one occasion, each for a pulmonary exacerbation during the study.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			new genotype at recurrence; proportion of patients free of *Pseudomonas aeruginosa* one month after the end of treatment for sputum and non-sputum producers and by baseline characteristics, lung function and infection status; number and length of hospital admissions for respiratory indications	No major short- or long-term changes in spirometric parameters were observed during the study period.
Hodson et al.[44] (2002) Tobramycin inhalation solution 300 mg BID vs colistin nebulized solution 80 mg inhaled BID	RCT Patients older than six years of age with cystic fibrosis, FEV_1>25%; *Pseudomonas aeruginosa* positive sputum culture	N=115 4 weeks	Primary: Mean change from baseline to week four in FEV_1 percent predicted Secondary: Change in sputum *Pseudomonas aeruginosa* density, tobramycin/colistin MICs, and safety assessment	Primary: Tobramycin inhalation solution produced a mean 6.7% improvement in lung function (P=0.006), while there was no significant improvement in the colistin-treated patients (mean change 0.37%). Secondary: Both nebulized antibiotic regimens produced a significant decrease in the sputum *Pseudomonas aeruginosa* density, and there was no development of highly resistant strains over the course of the study. No significant difference was detected between groups with respect to incidence of adverse events.
Berlana et al.[45] (2011)	OBS, PRO Adult patients with	N=81 4 years	Primary: Frequency and duration of	Primary: Significant differences were observed in the mean yearly rates for hospitalizations, duration of hospitalization, and duration of antibiotic use

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Tobramycin inhalation solution vs colistin inhalation solution vs tobramycin inhalation solution plus colistin inhalation solution	cystic fibrosis who received inhaled colistin, inhaled tobramycin or both to treat *Pseudomonas aeruginosa* bronchial colonization, a history of chronic *Pseudomonas aeruginosa* bronchial colonization, a diagnosis of bronchiectasis or chronic obstructive pulmonary disease, and who were receiving long-term treatment (≥12 weeks) of outpatient inhaled antibiotic therapy		hospitalizations for respiratory exacerbations Secondary: Emergence of bacterial resistance, antibiotic use during admission, emergence of other opportunistic microorganisms, achievement of sustained *Pseudomonas aeruginosa* eradication in the airways, mortality, safety, and changes in respiratory function	between the tobramycin and colistin plus tobramycin groups. No significant differences were found in hospitalizations, hospitalization days, or days of antibiotic use between tobramycin and colistin treatment. Secondary: Of the 93 microbiologically assessable antibiotic courses, 10 episodes of *Pseudomonas aeruginosa* were classified as eradicated, 20 reduced, 17 maintained negative, and 46 no response. Antimicrobial resistance was assessable in 72 episodes. The frequency of emergence of resistant strains differed significantly according to the antibiotic received (48% for tobramycin and 8% for colistin). The highest rate of emergence of other microorganisms was seen in the colistin plus tobramycin group. Only one patient was treated to control persistent isolation of *Aspergillus* species. Neither *Pseudomonas aeruginosa* eradication nor emergence of other microorganisms was linked to the inhaled antibiotic treatment received. No significant differences were found in the mean change/year in pulmonary function tests between the treatment groups. The overall frequency of patients experiencing an adverse event was 40%. A total of 12 patients (14.8%) died during the study, all for respiratory causes. There were no significant differences in mortality between the study groups, and FEV_1 percent was linked to mortality (HR, 0.93; 95% CI, 0.86 to 0.98).
Smyth et al.[46] (2005) Tobramycin 10 mg/kg/day IV administered TID for 14 days plus ceftazidime	DB, RCT Patients older than five years of age with cystic fibrosis who had a pulmonary exacerbation	N=244 14 days	Primary: Change in FEV_1 over 14 days of treatment, mean change in baseline FEV_1 Secondary: Change in serum	Primary: The mean change in FEV_1 (percent predicted) over 14 days was similar between the two regimens (10.4% [once daily] vs 10.0% [TID] (adjusted mean difference, 0.4%; 95% CI, –3.3 to 4.1). Mean % change in FEV_1 from baseline was also similar in both treatments (21.9 vs 22.1%; –0.1%; –8.0 to 7.9). Secondary: There was no significant difference in percent change in creatinine from

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs tobramycin 10 mg/kg/day IV once daily for 14 days plus ceftazidime IV			creatinine	baseline (–1.5% [once daily] vs 1.7% [TID]). In children, once-daily treatment was significantly less nephrotoxic than TID treatment (mean percent change in creatine, –4.5% [once daily] vs 3.7% [TID] (adjusted mean difference, –8.0%; 95% CI, –15.7 to –0.4; P=0.04).
Konstan et al.[47] (2011) Tobramycin inhalation powder 112 µg via T-326 inhaler BID for three treatment cycles (28 days on-drug, 28 days off-drug) vs tobramycin inhalation solution 300 mg/5 mL via PARI LC PLUS nebulizer BID for three treatment cycles (28 days on-drug, 28 days off-drug)	OL, RCT Patients ages six years and older with cystic fibrosis with *Pseudomonas aeruginosa* infection with FEV_1 ≥25 to ≤75% predicted	N=553 24 weeks	Primary: Safety assessments; relative chance in FEV_1 percent predicted from baseline, change in sputum *Pseudomonas aeruginosa* density, tobramycin susceptibility to *Pseudomonas aeruginosa* using MIC, antipseudomonal antibiotic use, respiratory-related hospitalizations Secondary: Not reported	Primary: More patients in the tobramycin inhalation powder group reported adverse events compared to tobramycin inhalation solution group (90.3 vs 84.2%; P<0.05). The percentage of adverse events was highest in cycle 1, 77.9% with tobramycin inhalation powder group and 66.5% with tobramycin inhalation solution group and decreased with cycles 2 and 3 (cycle 2: 67.0 vs 66.3%; cycle 3: 65.8 vs 58.5%, respectively). The most frequently reported adverse event was cough during the study period (tobramycin inhalation powder: 48.4% vs tobramycin inhalation solution: 31.1%). The rate of cough suspected to be study drug related was higher in tobramycin inhalation powder group (25.3 vs 4.3%). Twelve out of 308 (4%) tobramycin inhalation powder-treated patients discontinued due to cough vs 1% (2/209) of tobramycin inhalation solution-treated patients. Dysphonia (13.6 vs 3.8%) and dysgeusia (3.9 vs 0.5%) were also more commonly reported in the tobramycin inhalation powder group. The incidence of serious adverse events was similar in both groups. Both treatment groups had similar increases in FEV_1 percent predicted from baseline to day 28 of cycle 3 (least squares mean difference, 1.1% relative change [standard error, 1.75]). On day 28 of cycle 3, 11.6% tobramycin inhalation powder-treated patients and 9.9% tobramycin inhalation solution-treated patients had negative *Pseudomonas aeruginosa* cultures. The proportion of patients requiring any new antipseudomonal antibiotic was significantly higher with tobramycin inhalation powder group (64.9 vs 54.5%; P=0.0148). The number of patients hospitalized for respiratory-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				related events was similar in the tobramycin inhalation powder group vs tobramycin inhalation solution group (24.4 vs 22.0%). Administration time was significantly less for tobramycin inhalation powder compared to the solution formulation (mean, 5.6 vs 19.7 minutes; P<0.0001). Secondary: Not reported
Mazurek et al.[48] (2014) Tobramycin nebulization solution 300 mg/4 mL (28 days on-drug, 28 days off-drug) vs tobramycin nebulization solution 300 mg/5 mL (28 days on-drug, 28 days off-drug) Subset of patients continued receiving tobramycin nebulization solution 300 mg/4 mL only.	MC, OL, RCT (core phase) SA (extension phase) Patients ages six years and older with cystic fibrosis with *Pseudomonas aeruginosa* infection with FEV_1 ≥40 and ≤80% predicted	N=321 (N=321: core phase; N=209: extension phase) 56 weeks (8 weeks: core phase; 48 weeks: extension phase)	Primary: Core phase: absolute change in FEV_1 percent predicted from baseline to week four; extension phase: long term safety of tobramycin nebulization solution 300 mg/4 mL; both phases: microbiological assessments, adverse events, and audiometry findings Secondary: Not reported	Primary: In the core phase, FEV_1 percent predicted increased similarly from baseline (absolute change) following a single on-treatment cycle for both groups: tobramycin nebulization solution 300 mg/4 mL, 7.0% vs tobramycin nebulization solution 300 mg/5 mL, 7.5% (difference between treatments, -0.5; 95% CI, -2.6 to 1.6). The baseline- and country-adjusted mean of absolute change from baseline to week four in FEV_1 percent predicted was 4.7 and 5.2% for 4 and 5 mL solution, respectively, with a significant (P<0.001) improvement vs baseline for both groups. These improvements were maintained throughout the extension phase. *Pseudomonas aeruginosa* sputum count reductions ranged between 0.6 (95% CI, 0.2 to 0.9) to 2.3 (95% CI, 2.0 to 2.6) log_{10} colony forming unit/g throughout the 56 weeks. No remarkable safety issues were identified throughout both study phases, with similar percentages of patients reporting adverse events in the two treatment groups during the core phase (4 mL, 31.4%; 5 mL, 28.0%; P=0.579). The adverse events that were judged to be related to the drug were also similar between the two groups (4 mL, 6.4%; 5 mL, 6.0%; P=1.000). Cough, rhinitis, pharyngitis, and pulmonary exacerbations were the most commonly reported adverse events, proportionally similar between the two groups. Serious adverse events occurred in six (3.8%) and two (1.2%) of patients treated with 4 and 5 mL solution, respectively (Fisher's test, P=0.161). During the extension phase, adverse events were reported by 148 patients (70.8%). Similar to the core phase, the most commonly reported adverse events included pulmonary exacerbation (24.9%), rhinitis (12.4%), cough (11%), pyrexia (7.7%), and bronchitis (7.2%). Bronchospasm and death

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				was not reported in either core or extension phase. Secondary: Not reported
Galeva et al.[49] (2013) Tobramycin inhalation powder 112 µg, as capsules administered via dry powder inhaler, BID vs placebo	DB, MC, PC, Phase 3, RCT Patients six to 21 years of age with cystic fibrosis with FEV_1 ≥25 and ≤80% and a positive sputum or throat culture for *Pseudomonas aeruginosa* within six months of screening and a positive sputum culture for *Pseudomonas aeruginosa* at the screening visit	N=62 Duration not specified	Primary: Relative change in FEV_1 percent predicted from baseline to day 29 Secondary: Relative change in forced vital capacity percent predicted and forced expiratory flow 25 to 75% predicted from baseline to day 29; change from baseline in sputum density of *Pseudomonas aeruginosa*; rates of antipseudomonal antibiotic use and hospitalizations due to respiratory events; safety assessments: the incidence and severity of all adverse events and serious adverse events and regular monitoring	Primary: Mean treatment difference was 5.9% (95% CI, -2.2 to 14.0; P=0.148) for relative change in FEV_1 percent predicted. Secondary: Mean treatment difference was 4.4% (95% CI, 0.0 to 8.8; P<0.05) for absolute change in FEV_1 percent predicted. Tobramycin inhalation powder significantly reduced sputum *Pseudomonas aeruginosa* density by -1.2 log_{10} colony forming unit (P=0.002). The tobramycin group had higher clearance rate for *Pseudomonas aeruginosa* compared to placebo (41.4 vs 0% at day 29). Antipseudomonal antibiotic use was reported to be used in three patients in each of the treatment groups. Hospitalization due to respiratory events occurred in one patient in the placebo group. Adverse events were mild to moderate in severity and they occurred in 26.7% patients in the tobramycin group compared to 34.4% patients in the placebo group. Drug-related adverse events occurred in five (16.7%) tobramycin-treated patients compared to two (6.3%) patients in the placebo group; the difference was due to adverse event of cough that was reported in three patients in the tobramycin group to be drug-related. There was no difference between the groups in serious adverse events. There were no major differences that were observed between the groups in any hematology, renal or biochemistry variables, or acuity.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			of hematology, blood chemistry and urine protein, vital signs, physical condition, and bodyweight	
Chuchalin et al.[50] [abstract] (2007) Tobramycin inhalation solution 300 mg/4 mL vs placebo Four-week treatment periods ('on' cycles) were followed by four-week periods without treatment ('off' cycles)	DB, MC, PC Patients with cystic fibrosis with chronic *Pseudomonas aeruginosa* infection	N=247 24 weeks Endpoint time assessment was at week 20	Primary: FEV_1 percent predicted normal Secondary: Forced vital capacity, forced expiratory flow at 25 to 75% of forced vital capacity, *Pseudomonas aeruginosa* susceptibility, MIC required to inhibit 90% of strains, rates of *Pseudomonas aeruginosa* - negative culture, *P. aeruginosa* persistence and superinfection, need for hospitalization and parenteral antipseudomonal antibiotics, loss of school/working days due to the disease, and	Primary: FEV_1 was significantly increased in the tobramycin group and the adjusted mean difference between groups in the intention-to-treat population was statistically significant (P<0.001). Secondary: Tobramycin group had clinically relevant improvements in forced vital capacity (P=0.022) and forced expiratory flow at 25 to 75% of forced vital capacity (P=0.001). The microbiologic outcomes at the end of the last 'on' cycle period were better in the tobramycin group than the placebo group (P=0.024). There was a concomitant trend toward an increase in the minimum concentration required to inhibit 90% of strains of isolated *Pseudomonas aeruginosa* strains. Tobramycin group had a lower percentage of patients hospitalized (P=0.002) and had a lower need for parenteral antipseudomonal antibiotics (P=0.009) compared to the placebo group. Tobramycin group patients had fewer lost school/working days due to the disease (P<0.001). Compared to placebo, there was a favorable effect of tobramycin in terms of an increase in bodyweight and body mass index at all time points (P<0.01 and P<0.001, respectively). There were no significant changes in serum creatinine and auditory function. The proportion of patients with drug-related adverse events was 15% in both treatment groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			nutritional status (bodyweight and body mass index); safety parameters including adverse events, audiometry, and renal function	
Lenoir et al.[51] (2007) Tobramycin inhalation solution 300 mg/4 mL BID for four weeks vs placebo BID	DB, MC, PC, PG, PRO, RCT Patients six years of age and older with cystic fibrosis with a FEV_1 ≥40 and ≤80% of predicted normal with *Pseudomonas aeruginosa* infection	N=59 8 weeks	Primary: Pulmonary function as measured by FEV_1, forced vital capacity, and forced expiratory flow at the midportion of vital capacity, *Pseudomonas aeruginosa* susceptibility, microbiologic results, and in vitro MIC for 90% of strains; safety as monitored by the recording of adverse events, audiometry (bone conduction at 250 to 8,000 Hz frequency), laboratory tests, physical examination, and general health	Primary: The tobramycin group had a significant increase in FEV_1 from baseline compared to the placebo group: the absolute difference between groups (intent-to-treat population) of predicted normal was 13.2% at week two (95% CI, 4.88 to 21.54; P=0.002) and 13.3% at week four (95% CI, 4.74 to 21.81; P=0.003). The forced vital capacity and forced expiratory flow at the midportion of vital capacity also increased in the tobramycin group compared to the placebo group: the estimated differences at week four visit were 10.65% (95% CI, 1.94 to 19.37; P=0.017) and 15.78% (95% CI, 5.24 to 26.32; P=0.004) for the two variables, respectively. There was no significant effects in terms of maintenance of *Pseudomonas aeruginosa* negative cultures at the end of the run-out phase in the tobramycin group (P=0.202 between-group comparison). There was no differences between treatments in the mean changes from baseline of MIC for 90% at the end of week four in patients with persistent *Pseudomonas aeruginosa* (P=0.780). There was no difference between the treatment groups in terms of drug-related adverse events (P=0.184). Results of audiometric tests did not show statistically significant differences between groups. There were no differences between treatment groups in increase in serum creatinine levels (P=0.850). There were no clinically significant changes in heart rate and blood pressure in either group at any time. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			condition Secondary: Not reported	Not reported
Miscellaneous Infections				
Sullam et al.[52] (1986) Paromomycin 25 to 35 mg/kg daily in three divided doses for seven days	PRO Homosexual men with *Entamoeba histolytica* cysts or trophozoites in stool specimens with mild to moderate intestinal amebiasis	N=114 6 weeks	Primary: Symptomatic response to therapy and side effects of therapy Secondary: Not reported	Primary: Seventy percent (80/114) of the patients had gastrointestinal symptoms at the onset of therapy with range from mild softening of stools to severe diarrhea with ten or more watery stools per day; 34 men were asymptomatic. Forty-six of 66 (70%) men who were symptomatic initially reported improvement or resolution of symptoms after one week of paromomycin therapy. After four to six weeks of treatment, 55 of the patients with symptoms were asymptomatic, 14 had gastrointestinal complaints, and 11 were lost to follow-up. Four out of 14 patients with persistent symptoms at six weeks had proved *Entamoeba histolytica* infection after therapy. Two out of the remaining 10 patients became asymptomatic within 12 weeks after paromomycin therapy, without additional medication. One man responded to empiric therapy with metronidazole and iodoquinol, one man had *Giardia lamblia* on follow-up stool examination, three men responded to empiric therapy for giardiasis with quinacrine; one man was diagnosed with cryptosporidiosis secondary to acquired immunodeficiency syndrome and another man was not available for further evaluation. Fifty-four out of 80 men with initial symptoms at treatment onset were successfully treated; six were treatment failures (success rate, 90 vs 95% for asymptomatic patients; P>0.5). Mild diarrhea during therapy was reported by 67% of the patients and paromomycin treatment was generally well-tolerated. Secondary: Not reported
Pamba et al.[53]	RCT	N=417	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1990) Aminosidine (paromomycin) vs etophamide vs nimorazole vs nimorazole + aminosidine vs nimorazole + etophamide vs etophamide + aminosidine The medications were given orally at the following doses under medical supervision for a total of five days: aminosidine: 500 mg BID (adults), 15 mg/kg of body	Patients six to 80 years of age with *Entamoeba histolytica* intestinal infection	60 days	Clinical cure, defined as the disappearance of all symptoms present on entry; parasitological cure as defined by disappearance of all parasitic forms from stools or ulcer scrapings; anatomical cure as defined by healing of previous ulceration Secondary: Not reported	Clinical cure with the different treatments varied from 98 to 100%. Parasitological cure was 100% in the nimorazole+aminosidine group, 100% in the etophamide+aminosidine group, and 98% in aminosidine group. The incidence of relapses did not occur in the etophamide+aminosidine group, followed by 3% in nimorazole+aminosidine, and 6% in aminosidine group. Anatomical cure was 97.8% in the nimorazole+aminosidine group, 95.5% in the nimorazole group, and 88.5% in the aminosidine group. Etophamide + aminosidine combination produced diarrhea in 76.5% of patients, and as a result proper assessment of clinical cure was not conducted in this treatment group; all other treatments were well tolerated. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
weight BID (children); etophamide: 600 mg BID (adults), 15 mg/kg of body weight BID (children); nimorazole: 1 g BID (adults), 20 mg/kg of body weight BID (children)				
Tarao et al.[54] (1982) Paromomycin sulfate 2 g in four doses daily (250 mg after each meal and 250 mg at bedtime) vs placebo	DB, RCT Clinically stable cirrhotic patients with endotoxemia whose general hepatic status was not rapidly changing, as determined by liver function tests and clinical examination	N=24 4 weeks	Primary: Prevention of endotoxemia in cirrhotic patients with endotoxemia, adverse events Secondary: Not reported	Primary: More patients in the paromomycin group (10 out of 13, 76.9%) had disappearance of endotoxemia compared to the placebo group (three out of 11, 27.3%). This difference was statistically significant (P<0.05). Endogenous creatinine clearance and p-aminohippurate clearance was significantly increased in the patients whose endotoxemia disappeared on paromomycin administration (P<0.02). However, improvements in liver function tests or blood coagulation studies were not observed in either of the groups. No serious adverse events were observed in either of the treatment groups. Secondary: Not reported
Bode et al.[55] (1997) Paromomycin sulfate 1 g TID vs placebo	DB, PC Male patients between 18 and 65 years of age with alcoholic liver disease with an average daily alcohol consumption of 60 g or more for more	N=50 3 to 4 weeks	Primary: Efficacy as measured by plasma endotoxin concentration Secondary: Efficacy as measured by the following laboratory values:	Primary: Mean initial endotoxin concentrations were significantly elevated in both study groups (mean±SEM; paromomycin, 16.7±5.3 pg/mL; placebo, 17.5±6.9 pg/mL; healthy controls, 2.3±0.4 pg/mL). Although the mean endotoxin concentration was lower in the paromomycin group after one week (paromomycin, 8.0±1.9 pg/mL; placebo, 14.6±3.5 pg/mL; P>0.05), paromomycin treatment had no significant effect on endotoxin concentration or liver function tests during the four week study period. Secondary: There were no significant differences between the two overall groups for

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	than three years and evidence of alcoholic hepatitis with or without cirrhosis		γ-glutamyl-transferase, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, bilirubin, quick-test for prothrombin time, albumin and neutrophil leukocytes	any of the following biochemical tests at the end of three weeks: γ-glutamyltransferase, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, bilirubin, quick-test for prothrombin time, albumin and neutrophil leukocytes (P values for the placebo group vs treatment group were not reported).
Evans et al.[56] (1986) Amikacin vs gentamicin vs netilmicin vs sisomicin vs tobramycin	MA, RCT Patients with urinary tract infections, obstetric gynecologic infections, major gram-negative infections, and serious systemic infections	42 trials Variable duration	Primary: Efficacy (bacteriologic or clinical response), nephrotoxicity, auditory toxicity Secondary: Not reported	Primary: Efficacy was an end point in 33 trials. A statistically significant difference was found in only two of the 44 aminoglycoside comparisons. These two studies noted that sisomicin had greater efficacy than gentamicin. Nephrotoxicity was an end point in all 42 trials. Statistically significant differences were only found for four of the 53 aminoglycoside comparisons. Two studies noted a greater risk of nephrotoxicity among patients receiving gentamicin than those receiving amikacin (specific details including statistical analyses were not available). Another study noted that patients receiving gentamicin had a higher risk of nephrotoxicity than those receiving tobramycin. A fourth study noted a higher risk of nephrotoxicity among patients receiving tobramycin than among those receiving netilmicin. Auditory toxicity was an end point in 23 trials. Statistically significant results were found for only one of the 32 aminoglycoside comparisons. That study noted a greater risk of auditory toxicity in patients receiving tobramycin than in those receiving netilmicin. Secondary: Not reported
Contopoulos-	MA	N=995	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ioannidis et al.[57] (2004) Amikacin vs gentamicin vs tobramycin vs netilmicin Multiple-daily dosing and once-daily dosing for the aminoglycoside classes were compared.	Patients receiving aminoglycosides in different clinical settings (neonatal intensive care unit, cystic fibrosis, cancer, urinary tract infections, diverse infections, pediatric intensive care units)	(24 trials) Variable duration	Clinical failure rates, microbiologic failure rate and combined clinical or microbiologic failure rates Secondary: Safety endpoints of nephrotoxicity and ototoxicity	No significant difference between once-daily dosing and multiple-daily dosing in the clinical failure rate, microbiologic failure rate, and combined clinical or microbiologic failure rates, but trends favored once-daily dosing consistently. A statistically significant benefit was seen with once-daily dosing over multiple-daily dosing in trials using amikacin, whereas no statistical difference was seen in trials using other antibiotics. Secondary: There was no significant difference between once-daily dosing and multiple-daily dosing in the primary nephrotoxicity outcomes. Secondary nephrotoxicity outcomes were significantly better with once-daily dosing. There was no significant difference between once-daily dosing and multiple-daily dosing in the primary ototoxicity outcomes. Studies noting only the clinical impression of hearing impairment also failed to identify any toxicity (once-daily dosing: 114 cases; multiple-daily dosing: 114 cases).
King et al.[58] (1992) Amikacin vs tobramycin vs gentamicin	OBS, PRO All gram-negative bacilli isolates from any patient source during study period	N=11,641 resistant isolates 64 months	Primary: Resistance, bacteremic episodes, and bacteremia-associated deaths before and after institution of amikacin as the sole preferred aminoglycoside Secondary: Not reported	Primary: Resistance rates to gentamicin, tobramycin, and amikacin among aerobic and facultative gram-negative bacterial isolates were 12.8, 10.8, and 5.9%, respectively, before amikacin was adopted as the sole formulary aminoglycoside. After amikacin was adopted as the sole formulary aminoglycoside, over the next 30 months the rates of resistance to gentamicin, tobramycin, and amikacin were 6.3, 5.0, and 3.3%, respectively. (P=0.02) During the 30 months when amikacin had preferred status, the incidence of bacteremia-associated death decreased from 18.6 to 11.5% (P=0.003). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Gerding et al.[59] (1991) Amikacin vs tobramycin vs gentamicin	PRO All gram-negative bacilli isolates in a single hospital setting	N=25,000 aerobic and gram-negative bacillary isolates 10 years	Primary: Resistance rates Secondary: Not reported	Primary: Introduction of amikacin at a high level of usage in the 1980's was associated with a significant reduction in resistance to gentamicin and tobramycin among gram-negative bacilli. Gentamicin resistance decreased from 12.0 to 6.4% (P<0.001), tobramycin resistance decreased from 9.5 to 4.8% (P<0.001). Rapid introduction of gentamicin usage in 1982 after the use of amikacin was associated with a significant and rapid increase in gentamicin and tobramycin resistance. Gentamicin resistance increased from 6.4 to 9.2% (P<0.001) and tobramycin resistance increased from 4.8 to 6.0% (P<0.05). However, in 1986, gentamicin was again reintroduced to the institution and the usage of gentamicin was gradually increased over a 15-month period without significant change in resistance to gentamicin, tobramycin, or amikacin. Gentamicin resistance decreased from 5.8 to 5.7%, and tobramycin increased from 4.0 to 4.2% (P=not statistically significant). Secondary: Not reported
Sexton et al.[60] (1998) Gentamicin 3 mg/kg once daily plus ceftriaxone 2 g IV once daily for two weeks vs ceftriaxone 2 g IV once daily for four weeks	MC, OL, RCT Patients ≥18 years of age with endocarditis who had received <72 hours of parenteral antibiotic therapy	N=51 4 years	Primary: Clinical cure Secondary: Not reported	Primary: Clinical cure was observed for patients both at termination of therapy and at the three-month follow-up: 25 (96.2%) of the monotherapy patients and 24 (96%) of combination therapy patients were considered clinically cured. Ceftriaxone 2 g once daily for four weeks and ceftriaxone 2 g once daily plus gentamicin 3 mg/kg once daily for two weeks were both judged effective for treatment of streptococcal endocarditis. Secondary: Not reported
Mithani et al.[61]	RETRO	N=200	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1996) Gentamicin or tobramycin 1.5 to 2 mg/kg every eight hours vs gentamicin or tobramycin 6 mg/kg every 24 hours	All patients who received once-daily aminoglycoside therapy	1 year	Rates of clinical response, failure and relapse Secondary: Toxicity	Eighty-nine patients were cured or improved with once-daily administration vs 90 patients with conventional administration. Secondary: One patient in each group developed definite aminoglycoside-induced renal toxicity.
Song et al.[62] (1998) Gentamicin plus metronidazole vs cefuroxime plus metronidazole vs first generation or second generation cephalosporin vs third generation cephalosporin vs other antibiotic	MA Patients scheduled to undergo elective surgery of the colon	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 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
agents as monotherapy or combination therapy				
Mwengee et al.[63] (2006) Gentamicin 2.5 mg/kg IM every 12 hours for seven days vs doxycycline 100 mg (adults) or 2.2 mg/kg (children) orally every 12 hours for seven days	OL, RCT Adults and children with symptoms of bubonic, septicemic, or pneumonic plague lasting less than or equal to three days	N=65 2 weeks	Primary: Efficacy Secondary: Not reported	Primary: Three patients, two of whom were treated with gentamicin and one of whom was treated with doxycycline, died on the first or second day of treatment, and these deaths were attributed to advanced disease and complications including pneumonia, septicemia, hemorrhage, and renal failure at the start of therapy. All other patients experienced cure or an improved condition after receiving therapy, resulting in favorable response rates of 94% for gentamicin (95% CI, 81.1 to 99.0) and 97% for doxycycline (95% CI, 83.4 to 99.8). *Yersinia pestis* isolates obtained from 30 patients belonged to biotype *antiqua* and were susceptible to gentamicin and doxycycline, which had MICs of 0.13 mg/L and 0.25 to 0.5 mg/L, respectively. Serum concentrations of antibiotics were within therapeutic ranges, and adverse events were infrequent. Patients treated with gentamicin demonstrated a modest increase in the mean serum creatinine concentration after treatment (P<0.05). Both gentamicin and doxycycline were effective therapies for adult and pediatric plague, with high rates of favorable responses and low rates of adverse events. Secondary: Not reported
Roushan et al.[64] (2010) Gentamicin 5 mg/kg once daily for five days plus doxycycline 100 mg BID for eight weeks (gentamicin-doxycycline group)	RCT Patients >10 years of age with brucellosis	N=164 Up to 8 weeks	Primary: Therapeutic failure due to lack of efficacy and relapse Secondary: Safety	Primary: Therapeutic failure was seen in two (2.4%) patients from the gentamicin-doxycycline group and in four (4.9%) patients from the streptomycin-doxycycline group (P=0.68). Relapse occurred in two (2.4%) patients from the gentamicin-doxycycline group and in five (6.1%) patients from the streptomycin-doxycycline group (P=0.44). Success occurred in 78 (95.12%) patients in the gentamicin-doxycycline

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs streptomycin 1 g IM for two weeks plus doxycycline 100 mg BID for 45 days (streptomycin-doxycycline group)				group and in 73 (89%) patients in the streptomycin-doxycycline group (P=0.25). Secondary: The rates of adverse effects were similar in the gentamicin-doxycycline group (28%) and in the streptomycin-doxycycline group (22%; P=0.5).
Lewis[65] (2002) Neomycin 2 g orally vs amikacin 1 g IV vs metronidazole 2 g orally vs metronidazole 1 g IV vs placebo	MA 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 (RR, 0.29; 95% CI, 0.11 to 0.75; P<0.01). 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 RR 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
Boulanger et al.[66] (2004) Streptomycin vs	RETRO Patients with plague whose cases were reported in New	N=75 Duration varied	Primary: Mean number of hospital days, fever days, complications, and deaths	Primary: The mean number of fever days after the initiation of antimicrobial treatment was 3.5 days for the streptomycin group, 2.6 days for the gentamicin group, 1.9 days for the gentamicin-tetracycline group and 2.6 days for the tetracycline group (P=0.23).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
gentamicin vs tetracycline vs gentamicin plus tetracycline	Mexico during 1985 to 1999		Secondary: Not reported	The mean duration of hospital days was 6.2 days in the streptomycin group, 7.2 days in the gentamicin group, and 6.0 days in the gentamicin-tetracycline group (P=0.57). There were no deaths among the 50 patients in the four treatment groups. The mean numbers of fever days, hospital days, and complications and the number of deaths did not differ between patients treated with streptomycin and those treated with gentamicin. Secondary: Not reported
Mwengee et al.[67] (2006) Doxycycline 100 mg (adults) and 2.2 mg/kg (children) by mouth BID for seven days vs gentamicin 2.5 mg/kg IM BID for seven days	OL, RCT Adults and children with symptoms of bubonic, septicemic, or pneumonic plague	N=65 2 weeks	Primary: Efficacy (resolution of fever, bubo swelling, and all other plague symptoms) Secondary: Not reported	Primary: Three patients, two of whom were treated with gentamicin and one of whom was treated with doxycycline, died on the first or second day of treatment, and these deaths were attributed to advanced disease and complications including pneumonia, septicemia, hemorrhage, and renal failure at the start of therapy. All other patients experienced cure or an improved condition after receiving therapy, resulting in favorable response rates of 94% for gentamicin and 97% for doxycycline. Secondary: Not reported
Festi et al.[68] (1993) <u>Study 1</u> Rifaximin 1,200 mg/day for 21 days <u>Study 2</u> Rifaximin 1,200 mg/day for 21 days	OL (Study 1), RCT (Study 2 and 3) Patients 40 to 75 years of age with clinical and biochemical signs of mild hepatic encephalopathy and	N=136 21 days	Primary: Neurological signs, electro-encephalographic abnormalities, ammonia levels Secondary: Not reported	Primary: <u>Study 1</u> Rifaximin significantly reduced the frequency of neurologic signs. After five days of treatment, the percentage of patients who exhibited asterixis was significantly lower than at baseline; after 15 days of treatment, no patients showed this neurologic sign. After seven days, a significantly lower percentage of patients exhibited electroencephalography abnormalities. Blood ammonia levels were significantly improved with rifaximin after

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs neomycin 3,000 mg/day for 21 days Study 3 Rifaximin 1,200 mg/day for 21 days vs lactulose 40 g/day for 21 days	liver cirrhosis			five days. Blood ammonia concentrations reached normal values and remained within the normal range throughout the study. Study 2 Both rifaximin and neomycin reduced the neurologic signs of hepatic encephalopathy, but at different rates. Treatment with rifaximin led to a significant reduction in the frequency of asterixis after three days compared to five days with neomycin. A significantly lower percentage of patients exhibited electro-encephalographic abnormalities with rifaximin and neomycin compared to baseline (P<0.001). Ammonia levels were significantly reduced by rifaximin and neomycin. Normal values were achieved after seven days of treatment. Study 3 Both rifaximin and lactulose reduced the neurologic signs of hepatic encephalopathy compared to baseline (P<0.05). Electro-encephalographic abnormalities significantly decreased in frequency with rifaximin and lactulose compared to baseline. Ammonia levels were significantly decreased with both treatments (P<0.01). Secondary: Not reported
Miglio et al.[69] (1997) Rifaximin 400 mg TID for 14 days each month vs	DB, RCT Patients with cirrhosis and chronic hepatic encephalopathy of grade 1 or 2	N=60 6 months	Primary: Improvement of at least one grade of hepatic encephalopathy, neurological signs, Reitan test, ammonia levels, liver function tests	Primary: There was a progressive reduction in hepatic encephalopathy grade with rifaximin and neomycin. There was no significant difference between the two treatment groups. The improvement in hepatic encephalopathy was significant after 30 days (P<0.001 for each group). In both groups, the disturbances in speech, memory, behavior and mood, gait, asterixis, writing, serial subtraction of 7s and five-pointed star tests showed the highest improvement (P<0.001). The Reitan test only showed

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
neomycin 1 g TID for 14 days each month			Secondary: Not reported	a significant improvement in the rifaximin group (P<0.02). Blood ammonia levels were decreased from 210.2 to 88.9 µg/100 mL in the rifaximin group (P<0.001) and from 202.1 to 86.2 µg/100 mL in the neomycin group (P<0.001). There was no significant difference between the treatment groups. There were significant decreases in aspartate aminotransferase (P<0.02) and alanine transaminase (P<0.01 in the rifaximin group and P<0.03 in the neomycin group). Secondary: Not reported

Drug regimen abbreviations: BID=twice daily, IM=intramuscular, IV=intravenous, TID=three times daily.
Study abbreviations: AOR=adjusted odds ratio, CI=confidence interval, DB=double-blind, HR=hazard ratio, MA=meta-analysis, MC=multicenter, OBS=observational, OL=open-label, OR=odds ratio, PC=placebo- controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=risk ratio, SA=single arm, SEM=standard error of the mean.
Miscellaneous abbreviations: FEV_1=forced expiratory volume in one second, MIC=minimum inhibitory concentration.

Additional Evidence

Dose Simplification
Once-daily dosing of aminoglycosides is possible due to their rapid concentration-dependent killing and post-antibiotic effect. There was no significant difference between once-daily dosing and multiple daily dosing regimens with regards to clinical failure rates, microbiologic failure rates, or the combined clinical/microbiologic failure rates. Studies have demonstrated that once-daily dosing regimens are as safe as multiple daily dosing regimens with similar efficacy.[7,31-32]

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 Aminoglycosides

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Amikacin	injection	N/A	N/A	$$$$$
Gentamicin	injection	N/A	N/A	$$$$
Neomycin	tablet	N/A	N/A	$
Paromomycin	capsule	N/A	N/A	$$$$$
Streptomycin	injection	N/A	N/A	$$$$$
Tobramycin	inhalation solution, inhalation powder, injection	Bethkis®, Kitabis®*, TOBI®*, TOBI Podhaler®	$$$$$	$$$$$

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

X. Conclusions

The parenteral aminoglycosides are often used empirically as monotherapy or in combination with other antibacterial agents to treat serious infections, such as septicemia, respiratory tract infections, and complicated

urinary tract infections. All of the aminoglycosides are available in a generic formulation, with the exception of tobramycin inhalation powder.

There are many guidelines that define the appropriate place in therapy for the oral/parenteral aminoglycosides. The agent that is recommended is dependent upon the infectious organism being treated and the corresponding spectrum of activity of the aminoglycoside. The parenteral aminoglycosides are recommended as an initial empiric treatment option for serious infections, including acute pyelonephritis, community-acquired pneumonia, nosocomial pneumonia, and febrile neutropenia.[21,25,26,31] They are also recommended as specific therapy for the treatment of susceptible pathogens causing endocarditis, encephalitis, meningitis, pelvic inflammatory disease, and plague.[12,13,15-18,20,25,27,30,33] The aminoglycosides are recommended as an alternative treatment option for skin and soft-tissue infections, granuloma inguinale, tuberculosis, and for surgical prophylaxis.[19,20,27,28,34] Neomycin is recommended for the treatment of hepatic encephalopathy, as well as for the prophylaxis for colorectal surgery.[34,35] Clinical trials have demonstrated comparable efficacy when the oral/parenteral aminoglycosides have been compared to each other, as well as to antibacterial agents in other classes.[56,57,61-64] Paromomycin has been evaluated in clinical trials that demonstrates it efficacy and safety for the treatment of intestinal amebiasis and for the management of endotoxemia.[52-55]

The European Society of Cardiology guidelines for infective endocarditis note that the indications and pattern of use of aminoglycosides have changed. Aminoglycosides are no longer recommended in staphylococcal native valve endocarditis because their clinical benefits have not been demonstrated, but they can increase renal toxicity; and, when they are indicated in other conditions, aminoglycosides should be given in a single daily dose in order to reduce nephrotoxicity.[12]

The chronic use of inhaled tobramycin is recommended for patients six years of age and older with cystic fibrosis colonized with *Pseudomonas aeruginosa* regardless of the severity of lung disease.[23] Treatment with tobramycin has been associated with improvements in pulmonary function, improved quality of life, decreased requirement for intravenous anti-pseudomonal antibiotics, and a decrease in hospitalizations compared to placebo.[36-41] Open-label studies following patients for up to two years have also demonstrated continued benefit over time.[39,40] Tobramycin inhalation powder provides a dosing option with decreased medication administration time, compared to the tobramycin inhalation solution.[5,6] However, there is no clinical evidence of differences in efficacy with the various inhaled tobramycin formulations.[47-51]

Patients treated with parenteral aminoglycosides should be under close clinical observation because of the potential ototoxicity, nephrotoxicity, and neurotoxicity associated with their use.[1] Safety for treatment periods which are longer than 14 days has not been established.

Therefore, all brand aminoglycosides products 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. Tobramycin inhalation solution and inhalation powder has been shown to improve lung function and reduce exacerbations in cystic fibrosis patients colonized with *Pseudomonas aeruginosa*.[4-8,47-51] Therefore, these patients should be allowed approval for inhalation solution and inhalation powder through the medical justification portion of the prior authorization process.

XI. Recommendations

No brand aminoglycosides 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.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Cephalosporins
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I. Overview

The cephalosporins are approved to treat a variety of infections, including central nervous system, dermatologic, genitourinary, respiratory, as well as several miscellaneous infections.[1-13] They exert their bactericidal action by binding to penicillin-binding proteins, which leads to inhibition of cell-wall synthesis.

The cephalosporins have been shown to be active against a wide range of gram-positive and gram-negative organisms.[1-14] They are frequently grouped into generations based on their spectrum of activity. The first generation cephalosporins (cefadroxil, cefazolin, and cephalexin) are most active against gram-positive aerobes with limited activity against gram-negative aerobes. The second generation cephalosporins (cefaclor, cefprozil, and cefuroxime) have a greater gram-negative spectrum than first generation agents while retaining some activity against gram-positive cocci. They are also more resistant to beta-lactamases. The third generation cephalosporins (cefdinir, cefixime, cefotaxime, cefpodoxime, ceftazidime, ceftibuten, and ceftriaxone) have a broad spectrum of activity and enhanced activity against gram-negative organisms. Cefepime is a fourth generation cephalosporin, which is an extended-spectrum agent with similar activity against gram-positive organisms as first generation cephalosporins. It also has a greater resistance to beta-lactamases than the third generation cephalosporins. Ceftaroline is a fifth generation cephalosporin with a spectrum of activity similar to ceftriaxone. It has greater activity against gram-positive organisms, including methicillin-resistant *Staphylococcus aureus* and vancomycin-intermediate *Staphylococcus aureus*. Although the concept of "generations" was initially helpful, differences in antimicrobial spectra and pharmacokinetic properties within each generation exist. Additionally, there is an overlap in the spectra between generations.

Since this class was last reviewed, Zerbaxa® (ceftolozane-tazobactam) and Avycaz® (ceftazidime-avibactam) were FDA-approved, both with the indications of complicated intra-abdominal infections when used in combination with metronidazole and complicated urinary tract infections including pyelonephritis.[2,12,13] Ceftolozane-tazobactam has demonstrated activity against gram-negative and gram-positive microorganisms, including *Pseudomonas aeruginosa*. Tazobactam and avibactam are β-lactamase inhibitors. β-lactamase inhibitors have a high, irreversible binding affinity for the β-lactamase enzyme and prevent hydrolysis of the β-lactam ring. They also bind to the penicillin-binding proteins of the bacteria, increasing the effectiveness of certain cephalosporins. However, they have little clinically relevant in vitro activity against bacteria themselves.[1-3,12,13]

The cephalosporins that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All of the cephalosporins are available in a generic formulation with the exception of ceftaroline and the combination products. This class was last reviewed in August 2014.

Table 1. Cephalosporins Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Cefaclor	capsule, extended-release tablet, suspension	N/A	cefaclor
Cefadroxil	capsule, suspension, tablet	N/A	cefadroxil
Cefazolin	injection	N/A	cefazolin
Cefdinir	capsule, suspension	N/A	cefdinir
Cefepime	injection	Maxipime®*	cefepime
Cefixime	capsule, chewable tablet, suspension	Suprax®*	cefixime
Cefotaxime	injection	Claforan®*	cefotaxime
Cefpodoxime	suspension, tablet	N/A	cefpodoxime

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Cefprozil	suspension, tablet	N/A	cefprozil
Ceftaroline	injection	Teflaro®	none
Ceftazidime	injection	Fortaz®*, Tazicef®*	ceftazidime
Ceftibuten	capsule, suspension	Cedax®*	ceftibuten
Ceftriaxone	injection	N/A	ceftriaxone
Cefuroxime	injection, suspension, tablet	Ceftin®*, Zinacef®*	cefuroxime
Cephalexin	capsule, suspension, tablet	Keflex®*	cephalexin
Combination Products			
Ceftazidime and Avibactam	injection	Avycaz®	none
Ceftolozane and Tazobactam	injection	Zerbaxa®	none

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

The cephalosporins have been shown to be active against the strains of microorganisms 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 cephalosporins that are noted in Table 5. 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 Cephalosporins[1-13]

Organism	Cefaclor	Cefadroxil	Cefazolin	Cefdinir	Cefepime	Cefixime	Cefotaxime	Cefpodoxime
Gram-Positive Aerobes								
Enterococcus species							✔	
Staphylococci	✔	✔						
Staphylococcus aureus	✔		✔	✔	✔		✔	✔
Staphylococcus epidermidis							✔	
Staphylococcus saprophyticus								✔
Streptococci		✔	✔		✔		✔	
Streptococcus pneumoniae	✔	✔	✔	✔	✔	✔	✔	✔
Streptococcus pyogenes	✔	✔		✔	✔	✔	✔	✔
Gram-Negative Aerobes								
Acinetobacter species							✔	
Citrobacter species							✔	
Enterobacter species			✔		✔		✔	
Enterococci			✔					
Escherichia coli	✔	✔	✔		✔	✔	✔	✔
Haemophilus influenzae	✔		✔	✔		✔	✔	✔
Haemophilus parainfluenzae				✔			✔	
Klebsiella species	✔	✔	✔				✔	
Klebsiella pneumoniae					✔			✔
Moraxella catarrhalis		✔		✔		✔		✔
Morganella morganii							✔	
Neisseria gonorrhoeae						✔	✔	✔
Neisseria meningitidis							✔	
Proteus species							✔	
Proteus mirabilis	✔	✔	✔		✔	✔	✔	✔
Proteus vulgaris							✔	
Providencia rettgeri							✔	
Providencia stuartii							✔	
Pseudomonas species							✔	
Pseudomonas aeruginosa					✔		✔	
Serratia marcescens							✔	

Organism	Cefaclor	Cefadroxil	Cefazolin	Cefdinir	Cefepime	Cefixime	Cefotaxime	Cefpodoxime
Anaerobes								
Bacteroides species							✔	
Bacteroides fragilis					✔			
Clostridium species							✔	
Fusobacterium species							✔	
Peptococcus species							✔	
Peptostreptococcus species							✔	

Table 3. Microorganisms Susceptible to the Cephalosporins (cont.)[1-13]

Organism	Cefprozil	Ceftaroline	Ceftazidime	Ceftibuten	Ceftolozane	Ceftriaxone	Cefuroxime	Cephalexin
Gram-Positive Aerobes								
Staphylococcus aureus	✔		✔			✔	✔	✔
Staphylococcus aureus (including methicillin-resistant isolates)		✔						
Staphylococcus epidermidis						✔		
Staphylococcus saprophyticus								
Streptococci						✔		
Streptococcus anginosus					✔			
Streptococcus agalactiae		✔	✔					
Streptococcus constellatus					✔			
Streptococcus pneumoniae	✔		✔	✔		✔	✔	✔
Streptococcus pyogenes	✔	✔	✔	✔		✔	✔	✔
Streptococcus salivarius					✔			
Gram-Negative Aerobes								
Acinetobacter calcoaceticus						✔		
Citrobacter species			✔					
Enterobacter species			✔			✔		
Enterobacter aerogenes						✔		
Enterobacter cloacae					✔	✔		
Escherichia coli		✔	✔		✔	✔	✔	✔
Haemophilus influenzae	✔	✔	✔	✔		✔	✔	✔
Haemophilus parainfluenzae						✔	✔	
Klebsiella species			✔					
Klebsiella oxytoca		✔			✔	✔		
Klebsiella pneumoniae		✔			✔	✔	✔	✔
Moraxella catarrhalis	✔			✔		✔	✔	✔
Morganella morganii						✔		
Neisseria gonorrhoeae						✔	✔	

Organism	Cefprozil	Ceftaroline	Ceftazidime	Ceftibuten	Ceftolozane	Ceftriaxone	Cefuroxime	Cephalexin
Neisseria meningitidis			✔			✔		
Proteus species			✔					
Proteus mirabilis			✔		✔	✔		✔
Proteus vulgaris			✔			✔		
Pseudomonas species			✔					
Pseudomonas aeruginosa			✔		✔	✔		
Serratia species			✔					
Serratia marcescens						✔		
Anaerobes								
Bacteroides species			✔					
Bacteroides fragilis					✔	✔		
Clostridium species						✔		
Peptostreptococcus species						✔		
Spirochete								
Borrelia burgdorferi							✔	

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the cephalosporins are summarized in Table 4.

Table 4. Treatment Guidelines Using the Cephalosporins

Clinical Guideline	Recommendation(s)

European Society of Cardiology: **Guidelines for the Management of Infective Endocarditis (2015)**[15]	Main principles of prevention if infective endocarditis
	• The principle of antibiotic prophylaxis when performing procedures at risk of infective endocarditis (IE) in patients with predisposing cardiac conditions is maintained.
	• Antibiotic prophylaxis must be limited to patients with the highest risk of IE undergoing the highest risk dental procedures (dental procedures requiring manipulation of the gingival or periapical region of the teeth or perforation of the oral mucosa).
	  o Patients with a prosthetic valve, including transcatheter valve, or a prosthetic material used for cardiac valve repair.
	  o Patients with previous IE.
	  o Patients with congenital heart disease.
	• Good oral hygiene and regular dental review are more important than antibiotic prophylaxis to reduce the risk of IE.
	• Aseptic measures are mandatory during venous catheter manipulation and during any invasive procedures in order to reduce the rate of health care-associated IE.
	• Recommended prophylaxis for dental procedures at high-risk:
	  o Single-dose amoxicillin or penicillin 30 to 60 minutes before procedure.
	  o If allergy to penicillin or ampicillin, single-dose clindamycin 30 to 60 minutes before procedure.
	
	Antimicrobial therapy: principles
	• The treatment of infective endocarditis relies on the combination of prolonged antimicrobial therapy and - in about half of patients - surgical eradication of the infected tissues.
	• Prolonged therapy with a combination of bactericidal drugs is the basis of IE treatment. Drug treatment of prosthetic valve endocarditis (PVE) should last longer (at least six weeks) than that of native valve endocarditis (NVE) (two to six weeks).
	• In both NVE and PVE, the duration of treatment is based on the first day of effective antibiotic therapy, not on the day of surgery. A new full course of treatment should only start if valve cultures are positive, the choice of antibiotic being based on the susceptibility of the latest recovered bacterial isolate.
	• The indications and pattern of use of aminoglycosides have changed. They are no longer recommended in staphylococcal NVE because their clinical benefits have not been demonstrated but they can increase renal toxicity; and, when they are indicated in other conditions, aminoglycosides should be given in a single daily dose in order to reduce nephrotoxicity.
	• New antibiotic regimens have emerged in the treatment of staphylococcal IE, including daptomycin and the combination of high-doses of cotrimoxazole plus clindamycin, but additional investigations are necessary in large series before they can be recommended in all patients.
	
	Antimicrobial therapy: regimens
	• Antibiotic treatment of infective endocarditis due to oral streptococci and *Streptococcus* bovis group:
	  o Penicillin-susceptible strains:
	  ▪ Penicillin G, amoxicillin, or ceftriaxone for four weeks.
	  ▪ Penicillin G, amoxicillin, or ceftriaxone plus gentamicin or netilmicin for two weeks.
	  ▪ Vancomycin for four weeks (in beta-lactam allergic patients).

Clinical Guideline	Recommendation(s)
	o Penicillin-resistant strains: ▪ Penicillin G, amoxicillin, or ceftriaxone for four weeks plus gentamicin for two weeks. ▪ Vancomycin for four weeks plus gentamicin for two weeks (in beta-lactam allergic patients). • Antibiotic treatment of infective endocarditis due to *Staphylococcus* species: o Methicillin-susceptible strains (native valves): ▪ Flucloxacillin or oxacillin for four to six weeks. ▪ Cotrimoxazole intravenous for one week and oral for five weeks plus clindamycin for one week (for *Staphylococcus aureus*). o Penicillin-allergic patients or methicillin-resistant staphylococci (native valves): ▪ Vancomycin for four to six weeks. ▪ Alternative: Daptomycin for four to six weeks. ▪ Cotrimoxazole intravenous for one week and oral for five weeks plus clindamycin for one week (for *Staphylococcus aureus*). o Methicillin-susceptible strains (prosthetic valves): ▪ Flucloxacillin or oxacillin for at least six weeks, rifampin for at least six weeks, and gentamicin for two weeks. o Penicillin-allergic patients or methicillin-resistant staphylococci (prosthetic valves): ▪ Vancomycin for at least six weeks, rifampin for at least six weeks, and gentamicin for two weeks. • Antibiotic treatment of infective endocarditis due to *Enterococcus* species: o Beta-lactam and gentamicin susceptible strains: ▪ Amoxicillin for four to six weeks plus gentamicin for two to six weeks. ▪ Ampicillin plus gentamicin for six weeks. ▪ Vancomycin plus gentamicin for six weeks. • Antibiotic treatment of blood culture-negative infective endocarditis: o *Brucella* species: ▪ Doxycycline, cotrimoxazole, and rifampin for ≥3 months. o *Coxiella burnetii* (agent of Q fever): ▪ Doxycycline plus hydroxychloroquine for >18 months. ▪ o *Bartonella* species: ▪ Doxycycline orally for four weeks plus gentamicin for two weeks. o *Legionella* species: ▪ Levofloxacin intravenous for ≥6 weeks or clarithromycin intravenous for two weeks then orally for four weeks plus rifampin. o *Mycoplasma* species: ▪ Levofloxacin for ≥6 months. o *Tropheryma whipplei* (agent of Whipple's disease): ▪ Doxycycline plus hydroxychloroquine orally for ≥18 months. • Proposed antibiotic regimens for initial empirical treatment of infective endocarditis in acute severely ill patients (before pathogen identification): o Community-acquired native valves or late prosthetic valves (≥12 months post surgery) endocarditis: ▪ Ampicillin intravenous plus flucloxacillin or oxacillin intravenous plus gentamicin intravenous for once dose. ▪ Vancomycin intravenous plus gentamicin intravenous (for penicillin allergic patients). o Early PVE (<12 months post surgery) or nosocomial and non-nosocomial healthcare associated endocarditis:

Clinical Guideline	Recommendation(s)
	▪ Vancomycin intravenous, gentamicin intravenous, and rifampin orally.
American College of Cardiology/ American Heart Association: **2008 Focused Update Incorporated Into the American College of Cardiology/ American Heart Association 2006 Guidelines for the Management of Patients With Valvular Heart Disease (2008)**[16] American College of Cardiology/ American Heart Association: **Guideline for the Management of Patients With Valvular Heart Disease (2014)**[17] **(although a more current guideline more detailed information was included as part of the 2008 Focused update; as such both are summarized together)**	<u>Rheumatic fever prophylaxis</u> • Primary prevention of rheumatic heart disease: o Penicillin G benzathine intramuscular once or penicillin V orally for 10 days. o Erythromycin estolate or erythromycin ethylsuccinate orally for 10 days, or azithromycin orally for five days in patients who are allergic to penicillin. • Secondary prevention of rheumatic fever: o Penicillin G benzathine intramuscular every four weeks, or penicillin V orally twice daily, or sulfadiazine orally once daily. o Erythromycin orally twice daily for patients who are allergic to penicillin. <u>Endocarditis prophylaxis</u> • Prophylaxis against infective endocarditis is reasonable for the following patients at highest risk for adverse outcomes from infective endocarditis who undergo dental procedures that involve manipulation of either gingival tissue or the periapical region of teeth or perforation of the oral mucosa: o Patients with prosthetic cardiac valve or prosthetic material used for cardiac valve repair. o Patients with previous infective endocarditis. o Patients with congenital heart disease. o Cardiac transplant recipients with valve regurgitation due to a structurally abnormal valve. • Prophylaxis against infective endocarditis is not recommended for non-dental procedures (such as transesophageal echocardiogram, esophagogastroduodenoscopy, or colonoscopy) in the absence of active infection. • Regimens for dental procedures (single dose 30 to 60 minutes before procedure): o Oral: amoxicillin. o Unable to take oral medications: ampicillin, cefazolin or ceftriaxone. o Allergic to penicillin or ampicillin (oral): cephalexin, clindamycin, or azithromycin. o Allergic to penicillins or ampicillin and unable to take oral medication: cefazolin, ceftriaxone, or clindamycin. • Therapy of native valve endocarditis caused by highly penicillin-susceptible viridans group streptococci and *Streptococcus bovis:* o Penicillin G or ceftriaxone for four weeks. o Ceftriaxone plus gentamicin for two weeks. o Vancomycin for four weeks in patients allergic to penicillin. • Therapy of native valve endocarditis caused by strains of viridans group streptococci and *Streptococcus bovis* relatively resistant to penicillin: o Penicillin G or ceftriaxone for four weeks plus gentamicin for two weeks. o Vancomycin for four weeks in patients allergic to penicillin. • Therapy for native valve or prosthetic valve enterococcal endocarditis caused by strains susceptible to penicillin, gentamicin, and vancomycin: o Ampicillin for four to six weeks or penicillin G plus gentamicin for four to six weeks. o Vancomycin plus gentamicin for six weeks in patients allergic to penicillin. • Therapy for endocarditis caused by staphylococci in the absence of prosthetic materials: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin for six weeks plus the optional addition of gentamicin for three to five days. ▪ Cefazolin for six weeks with the optional addition of gentamicin

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	in patients allergic to penicillin. o Oxacillin-resistant strains: ▪ Vancomycin for six weeks. • Therapy for prosthetic valve endocarditis caused by staphylococci: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin, rifampin, and gentamicin for ≥6 weeks. o Oxacillin-resistant strains: ▪ Vancomycin, rifampin, and gentamicin for ≥6 weeks. • Therapy for both native and prosthetic valve endocarditis caused by *Haemophilus* species *(Haemophilus parainfluenzae, Haemophilus aphrophilus, Haemophilus paraphrophilus), Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* species microorganisms: o Ceftriaxone for four weeks. o Ampicillin-sulbactam for four weeks. o Ciprofloxacin for four weeks. • Therapy for culture-negative endocarditis including *Bartonella* endocarditis: o Native valve: ▪ Ampicillin-sulbactam plus gentamicin (or vancomycin for patients allergic to penicillin) plus ciprofloxacin for four to six weeks. o Prosthetic valve (early; ≤1 year): ▪ Vancomycin for six weeks, plus gentamicin for two weeks, plus cefepime for six weeks, plus rifampin for six weeks. o Prosthetic valve (late; >1 year): ▪ Suspected *Bartonella*, culture negative: • Ceftriaxone for six weeks plus gentamicin with/without doxycycline for six weeks. ▪ Documented *Bartonella*, culture positive: • Doxycycline for six weeks plus gentamicin for two weeks.
American Heart Association: **Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications (2015)**[18]	• Therapy for native valve endocarditis caused by viridans group streptococci and *Streptococcus gallolyticus* (Formerly Known as *Streptococcus bovis)*: o Highly penicillin-susceptible strains: ▪ Penicillin G or ceftriaxone for four weeks. ▪ Penicillin G or ceftriaxone plus gentamicin for two weeks (in patients with uncomplicated infective endocarditis, rapid response to therapy, and no underlying renal disease). ▪ Vancomycin for four weeks (recommended only for patients unable to tolerate penicillin or ceftriaxone therapy). o Relatively penicillin-resistant strains: ▪ Penicillin for four weeks plus gentamicin for the first two weeks. ▪ If the isolate is ceftriaxone susceptible, then ceftriaxone alone may be considered. ▪ Vancomycin for four weeks (recommended only for patients unable to tolerate beta-lactam therapy). • Therapy for native valve endocarditis caused by *A defectiva* and *Granulicatella* Species and viridans group streptococci: o For patients with infective endocarditis caused by *A defectiva*, *Granulicatella* species, and viridans group streptococci with a penicillin MIC ≥0.5 µg/mL, treat with a combination of ampicillin or penicillin plus gentamicin as done for enterococcal infective endocarditis with infectious diseases consultation. o If vancomycin is used in patients intolerant of ampicillin or penicillin, then the addition of gentamicin is not needed. o Ceftriaxone combined with gentamicin may be a reasonable alternative treatment option for isolates that are susceptible to ceftriaxone.

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	• Therapy for endocarditis of prosthetic valves or other prosthetic material caused by viridans group streptococci and *Streptococcus gallolyticus* (Formerly Known as *Streptococcus bovis)*: o Penicillin for six weeks plus gentamicin for the first two weeks. o Extend gentamicin to six weeks if the MIC is >0.12 µg/mL for the infecting strain. o Vancomycin can be used in patients intolerant of penicillin, ceftriaxone, or gentamicin. • Therapy for endocarditis of prosthetic valves or other prosthetic material caused by *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and Groups B, C, F, and G β-Hemolytic Streptococci: o Penicillin, cefazolin, or ceftriaxone for four weeks is reasonable for infective endocarditis caused by *S pneumoniae*; vancomycin can be useful for patients intolerant of β-lactam therapy. o Six weeks of therapy is reasonable for prosthetic valve endocarditis caused by *S pneumoniae*. o High-dose penicillin or a third-generation cephalosporin is reasonable in patients with infective endocarditis caused by penicillin-resistant *S pneumoniae* without meningitis; if meningitis is present, then high doses of cefotaxime (or ceftriaxone) are reasonable. o The addition of vancomycin and rifampin to cefotaxime (or ceftriaxone) may be considered in patients with infective endocarditis caused by *S pneumoniae* that are resistant to cefotaxime. o Because of the complexities of infective endocarditis caused by *S pneumoniae*, consultation with an infectious diseases specialist is recommended. o For infective endocarditis caused by *S pyogenes*, four to six weeks of therapy with aqueous crystalline penicillin G or ceftriaxone is reasonable; vancomycin is reasonable only in patients intolerant of β-lactam therapy. o For infective endocarditis caused by group B, C, or G streptococci, the addition of gentamicin to penicillin G or ceftriaxone for at least the first two weeks of a four to six week treatment course may be considered. o Consultation with an infectious diseases specialist to guide treatment is recommended in patients with infective endocarditis caused by β-hemolytic streptococci. • Therapy for endocarditis caused by staphylococci in the absence of prosthetic valves or other prosthetic material: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin for six weeks. ▪ For penicillin-allergic individuals: cefazolin for six weeks. o Oxacillin-resistant strains ▪ Vancomycin for six weeks. ▪ Daptomycin for six weeks. • Therapy for prosthetic valve endocarditis caused by staphylococci: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin plus rifampin (for at least six weeks) and gentamicin (for two weeks). o Oxacillin-resistant strains: ▪ Vancomycin plus rifampin (for at least six weeks) and gentamicin (for two weeks). • Therapy for native valve or prosthetic valve enterococcal endocarditis: o Strains susceptible to penicillin and gentamicin: ▪ Ampicillin or penicillin G plus gentamicin for four to six weeks. ▪ Double β-lactam ampicillin plus ceftriaxone for six. o Strains susceptible to penicillin and resistant to aminoglycosides or streptomycin-susceptible gentamicin-resistant in patients able to tolerate

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	β-Lactam therapy: ▪ Ampicillin plus ceftriaxone for six weeks. ▪ Ampicillin or penicillin G plus streptomycin for four to six weeks. o Vancomycin and aminoglycoside-susceptible penicillin-resistant enterococcus species in patients unable to tolerate β-lactam : ▪ Unable to tolerate β-lactams: • Vancomycin plus gentamicin for six weeks (vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone therapy). ▪ Intrinsic penicillin resistance: • Vancomycin plus gentamicin for six weeks. o Strains Resistant to Penicillin, Aminoglycosides, and Vancomycin: ▪ Linezolid or daptomycin for at least six weeks. • Therapy for both native and prosthetic valve endocarditis caused by *Haemophilus* species *(Haemophilus parainfluenzae, Haemophilus aphrophilus, Haemophilus paraphrophilus), Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* species microorganisms: o Ceftriaxone (cefotaxime or another third- or fourth-generation cephalosporin may be substituted) or ampicillin or ciprofloxacin for four weeks. Fluoroquinolone therapy recommended only for patients unable to tolerate cephalosporin and ampicillin therapy; levofloxacin or moxifloxacin may be substituted. • Therapy for culture-negative endocarditis including *Bartonella* endocarditis: o For patients with acute (days) clinical presentations of native valve infection, coverage for *S aureus*, β-hemolytic streptococci, and aerobic Gram-negative bacilli is reasonable. o For patients with a subacute (weeks) presentation of native valve endocarditis, coverage of *S aureus*, viridans group streptococci, HACEK, and enterococci is reasonable. o For patients with culture-negative prosthetic valve endocarditis, coverage for staphylococci, enterococci, and aerobic Gram-negative bacilli is reasonable if onset of symptoms is within one year of prosthetic valve placement. o If symptom onset is >1 year after valve placement, then infective endocarditis is more likely to be caused by staphylococci, viridans group streptococci, and enterococci, and antibiotic therapy for these potential pathogens is reasonable.
Infectious Diseases Society of America: **Clinical Practice Guidelines: Management of Encephalitis (2008)**[19] **(Was reviewed and deemed current as of July 2011)**	<u>Empirical therapy</u> • Acyclovir should be initiated in all patients with suspected encephalitis, pending results of diagnostic studies. • Other empirical antimicrobial agents should be initiated on the basis of specific epidemiologic or clinical factors, including appropriate therapy for presumed bacterial meningitis, if clinically indicated. • In patients with clinical clues suggestive of rickettsial or ehrlichial infection during the appropriate season, doxycycline should be added to empirical treatment regimens. <u>Bacteria</u> • *Bartonella bacilliformis:* chloramphenicol, ciprofloxacin, doxycycline, ampicillin, or sulfamethoxazole-trimethoprim is recommended. • *Bartonella henselae:* doxycycline or azithromycin, with or without rifampin, can be considered. • *Listeria monocytogenes:* ampicillin plus gentamicin is recommended; sulfamethoxazole-trimethoprim is an alternative in the penicillin-allergic patient.

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	• *Mycoplasma pneumoniae:* antimicrobial therapy (azithromycin, doxycycline, or a fluoroquinolone) can be considered. • *Tropheryma whipplei:* ceftriaxone, followed by either sulfamethoxazole-trimethoprim or cefixime, is recommended. <u>Helminths</u> • *Baylisascaris procyonis:* albendazole plus diethylcarbamazine can be considered; adjunctive corticosteroids should also be considered. • *Gnathostoma* species: albendazole or ivermectin is recommended. • *Taenia solium:* need for treatment should be individualized; albendazole and corticosteroids are recommended; praziquantel can be considered as an alternative. <u>Rickettsioses and ehrlichiosis</u> • *Anaplasma phagocytophilum:* doxycycline is recommended. • *Ehrlichia chaffeensis:* doxycycline is recommended. • *Rickettsia rickettsii:* doxycycline is recommended; chloramphenicol can be considered an alternative in selected clinical scenarios, such as pregnancy. • *Coxiella burnetii:* doxycycline plus a fluoroquinolone plus rifampin is recommended. <u>Spirochetes</u> • *Borrelia burgdorferi:* ceftriaxone, cefotaxime, or penicillin G is recommended. • *Treponema pallidum:* penicillin G is recommended; ceftriaxone is an alternative. <u>Protozoa</u> • *Acanthamoeba:* sulfamethoxazole-trimethoprim plus rifampin plus ketoconazole or fluconazole plus sulfadiazine plus pyrimethamine can be considered. • *Balamuthia mandrillaris:* pentamidine, combined with a macrolide (azithromycin or clarithromycin), fluconazole, sulfadiazine, flucytosine, and a phenothiazine can be considered. • *Naegleria fowleri:* amphotericin B (intravenous and intrathecal) and rifampin, combined with other agents, can be considered. • *Plasmodium falciparum:* quinine, quinidine, or artemether is recommended; atovaquone-proguanil is an alternative; exchange transfusion is recommended for patients with 110% parasitemia or cerebral malaria; corticosteroids are not recommended. • *Toxoplasma gondii:* pyrimethamine plus either sulfadiazine or clindamycin is recommended; sulfamethoxazole-trimethoprim alone and pyrimethamine plus atovaquone, clarithromycin, azithromycin, or dapsone are alternatives. • *Trypanosoma brucei gambiense:* eflornithine is recommended; melarsoprol is an alternative. • *Trypanosoma brucei rhodesiense:* melarsoprol is recommended.
European Federation of Neurological Societies: **Guideline on the Management of Community-acquired Bacterial Meningitis (2008)**[20]	<u>Empirical therapy</u> • Ceftriaxone 2 g every 12 to 24 hours or cefotaxime 2 g every six to eight hours. • Alternative therapy: meropenem 2 g every eight hours or chloramphenicol 1 g every six hours. • If penicillin or cephalosporin-resistant pneumococcus is suspected, use ceftriaxone or cefotaxime plus vancomycin 60 mg/kg every 24 hours after a loading dose of 15 mg/kg. • Ampicillin-amoxicillin 2 g every four hours if *Listeria* is suspected. <u>Pathogen specific therapy</u> • Penicillin-sensitive pneumococcal meningitis: o Benzyl penicillin 250,000 U/kg/day, ampicillin-amoxicillin 2 g every four hours, ceftriaxone 2 g every 12 hours or cefotaxime 2 g every six to eight

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	hours. o Alternative therapy: meropenem 2 g every eight hours or vancomycin 60 mg/kg every 24 hours as a continuous infusion after a 15 mg/kg loading dose plus rifampicin 600 mg every 12 hours, or moxifloxacin 400 mg daily. • Pneumococcus with reduced susceptibility to penicillin or cephalosporins: o Ceftriaxone or cefotaxime plus vancomycin±rifampicin. o Alternative therapy: moxifloxacin, meropenem or linezolid 600 mg combined with rifampicin. • Meningococcal meningitis: o Benzyl penicillin, ceftriaxone, or cefotaxime. o Alternative therapy: meropenem, chloramphenicol, or moxifloxacin. • *Haemophilus influenzae* type B: o Ceftriaxone or cefotaxime. o Alternative therapy: chloramphenicol–ampicillin-amoxicillin. • Listerial meningitis: o Ampicillin or amoxicillin 2 g every four hours±gentamicin 1 to 2 mg every eight hours for the first seven to 10 days. o Alternative therapy: sulfamethoxazole-trimethoprim 10 to 20 mg/kg every six to 12 hours or meropenem. • *Staphylococcal* species: o Flucloxacillin 2 g every four hours or vancomycin if penicillin allergy is suspected. o Rifampicin should also be considered in addition to either agent. Linezolid should be considered for methicillin-resistant staphylococcal meningitis. • Gram-negative *Enterobacteriaceae*: o Ceftriaxone, cefotaxime or meropenem. • Pseudomonal meningitis: o Meropenem±gentamicin.
Infectious Diseases Society of America: **Practice Guidelines for the Management of Bacterial Meningitis (2004)**[21]	<u>Empiric therapy</u> • Empirical antimicrobial therapy is initiated either when the lumbar puncture is delayed or for patients with purulent meningitis and a negative cerebrospinal fluid gram stain result: o Age <1 month: ampicillin plus cefotaxime or ampicillin plus an aminoglycoside. o Age one to 23 months: vancomycin plus a third-generation cephalosporin. o Age two to 50 years: vancomycin plus a third-generation cephalosporin. o Age >50 years: vancomycin plus ampicillin plus a third-generation cephalosporin. o Basilar skull fracture: vancomycin plus a third-generation cephalosporin. o Penetrating head trauma: vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem. o Post neurosurgery: vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem. o Cerebrospinal fluid shunt: vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem. <u>Specific therapy</u> • Recommendations for specific antimicrobial therapy in bacterial meningitis are based on isolated pathogens and susceptibility. • *Streptococcus pneumoniae* o Penicillin minimum inhibitory concentrations <0.1 µg/mL: standard therapy includes penicillin G or ampicillin; alternative therapies include ceftriaxone, cefotaxime, or chloramphenicol. o Penicillin minimum inhibitory concentrations 0.1 to 1.0 µg/mL: standard therapy includes ceftriaxone or cefotaxime; alternative therapies include

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	cefepime or meropenem. o Penicillin minimum inhibitory concentrations ≥2 µg/mL: standard therapies include vancomycin plus ceftriaxone or cefotaxime; alternative therapies include gatifloxacin or moxifloxacin. o Cefotaxime or ceftriaxone minimum inhibitory concentrations ≥1.0 µg/mL: standard therapies include vancomycin plus ceftriaxone or cefotaxime (consider addition of rifampin if minimum inhibitory concentrations of ceftriaxone is >2 µg/mL); alternative therapies include gatifloxacin or moxifloxacin. • *Neisseria meningitides* o Penicillin minimum inhibitory concentrations <0.1 µg/mL: standard therapy includes penicillin G or ampicillin; alternative therapy includes ceftriaxone, cefotaxime or chloramphenicol. o Penicillin minimum inhibitory concentrations 0.1 to 1.0 µg/mL: standard therapy includes ceftriaxone or cefotaxime; alternative therapies include chloramphenicol, a fluoroquinolone or meropenem. • *Listeria monocytogenes* o Standard therapy includes ampicillin or penicillin G; alternative therapies include sulfamethoxazole-trimethoprim or meropenem. • *Streptococcus agalactiae* o Standard therapy includes ampicillin or penicillin G; alternative therapies include ceftriaxone or cefotaxime. • *Escherichia coli* and other Enterobacteriaceae o Standard therapy includes a third-generation cephalosporin; alternative therapies include aztreonam, fluoroquinolone, meropenem, sulfamethoxazole-trimethoprim or ampicillin. • *Pseudomonas aeruginosa* o Standard therapies include cefepime or ceftazidime; alternative therapies include aztreonam, ciprofloxacin, or meropenem (addition of an aminoglycoside should be considered). • *Haemophilus influenzae* β-lactamase negative strains o Standard therapy includes ampicillin; alternative therapies include ceftriaxone, cefotaxime, cefepime, chloramphenicol or a fluoroquinolone. • *Haemophilus influenzae* β-lactamase positive strains o Standard therapy includes a third-generation cephalosporin; alternative therapies include cefepime, chloramphenicol or a fluoroquinolone. • *Staphylococcus aureus* methicillin susceptible o Standard therapy includes nafcillin or ofloxacin; alternative therapies include vancomycin or meropenem. • *Staphylococcus aureus* methicillin resistant o Standard therapy includes vancomycin (consider addition of rifampin); alternative therapies include sulfamethoxazole-trimethoprim or linezolid. • *Staphylococcus epidermidis* o Standard therapy includes vancomycin (consider addition of rifampin); alternative therapy includes linezolid. • *Enterococcus* species ampicillin susceptible o Standard therapy includes ampicillin plus gentamicin. • *Enterococcus* species ampicillin resistant o Standard therapy includes vancomycin plus gentamicin. • *Enterococcus* species ampicillin and vancomycin resistant o Standard therapy includes linezolid.
Infectious Diseases Society of America: **Practice Guidelines for the Diagnosis**	Impetigo and ecthyma • Gram stain and culture of the pus or exudates from skin lesions of impetigo and ecthyma are recommended to help identify whether *Staphylococcus aureus* and/or a β-hemolytic *Streptococcus* is the cause (strong, moderate), but

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and Management of Skin and Soft-Tissue Infections (2014)[22]	treatment without these studies is reasonable in typical cases.
	• Bullous and nonbullous impetigo can be treated with oral or topical antimicrobials, but oral therapy is recommended for patients with numerous lesions or in outbreaks affecting several people to help decrease transmission of infection. Treatment for ecthyma should be an oral antimicrobial.
	  o Treatment of bullous and nonbullous impetigo should be with either mupirocin or retapamulin twice daily for five days.
	  o Oral therapy for ecthyma or impetigo should be a seven-day regimen with an agent active against *S. aureus* unless cultures yield streptococci alone (when oral penicillin is the recommended agent). Because *S. aureus* isolates from impetigo and ecthyma are usually methicillin susceptible, dicloxacillin or cephalexin is recommended. When MRSA is suspected or confirmed, doxycycline, clindamycin, or sulfamethoxazole-trimethoprim is recommended.
	
	Purulent skin and soft-tissue infections (cutaneous abscesses, furuncles, carbuncles, and inflamed epidermoid cysts)
	• Gram stain and culture of pus from carbuncles and abscesses are recommended, but treatment without these studies is reasonable in typical cases. Gram stain and culture of pus from inflamed epidermoid cysts are not recommended.
	• Incision and drainage is the recommended treatment for inflamed epidermoid cysts, carbuncles, abscesses, and large furuncles.
	• The decision to administer antibiotics directed against *S. aureus* as an adjunct to incision and drainage should be made based upon presence or absence of systemic inflammatory response syndrome (SIRS), such as temperature >38°C or <36°C, tachypnea >24 breaths per minute, tachycardia >90 beats per minute, or white blood cell count >12 000 or <400 cells/µL. An antibiotic active against MRSA is recommended for patients with carbuncles or abscesses who have failed initial antibiotic treatment or have markedly impaired host defenses or in patients with SIRS and hypotension.
	
	Recurrent skin abscesses
	• A recurrent abscess at a site of previous infection should prompt a search for local causes such as a pilonidal cyst, hidradenitis suppurativa, or foreign material.
	• Recurrent abscesses should be drained and cultured early in the course of infection.
	• After obtaining cultures of recurrent abscess, treat with a five to ten day course of an antibiotic active against the pathogen isolated.
	• Consider a five-day decolonization regimen twice daily of intranasal mupirocin, daily chlorhexidine washes, and daily decontamination of personal items such as towels, sheets, and clothes for recurrent *S. aureus* infection.
	• Adult patients should be evaluated for neutrophil disorders if recurrent abscesses began in early childhood.
	
	Erysipelas and cellulitis
	• Cultures of blood or cutaneous aspirates, biopsies, or swabs are not routinely recommended except in patients with malignancy on chemotherapy, neutropenia, severe cell-mediated immunodeficiency, immersion injuries, and animal bites.
	• Typical cases of cellulitis without systemic signs of infection should receive an antimicrobial agent that is active against streptococci. For cellulitis with systemic signs of infection (moderate nonpurulent), systemic antibiotics are indicated. Many clinicians could include coverage against methicillin-susceptible *S. aureus* (MSSA). For patients whose cellulitis is associated with

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	penetrating trauma, evidence of MRSA infection elsewhere, nasal colonization with MRSA, injection drug use, or SIRS (severe nonpurulent), vancomycin or another antimicrobial effective against both MRSA and streptococci is recommended. In severely compromised patients, broad-spectrum antimicrobial coverage may be considered. Vancomycin plus either piperacillin-tazobactam or imipenem/meropenem is recommended as a reasonable empiric regimen for severe infections. • The recommended duration of antimicrobial therapy is five days, but treatment should be extended if the infection has not improved within this time period. Surgical site infections • Suture removal plus incision and drainage should be performed for surgical site infections. • Adjunctive systemic antimicrobial therapy is not routinely indicated, but in conjunction with incision and drainage may be beneficial for surgical site infections associated with a significant systemic response. • A brief course of systemic antimicrobial therapy is indicated in patients with surgical site infections following clean operations on the trunk, head and neck, or extremities that also have systemic signs of infection. • A first-generation cephalosporin or an antistaphylococcal penicillin for MSSA, or vancomycin, linezolid, daptomycin, telavancin, or ceftaroline where risk factors for MRSA are high (nasal colonization, prior MRSA infection, recent hospitalization, recent antibiotics), is recommended. • Agents active against gram-negative bacteria and anaerobes, such as a cephalosporin or fluoroquinolone in combination with metronidazole, are recommended for infections following operations on the axilla, gastrointestinal tract, perineum, or female genital tract. Necrotizing fasciitis • Empiric antibiotic treatment should be broad (e.g., vancomycin or linezolid plus piperacillin-tazobactam or a carbapenem; or plus ceftriaxone and metronidazole), as the etiology can be polymicrobial (mixed aerobic–anaerobic microbes) or monomicrobial (group A streptococci, community-acquired MRSA). • Penicillin plus clindamycin is recommended for treatment of documented group A streptococcal necrotizing fasciitis. Pyomyositis • Cultures of blood and abscess material should be obtained. • Vancomycin is recommended for initial empirical therapy. An agent active against enteric gram-negative bacilli should be added for infection in immunocompromised patients or following open trauma to the muscles. • Cefazolin or antistaphylococcal penicillin (e.g., nafcillin or oxacillin) is recommended for treatment of pyomyositis caused by MSSA. • Antibiotics should be administered intravenously initially, but once the patient is clinically improved, oral antibiotics are appropriate for patients in whom bacteremia cleared promptly and there is no evidence of endocarditis or metastatic abscess. Two to three weeks of therapy is recommended. Clostridial gas gangrene or myonecrosis • Urgent surgical exploration of the suspected gas gangrene site and surgical debridement of involved tissue should be performed. • In the absence of a definitive etiologic diagnosis, broad-spectrum treatment with vancomycin plus either piperacillin-tazobactam, ampicillin-sulbactam, or a carbapenem antimicrobial is recommended. Definitive antimicrobial therapy

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	with penicillin and clindamycin is recommended for treatment of clostridial myonecrosis. Animal bites • Preemptive early antimicrobial therapy for three to five days is recommended for patients who: o are immunocompromised; o are asplenic; o have advanced liver disease; o have preexisting or resultant edema of the affected area; o have moderate to severe injuries, especially to the hand or face; or o have injuries that may have penetrated the periosteum or joint capsule. • 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 o β-lactam-β-lactamase combinations, piperacillin-tazobactam, second-generation cephalosporins, and carbapenems. • Tetanus toxoid should be administered to patients without toxoid vaccination within 10 years. Tetanus, diphtheria, and tetanus (Tdap) is preferred over Tetanus and diphtheria (Td) if the former has not been previously given. Cutaneous anthrax • Oral penicillin V 500 mg four times daily for seven to 10 days is the recommended treatment for naturally acquired cutaneous anthrax. • Ciprofloxacin 500 mg by mouth twice daily or levofloxacin 500 mg intravenously/orally every 24 hours for 60 days is recommended for bioterrorism cases because of presumed aerosol exposure. Bacillary angiomatosis and cat scratch disease • Azithromycin is recommended for cat scratch disease (strong, moderate) according to the following dosing protocol: o Patients >45 kg: 500 mg on day one followed by 250 mg for four additional days. o Patients <45 kg: 10 mg/kg on day one and 5 mg/kg for four more days. • Erythromycin 500 mg four times daily or doxycycline 100 mg bid for two weeks to two months is recommended for treatment of bacillary angiomatosis. Erysipeloid • Penicillin (500 mg four times daily) or amoxicillin (500 mg three times daily [tid]) for seven to 10 days is recommended for treatment of erysipeloid. Glanders • Ceftazidime, gentamicin, imipenem, doxycycline, or ciprofloxacin is recommended based on in vitro susceptibility. Bubonic plague • Bubonic plague should be diagnosed by Gram stain and culture of aspirated material from a suppurative lymph node. Streptomycin (15 mg/kg intramuscularly [IM] every 12 hours) or doxycycline (100 mg twice daily by

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	mouth) is recommended for treatment of bubonic plague. Gentamicin could be substituted for streptomycin. Tularemia • Streptomycin (15 mg/kg every 12 hours intramuscularly) or gentamicin (1.5 mg/kg every 8 hours intravenously) is recommended for treatment of severe cases of tularemia. • Tetracycline (500 mg four times daily) or doxycycline (100 mg twice daily by mouth) is recommended for treatment of mild cases of tularemia.
Infectious Diseases Society of America: **Diagnosis and Treatment of Diabetic Foot Infections (2012)**[23]	• Empirical antibiotic regimens should be based on the clinical severity of the infection. • Current clinical data does not allow for the recommendation of any specific antibiotic regimen for diabetic foot infections. • Suggested agents are derived from available published clinical trials and expert experience. • Definitive regimens should consider results of culture and susceptibility tests, as well as the clinical response to the empirical regimen. Similar agents of the same drug class may be substituted. Some of these regimens may not have Food and Drug Administration approval for complicated skin and skin-structure infections, and only linezolid, ertapenem and piperacillin-tazobactam are currently specifically approved for diabetic foot infections. • Suggested empirical antibiotic regimens for mild infections: dicloxacillin, clindamycin, cephalexin, sulfamethoxazole-trimethoprim, amoxicillin-clavulanate, levofloxacin and doxycycline. • Suggested empirical antibiotic regimens for moderate infections: levofloxacin, cefoxitin, ceftriaxone, ampicillin-sulbactam, moxifloxacin, tigecycline, linezolid, daptomycin, ertapenem, ticarcillin-clavulanate, piperacillin-tazobactam, levofloxacin or ciprofloxacin with clindamycin, imipenem-cilastatin, vancomycin, ceftazidime, cefepime, aztreonam. • Suggested empirical antibiotic regimens for severe infections: piperacillin-tazobactam, vancomycin, ceftazidime, cefepime, aztreonam or a carbapenem.

World Gastroenterology Organization: **Acute Diarrhea (2012)**[24]	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.
	• 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.
	
	Antimicrobial agents for the treatment of specific causes of diarrhea
	• 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

Clinical Guideline	Recommendation(s)
	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)**[25]	Chemoprophylaxis • 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. Treatment • 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. • 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)**[26]	Recommendations for therapy against specific pathogens • *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.

Clinical Guideline	Recommendation(s)
	o Fluoroquinolone. • *Campylobacter* species: o Erythromycin. • *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 (2015)**[27]	Arthritis and arthritis-dermatitis syndrome • Recommended regimen: o Ceftriaxone 1 g intramuscular or intravenous every 24 hours plus azithromycin 1 g orally in a single dose. • Alternative regimen: o Cefotaxime 1 g intravenous every eight hours or ceftizoxime 1 g intravenous every eight hours plus azithromycin 1 g orally in a single dose. Bacterial vaginosis • Recommended regimens: o Metronidazole 500 mg orally twice a day for seven days. o Metronidazole gel 0.75%, one full applicator (5 g) intravaginally, once a day for five days. o Clindamycin cream 2%, one full applicator (5 g) intravaginally at bedtime for seven days. • Alternative regimens: o Tinidazole 2 g orally once daily for two days. o Tinidazole 1 g 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. Cervicitis • Recommended regimens for presumptive treatment: o Azithromycin 1 g orally in a single dose. o Doxycycline 100 mg orally twice a day for seven days. Chancroid • Recommended regimens: o Azithromycin 1 g 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.

Clinical Guideline	Recommendation(s)
	o Erythromycin base 500 mg orally three times a day for seven days. Chlamydial infections • Recommended regimens: o Azithromycin 1 g 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. Chlamydial infections among children • 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 g orally in a single dose. • Recommended regimens for children ≥8 years of age: o Azithromycin 1 g orally in a single dose. o Doxycycline 100 mg orally twice a day for seven days. Disseminated gonococcal infection • Recommended regimen: o Ceftriaxone 1 g intramuscular or intravenous every 24 hours. • Alternative regimens: o Cefotaxime 1 g intravenous every eight hours. o Ceftizoxime 1 g intravenous every eight hours. Epididymitis • 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. Granuloma inguinale (Donovanosis) • Recommended regimen: o Azithromycin 1 g orally once per week or 500 mg daily for at least three weeks and until all lesions have completely healed. • Alternative regimens: o Doxycycline 100 mg orally twice a day 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.

Clinical Guideline	Recommendation(s)
	Gonococcal conjunctivitis • Recommended regimen: o Ceftriaxone 1 g intramuscular in a single dose plus azithromycin 1 g orally 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 25 to 50 mg/kg intravenous or intramuscular in a single dose, not to exceed 125 mg. • Recommended regimen for children who weigh ≤45 kg and who have bacteremia or arthritis: o Ceftriaxone 50 mg/kg (maximum dose: 1 g) 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 g intravenous every 12 hours plus azithromycin 1 g orally in a single dose. 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 g 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. • Alternative regimen: o Azithromycin suspension, 20 mg/kg/day orally, one dose daily for three days. Pelvic inflammatory disease • Recommended parenteral regimen A: o Cefotetan 2 g intravenous every 12 hours.

Clinical Guideline	Recommendation(s)
	o Cefoxitin 2 g 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 g 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 g intramuscular in a single dose and probenecid, 1 g 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 g orally in a single dose. o Tinidazole 2 g orally in a single dose plus azithromycin 1 g orally in a single dose (if not used for initial episode). <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.

Clinical Guideline	Recommendation(s)
	Tertiary syphilis • 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. Trichomoniasis • Recommended regimen: o Metronidazole 2 g orally in a single dose. o Tinidazole 2 g orally in a single dose. • Alternative regimen: o Metronidazole 500 mg orally twice a day for seven days. Neurosyphilis • 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. Uncomplicated gonococcal infections of the cervix, urethra, and rectum • 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 1g orally in a single dose or doxycycline 100 mg orally twice a day for seven days. Uncomplicated gonococcal infections of the pharynx • Recommended regimens: o Ceftriaxone 250 mg intermuscular in a single dose plus azithromycin 1g orally in a single dose or doxycycline 100 mg orally twice a day for seven 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)**[28] Reviewed and deemed current as of 07/2013	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 g 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.

Clinical Guideline	Recommendation(s)
	• Amoxicillin or ampicillin should not be used for empirical treatment given the relatively poor efficacy and the very high prevalence of antimicrobial resistance to these agents worldwide. Acute pyelonephritis • 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 g 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 g 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 g 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 g 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.

American College of Obstetricians and Gynecologists: **Treatment of Urinary Tract Infections in Nonpregnant Women (2008)**[29]	• 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 g dose (powder) single dose.

American Academy of Pediatrics/ American Academy of Family Physicians: **Diagnosis and Management of Acute Otitis Media (2013)**[30]	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.

Clinical Guideline	Recommendation(s)
	• 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: **Practice Guidelines for the Diagnosis and Management of Group A Streptococcal Pharyngitis (2012)**[31] Reviewed and deemed current as of 05/2015	• Patients with acute streptococcal pharyngitis should receive therapy with an antimicrobial agent in a dose and for a duration that is likely to eradicate the infecting organism from the pharynx. • Penicillin or amoxicillin are the agents of choice because of their proven efficacy, safety, and narrow spectrum. • Treatment of acute streptococcal pharyngitis is penicillin-allergic patients should include a first generation cephalosporin for ten days, clindamycin or clarithromycin for ten days or azithromycin for five days. • Intramuscular administration of benzathine penicillin G is preferred for patients who are unlikely to complete a full 10-day course of oral therapy. • Most oral antibiotic therapy must be administered for the conventional 10 days to achieve maximal rates of pharyngeal eradication of group A streptococci. • When multiple episodes occur over the course of months or years, it may be difficult to differentiate viral pharyngitis in a *Streptococcus* carrier from true group A streptococcal pharyngitis. Therapy with certain antimicrobial agents, such as clindamycin and amoxicillin-clavulanate, may be beneficial, because they have been shown to yield high rates of eradication of streptococci from the pharynx under these particular circumstances.
American Academy of Otolaryngology–Head and Neck Surgery Foundation: **Clinical Practice Guideline: Adult Sinusitis (2015)**[32]	Symptomatic relief of viral rhinosinusitis • Management of viral rhinosinusitis is primarily symptomatic, with an analgesic or antipyretic provided for pain or fever, respectively. • Nasal saline may be palliative and cleansing with low risk of adverse reactions. • Oral decongestants may provide symptomatic relief and should be considered barring any medical contraindications, such as hypertension or anxiety. The use of topical decongestant is likely to be palliative, but continuous duration of use should not exceed three to five days, as recommended by the manufacturers, to avoid rebound congestion and rhinitis medicamentosa. • Clinical experience suggests oral antihistamines may provide symptomatic relief of excessive secretions and sneezing, although there are no clinical studies supporting the use of antihistamines in acute viral rhinosinusitis. • Guaifenesin (an expectorant) and dextromethorphan (a cough suppressant) are often used for symptomatic relief of viral rhinosinusitis symptoms, but evidence of clinical efficacy is lacking. Symptomatic relief of acute bacterial rhinosinusitis • Symptomatic treatments for acute bacterial rhinosinusitis include analgesics, topical intranasal steroids, and/or nasal saline irrigation. None of these products has been specifically approved by the FDA for use in acute rhinosinusitis (as of March 2014), and only some have data from controlled clinical studies supporting this use. • Over-the-counter analgesics, such as nonsteroidal anti-inflammatory drugs or acetaminophen, are usually sufficient to relieve facial pain associated with acute bacterial rhinosinusitis. • Antihistamines have no role in the symptomatic relief of acute bacterial

Clinical Guideline	Recommendation(s)
	rhinosinusitis in nonatopic patients. No studies support their use in an infectious setting, and antihistamines may worsen congestion by drying the nasal mucosa. Initial management of acute bacterial rhinosinusitis • Offer watchful waiting (without antibiotics) or prescribe initial antibiotic therapy for adults with uncomplicated acute bacterial rhinosinusitis. Watchful waiting should be offered only when there is assurance of follow-up, such that antibiotic therapy is started if the patient's condition fails to improve by seven days after acute bacterial rhinosinusitis diagnosis or if it worsens at any time. Choice of antibiotic for acute bacterial rhinosinusitis • If a decision is made to treat acute bacterial rhinosinusitis with an antibiotic, the clinician should prescribe amoxicillin with or without clavulanate as first-line therapy for five to ten days for most adults. • For penicillin-allergic patients, either doxycycline or a respiratory fluoroquinolone (levofloxacin or moxifloxacin) is recommended as an alternative agent for empiric antimicrobial therapy. Treatment failure for acute bacterial rhinosinusitis • If the patient worsens or fails to improve with the initial management option by seven days after diagnosis or worsens during the initial management, the clinician should reassess the patient to confirm acute bacterial rhinosinusitis, exclude other causes of illness, and detect complications. • If acute bacterial rhinosinusitis is confirmed in the patient initially managed with observation, the clinician should begin antibiotic therapy. • If the patient was initially managed with an antibiotic, the clinician should change the antibiotic.
American Academy of Allergy, Asthma, and Immunology/ American College of Allergy, Asthma and Immunology/ Joint Council on Allergy, Asthma and Immunology: **The Diagnosis and Management of Sinusitis: A Practice Parameter Update (2014)**[33]	• Treat acute bacterial rhinosinusitis if symptoms last longer than 10 days or with recrudescence of symptoms after progressive improvement. • The most commonly reported bacterial pathogens in acute bacterial rhinosinusitis are *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Staphylococcus aureus*. • The antibiotics currently approved by the FDA for acute bacterial rhinosinusitis are azithromycin, clarithromycin, amoxicillin-clavulanate, cefprozil, cefuroxime axetil, loracarbef, levofloxacin, trimethoprim-sulfamethoxazole, and moxifloxacin. Although some studies have reported comparisons of different antibiotics for adult acute bacterial rhinosinusitis, not one was found to be superior. • Owing to concerns over bacterial resistance, the Infectious Diseases Society of America no longer recommends the use of macrolides for empiric treatment of acute bacterial rhinosinusitis. That organization recommends amoxicillin-clavulanate as first-line therapy and doxycycline, levofloxacin, and moxifloxacin in patients allergic to penicillin. • The Infectious Diseases Society of America recommends five to seven days of treatment with antibiotics for uncomplicated acute bacterial rhinosinusitis in adults and 10 to 14 days in children. • Use intranasal steroids for treatment of acute rhinosinusitis as monotherapy or with antibiotics.
American Academy of Pediatrics: **Clinical Practice Guideline for the Diagnosis and Management of Acute Bacterial Sinusitis in**	• Antibiotic therapy should be prescribed for acute bacterial sinusitis in children with severe onset or worsening course (signs, symptoms or both). • Antibiotic therapy or additional outpatient observation for three days should be utilized for children with persistent illness (nasal discharge of any quality, cough or both for at least 10 days). • When a decision has been made to initiate antibiotic therapy for the treatment of acute bacterial sinusitis, amoxicillin with or without clavulanate is considered first-line.

Clinical Guideline	Recommendation(s)
Children Aged 1 to 18 years (2013)[34]	• For children ≥2 years of age with uncomplicated acute bacterial sinusitis that is mild to moderate in severity who do not attend child care and have not received antibiotics in the previous four weeks, amoxicillin 45 mg/kg/day in two divided doses is recommended. In communities with high prevalence of *Streptococcus pneumoniae* (>10%, including intermediate and high level resistance), amoxicillin may be initiated at 80 to 90 mg/kg/day in two divided doses with a maximum of 2 g per dose. • Patients with moderate to severe illness and those <2 years of age who are attending child care or have recently received antibiotics, amoxicillin-clavulanate (80 to 90 mg/kg/day of amoxicillin with 6.4 mg/kg/day of clavulanate to a maximum of 2 g per dose) may be used. • A single dose of ceftriaxone 50 mg/kg intravenous or intramuscular may be used for children who are vomiting, unable to tolerate oral medication or unlikely to adhere to initial doses of antibiotic.
Global Initiative for Chronic Obstructive Lung Disease: **Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2016)[35]**	• Prophylactic, continuous use of antibiotics has been shown to have no effect on the frequency of exacerbations in chronic obstructive pulmonary disease. • The use of antibiotics, other than for treating infectious exacerbations of chronic obstructive pulmonary disease and other bacterial infections, is currently not indicated. • Based on current available evidence, antibiotics should be given to: o Patients with exacerbations of chronic obstructive pulmonary disease with the following three cardinal symptoms: dyspnea, sputum volume, and sputum purulence. o Patients with exacerbations of chronic obstructive pulmonary disease with two of the cardinal symptoms, if the increased purulence of sputum is one of the two symptoms. o Patients with a severe exacerbation of chronic obstructive pulmonary disease that requires mechanical ventilation (invasive or noninvasive). • The recommended length of antibiotic therapy is usually five to 10 days. • The choice of antibiotic should be based on local bacterial resistance patterns. • Initial empiric treatment may include an aminopenicillin with or without clavulanic acid, macrolide, or tetracycline. In patients with frequent exacerbations, severe airflow limitation, and/or exacerbations requiring mechanical ventilation, sputum cultures or cultures from other materials from the lung should be performed, as gram-negative bacteria or resistant pathogens that may not be sensitive to the afore-mentioned antibiotics may be present.
Infectious Diseases Society of America: **Management of Community-Acquired Pneumonia in Infants and Children Older Than 3 Months of Age (2011)[36]** Reviewed and deemed current as of 04/2013	<u>Outpatient treatment</u> • Antimicrobial therapy is not routinely required for preschool-aged children with community-acquired pneumonia, because viral pathogens are responsible for the great majority of clinical disease. • Amoxicillin should be used as first-line therapy for previously healthy, appropriately immunized infants and preschool children with mild to moderate community-acquired pneumonia suspected to be of bacterial origin. Amoxicillin provides appropriate coverage for *Streptococcus pneumoniae*. • For patients allergic to amoxicillin, the following agents are considered alternative treatment options: o Second- or third-generation cephalosporin (cefpodoxime, cefuroxime, cefprozil). o Levofloxacin (oral therapy). o Linezolid (oral therapy). • Macrolide antibiotics should be prescribed for treatment of children (primarily school-aged children and adolescents) evaluated in an outpatient setting with findings compatible with community-acquired pneumonia caused by atypical pathogens.

Clinical Guideline	Recommendation(s)
	Inpatient treatment • Ampicillin or penicillin G should be administered to the fully immunized infant or school-aged child admitted to a hospital ward with community-acquired pneumonia when local epidemiologic data document lack of substantial high-level penicillin resistance for invasive *Streptococcus pneumoniae*. • Empiric therapy with a third-generation parenteral cephalosporin (ceftriaxone or cefotaxime) should be prescribed for hospitalized infants and children who are not fully immunized, in regions where local epidemiology of invasive pneumococcal strains documents high-level penicillin resistance, or for infants and children with life-threatening infection, including those with empyema. • Non–β-lactam agents, such as vancomycin, have not been shown to be more effective than third-generation cephalosporins in the treatment of pneumococcal pneumonia for the degree of resistance noted currently in North America. • Empiric combination therapy with a macrolide (oral or parenteral), in addition to a β-lactam antibiotic, should be prescribed for the hospitalized child for whom *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* are significant considerations. • Vancomycin or clindamycin (based on local susceptibility data) should be provided in addition to β-lactam therapy if clinical, laboratory, or imaging characteristics are consistent with infection caused by *Staphylococcus aureus*.

Infectious Diseases Society of America/American Thoracic Society: **Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults (2007)**[37]	Empirical antimicrobial therapy
	• Recommendations are generally for a class of antibiotics rather than for a specific drug, unless outcome data clearly favor one drug.
	• Because overall efficacy remains good for many classes of agents, the more potent drugs are given preference because of their benefit in decreasing the risk of selection for antibiotic resistance.
	• Outpatient treatment
	  o Previously healthy and no risk factors for drug-resistant *Streptococcus pneumoniae* infection:
	  ▪ Macrolide (azithromycin, clarithromycin, or erythromycin).
	  ▪ Doxycycline.
	  o Presence of comorbidities, such as chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressing conditions or use of immunosuppressing drugs; use of antimicrobials within the previous three months (in which case an alternative from a different class should be selected); or other risks for drug-resistant Streptococcus pneumoniae infection:
	  ▪ Respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin).
	  ▪ β-lactam plus a macrolide (high-dose amoxicillin or amoxicillin-clavulanate is preferred; alternatives include ceftriaxone, cefpodoxime, and cefuroxime; doxycycline is an alternative to the macrolide).
	  o In regions with a high rate of infection with high-level macrolide-resistant *Streptococcus pneumoniae,* consider the use of alternative agents listed above for any patient, including those without comorbidities.
	• Inpatient, non-intensive care unit treatment
	  o Respiratory fluoroquinolone.
	  o β-lactam plus a macrolide (preferred β-lactam agents include cefotaxime, ceftriaxone, and ampicillin; ertapenem for selected patients; with doxycycline as an alternative to the macrolide. A respiratory fluoroquinolone should be used for penicillin-allergic patients).
	• Inpatient, intensive care unit treatment
	  o β-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) plus either azithromycin or a fluoroquinolone (for penicillin-allergic patients, a respiratory fluoroquinolone and aztreonam are recommended).

Clinical Guideline	Recommendation(s)
	o For *Pseudomonas* infection, use an antipneumococcal, antipseudomonal β-lactam (piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin; OR o Antipneumococcal, antipseudomonal β-lactam (listed above) plus an aminoglycoside and azithromycin; OR o Antipneumococcal, antipseudomonal β-lactam (listed above) plus an aminoglycoside and an antipneumococcal fluoroquinolone (for penicillin-allergic patients, substitute aztreonam for the above β-lactam). o For community-acquired methicillin-resistant *Staphylococcus aureus* infection, add vancomycin or linezolid.
American Thoracic Society/ Infectious Diseases Society of America: **Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia (2005)**[38]	• Select an initial empiric therapy based on the absence or presence of risk factors for multidrug-resistant pathogens. These risk factors include prolonged duration of hospitalization (five days or more), admission from a healthcare-related facility, and recent prolonged antibiotic therapy. • Patients with healthcare-related pneumonia should be treated for potentially drug-resistant organisms, regardless of when during the hospital stay the pneumonia begins. • In selecting empiric therapy for patients who have recently received an antibiotic, an effort should be made to use an agent from a different antibiotic class, because recent therapy increases the probability of inappropriate therapy and can predispose to resistance to that same class of antibiotics. • Initial empiric antibiotic therapy for hospital-acquired pneumonia or ventilator-associated pneumonia in patients with no known risk factors for multidrug-resistant pathogens, early onset, and any disease severity: o Ceftriaxone; OR o Levofloxacin, moxifloxacin, ciprofloxacin; OR o Ampicillin-sulbactam; OR o Ertapenem. • Initial empiric antibiotic therapy for hospital-acquired pneumonia, ventilator-associated pneumonia, and healthcare-associated pneumonia in patients with late-onset disease or risk factors for multidrug-resistant pathogens and all disease severity–combination antibiotic therapy is recommended as follows: o Antipseudomonal cephalosporin (cefepime, ceftazidime) or antipseudomonal carbapenem (imipenem or meropenem) or β-lactam-β-lactamase inhibitor (piperacillin-tazobactam) plus antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) or aminoglycoside (amikacin, gentamicin, or tobramycin) plus linezolid or vancomycin if methicillin-resistant *Staphylococcus aureus* risk factors are present or there is a high incidence locally.
Infectious Diseases Society of America: **Diagnosis and Management of Complicated Intra-abdominal Infection in Adults and Children (2010)**[39]	<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

Clinical Guideline	Recommendation(s)
	recommended in adults or children with community-acquired intra-abdominal infections. Community-acquired infection in adults: high severity • 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. Community-acquired infection in pediatric patients • 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 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:

Clinical Guideline	Recommendation(s)
	• 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: **Management of Patients with Infections Caused by Methicillin-Resistant *Staphylococcus Aureus* (2011)**[40]	Skin and soft-tissue infections • For a cutaneous abscess, incision and drainage is the primary treatment. For simple abscesses or boils, incision and drainage alone is likely to be adequate. • Antibiotic therapy is recommended for abscesses associated with the following conditions: severe or extensive disease (e.g., involving multiple sites of infection) or rapid progression in presence of associated cellulitis, signs and symptoms of systemic illness, associated comorbidities or immunosuppression, extremes of age, abscess in an area difficult to drain (e.g., face, hand, and genitalia), associated septic phlebitis, and lack of response to incision and drainage alone. • For outpatients with purulent cellulitis, empirical therapy for community-acquired methicillin-resistant *Staphylococcus aureus* is recommended pending culture results. Empirical therapy for infection due to beta-hemolytic streptococci is likely to be unnecessary. • For outpatients with non-purulent cellulitis, empirical therapy for infection due to beta-hemolytic streptococci is recommended. Empirical coverage for community-acquired methicillin-resistant *Staphylococcus aureus* is recommended in patients who do not respond to beta-lactam therapy and may be considered in those with systemic toxicity. • For empirical coverage of community-acquired methicillin-resistant *Staphylococcus aureus* in outpatients with skin and soft-tissue infections, oral antibiotic options include the following: clindamycin, sulfamethoxazole-trimethoprim, a tetracycline (doxycycline or minocycline), and linezolid. If coverage for both beta-hemolytic streptococci and community-acquired methicillin-resistant *Staphylococcus aureus* is desired, options include the following: clindamycin alone or sulfamethoxazole-trimethoprim or a tetracycline in combination with a beta-lactam (e.g., amoxicillin) or linezolid alone. • The use of rifampin as a single agent or as adjunctive therapy for the treatment of skin and soft-tissue infections is not recommended. • For hospitalized patients with complicated skin and soft-tissue infections, in addition to surgical debridement and broad-spectrum antibiotics, empirical therapy for methicillin-resistant *Staphylococcus aureus* should be considered pending culture data. Options include the following: vancomycin intravenous, linezolid oral or intravenous, daptomycin intravenous, telavancin intravenous, and clindamycin intravenous or oral. A beta-lactam antibiotic (e.g., cefazolin) may be considered in hospitalized patients with non-purulent cellulitis with modification to methicillin-resistant *Staphylococcus aureus*-active therapy if there is no clinical response. • For children with minor skin infections (such as impetigo) and secondarily infected skin lesions (such as eczema, ulcers, or lacerations), mupirocin 2% topical ointment can be used. • Tetracyclines should not be used in children <8 years of age. • In hospitalized children with skin and soft-tissue infections, vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, empirical therapy with clindamycin intravenous is an option if the clindamycin resistance rate is low (<10%) with transition to oral therapy if the strain is susceptible. Linezolid oral or intravenous is an alternative. Methicillin-resistant Staphylococcus aureus and infective endocarditis (native valve) • For adults with uncomplicated bacteremia, vancomycin or daptomycin intravenous for at least two weeks is recommended. For complicated bacteremia, four to six weeks of therapy is recommended, depending on the extent of infection. • For adults with infective endocarditis, intravenous vancomycin or daptomycin for six weeks is recommended.

Clinical Guideline	Recommendation(s)
	• Addition of gentamicin to vancomycin is not recommended for bacteremia or native valve infective endocarditis. Methicillin-resistant *Staphylococcus aureus* bacteremia and infective endocarditis (prosthetic valve) • Intravenous vancomycin plus rifampin oral or intravenous for at least six weeks plus gentamicin intravenous for two weeks. • In children, vancomycin intravenous is recommended for the treatment of bacteremia and infective endocarditis. Duration of therapy may range from two to six weeks depending on source, presence of endovascular infection, and metastatic foci of infection. • Data regarding the safety and efficacy of alternative agents in children are limited, although daptomycin intravenous may be an option. Clindamycin or linezolid should not be used if there is concern for infective endocarditis or endovascular source of infection, but may be considered in children whose bacteremia rapidly clears and is not related to an endovascular focus. • Data are insufficient to support the routine use of combination therapy with rifampin or gentamicin in children with bacteremia or infective endocarditis. Management of methicillin-resistant *Staphylococcus aureus* pneumonia • For hospitalized patients with severe community-acquired pneumonia, empirical therapy for methicillin-resistant *Staphylococcus aureus* is recommended pending sputum and/or blood culture results. • For health care–associated methicillin-resistant *Staphylococcus aureus* or community-acquired methicillin-resistant *Staphylococcus aureus* pneumonia, intravenous vancomycin or linezolid oral or intravenous or clindamycin oral or intravenous, if the strain is susceptible, is recommended for seven to 21 days, depending on the extent of infection. • In children, intravenous vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, clindamycin intravenous can be used as empirical therapy if the clindamycin resistance rate is low (<10%) with transition to oral therapy if the strain is susceptible. Linezolid oral or intravenous is an alternative. Management of methicillin-resistant *Staphylococcus aureus* bone and joint infections • Antibiotics available for parenteral administration include intravenous vancomycin and daptomycin. • Some antibiotic options with parenteral and oral routes of administration include the following: sulfamethoxazole-trimethoprim in combination with rifampin, linezolid, and clindamycin. Some experts recommend the addition of rifampin. For patients with concurrent bacteremia, rifampin should be added after clearance of bacteremia. • A minimum eight-week course is recommended. Some experts suggest an additional one to three months (and possibly longer for chronic infection or if debridement is not performed) of oral rifampin-based combination therapy with sulfamethoxazole-trimethoprim, doxycycline-minocycline, clindamycin, or a fluoroquinolone, chosen on the basis of susceptibilities. • For septic arthritis, refer to antibiotic choices for osteomyelitis. A three to four-week course of therapy is suggested. Management of methicillin-resistant *Staphylococcus aureus* infections of the central nervous system • Meningitis o Intravenous vancomycin for two weeks is recommended. Some experts recommend the addition of rifampin.

Clinical Guideline	Recommendation(s)
	o Alternatives include the following: linezolid or sulfamethoxazole-trimethoprim. o For central nervous system shunt infection, shunt removal is recommended, and it should not be replaced until cerebrospinal fluid cultures are repeatedly negative. • Brain abscess, subdural empyema, spinal epidural abscess o Intravenous vancomycin for four to six weeks is recommended. Some experts recommend the addition of rifampin. o Alternatives include the following: linezolid and sulfamethoxazole-trimethoprim. • Septic thrombosis of cavernous or dural venous sinus o Intravenous vancomycin for four to six weeks is recommended. Some experts recommend the addition of rifampin. o Alternatives include the following: linezolid and sulfamethoxazole-trimethoprim. o Intravenous vancomycin is recommended in children.
Infectious Diseases Society of America: **Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer (2010)**[41] Reviewed and deemed current as of 04/2013	Initial antibiotic therapy • Oral route: o For low-risk adults only; use ciprofloxacin plus amoxicillin-clavulanate. • Monotherapy with vancomycin not indicated: o Choose therapy with one of the following agents: cefepime or ceftazidime, or imipenem or meropenem. • Two drugs without vancomycin: o Choose an aminoglycoside plus antipseudomonal penicillin, cephalosporin (cefepime or ceftazidime), or carbapenem. • Vancomycin plus one or two antibiotics: o Choose cefepime or ceftazidime plus vancomycin, with or without an aminoglycoside; carbapenem plus vancomycin, with or without an aminoglycoside; or antipseudomonal penicillin plus an aminoglycoside and vancomycin. Modification of therapy during the first week of treatment • Patient becomes afebrile in three to five days: o Adjust therapy to the most appropriate drug(s). If no etiologic agent is identified and if the patient is at low risk initially, and oral antibiotic treatment was begun with no subsequent complications, continue use of the same drugs. o If the patient was at low risk initially and therapy with intravenous drugs was begun with no subsequent complications, the regimen may be changed after 48 hours to oral ciprofloxacin plus amoxicillin-clavulanate for adults or cefixime for children. o If the patient is at high risk initially with no subsequent complications, continue use of the same intravenous drugs. • Persistent fever throughout the first three to five days: o Reassess therapy on day three. If there is no clinical worsening, continue use of the same antibiotics; stop vancomycin use if cultures do not yield organisms. o If there is progressive disease, change antibiotics. o If the patient is febrile after five days, consider adding an antifungal drug. Antibiotic prophylaxis for afebrile neutropenic patients • Use of antibiotic prophylaxis is not routine because of emerging antibiotic resistance, except for the use of sulfamethoxazole-trimethoprim to prevent *Pneumocystis carinii* pneumonitis.
National Comprehensive	Low infection risk prophylaxis • Antimicrobial prophylaxis is not recommended in patients with low infection risk.

Clinical Guideline	Recommendation(s)

Cancer Network: **Prevention and Treatment of Cancer-Related Infections (2016)**[42]	Intermediate infection risk prophylaxis
	• Consider using fluoroquinolone prophylaxis.
	
	High infection risk prophylaxis
	• Consider using fluoroquinolone prophylaxis.
	• Additional prophylaxis may be necessary.
	
	Pneumocystis jirovecii prophylaxis
	• Sulfamethoxazole-trimethoprim is the preferred treatment. Sulfamethoxazole-trimethoprim has the additional benefit of activity against other pathogens including Nocardia, Toxoplasma, and Listeria.
	• Atovaquone, dapsone, and pentamidine are potential alternatives as prophylaxis for patients intolerant to sulfamethoxazole-trimethoprim.
	• Consider sulfamethoxazole-trimethoprim desensitization or atovaquone, dapsone, or pentamidine when *Pneumocystis* prophylaxis is required in patients who are sulfamethoxazole-trimethoprim intolerant. For patients receiving dapsone, consider assessing G6PD levels.
	
	Pneumococcal infection prophylaxis
	• Prophylaxis for pneumococcal infection should begin three months after patients undergo hematopoietic stem cell transplantation with penicillin, and prophylaxis should continue for at least one year after the transplant.
	• In regions that have pneumococcal isolates with intermediate or high-level resistance to penicillin, sulfamethoxazole-trimethoprim will likely be adequate for pneumococcal prophylaxis.
	
	Initial empiric antibiotic therapy
	• Patients with neutropenia should begin empiric treatment with broad spectrum antibiotics at the first sign of infection.
	• Intravenous antibiotic monotherapy for uncomplicated infections (choose one):
	  o Cefepime.
	  o Imipenem-cilastatin.
	  o Meropenem.
	  o Piperacillin-tazobactam.
	  o Ceftazidime.
	• Oral antibiotic combination therapy for low-risk patients with uncomplicated infections:
	  o Ciprofloxacin plus amoxicillin-clavulanate.
	  o Moxifloxacin.
	  o Oral antibiotic regimen recommended should not be used if quinolone prophylaxis was used.
	• Complicated infections (choose based on local antibiotic susceptibility patterns):
	  o Intravenous antibiotic monotherapy is preferred.
	  o Intravenous combination therapy could be considered especially in cases of resistance.
	
	Antibacterial agents: empiric gram-positive activity
	• Vancomycin
	  o Gram-positive organisms with the exception of VRE and a number of rare organisms.
	  o Should not be considered as routine therapy for neutropenia and fever unless certain risk factors present.
	  o Dosing individualized with monitoring of levels; loading dose may be considered.

Clinical Guideline	Recommendation(s)

	• Daptomycin
	  o Has in vitro activity against VRE but is not FDA-approved for this indication.
	  o Weekly creatine phosphokinase (CPK) to monitor for rhabdomyolysis.
	  o Not indicated for pneumonia due to inactivation by pulmonary surfactant.
	• Linezolid
	  o Gram-positive organisms including VRE.
	  o Hematologic toxicity (typically with prolonged cases over two weeks) may occur.
	  o Not routinely use in fever and neutropenia, although may impair neutrophil and platelet recovery for extended use.
	  o Treatment option for VRE and MRSA.
	  o Peripheral/optic neuropathy with long-term use.
	
	<u>Antibacterial agents: anti-pseudomonal</u>
	• Cefepime
	  o Broad-spectrum activity against most gram-positive and negative organisms (not active against most anaerobes and *Enterococcus* species).
	  o Use for suspected/proven CNS infection with susceptible organism.
	  o Empiric therapy for neutropenic fever.
	• Ceftazidime
	  o Relatively poor gram-positive activity (not active against most anaerobes and *Enterococcus* species).
	  o Use for suspected/proven CNS infection with susceptible organism.
	  o Empiric therapy for neutropenic fever (resistance among gram-negative rods at some centers).
	• Imipenem-cilastatin/ meropenem/ doripenem
	  o Broad spectrum activity against most gram-positive, gram-negative, and anaerobic organisms.
	  o Preferred against extended spectrum beta-lactamase and serious *Enterobacter* infections.
	  o Carbapenem-resistant gram-negative rod infections are an increasing problem at a number of centers.
	  o Use for suspected intra-abdominal source.
	  o Meropenem is preferred over imipenem for suspected/proven CNS infection.
	  o Effective in nosocomial pneumonia and intra-abdominal infections.
	• Piperacillin-tazobactam
	  o Broad spectrum activity against most gram-positive, gram-negative, and anaerobic organisms.
	  o Use for suspected intra-abdominal source.
	
	<u>Antibacterial agents: other</u>
	• Aminoglycosides
	  o Activity primarily against gram-negative organisms.
	  o Often used as empiric therapy in seriously ill or hemodynamically unstable patients.
	• Ciprofloxacin in combination with amoxicillin-clavulanate
	  o Good activity against gram-negative and atypical organisms. Less active than “respiratory” fluoroquinolones against gram-positive organisms.
	  o Ciprofloxacin alone has no activity against anaerobes.
	  o Avoid for empiric therapy if patient recently treated with fluoroquinolone prophylaxis.
	• Levofloxacin/ moxifloxacin
	  o Good activity against gram-negative and atypical organisms.
	  o Levofloxacin has no activity against anaerobes. Moxifloxacin has limited

Clinical Guideline	Recommendation(s)
	activity against Pseudomonas. o Prophylaxis may increase bacterial resistance and superinfection. • Metronidazole o Good activity against anaerobic organisms. • Sulfamethoxazole-trimethoprim o Highly effective as prophylaxis against *Pneumocystis jiroveci* in high-risk patients. o Monitor for myelosuppression, hepatotoxicity, and hyperkalemia.
Infectious Diseases Society of America: **Clinical Assessment, Treatment, and Prevention of Lyme Disease, Human Granulocytic Anaplasmosis, and Babesiosis (2006)**[43]	• Doxycycline, amoxicillin or cefuroxime axetil for 14 days is recommended for the treatment of adult patients with early localized or early disseminated Lyme disease associated with erythema migrans, in the absence of specific neurologic manifestations (see Lyme meningitis, below) or advanced atrioventricular heart block. • Each of these antimicrobial agents has been shown to be highly effective for the treatment of erythema migrans and associated symptoms in prospective studies. • Doxycycline has the advantage of being effective for treatment of Human Granulocytic Anaplasmosis (but not for babesiosis), which may occur simultaneously with early Lyme disease.
American Society of Health-System Pharmacists/ Infectious Diseases Society of America/ Surgical Infection Society/ Society for Healthcare Epidemiology of America: **Clinical practice guidelines for antimicrobial prophylaxis in surgery (2013)**[44]	Common principles • The optimal time for administration of preoperative doses is within 60 minutes before surgical incision. Some agents, such as fluoroquinolones and vancomycin, require administration over one to two hours; therefore, the administration of these agents should begin within 120 minutes before surgical incision. • The selection of an appropriate antimicrobial agent for a specific patient should take into account the characteristics of the ideal agent, the comparative efficacy of the antimicrobial agent for the procedure, the safety profile, and the patient's medication allergies. • For most procedures, cefazolin is the drug of choice for prophylaxis because it is the most widely studied antimicrobial agent, with proven efficacy. It has a desirable duration of action, spectrum of activity against organisms commonly encountered in surgery, reasonable safety, and low cost. • There is little evidence to suggest that broad-spectrum antimicrobial agents (i.e., agents with broad in vitro antibacterial activity) result in lower rates of postoperative SSI compared with older antimicrobial agents with a narrower spectrum of activity. However, comparative studies are limited by small sample sizes, resulting in difficulty detecting a significant difference between antimicrobial agents. Cardiac procedures • For patients undergoing cardiac procedures, the recommended regimen is a single preincision dose of cefazolin or cefuroxime with appropriate intraoperative redosing. • For patients with serious allergy or adverse reaction to β-lactams, vancomycin or clindamycin may be an acceptable alternative. • Vancomycin should be used for prophylaxis in patients known to be colonized with MRSA. • Mupirocin should be given intranasally to all patients with documented *S. aureus* colonization. Thoracic procedures • In patients undergoing thoracic procedures, a single dose of cefazolin or ampicillin–sulbactam is recommended. • For patients with serious allergy or adverse reaction to β-lactams, vancomycin or

Clinical Guideline	Recommendation(s)
	clindamycin may be an acceptable alternative. • Vancomycin should be used for prophylaxis in patients known to be colonized with MRSA. Gastroduodenal procedures • Antimicrobial prophylaxis in gastroduodenal procedures should be considered for patients at highest risk for postoperative infections, including risk factors such as increased gastric pH (e.g., patients receiving acid-suppression therapy), gastroduodenal perforation, decreased gastric motility, gastric outlet obstruction, gastric bleeding, morbid obesity, ASA classification of ≥3, and cancer. • A single dose of cefazolin is recommended in procedures during which the lumen of the intestinal tract is entered. A single dose of cefazolin is recommended in clean procedures, such as highly selective vagotomy, and antireflux procedures only in patients at high risk of postoperative infection due to the presence of the above risk factors. • Alternative regimens for patients with β -lactam allergy include clindamycin or vancomycin plus gentamicin, aztreonam, or a fluoroquinolone. • Higher doses of antimicrobials are uniformly recommended in morbidly obese patients undergoing bariatric procedures. Higher doses of antimicrobials should be considered in significantly overweight patients undergoing gastroduodenal and endoscopic procedures. Biliary tract procedures • A single dose of cefazolin should be administered in patients undergoing open biliary tract procedures. • Alternatives include ampicillin–sulbactam and other cephalosporins (cefotetan, cefoxitin, and ceftriaxone). Alternative regimens for patients with β -lactam allergy include clindamycin or vancomycin plus gentamicin, aztreonam, or a fluoroquinolone; or metronidazole plus gentamicin or a fluoroquinolone. Appendectomy procedures • For uncomplicated appendicitis, the recommended regimen is a single dose of a cephalosporin with anaerobic activity (cefoxitin or cefotetan) or a single dose of a first-generation cephalosporin (cefazolin) plus metronidazole. • For β -lactam-allergic patients, alternative regimens include clindamycin plus gentamicin, aztreonam, or a fluoroquinolone; and metronidazole plus gentamicin or a fluoroquinolone (ciprofloxacin or levofloxacin). Small intestine procedures • For small bowel surgery without obstruction, the recommended regimen is a first generation cephalosporin (cefazolin). For small bowel surgery with intestinal obstruction, the recommended regimen is a cephalosporin with anaerobic activity (cefoxitin or cefotetan) or the combination of a first-generation cephalosporin (cefazolin) plus metronidazole. • For β -lactam-allergic patients, alternative regimens include clindamycin plus gentamicin, aztreonam, or a fluoroquinolone; and metronidazole plus gentamicin or a fluoroquinolone (ciprofloxacin or levofloxacin). Hernia repair procedures • For hernioplasty and herniorrhaphy, the recommended regimen is a single dose of a first-generation cephalosporin (cefazolin). For patients known to be colonized with MRSA, it is reasonable to add a single preoperative dose of vancomycin to the recommended agent. For β –lactam-allergic patients, alternative regimens include clindamycin and vancomycin.

Clinical Guideline	Recommendation(s)

	Colorectal procedures
	• A single dose of second-generation cephalosporin with both aerobic and anaerobic activities (cefoxitin or cefotetan) or cefazolin plus metronidazole is recommended for colon procedures.
	• In institutions where there is increasing resistance to first- and second-generation cephalosporins among gram-negative isolates from SSIs, a single dose of ceftriaxone plus metronidazole is recommended over routine use of carbapenems. An alternative regimen is ampicillin–sulbactam.
	• In most patients, mechanical bowel preparation combined with a combination of oral neomycin sulfate plus oral erythromycin base or oral neomycin sulfate plus oral metronidazole should be given in addition to intravenous prophylaxis. The oral antimicrobial should be given as three doses over approximately 10 hours the afternoon and evening before the operation and after the mechanical bowel preparation.
	• Alternative regimens for patients with β–lactam allergies include (1) clindamycin plus an aminoglycoside, aztreonam, or a fluoroquinolone and (2) metronidazole plus an aminoglycoside or a fluoroquinolone. Metronidazole plus aztreonam is not recommended as an alternative because this combination has no aerobic gram-positive activity.
	
	Head and neck procedures
	• Clean procedures:
	  o Antimicrobial prophylaxis is not required.
	• Clean-contaminated procedures:
	  o Antimicrobial prophylaxis has not been shown to benefit patients undergoing tonsillectomy or functional endoscopic sinus procedures.
	  o The preferred regimens for patients undergoing other clean-contaminated head and neck procedures are (1) cefazolin or cefuroxime plus metronidazole and (2) ampicillin–sulbactam.
	  o Clindamycin is a reasonable alternative in patients with a documented β-lactam allergy. The addition of an aminoglycoside to clindamycin may be appropriate when there is an increased likelihood of gram-negative contamination of the surgical site.
	
	Neurosurgery procedures
	• A single dose of cefazolin is recommended for patients undergoing clean neurosurgical procedures, CSF-shunting procedures, or intrathecal pump placement. Clindamycin or vancomycin should be reserved as an alternative agent for patients with a documented β-lactam allergy (vancomycin for MRSA-colonized patients).
	
	Cesarean delivery procedures
	• The recommended regimen for all women undergoing cesarean delivery is a single dose of cefazolin administered before surgical incision. For patients with β-lactam allergies, an alternative regimen is clindamycin plus gentamicin.
	
	Hysterectomy procedures
	• The recommended regimen for women undergoing vaginal or abdominal hysterectomy, using an open or laparoscopic approach, is a single dose of cefazolin.
	• Cefoxitin, cefotetan, or ampicillin–sulbactam may also be used. Alternative agents for patients with a b-lactam allergy include (1) either clindamycin or vancomycin plus an aminoglycoside, aztreonam, or a fluoroquinolone and (2) metronidazole plus an aminoglycoside or a fluoroquinolone.
	
	Ophthalmic procedures
	• Due to the lack of robust data from trials, specific recommendations cannot be

Clinical Guideline	Recommendation(s)
	made regarding choice, route, or duration of prophylaxis. • As a general principle, the antimicrobial prophylaxis regimens used in ophthalmic procedures should provide coverage against common ocular pathogens, including *Staphylococcus* species and gram-negative organisms, particularly *Pseudomonas* species. Orthopedic procedures • Antimicrobial prophylaxis is not recommended for patients undergoing clean orthopedic procedures, including knee, hand, and foot procedures, arthroscopy, and other procedures without instrumentation or implantation of foreign materials. • Antimicrobial prophylaxis is recommended for orthopedic spinal procedures with and without instrumentation. The recommended regimen is cefazolin. • The recommended regimen in hip fracture repair or other orthopedic procedures involving internal fixation is cefazolin. Clindamycin and vancomycin should be reserved as alternative agents. • The recommended regimen for patients undergoing total hip, elbow, knee, ankle, or shoulder replacement is cefazolin. Clindamycin and vancomycin should be reserved as alternative agents. Urologic procedures • No antimicrobial prophylaxis is recommended for clean urologic procedures in patients without risk factors for postoperative infections. • Patients with preoperative bacteriuria or UTI should be treated before the procedure, when possible, to reduce the risk of postoperative infection. • For patients undergoing lower urinary tract instrumentation with risk factors for infection, the use of a fluoroquinolone or trimethoprim– sulfamethoxazole (oral or intravenous) or cefazolin (intravenous or intramuscular) is recommended. Vascular procedures • The recommended regimen for patients undergoing vascular procedures associated with a higher risk of infection, including implantation of prosthetic material, is cefazolin. Heart, lung, heart-lung, liver, pancreas, and kidney transplantation • Antimicrobial prophylaxis is indicated for all patients undergoing heart transplantation. The recommended regimen is a single dose of cefazolin. Alternatives include vancomycin or clindamycin with or without gentamicin, aztreonam, or a single fluoroquinolone dose. • Adult patients undergoing lung transplantation should receive antimicrobial prophylaxis, because of the high risk of infection. Patients with negative pretransplantation cultures should receive antimicrobial prophylaxis as appropriate for other types of cardiothoracic procedures. The recommended regimen is a single dose of cefazolin. • The recommended agents for patients undergoing liver transplantation are (1) piperacillin–tazobactam and (2) cefotaxime plus ampicillin. The duration of prophylaxis should be restricted to 24 hours or less. • The recommended regimen for patients undergoing pancreas or SPK transplantation is cefazolin. • The recommended agent for patients undergoing kidney transplantation is cefazolin. Plastic surgery and breast procedures • Antimicrobial prophylaxis is not recommended for most clean procedures in patients without additional postoperative infection risk factors. • Although no studies have demonstrated antimicrobial efficacy in these procedures,

Clinical Guideline	Recommendation(s)
	expert opinion recommends that patients with risk factors undergoing clean plastic procedures receive antimicrobial prophylaxis. The recommendation for clean-contaminated procedures, breast cancer procedures, and clean procedures with other risk factors is a single dose of cefazolin or ampicillin–sulbactam.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the cephalosporins are noted in Tables 5 through 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 5. FDA-Approved Indications for the Single Entity Cephalosporins[1-13]

Indication	Cefaclor	Cefadroxil	Cefazolin	Cefdinir	Cefepime	Cefixime	Cefotaxime
Central Nervous System Infections							
Central nervous system infections							✔
Dermatological Infections							
Skin and skin-structure infections	✔ †‡	✔	✔	✔	✔		✔
Genitourinary Infections							
Endometritis							✔
Genital infections			✔				
Gonorrhea						✔	✔
Pelvic cellulitis							✔
Pelvic inflammatory disease							✔
Urinary tract infections	✔ †§	✔	✔		✔	✔	✔
Respiratory Infections							
Acute bronchitis	✔ ‡						
Acute exacerbations of chronic bronchitis	✔ ‡			✔		✔	
Otitis media	✔ †§			✔		✔	
Pharyngitis and/or tonsillitis	✔ †‡§	✔		✔		✔	
Pneumonia	✔ ‡				✔		✔
Pneumonia (community-acquired)				✔			
Sinusitis				✔			
Respiratory tract infections (lower)	✔ †§		✔				✔
Respiratory tract infections (upper)			✔				
Miscellaneous Infections							
Bacteremia/Septicemia			✔				✔
Biliary tract infections			✔				
Bone and/or joint infections			✔				✔
Empiric therapy for febrile neutropenic patients					✔		
Endocarditis			✔				
Intra-abdominal infections					✔		✔
Perioperative prophylaxis			✔				✔

†Capsule formulation.
‡Extended-release tablet formulation.
§Suspension formulation.

Table 6. FDA-Approved Indications for the Single Entity Cephalosporins (cont.)[1-13]

Indication	Cefpodoxime	Cefprozil	Ceftaroline	Ceftazidime	Ceftibuten	Ceftriaxone	Cefuroxime	Cephalexin
Central Nervous System Infections								
Central nervous system infections				✔				
Meningitis				✔		✔	✔ §	
Dermatological Infections								
Impetigo							✔ ‡	
Skin and skin-structure infections	✔	✔	✔	✔		✔	✔ †§	✔
Genitourinary Infections								
Genitourinary infections								✔
Gonorrhea	✔					✔	✔ †§	
Gynecologic infections				✔		✔		
Urinary tract infections	✔			✔		✔	✔ †§	
Respiratory Infections								
Acute bronchitis		✔						
Acute exacerbations of chronic bronchitis	✔	✔			✔		✔ †	
Otitis media	✔	✔			✔	✔	✔ †‡	✔
Pharyngitis and/or tonsillitis	✔	✔			✔		✔ †‡	
Pneumonia				✔				
Pneumonia (community-acquired)	✔		✔					
Sinusitis	✔	✔					✔ †	
Respiratory tract infections (lower)				✔		✔	✔ §	✔
Respiratory tract infections (upper)								✔
Miscellaneous Infections								
Bone and/or joint infections				✔		✔	✔ §	✔
Intra-abdominal infections				✔		✔		
Lyme disease (early)							✔ †	
Perioperative prophylaxis						✔	✔ §	
Septicemia				✔		✔	✔ §	

§Injection formulation.
‡Suspension formulation.
†Tablet formulation.

Table 7. FDA-Approved Indications for the Combination Product Cephalosporins[1-13]

Indication	Ceftazidime and Avibactam	Ceftolozane and Tazobactam
Complicated intra-abdominal infections, used in combination with metronidazole	✔	✔
Complicated urinary tract infections, including pyelonephritis	✔	✔

IV. Pharmacokinetics

The pharmacokinetic parameters of the cephalosporins are listed in Table 8.

Table 8. Pharmacokinetic Parameters of the Cephalosporins[1-13]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents					
Cefaclor	Well absorbed	25	Not reported	Renal (50 to 80) Bile	0.5 to 1.0
Cefadroxil	Well absorbed	20	Not reported	Renal (85)	1.2 to 1.7
Cefazolin	Not reported	80 to 86	Not metabolized	Renal (70 to 80)	1.5 to 2.5
Cefdinir	21 to 25	60 to 73	Not reported	Renal	1.7
Cefepime	IM: Complete	16 to 20	Liver	Renal (70 to 99)	2
Cefixime	40 to 50	50 to 65	Not reported	Renal (50) Bile (5)	3 to 4
Cefotaxime	Not reported	27 to 38	Liver	Renal (50 to 85)	0.8 to 1.4
Cefpodoxime	41 to 64	18 to 33	Not reported	Renal (29 to 33)	2 to 3
Cefprozil	89 to 95	35 to 45	Not reported	Renal (60 to 70)	1 to 2
Ceftaroline	Not reported	20	Plasma	Renal (88) Feces (6)	2.6
Ceftazidime	IM: 91	5 to 17	Not metabolized	Renal (90 to 96)	1.6 to 2.0
Ceftibuten	80	65 to 77	Not reported	Renal (56)	1.53 to 2.50
Ceftriaxone	IM: 100 SC: 92	83 to 96	Intestinal wall	Renal (33 to 67) Bile (35 to 45)	5.8 to 8.7
Cefuroxime	37 to 52	50	Intestinal wall	Renal (66 to 100)	1.2 to 1.9
Cephalexin	Well absorbed	15 to 20	Not reported	Renal (>90)	0.9
Combination Products					
Ceftazidime and Avibactam	Not reported	C: <10 A: 5.7 to 8.2	Not reported	C: Renal (80 to 90) A: Renal (97)	C: 2.8 to 3.3 A: 2.2 to 2.7
Ceftolozane and Tazobactam	Not reported	C: 16 to 21 T: 30	C: Not metabolized T: Hydrolysis	C: Renal (>95) T: Renal (80)	C: 3.12 T: 1.03

IM=intramuscular, SC=subcutaneous.

V. Drug Interactions

Major drug interactions with the cephalosporins are listed in Table 9.

Table 9. Major Drug Interactions with the Cephalosporins[2]

Generic Name(s)	Interaction	Mechanism
Cephalosporins (cefadroxil, cefdinir, cefepime, cefixime, cefotaxime, cefpodoxime, ceftazidime, ceftibuten, cephalexin)	Warfarin	Concurrent use of cefadroxil and warfarin may result in an increased risk of bleeding.

Generic Name(s)	Interaction	Mechanism
Ceftriaxone	Calcium salts	Isolated neonatal deaths have been reported due to potential pulmonary and renal precipitation. Simultaneous administration of calcium-containing intravenous solutions and ceftriaxone in the same intravenous line should be avoided. A potential risk exists for calcium-ceftriaxone precipitation leading to gall bladder sludging, as well as precipitation, in the lungs and kidneys.
Cephalexin	Probenecid	Concurrent use of cephalexin and probenecid may result in increased cephalexin exposure.

VI. Adverse Drug Events

The most common adverse drug events reported with the cephalosporins are listed in Tables 10 through 12.

Table 10. Adverse Drug Events (%) Reported with the Cephalosporins[1-13]

Adverse Events	Cefaclor	Cefadroxil	Cefazolin	Cefdinir	Cefditoren	Cefepime	Cefixime	Cefotaxime
Cardiovascular								
Arrhythmia	-	-	-	-	-	-	-	<1
Cardiac failure	-	-	-	<1	-	-	-	-
Chest pain	-	-	-	<1	-	-	-	-
Hypertension	-	-	-	<1	-	-	-	-
Myocardial infarction	-	-	-	≤1	-	-	-	-
Shock	-	-	-	<1	-	<1	-	-
Central Nervous System								
Agitation	<1	-	-	-	-	-	-	-
Coma	-	-	-	-	-	<1	-	-
Confusion	<1	-	-	-	-	<1	-	-
Dizziness	<1	-	-	<1	-	-	<2	-
Encephalopathy	-	-	-	-	-	<1	-	-
Fever	-	<1	✔	<1	-	1	<2	<1
Hallucinations	<1	-	-	-	-	<1	-	-
Headache	-	-	-	2	2 to 3	1	<2	<1
Hyperactivity	<1	-	-	-	-	-	-	-
Insomnia	<1	-	-	<1	-	-	-	-
Irritability	<1	-	-	-	-	-	-	-
Loss of consciousness	-	-	-	<1	-	-	-	-
Nervousness	<1	-	-	-	-	-	-	-
Paresthesias	<1	-	-	-	-	-	-	-
Seizures	<1	-	✔	-	-	<1	<2	-
Somnolence	<1	-	-	<1	-	-	-	-
Stupor	-	-	-	-	-	<1	-	-
Dermatological								
Angioedema	<1	<1	-	-	-	-	<2	-
Cutaneous moniliasis	-	-	-	<1	-	-	-	-
Erythema at injection site	-	-	-	-	-	1	-	-
Erythema multiforme	-	<1	-	<1	<1	-	<2	<1
Erythema nodosum	-	-	-	<1	-	-	-	-
Exfoliative dermatitis	-	-	-	<1	-	-	-	-

Adverse Events	Cefaclor	Cefadroxil	Cefazolin	Cefdinir	Cefditoren	Cefepime	Cefixime	Cefotaxime
Facial edema	-	-	-	<1	-	-	<2	-
Pruritus	<1	<1	✔	<1	-	1	-	1 to 10
Rash	1 to 2	<1	✔	≤3	<1	1 to 4	<2	1 to 10
Stevens-Johnson syndrome	<1	<1	✔	<1	<1	-	<2	<1
Toxic epidermal necrolysis	<1	-	-	<1	<1	-	<2	<1
Urticaria	<1	<1	-	-	-	<1	<2	<1
Gastrointestinal								
Abdominal pain	-	<1	✔	≤1	2	-	2 to 10	-
Anorexia	-	-	✔	<1	-	-	-	-
Bloody diarrhea	-	-	-	<1	-	-	-	-
Colitis	-	-	-	-	-	<1	-	1 to 10
Constipation	-	-	-	<1	-	-	-	-
Diarrhea	3	1 to 10	✔	8 to 15	11 to 15	≤3	16	1 to 10
Dyspepsia	-	<1	-	<1	1 to 2	-	2 to 10	-
Enterocolitis	-	-	-	<1	-	-	-	-
Flatulence	-	-	-	<1	-	-	2 to 10	-
GI bleed	-	-	-	<1	-	-	-	-
Hemorrhagic colitis	-	-	-	<1	-	-	-	-
Ileus	-	-	-	<1	-	-	-	-
Loose stools	-	-	-	-	-	-	2 to 10	-
Melena	-	-	-	<1	-	-	-	-
Nausea	<1	<1	✔	≤3	4 to 6	≤2	2 to 10	1 to 10
Oral candidiasis	-	-	✔	-	-	-	-	-
Oral moniliasis	-	-	-	-	-	<1	-	-
Peptic ulcer	-	-	-	<1	-	-	-	-
Pseudomonas colitis	<1	<1	✔	<1	<1	<1	-	<1
Stomatitis	-	-	-	<1	-	-	-	-
Stools abnormal	-	-	-	<1	-	-	-	-
Vomiting	<1	<1	✔	≤1	1	≤1	<2	1 to 10
Xerostomia	-	-	-	<1	-	-	-	-
Genitourinary								
Glycosuria	-	-	-	≤1	-	-	-	-
Hematuria	-	-	-	-	3	-	-	-
Interstitial nephritis	<1	-	-	-	-	-	-	<1
Leukorrhea	-	-	-	<1	<1	-	-	-
Microhematuria	-	-	-	≤1	-	-	-	-
Nephropathy	-	-	-	<1	-	-	-	-

Adverse Events	Cefaclor	Cefadroxil	Cefazolin	Cefdinir	Cefditoren	Cefepime	Cefixime	Cefotaxime
Proteinuria	-	-	-	≤1	-	-	-	-
Pyuria	-	-	-	-	2	-	-	-
Renal failure	-	-	✔	<1	<1	-	<2	-
Urine leukocytes increased	-	-	-	≤2	-	-	-	-
Urine pH increased	-	-	-	≤1	-	-	-	-
Urine specific gravity decreased	-	-	-	<1	-	-	-	-
Urine specific gravity increased	-	-	-	≤1	-	-	-	-
Vaginal moniliasis	-	-	-	<4	3 to 6	-	-	-
Vaginitis	2	<1	✔	≤1	-	<1	<2	<1
Hematologic								
Agranulocytosis	<1	<1	-	-	-	<1	-	-
Aplastic anemia	<1	-	-	-	-	-	-	-
Coagulation disorder	-	-	-	<1	-	-	-	-
Coagulation time increased	-	-	-	-	<1	-	-	-
Disseminated intravascular coagulation	-	-	-	<1	-	-	-	-
Eosinophilia	2	-	✔	1	-	2	<2	<1
Granulocytopenia	-	-	-	<1	-	-	-	-
Hematocrit decreased	-	-	-	-	2	<1	-	-
Hemoglobin decreased	-	-	-	<1	-	-	-	-
Hemolytic anemia	<1	-	-	<1	-	-	-	-
Leukocytosis	-	-	-	≤1	-	-	-	-
Leukopenia	-	-	✔	≤1	<1	<1	<2	-
Lymphocytes decreased	-	-	-	1	-	-	-	-
Lymphocytes increased	-	-	-	≤2	-	-	-	-
Monocytes increased	-	-	-	<1	-	-	-	-
Neutropenia	<1	<1	✔	-	-	<1	<2	<1
Pancytopenia	-	-	-	<1	-	-	-	-
Prothrombin time abnormal	-	-	-	-	-	1	-	-
Prothrombin time prolonged	<1	-	-	-	-	-	<2	-
Partial thromboplastin time abnormal	-	-	-	-	-	2	-	-
Thrombocythemia	-	-	-	-	<1	-	-	-
Thrombocytopenia	<1	<1	✔	<1	<1	<1	<2	<1
Thrombocytopenia purpura	-	-	-	<1	-	-	-	-
Thrombocytosis	-	-	✔	≤1	-	-	-	-
White blood cells decreased	-	-	-	<1	<1	-	-	-
White blood cells increased	-	-	-	<1	<1	-	-	-

Adverse Events	Cefaclor	Cefadroxil	Cefazolin	Cefdinir	Cefditoren	Cefepime	Cefixime	Cefotaxime
Hepatic								
Cholestasis	-	<1	-	<1	-	-	-	-
Hepatic failure	-	-	-	<1	-	-	-	-
Hepatitis	<1	-	✔	<1	-	-	<2	-
Jaundice	<1	-	-	<1	-	-	<2	-
Laboratory Test Abnormalities								
Albumin decreased	-	-	-	-	<1	-	-	-
Alkaline phosphatase increased	-	-	-	≤1	-	<1	-	-
Amylase increased	-	-	-	<1	-	-	-	-
Bicarbonate decreased	-	-	-	≤1	-	-	-	-
Blood urea nitrogen increased	-	-	✔	<1	<1	<1	<2	<1
Gamma-glutamyl transferase increased	-	-	-	≤1	-	-	-	-
Hyperbilirubinemia	-	-	-	-	-	<1	<2	-
Hyperglycemia	-	-	-	≤1	1 to 2	-	-	-
Hyperkalemia	-	-	-	<1	<1	<1	-	-
Hyperphosphatemia	-	-	-	≤1	-	<1	-	-
Hypocalcemia	-	-	-	<1	<1	<1	-	-
Hyponatremia	-	-	-	-	<1	-	-	-
Hypophosphatemia	-	-	-	<1	-	3	-	-
Lactate dehydrogenase increased	-	-	-	≤1	-	-	-	-
Positive Coombs' test	-	-	-	-	<1	16	-	-
Serum creatinine increased	-	-	✔	-	-	<1	<2	<1
Transaminases increased	3	<1	✔	<1	-	2 to 3	<2	<1
Musculoskeletal								
Arthralgia	<1	<1	-	-	<1	-	-	-
Hyperkinesia	-	-	-	<1	-	-	-	-
Involuntary movement	-	-	-	<1	-	-	-	-
Myoclonus	-	-	-	-	-	<1	-	-
Rhabdomyolysis	-	-	-	<1	-	-	-	-
Respiratory								
Asthma	-	-	-	<1	<1	-	-	-
Eosinophilic pneumonia	-	-	-	<1	<1	-	-	-
Interstitial pneumonia	-	-	-	<1	<1	-	-	-
Pneumonia	-	-	-	<1	-	-	-	-
Respiratory failure	-	-	-	<1	-	-	-	-
Other								
Allergic reaction	-	-	-	-	<1	-	-	-

Adverse Events	Cefaclor	Cefadroxil	Cefazolin	Cefdinir	Cefditoren	Cefepime	Cefixime	Cefotaxime
Allergic vasculitis	-	-	-	<1	-	-	-	-
Anaphylaxis	<1	<1	✔	<1	-	<1	<2	<1
Bleeding tendency	-	-	-	<1	-	-	-	-
Candidiasis	-	-	-	-	-	-	<2	<1
Conjunctivitis	-	-	-	<1	-	-	-	-
Fungal infection	-	-	-	-	<1	-	-	-
Laryngeal edema	-	-	-	<1	-	-	-	-
Moniliasis	2	-	-	<1	-	-	-	-
Pain at injection site	-	-	✔	-	-	1	-	1 to 10
Phlebitis	-	-	✔	-	-	1	-	<1
Serum sickness-like reaction	<1	<1	-	<1	-	-	<2	-

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

Table 11. Adverse Drug Events (%) Reported with the Cephalosporins (cont.)[1-13]

Adverse Events	Cefpodoxime	Cefprozil	Ceftaroline	Ceftazidime	Ceftibuten	Ceftriaxone	Cefuroxime	Cephalexin
Cardiovascular								
Bradycardia	-	-	<2	-	-	-	-	-
Chest pain	<1	-	-	-	-	-	-	-
Edema	-	-	-	-	-	<1	-	-
Hypotension	<1	-	-	-	-	-	-	-
Palpitation	-	-	<2	-	-	<1	-	-
Tachycardia	-	-	-	-	-	-	<1	-
Central Nervous System								
Agitation	-	-	-	-	<1	-	-	✔
Anxiety	<1	-	-	-	-	-	-	-
Confusion	-	<1	-	-	-	-	-	✔
Dizziness	<1	1	<2	<1	≤1	<1	-	✔
Encephalopathy	-	-	-	<1	-	-	-	-
Fatigue	<1	-	-	-	<1	-	-	✔
Fever	<1	<1	<2	<1	<1	<1	<1	-
Hallucinations	-	-	-	-	-	-	-	✔
Headache	1	<1	3 to 5	<1	≤3	<1	-	✔
Hyperactivity	-	<1	-	-	-	-	-	-
Insomnia	<1	<1	3 to 4	-	<1	-	-	-
Irritability	-	-	-	-	<1	-	-	-
Nightmares	<1	-	-	-	-	-	-	-
Paresthesias	-	-	-	<1	<1	-	-	-

Adverse Events	Cefpodoxime	Cefprozil	Ceftaroline	Ceftazidime	Ceftibuten	Ceftriaxone	Cefuroxime	Cephalexin
Psychosis	-	-	-	-	<1	-	-	-
Seizures	-	-	<2	-	-	<1	<1	-
Somnolence	-	<1	-	-	<1	-	-	-
Dermatological								
Allergic dermatitis	-	-	-	-	-	<1	-	-
Angioedema	-	<1	-	<1	-	-	<1	✔
Diaper rash	12	2	-	-	<1	-	3	-
Erythema multiforme	-	<1	-	<1	-	<1	<1	✔
Exanthema	-	-	-	-	-	<1	-	-
Flushing	<1	-	-	-	-	<1	-	-
Lyell's syndrome	-	-	-	-	-	<1	-	-
Pruritus	<1	-	3 to 4	<1	<1	<1	-	-
Rash	1	<1	3	<1	<1	2	<1	✔
Stevens-Johnson syndrome	-	<1	-	<1	<1	<1	<1	✔
Toxic epidermal necrolysis	-	-	-	<1	<1	<1	<1	✔
Urticaria	-	<1	<2	-	<1	<1	<1	✔
Gastrointestinal								
Abdominal pain	2	1	<2	-	1 to 2	<1	<1	✔
Anorexia	-	-	-	-	<1	-	-	-
Aphasia	-	-	-	-	<1	-	-	-
Appetite decrease	<1	-	-	-	-	-	-	-
Clostridium difficile-associated diarrhea	-	-	<2	-	-	-	-	-
Colitis	-	-	-	-	-	<1	<1	-
Constipation	-	-	2	-	<1	-	-	-
Dehydration	-	-	-	-	<1	-	-	-
Diarrhea	7 to 15	3	5	1	3 to 4	3	4 to 11	✔
Dysgeusia	-	-	-	-	-	<1	-	-
Dyspepsia	-	-	-	-	≤2	<1	-	✔
Eructation	-	-	-	-	<1	-	-	-
Flatulence	<1	-	-	-	<1	<1	-	-
Gastritis	-	-	-	-	-	-	-	✔
Gastrointestinal bleed	-	-	-	-	-	-	<1	-
Glossitis	-	-	-	-	-	<1	-	-
Loose stools	-	-	-	-	≤2	-	-	-
Melena	-	-	-	-	<1	-	-	-
Nausea	4	4	4	<1	≤4	<1	3 to 7	✔
Pseudomonas colitis	<1	<1	-	<1	<1	<1	<1	✔

Adverse Events	Cefpodoxime	Cefprozil	Ceftaroline	Ceftazidime	Ceftibuten	Ceftriaxone	Cefuroxime	Cephalexin
Salivation decreased	<1	-	-	-	-	-	-	-
Stomatitis	-	-	-	-	-	<1	-	-
Taste alteration	<1	-	-	-	<1	-	-	-
Tongue swelling	-	-	-	-	-	-	<1	-
Vomiting	1 to 2	1	2	<1	1 to 2	<1	3 to 7	✔
Xerostomia	-	-	-	-	<1	-	-	-
Genitourinary								
Dysuria	-	-	-	-	<1	-	-	-
Genital moniliasis	-	-	-	-	-	-	-	✔
Genital pruritus	-	2	-	-	-	-	-	✔
Glycosuria	-	-	-	-	-	<1	-	-
Hematuria	-	-	-	-	<1	<1	-	-
Interstitial nephritis	-	-	-	-	-	-	<1	✔
Nephrolithiasis	-	-	-	-	-	<1	-	-
Oliguria	-	-	-	-	-	<1	-	-
Purpuric nephritis	<1	-	-	-	-	-	-	-
Renal dysfunction	-	-	-	-	-	-	<1	-
Renal failure	-	-	<2	-	-	-	-	-
Renal precipitations	-	-	-	-	-	<1	-	-
Urinary casts	-	-	-	-	-	<1	-	-
Vaginal candidiasis	<1	-	-	-	-	-	-	-
Vaginal discharge	-	-	-	-	-	-	-	✔
Vaginal infection	3	-	-	-	-	-	-	-
Vaginitis	-	1 to 10	-	<1	<1	<1	≤5	✔
Hematologic								
Agranulocytosis	-	-	-	-	-	<1	-	-
Anemia	-	-	<2	-	-	<1	-	-
Basophilia	-	-	-	-	-	<1	-	-
Eosinophilia	-	<1	<2	<1	3	6	7	✔
Hematocrit decreased	-	-	-	-	-	-	10	-
Hemoglobin decreased	-	-	-	-	1 to 2	-	10	-
Hemolytic anemia	-	-	-	<1	-	<1	<1	✔
Leukocytosis	-	-	-	-	-	<1	-	-
Leukopenia	-	<1	-	<1	<1	2	<1	-
Lymphocytosis	-	-	-	-	-	<1	-	-
Lymphopenia	-	-	-	-	-	<1	-	-
Monocytosis	-	-	-	-	-	<1	-	-

Adverse Events	Cefpodoxime	Cefprozil	Ceftaroline	Ceftazidime	Ceftibuten	Ceftriaxone	Cefuroxime	Cephalexin
Neutropenia	-	-	<2	-	-	<1	<1	✔
Pancytopenia	-	-	-	-	-	-	<1	-
Prothrombin time decreased	-	-	-	-	-	<1	-	-
Prothrombin time prolonged	-	-	-	-	-	<1	<1	-
Thrombocytopenia	-	<1	<2	-	<1	<1	<1	✔
Thrombocytosis	-	-	-	<1	≤1	5	-	-
Hepatic								
Cholestasis	-	-	-	-	-	-	<1	-
Hepatitis	-	-	<2	-	-	-	<1	✔
Jaundice	-	<1	-	<1	<1	<1	<1	✔
Laboratory Test Abnormalities								
Alkaline phosphatase increased	-	-	-	-	<1	<1	2	-
Blood urea nitrogen increased	-	<1	-	<1	2 to 4	1	<1	-
Hyperbilirubinemia	-	-	-	<1	≤1	<1	<1	-
Hyperglycemia	-	-	<2	-	-	-	-	-
Hyperkalemia	-	-	<2	-	-	-	-	-
Hypokalemia	-	-	2	-	-	-	-	-
Lactate dehydrogenase increased	-	-	-	-	-	-	1	-
Positive Coombs' test	-	-	11	-	-	-	<1	-
Serum creatinine increased	-	<1	-	<1	<1	<1	<1	-
Transaminases increased	-	2	2	<1	≤1	3	2 to 4	✔
Musculoskeletal								
Arthralgia	-	<1	-	-	-	-	-	✔
Arthritis	-	-	-	-	-	-	-	✔
Asterixis	-	-	-	<1	-	-	-	-
Hyperkinesia	-	-	-	-	<1	-	-	-
Joint disorder	-	-	-	-	-	-	-	✔
Malaise	<1	-	-	-	-	-	-	-
Myoclonus	-	-	-	<1	-	-	-	-
Neuromuscular excitability	-	-	-	<1	-	-	-	-
Rigors	-	-	-	-	<1	-	-	-
Weakness	<1	-	-	-	-	-	-	-
Respiratory								
Allergic pneumonitis	-	-	-	-	-	<1	-	-
Bronchospasm	-	-	-	-	-	<1	-	-
Cough	<1	-	-	-	-	-	-	-
Dyspnea	-	-	-	-	<1	-	<1	-

Adverse Events	Cefpodoxime	Cefprozil	Ceftaroline	Ceftazidime	Ceftibuten	Ceftriaxone	Cefuroxime	Cephalexin
Nasal congestion	-	-	-	-	<1	-	-	-
Pulmonary precipitations	-	-	-	-	-	<1	-	-
Stridor	-	-	-	-	<1	-	-	-
Other								
Allergic reactions	-	-	-	-	-	-	-	✔
Anaphylaxis	<1	<1	<2	<1	-	<1	<1	✔
Biliary lithiasis	-	-	-	-	-	<1	-	-
Candidiasis	-	-	-	<1	-	-	-	-
Chills	-	-	-	-	-	<1	-	-
Diaphoresis	-	-	-	-	-	<1	-	-
Epistaxis	<1	-	-	-	-	<1	-	-
Eye itching	<1	-	-	-	-	-	-	-
Fungal infection	<1	-	-	-	-	-	-	-
Gallbladder sludge	-	-	-	-	-	<1	-	-
Gallstones	-	-	-	-	-	<1	-	-
Hypersensitivity reactions	-	-	<2	2	-	-	<1	-
Moniliasis	-	-	-	-	<1	<1	-	-
Pain at injection site	-	-	-	1	-	1	<1	-
Pancreatitis	-	-	-	-	-	<1	-	-
Phlebitis	-	-	2	<1	-	<1	-	-
Serum sickness-like reaction	-	<1	-	-	<1	<1	-	-
Superinfection	-	1 to 10	-	-	-	-	-	-
Thrombophlebitis	-	-	-	-	-	-	2	-
Tinnitus	<1	-	-	-	-	-	-	-

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

Table 12. Adverse Drug Events (%) Reported with the Combination Product Cephalosporins (cont.)[1-13]

Adverse Events	Ceftazidime and Avibactam	Ceftolozane and Tazobactam
Cardiovascular		
Atrial fibrillation	-	0.2 to 1.2
Hypotension	-	0.4 to 1.7
Central Nervous System		
Anxiety	10	0.2 to 1.9
Dizziness	3 to 6	0.8 to 1.1
Headache	2	2.5 to 5.8
Insomnia	-	1.3 to 3.5

Adverse Events	Ceftazidime and Avibactam	Ceftolozane and Tazobactam
Dermatological		
Angioedema	✔	-
Erythema multiforme	✔	-
Pruritus	✔	-
Rash	✔	0.9 to 1.7
Stevens-Johnson syndrome	✔	-
Toxic epidermal necrolysis	✔	-
Urticaria	✔	-
Gastrointestinal		
Abdominal pain	1 to 7	0.8 to 1.2
Constipation	10	1.9 to 3.9
Diarrhea	8	1.9 to 6.2
Nausea	7	2.8 to 7.9
Upper abdominal pain	7	-
Vomiting	5	1.1 to 3.3
Genitourinary		
Acute renal failure	✔	-
Nephritis	✔	-
Renal impairment	✔	-
Hematologic		
Agranulocytosis	✔	-
Anemia	-	0.4 to 1.5
Eosinophilia	✔	-
Hemolytic anemia	✔	-
Leukopenia	✔	-
Lymphocytosis	✔	-
Neutropenia	✔	-
Thrombocytopenia	✔	-
Thrombocytosis	✔	0.4 to 1.9
Hepatic		
Jaundice	✔	-
Laboratory Test Abnormalities		
Hypokalemia	✔	0.8 to 3.3
Lactate dehydrogenase increased	✔	-
Positive Coombs' test	✔	-
Serum creatinine increased	-	-
Transaminases increased	✔	1 to 1.7

Adverse Events	Ceftazidime and Avibactam	Ceftolozane and Tazobactam
Other		
Candidiasis	✔	-
Phlebitis	✔	-
Pyrexia	-	1.7 to 5.6
Taste alterations	✔	-

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

VII. Dosing and Administration

The usual dosing regimens for the cephalosporins are listed in Table 13.

Table 13. Usual Dosing Regimens for the Cephalosporins[1-13]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Cefaclor	Acute bronchitis: Extended release tablet: 500 mg every 12 hours for seven days Acute exacerbations of chronic bronchitis: Extended release tablet: 500 mg every 12 hours for seven days Otitis media: Capsule, suspension: 250 mg every eight hours Pharyngitis and/or tonsillitis: Capsule, suspension: 250 mg every eight hours Suspension, extended release tablet: 375 mg every 12 hours for 10 days Respiratory tract infections (lower): Capsule, suspension: 250 mg every eight hours Skin and skin-structure infections: Capsule: 250 mg every eight hours Extended release tablet: 375 mg every 12 hours for seven to ten days Urinary tract infections: Capsule, suspension: 250 mg every eight hours	Otitis media: Capsule, suspension: 20 mg/kg/day in divided doses every eight hours Pharyngitis and/or tonsillitis: Capsule, suspension: 20 mg/kg/day in divided doses every eight hours Respiratory tract infections (lower): Capsule, suspension: 20 mg/kg/day in divided doses every eight hours Skin and skin-structure infections: Capsule: 20 mg/kg/day in divided doses every eight hours Urinary tract infections: Capsule, suspension: 20 mg/kg/day in divided doses every eight hours	Capsule: 250 mg 500 mg Extended release tablet: 500 mg Suspension: 125 mg/5 mL 250 mg/5 mL 375 mg/5 mL
Cefadroxil	Pharyngitis and/or tonsillitis: Capsule, suspension, tablet: 1 g per day in single (once daily) or divided doses (twice daily) for 10 days Skin and skin-structure infections (uncomplicated): Capsule, suspension, tablet: 1 g per day in single (once daily) or divided doses (twice daily)	Pharyngitis and/or tonsillitis: Capsule, suspension, tablet: 30 mg/kg/day in a single dose or in equally divided doses every 12 hours for 10 days Skin and skin-structure infections (uncomplicated): Capsule, suspension, tablet: 30 mg/kg/day in equally divided doses every 12 hours	Capsule: 500 mg Suspension: 250 mg/5 mL 500 mg/5 mL Tablet: 1 g

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Urinary tract infections (complicated): Capsule, suspension, tablet: complicated: 2 g per day in divided doses (twice daily) Urinary tract infections (uncomplicated): 1 or 2 g per day in single (once daily) or divided doses (twice daily)	Urinary tract infections: Capsule, suspension, tablet: 30 mg/kg/day in divided doses every 12 hours	
Cefazolin	Life-threatening infections: Injection: 1 to 1.5 g every six hours Mild infections: Injection: 250 to 500 mg every eight hours Moderate to severe infections: Injection: 500 mg to 1 g every six to eight hours Perioperative prophylaxis (preoperative): Injection:, 1 g IV/IM administered 30 minutes to one hour prior to the start of surgery Perioperative prophylaxis (intraoperative): Injection: 500 mg to 1 g IV/IM during surgery Perioperative prophylaxis (postoperative): Injection: 500 mg to 1 g IV/IM every six to eight hours for 24 hours Pneumonia: Injection: 500 mg every 12 hours Urinary tract infections (uncomplicated): Injection: 1 g every 12 hours	Mild to moderately severe infections in patients >1 month of age: Injection:, 25 to 50 mg/kg divided into three or four equal doses Severe infections >1 month of age: Injection: 25 to 100 mg/kg divided into three or four equal doses	Injection: 500 mg 1 g 10 g 20 g
Cefdinir	Acute exacerbations of chronic bronchitis: Capsule: 300 mg every 12 hours for five to 10 days or 600 mg every 24 hours for 10 days Pharyngitis and/or tonsillitis: Capsule: 300 mg every 12 hours for five to 10 days or 600 mg every 24 hours for 10 days	Otitis media in patients six months to 12 years of age: Suspension: 7 mg/kg every 12 hours for five to 10 days or 14 mg/kg every 24 hours for 10 days Pharyngitis and/or tonsillitis in patients six months to 12 years of age:	Capsule: 300 mg Suspension: 125 mg/5 mL 250 mg/5 mL

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Pneumonia (community-acquired): Capsule: 300 mg every 12 hours for 10 days Sinusitis: Capsule: 300 mg every 12 hours or 600 mg every 24 hours for 10 days Skin and skin-structure infections: Capsule: 300 mg every 12 hours or 600 mg every 24 hours for 10 days	Suspension: 7 mg/kg every 12 hours for five to ten days or 14 mg/kg every 24 hours for 10 days Sinusitis in patients six months to 12 years of age: Suspension: 7 mg/kg every 12 hours or 14 mg/kg every 24 hours for 10 days Skin and skin-structure infections (uncomplicated) in patients six months to 12 years of age: Suspension: 7 mg/kg every 12 hours for 10 days	
Cefepime	Empiric therapy for febrile neutropenic patients: Injection: 2 g IV every eight hours for seven days or until resolution of neutropenia Intra-abdominal infections (complicated): Injection: 2 g IV every 12 hours for seven to 10 days Pneumonia (moderate to severe): Injection: 1 to 2 g IV every 12 hours for 10 days Skin and skin-structure infections (moderate to severe): Injection: 2 g IV every 12 hours for 10 days Urinary tract infections (mild to moderate): Injection: 0.5 to 1 g IM/IV every 12 hours for seven to 10 days Urinary tract infections (severe): Injection: 2 g IV every 12 hours for 10 days	Empiric therapy for febrile neutropenic patients in patients two months to 16 years of age: Injection: 50 mg/kg IV every eight hours for seven days or until resolution of neutropenia Pneumonia in patients two months to 16 years of age: Injection: 50 mg/kg IV every 12 hours for 10 days Skin and skin-structure infections (uncomplicated) in patients two months to 16 years of age: Injection: 50 mg/kg IV every 12 hours for 10 days Urinary tract infections (mild to moderate) in patients two months to 16 years of age: Injection: mild to moderate, 50 mg/kg IV every 12 hours for seven to 10 days Urinary tract infections (severe) in patients two months to 16 years of age: Injection: severe, 50 mg/kg IV every 12 hours for 10 days	Injection: 1 g 2 g
Cefixime	Gonorrhea (Uncomplicated): Capsule, chewable tablet, suspension: 400 mg as a single dose Unspecified Infections: Capsule, chewable tablet, suspension: 400 mg once daily	Unspecified Infections: Six months to 12 years of age: Chewable tablet, suspension: 8 mg/kg once daily or 4 mg/kg every 12 hours	Capsule: 400 mg Chewable tablet: 100 mg 200 mg Suspension:

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	or 200 mg every 12 hours		100 mg/5 mL 200 mg/5 mL 500 mg/5 mL
Cefotaxime	Gonococcal infections (rectal): Injection: 0.5 g IM as a single dose in females and 1 g IM as a single dose in males Gonococcal infections (urethritis/cervicitis): Injection: 0.5 g IM as a single dose Life-threatening infections: Injection: 2 g IV every four hours Moderate to severe infections: Injection: 1 to 2 g IM/IV every eight hours Perioperative prophylaxis: Injection: 1 g IM/IV as a single dose administered 30 to 90 minutes prior to the start of surgery Uncomplicated infections: Injection: 1 g IM/IV every 12 hours	Unspecified infections in patients zero to one week of age: Injection: 50 mg/kg IV per dose every 12 hours Unspecified infections in patients one to four weeks of age: Injection: 50 mg/kg IV per dose every eight hours Unspecified infections in patients one month to 12 years of age: Injection: <50 kg, 50 to 180 mg/kg IM/IV divided into four to six equal doses; ≥50 kg, usual adult dosage	Injection: 500 mg 1 g 2 g 10 g
Cefpodoxime	Acute exacerbations of chronic bronchitis: Tablet: 200 mg every 12 hours for 10 days Gonococcal infections (rectal): Suspension, tablet: 200 mg as a single dose in females Uncomplicated gonorrhea: Suspension, tablet: 200 mg as a single dose Pharyngitis and/or tonsillitis: Suspension, tablet: 100 mg every 12 hours for five to 10 days Pneumonia (community-acquired): Suspension, tablet: 200 mg every 12 hours for 14 days Sinusitis: Suspension, tablet: 200 mg every 12 hours for 10 days	Acute exacerbations of chronic bronchitis in patients ≥12 years of age: Tablet: 200 mg every 12 hours for 10 days Gonococcal infections (rectal) in patients ≥12 years of age: Suspension, tablet: rectal, 200 mg as a single dose in females Uncomplicated gonorrhea in patients ≥12 years of age: Suspension, tablet: 200 mg as a single dose Otitis media in patients two months to 12 years of age: Suspension: 5 mg/kg every 12 hours for five days Pharyngitis and/or tonsillitis in patients two months to 12 years of age: Suspension: 5 mg/kg every 12 hours for five to 10 days	Suspension: 50 mg/5 mL 100 mg/5 mL Tablet: 100 mg 200 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Skin and skin-structure infections: Suspension, tablet: 400 mg every 12 hours for seven to 14 days Urinary tract infections (uncomplicated): Suspension, tablet: 100 mg every 12 hours for seven days	Pharyngitis and/or tonsillitis in patients ≥12 years of age: Suspension, tablet: 100 mg every 12 hours for five to 10 days Pneumonia (community-acquired in patients ≥12 years of age: Suspension, tablet: 200 mg every 12 hours for 14 days Sinusitis in patients two months to 12 years of age: Suspension: 5 mg/kg every 12 hours for 10 days Sinusitis in patients ≥12 years of age: Suspension, tablet: 200 mg every 12 hours for 10 days Skin and skin-structure infections in patients ≥12 years of age: Suspension, tablet: 400 mg every 12 hours for seven to 14 days Urinary tract infections (uncomplicated) in patients ≥12 years of age: Suspension, tablet: 100 mg every 12 hours for seven days	
Cefprozil	Acute bronchitis: Suspension, tablet: 500 mg every 12 hours for 10 days Acute exacerbations of chronic bronchitis: Suspension, tablet: 500 mg every 12 hours for 10 days Pharyngitis and/or tonsillitis: Suspension, tablet: 500 mg every 24 hours for 10 days Sinusitis: Suspension, tablet: 250 to 500 mg every 12 hours for 10 days Skin and skin-structure infections: Suspension, tablet: 250 to 500 mg every 12 hours or 500 mg every 24 hours for 10 days	Acute bronchitis in patients ≥13 years of age: Suspension, tablet: 500 mg every 12 hours for 10 days Acute exacerbations of chronic bronchitis in patients ≥13 years of age: Suspension, tablet: 500 mg every 12 hours for 10 days Otitis media in patients six months to 12 years of age: Suspension, tablet: 15 mg/kg every 12 hours for 10 days Pharyngitis and/or tonsillitis in patients two to 12 years of age: Suspension, tablet: 7.5 mg/kg every 12 hours for 10 days Pharyngitis and/or tonsillitis in patients ≥13 years of age:	Suspension: 125 mg/5 mL 250 mg/5 mL Tablet: 250 mg 500 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		Suspension, tablet: 500 mg every 24 hours for 10 days Sinusitis in patients six months to 12 years of age: Suspension, tablet: 7.5 mg/kg to 15 mg/kg every 12 hours for 10 days Sinusitis in patients ≥13 years of age: Suspension, tablet: 250 to 500 mg every 12 hours for 10 days Skin and skin-structure infections in patients two to 12 years of age: Suspension, tablet: 20 mg/kg every 24 hours for 10 days Skin and skin-structure infections in patients ≥13 years of age: Suspension, tablet: 250 to 500 mg every 12 hours or 500 mg every 24 hours for 10 days	
Ceftaroline	Pneumonia (community-acquired): Injection: 600 mg every 12 hours for five to seven days Skin and skin-structure infections: Injection: 600 mg every 12 hours for five to 14 days	Pneumonia (community-acquired): Injection: two to 18 years of age and >33 kg, 400 mg IV every eight hours or 600 mg IV every 12 hours; two to 18 years of age and ≤ 33 kg, 12 mg/kg/dose IV every eight hours; two months to <2 years of age, 8 mg/kg/dose IV every eight hours; all for five to 14 days Skin and skin-structure infections: Injection: two to 18 years of age and >33 kg, 400 mg IV every eight hours or 600 mg IV every 12 hours; two to 18 years of age and ≤ 33 kg, 12 mg/kg/dose IV every eight hours; two months to <2 years of age, 8 mg/kg/dose IV every eight hours; all for five to 14 days	Injection: 400 mg 600 mg
Ceftazidime	Bone and joint infections: Injection: 2 g IV every 12 hours Gynecologic infections (serious): Injection: 2 g IV every eight hours	Unspecified infections in patients zero to four weeks of age: Injection: 30 mg/kg IV every 12 hours Unspecified infections in	Injection: 500 mg 1 g 2 g 6 g

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Intra-abdominal infections (serious): Injection: 2 g IV every eight hours Life-threatening infections (very severe): Injection: 2 g IV every eight hours Lung infections (cystic fibrosis patients): Injection: 30 to 50 mg/kg IV every eight hours Meningitis: Injection: 2 g IV every eight hours Pneumonia (uncomplicated): Injection: 500 mg to 1 g IM/IV every eight hours Skin and skin-structure infections (mild): Injection: 500 mg to 1 g IM/IV every eight hours Urinary tract infections (uncomplicated): Injection: 250 mg IM/IV every 12 hours Urinary tract infections (complicated): Injection: 500 mg IM/IV every eight to 12 hours	patients one month to 12 years of age: Injection: 30 to 50 mg/kg IV every eight hours	
Ceftibuten	Acute exacerbations of chronic bronchitis: Capsule, suspension: 400 mg once daily for 10 days Otitis media: Capsule, suspension: 400 mg once daily for 10 days Pharyngitis and/or tonsillitis: Capsule, suspension: 400 mg once daily for 10 days	Otitis media in patients ≥6 months of age: Capsule, suspension: 9 mg/kg once daily for 10 days; patients weighing >45 kg should receive 400 mg once daily Pharyngitis and/or tonsillitis in patients ≥6 months of age: Capsule, suspension: 9 mg/kg once daily for 10 days; patients weighing >45 kg should receive 400 mg once daily	Capsule: 400 mg Suspension: 180 mg/5 mL
Ceftriaxone	Gonococcal infections (uncomplicated): Injection: 250 mg IM as a single dose	Meningitis: Injection: 100 mg/kg once daily or divided every 12 hours Otitis media:	Injection: 250 mg 500 mg 1 g 2 g

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Preoperative prophylaxis: Injection: 1 g IV as a single dose administered 30 minutes to two hours prior to surgery Unspecified infections: Injection: 1 to 2 g IM/IV once daily or in divided doses twice daily	Injection: 50 mg/kg IM as a single dose Skin and skin-structure infections: Injection: 50 to 75 mg/kg once daily or in equally divided doses twice daily Unspecified infections: Injection: 50 to 75 mg/kg/day given in divided doses every 12 hours	10 g
Cefuroxime	Acute bronchitis: Tablet: 250 to 500 mg twice daily for five to 10 days Acute exacerbations of chronic bronchitis: Tablet: 250 to 500 mg twice daily for 10 days Bone and joint infections: Injection: 1.5 g IM/IV every eight hours Gonococcal infections (disseminated): Injection: 750 mg IM/IV every eight hours Gonococcal infections (uncomplicated): Injection: 1.5 g IM as a single dose Tablet: 1,000 mg as a single dose Life-threatening infections: Injection: 1.5 g IM/IV every six hours Lyme disease (early): Tablet: 500 mg twice daily for 20 days Meningitis: Injection: 3 g IM/IV every eight hours Perioperative prophylaxis (clean-contaminated procedures: Injection: 1.5 g IV one hour prior to surgery, then 750 mg IM/IV every eight hours when	Acute bronchitis in patients ≥13 years of age: Tablet: 250 to 500 mg twice daily for five to 10 days Acute exacerbations of chronic bronchitis in patients ≥13 years of age: Tablet: 250 to 500 mg twice daily for 10 days Bone and joint infections in patients >3 months of age: Injection: 150 mg/kg/day IM/IV divided every eight hours Gonorrhea (uncomplicated) in patients ≥13 years of age: Tablet: 1,000 mg as a single dose Impetigo in patients three months to 12 years of age: Suspension: 30 mg/kg/day divided twice daily for 10 days Lyme disease (early) in patients ≥13 years of age: Tablet: 500 mg twice daily for 20 days Meningitis in patients >3 months of age: Injection: 200 to 240 mg/kg/day IV divided every six to eight hours Otitis media in patients three months to 12 years of age: Suspension: 30 mg/kg/day divided twice daily for 10 days Tablet: 250 mg twice daily for	Injection: 750 mg 1.5 g 7.5 g Suspension: 125 mg/5 mL 250 mg/5 mL Tablet: 250 mg 500 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	the surgery is prolonged Perioperative prophylaxis (open heart surgery): Injection: 1.5 g IV every 12 hours for a total of 6 g Pharyngitis and/or tonsillitis: Tablet: 250 mg twice daily for 10 days Pneumonia (uncomplicated): Injection: 750 mg IM/IV every eight hours Severe or complicated infections (unspecified): Injection: 1.5 g IM/IV every eight hours Sinusitis in patients ≥13 years of age: Tablet: 250 mg twice daily for 10 days Skin and skin-structure infections (uncomplicated): Injection: 750 mg IM/IV every eight hours Tablet: 250 to 500 mg twice daily for 10 days Unspecified infections: Injection: 750 mg to 1.5 g IM/IV every eight hours for five to 10 days Urinary tract infections (uncomplicated): Injection: 750 mg IM/IV every eight hours Tablet: 250 mg twice daily for seven to 10 days	10 days Pharyngitis and/or tonsillitis in patients three months to 12 years of age: Suspension: 20 mg/kg/day divided twice daily for 10 days Pharyngitis and/or tonsillitis in patients ≥13 years of age: Tablet: 250 mg twice daily for 10 days Sinusitis in patients three months to 12 years of age: Suspension: 30 mg/kg/day divided twice daily for 10 days Tablet: 250 mg twice daily for 10 days Sinusitis in patients ≥13 years of age: Tablet: 250 mg twice daily for 10 days Skin and skin-structure infections (uncomplicated) in patients ≥13 years of age: Tablet: 250 to 500 mg twice daily for 10 days Unspecified infections in patients >3 months of age: Injection: 50 to 100 mg/kg/day IM/IV divided every six to eight hours Urinary tract infections (uncomplicated) in patients ≥13 years of age: Tablet: 250 mg twice daily for seven to 10 days	
Cephalexin	Cystitis (uncomplicated): Capsule, suspension, tablet: 500 mg every 12 hours for seven to 14 days Skin and skin-structure infections: Capsule, suspension, tablet: 500 mg every 12 hours	Otitis media: Capsule, suspension, tablet: 75 to 100 mg/kg/day in four divided doses Streptococcal pharyngitis in patients >1 year of age: Capsule, suspension, tablet: 25 to 50 mg/kg/day every 12 hours for at least 10 days	Capsule: 250 mg 500 mg 750 mg Suspension: 125 mg/5 mL 250 mg/5 mL Tablet:

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Streptococcal pharyngitis: Capsule, suspension, tablet: 500 mg every 12 hours Unspecified infections: Capsule, suspension, tablet: 250 mg every six hours	Unspecified infections: Capsule, suspension, tablet: 25 to 50 mg/kg/day in divided doses	250 mg 500 mg
Combination Products			
Ceftazidime and Avibactam	Complicated intra-abdominal infections: Injection: 2.5 grams every eight hours for five to 14 days in conjunction with metronidazole Complicated urinary tract infections: Injection: 2.5 grams every eight hours for seven to 14 days	Safety and efficacy in pediatric patients have not been established	Injection: 2.5 g
Ceftolozane and Tazobactam	Complicated intra-abdominal infections: Injection: 1.5 grams every eight hours for four to 14 days in conjunction with metronidazole Complicated urinary tract infections: Injection: 1.5 grams every eight hours for seven days	Safety and efficacy in pediatric patients have not been established	Injection: 1.5 g

IM=intramuscular, IV=intravenous

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the cephalosporins are summarized in Table 14.

Table 14. Comparative Clinical Trials with the Cephalosporins

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Dermatological Infections				
Ballantyne[45] (1985) Cefaclor 250 mg PO TID vs cefadroxil 1,000 mg PO QD	OL, RCT Patients six to 80 years of age with skin and soft-tissue infections	N=200 10 days	Primary: Clinical and bacteriological efficacy, medication adherence Secondary: Not reported	Primary: There was no statistically significant difference in terms of clinical efficacy for patients treated with cefadroxil and cefaclor (91 vs 95%, respectively; P=0.41). Medication adherence was greater in patients treated with cefadroxil compared to patients treated with cefaclor based on the percentage of patients returning unused capsules (2 vs 77%, respectively). Secondary: Not reported
Ballantyne[46] (1980) Cefadroxil 500 mg PO BID vs cefadroxil 1,000 mg PO QD vs cefadroxil 1,000 mg PO BID vs cephalexin 500 mg PO QID	DB, MC (2 trials) Patients with skin and soft-tissue infections	N=224 10 days	Primary: Clinical evaluations, microbiologic evaluations Secondary: Adverse events	Primary: In study A, improvement in clinical and bacteriologic evaluations were reported in patients treated with cefadroxil and cephalexin (100 vs 91%, respectively). In study B, improvement in clinical and bacteriologic evaluations was reported in patients treated with both cefadroxil doses and cephalexin (98 vs 97 vs 98%, respectively). Based on the studies in this MA, overall clinical and bacteriologic response to cefadroxil and cephalexin were both reported as 96%. Secondary: No significant drug-related adverse events were reported.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
In study A, participants received either cefadroxil 1,000 mg BID or cephalexin; in study B, participants received either cefadroxil 500 mg BID or 1,000 mg QD or cephalexin.				
Bucko et al.[47] (2002) Cefadroxil 500 mg PO BID vs cefditoren 200 mg PO BID vs cefditoren 400 mg PO BID vs cefuroxime 250 mg PO BID In study A, participants received cefditoren	DB, MC, PG (2 trials) Patients with uncomplicated skin and skin structure infections	N=1,685 10 days	Primary: Clinical evaluation, microbiologic evaluation Secondary: Adverse events	Primary: Clinical cure rates were reported as 85, 83, 88, and 85% for patients treated with cefditoren 200 mg, cefditoren 400 mg, cefuroxime, and cefadroxil, respectively. At seven to 14 days after treatment completion, eradication rates were higher in patients treated with cefuroxime compared to patients treated with cefditoren 200 mg in study 1 (P=0.043). At seven to 14 days after treatment completion, eradication rates were higher for cefditoren 400 mg compared to patients treated with cefadroxil in study 2 (P=0.018). Secondary: A higher rate of drug-related adverse events were reported for patients treated with cefditoren 400 mg compared to all other treatment groups (P<0.05 for each comparison). The most common adverse events were mild cases of diarrhea, nausea, and headache.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
200 mg or cefuroxime; in study B, participants received cefditoren 400 mg or cefadroxil.				
Gooch et al.[48] (1991) Cefadroxil 500 mg PO BID vs cefuroxime 250 mg PO BID vs cephalexin 500 mg PO BID	DB, MC, PG, RCT Patients with mild to moderate infections of the skin or skin structures	N=330 10 days	Primary: Clinical and bacteriological response Secondary: Adverse events	Primary: A positive clinical outcome was achieved in 97, 89, and 94% of patients treated with cefuroxime, cephalexin, and cefadroxil, respectively (P=0.047, cefuroxime vs cephalexin). A positive bacteriological outcome was achieved in 96, 85, and 93% of patients treated with cefuroxime, cephalexin, and cefadroxil, respectively (P=0.026, cefuroxime vs cephalexin). Secondary: There was no significant difference in reported drug-related gastrointestinal adverse events by patients treated with cefuroxime, cephalexin, or cefadroxil (9.3 vs 7.2 vs 9.8%, respectively).
Leder et al.[49] (1998) Cefazolin 2 g IV BID	OS, PRO Patients 18 to 90 years of age with moderate to severe cellulitis using home-based therapy	N=57 3 to 13 days	Primary: Clinical efficacy Secondary: Adverse events	Primary: Clinical cure was reported in 93% of patients treated with cefazolin; failure occurred in three patients. Secondary: Cefazolin was well tolerated.
Tack et al.[50] (1997) Cefdinir 7 mg/kg PO BID vs	DB, MC, RCT Patients aged six months to 12 years diagnosed with uncomplicated mild to moderate skin or skin-structure infec-	N=231 10 days	Primary: Clinical cure rate, microbiologic eradication rate Secondary: Adverse events	Primary: Clinical cure rates were reported as 98.3 and 93.8% in patients treated with cefdinir and cephalexin, respectively (P=0.056). Microbiologic eradication rates were reported as 99.4 and 97.4% in patients treated with cefdinir and cephalexin, respectively (P=0.14). Secondary: Drug-related adverse events were reported in 16 and 11% of patients

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
cephalexin 10 mg/kg PO QID	tion warranting systemic anti-microbial therapy and/or drainage			treated with cefdinir and cephalexin, respectively (P=0.11). The most common side effect was diarrhea.
Giordano et al.[51] (2006) Cefdinir 300 mg BID vs cephalexin 250 mg QID	MC, RCT, SB Patients ≥13 years of age with mild to moderate uncomplicated skin and skin structure infections	N=391 24 days	Primary: Clinical cure rates in clinically evaluable patients at the test-of-cure visit Secondary: Bacteriological cure, pathogen eradication rates, adverse events	Primary: There were no statistically significant differences between the treatment groups in clinical response. At the test-of-cure visit, the clinical cure rate was 89% for cefdinir and 89% for cephalexin in clinically evaluable patients (95% CI, -6.7 to 7.3) and 88% among clinically and bacteriologically evaluable patients (95% CI, –7.7 to 7.5). In the intent-to-treat analysis, cure rates were 83% for cefdinir and 82% for cephalexin. Clinical cure rates for infections caused by methicillin-susceptible and methicillin-resistant *Staphylococcus aureus* were 93 and 92%, respectively for cefdinir compared to 91 and 90%, respectively for cephalexin (P>0.999 comparing treatment groups for methicillin-susceptible *Staphylococcus aureus*; P>0.999 comparing treatments for methicillin-resistant *Staphylococcus aureus*). Secondary: The treatment groups were similar based on patient bacteriological cure rates in the clinically and bacteriologically evaluable patients: 87% for cefdinir and 86% for cephalexin in patients with any isolate at baseline. The usefulness questionnaire demonstrated that cefdinir was more highly rated in the mean composite score (87.4 vs 83.6; P=0.04), with the difference primarily due to the respondents' preference for the convenience of taking the study medication (mean score 93.5 vs 74.1 for cephalexin, P<0.001). There were no statistically significant differences between treatment groups in the patient self-assessment questionnaire, the healthcare resource utilization questionnaire, and patient diary data. Both study drugs were well tolerated. The most common treatment-related adverse events were diarrhea, (10% cefdinir, 4% cephalexin; P=0.017), nausea (3 and 6%, respectively; P=0.203), and vaginal mycosis (3% and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				6% of females, respectively; P=0.500).
Gentry et al.[52] (1989) Cefotaxime 2 g IV TID and one placebo tablet PO BID vs ciprofloxacin 750 mg PO BID and placebo IV over 30 minutes TID	DB, MC, PRO, RCT Patients with culture-confirmed skin or skin structure infections requiring hospitalization	N=461 4 to 34 days	Primary: Clinical response, bacteriologic response, overall response rate Secondary: Adverse events	Primary: For patients treated with cefotaxime, clinical response was reported as 74, 20, and 6% characterized as resolution, improvement, and failure, respectively. For patients treated with ciprofloxacin, clinical response was reported as 81, 16, and 3% characterized as resolution, improvement, and failure, respectively. For all comparisons; P=NS. Bacteriologic eradication was reported as 87 and 84% for patients treated with ciprofloxacin and cefotaxime, respectively (P=0.0123). Overall efficacy rate was reported as 76 and 75% for patients treated with ciprofloxacin and cefotaxime, respectively. Overall failure rate was higher in patients treated with cefotaxime compared to ciprofloxacin (8 vs 2%, respectively; P=0.0081). Secondary: There was no statistically significant difference in adverse events for treatment groups. However, there was a higher incidence of metabolic and nutritional systems-related events in patients treated with ciprofloxacin (0.01<P<0.05).
Stevens et al.[53] (1993) Cefpodoxime 400 mg PO BID vs cefaclor 500 mg PO TID	DB, MC, PC, RCT Patients ≥12 years of age with acute single-site skin or skin-structure infections	N=371 7 to 10 days	Primary: Clinical evaluations, microbiologic evaluations Secondary: Not reported	Primary: Both cefpodoxime and cefaclor were highly effective for the treatment of single-site skin or skin-structure infections (99% pathogen eradication and 86% cure rate). There were no significant differences in the failure rate with cefpodoxime and cefaclor. Both active drug regimens were well tolerated. Secondary: Not reported
Corey et al.[54] (2010) Aztreonam 1 g	AC, DB, MC, RCT Patients ≥18 years of age with	N=702 Variable duration	Primary: Clinical cure rate at the test-of-cure visit (eight to 15	Primary: Clinical cure rates were similar for ceftaroline and vancomycin plus aztreonam in the clinically evaluable (91.1 vs 93.3%; 95% CI, -6.6 to 2.1) and modified intent-to-treat (86.6 vs 85.6%; 95% CI, -4.2 to 6.2)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
plus vancomycin 1 g every 12 hours for 5 to 14 days vs ceftaroline 600 mg every 12 hours for 5 to 14 days	complicated skin or skin structure infections who required ≥5 days of parenteral antibacterial therapy		days after administration of the last dose of study medication) in the clinically evaluable and modified intent-to-treat populations Secondary: Microbiological success rate, safety	populations, respectively. Secondary: The clinical cure rate for methicillin-resistant *Staphylococcus aureus* complicated skin or skin structure infections were 95.1% for ceftaroline and 95.2% for vancomycin plus aztreonam. Similar cure rates were found in patients with methicillin-susceptible *Staphylococcus aureus* (91.3 and 94.6%), as well as in the patients from whom Gram-negative pathogens were isolated. The microbiological success rate was similar for ceftaroline and vancomycin overall, and for methicillin-resistant *Staphylococcus aureus*. Among the microbiologically evaluable patients, the baseline pathogen(s) was eradicated or presumed eradicated at similar rates in both the microbiologically evaluable and modified intent-to-treat populations (91.8 and 86.3% for ceftaroline; 92.5 and 83.7% for vancomycin plus aztreonam; 95% CI, -5.7 to 4.4 and 95% CI, -3.4 to 8.9, respectively). The incidence of adverse events was similar in both study groups. The majority of adverse events were mild in severity and similar in type among study groups. Diarrhea occurred in 3.4 vs 3.2% of patients in the ceftaroline and vancomycin plus aztreonam treatment groups, respectively.
Wilcox et al.[55] (2010) Aztreonam 1 g plus vancomycin 1 g every 12 hours for 5 to 14 days vs ceftaroline 600 mg every 12 hours for 5 to 14 days	AC, DB, MC, RCT Patients ≥18 years of age with complicated skin or skin structure infections who required ≥5 days of parenteral antibacterial therapy	N=694 Variable duration	Primary: Clinical cure rate at the test-of-cure visit (eight to 15 days after administration of the last dose of study medication) in the clinically evaluable and modified intent-to-treat populations Secondary:	Primary: Cure rates at test-of-cure were comparable in both treatment groups across all study populations. In the clinically evaluable population, cure rates were 92.2 and 92.1% for ceftaroline and vancomycin plus aztreonam, respectively (95% CI, -4.4 to 4.5). In the modified intent-to-treat population, clinical cure rates for ceftaroline and vancomycin plus aztreonam were similar (85.1 vs 85.5%, respectively; 95% CI, -5.8 to 5.0). Secondary: In patients with methicillin-resistant *Staphylococcus aureus* isolated at baseline, cure rates were 91.4 and 93.3% for ceftaroline and vancomycin plus aztreonam, respectively. Similar cure rates were found in patients with methicillin-susceptible *Staphylococcus aureus* (94.4% in both groups) as well as in the patients from whom a Gram-negative pathogen

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Microbiological success rate, safety	was isolated. Baseline pathogens were eradicated or presumed eradicated at similar rates in both the microbiologically evaluable and modified intent-to-treat populations among Gram-positive and a limited number of Gram-negative pathogens (92.9 and 86.6% for ceftaroline; 95.0 and 88.4% for vancomycin plus aztreonam; 95% CI, -6.9 to 2.5 and 95% CI, -7.5 to 3.9, respectively). There were no microbiological reinfections or recurrences at the late follow-up visit in either treatment group. The incidence of adverse events was similar in both study groups. The majority of adverse events were mild in severity and similar in type among study groups. Diarrhea occurred in 6.5 vs 4.4% in the ceftaroline and vancomycin plus aztreonam treatment groups, respectively. Adverse events considered related to the study drug and occurring in ≥3% of patients were diarrhea and pruritus.
Corey et al.[56] (2010) Aztreonam 1 g plus vancomycin 1 g every 12 hours for 5 to 14 days vs ceftaroline 600 mg every 12 hours for 5 to 14 days	Pooled analysis (2 trials) Patients ≥18 years of age with complicated skin or skin structure infections who required ≥5 days of parenteral antibacterial therapy	N=1,378 Variable duration	Primary: Clinical cure rate at the test-of-cure visit (eight to 15 days after administration of the last dose of study medication) in the clinically evaluable and modified intent-to-treat populations Secondary: Microbiological success rate, safety	Primary: Clinical cure rates were similar for ceftaroline and vancomycin plus aztreonam in the clinically evaluable (91.6 vs 92.7%) and modified intent-to-treat (85.9 vs 85.5%) populations, respectively. Secondary: Clinical cure rates were similar for ceftaroline and vancomycin plus aztreonam in patients infected with methicillin-resistant *Staphylococcus aureus* (93.4 vs 94.3%). The efficacy of ceftaroline and vancomycin plus aztreonam against polymicrobial and monomicrobial infections was similar. Clinical relapse at the late follow-up visit was noted in 1.1% of patients in the ceftaroline group compared to 0.9% of patients in the vancomycin plus aztreonam group (clinically evaluable). Favorable microbiological response (microbiologically evaluable) was observed in 92.3% of patients in the ceftaroline group compared to 93.7%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				of patients in the vancomycin plus aztreonam group (95% CI, -4.8 to 2.0). Incidences of treatment-emergent adverse events were similar among the treatment groups. Diarrhea occurred in 4.9% of patients in the ceftaroline group and in 3.8% of patients in the vancomycin plus aztreonam group (modified intent-to-treat population). Adverse events considered to be related to study drug in ≥3% of patients were pruritus, nausea, and diarrhea.
Gentry et al.[57] (1989) Ceftazidime 2 g IV every 8eight hours vs ciprofloxacin 200 mg IV every 12 hours, then ciprofloxacin 750 mg PO every 12 hours	PRO, RCT Patients with serious infections of the skin and skin structures caused by gram-negative organisms	N=51 19 to 25 days	Primary: Cure rate Secondary: Adverse events	Primary: Cure rate was reported as 75 and 58% in patients treated with ciprofloxacin and ceftazidime, respectively (P<0.05). Bacteriologic cure was reported as 78 and 72% in patients treated with ciprofloxacin and ceftazidime, respectively. Superinfection was reported as 28 and 11% in patients treated with ciprofloxacin and ceftazidime, respectively (0.01<P<0.05). Secondary: Adverse events were reported in 6 and 5% of patients treated with ciprofloxacin and ceftazidime, respectively.
Eron et al.[58] (1983) Ceftriaxone 1 g IV BID vs ceftriaxone 2 g IV QD (children ≤15 years old: 50 mg/kg/day in divided doses)	PRO, XO Patients two to 86 years of age with bone or soft tissue infection	N=100 3 to 56 days	Primary: Clinical response Secondary: Adverse events	Primary: Positive clinical response was reported as 91% of patients for both the twice-daily and once-daily treatment groups; 89 vs 94%, respectively. Failed therapy was reported in nine patients caused by resistance, superinfection, or an underlying disease. IV therapy was continued in 41 patients in the outpatient setting. Secondary: Ten percent of patients treated with ceftriaxone reported diarrhea; of these, three patients required discontinuation of treatment.
Khawcharoenporn et al.[59]	RETRO	N=405	Primary: Treatment success	Primary: The overall treatment success rate with SMX-TMP was significantly

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2010) SMX-TMP one double strength tablet BID vs cephalexin 500 mg QID vs clindamycin 300 mg QID	Patients ≥18 years of age with cellulitis	Variable duration	rate, compliance, safety Secondary: Not reported	higher than the success rate with cephalexin (91 vs 74%; P<0.001). Clindamycin success rate was higher than that of cephalexin but did not reach statistical significance (85 vs 74%; P=0.22). The success rates of SMX-TMP and clindamycin were comparable. The treatment success rate with SMX-TMP was significantly more successful than cephalexin in patients who were male (P=0.001), were Pacific Islanders (P=0.001), had diabetes mellitus (P=0.001), were obese (P=0.002), had positive cultures for methicillin-resistant *Staphylococcus aureus* (P=0.01), and were cigarette smokers (P=0.04). The treatment success rate with clindamycin was higher than with cephalexin in patients who had methicillin-resistant *Staphylococcus aureus* infections (P<0.01), had moderately severe cellulitis (P<0.03), and were obese (P<0.04). MRSA was recovered in 62% of positive culture specimens. Compliance and adverse drug reaction rates were not significantly different among patients who received these three antibiotics. Factors associated with treatment failure included therapy with an antibiotic that was not active against community-associated methicillin-resistant *Staphylococcus aureus* (P<0.001) and severity of cellulitis (P<0.001). Secondary: Not reported
Genitourinary Infections				
Leigh et al.[60] (2000) Cefaclor 250 PO TID vs	DB, MC, PG, RCT Patients ≥13 years of age with uncomplicated urinary tract infections	N=383 5 days	Primary: Clinical and microbiologic efficacy Secondary: Adverse events	Primary: A greater number of pathogens were resistant to treatment with cefaclor compared to cefdinir (6.7 vs 3.7%, respectively; P<0.003). Isolates of *Escherichia coli* were more resistant to treatment with cefaclor compared to cefdinir (5.1 vs 2.0%, respectively; P<0.007). At five to nine days post treatment, patients treated with cefdinir and cefaclor reported statistically equivalent clinical (91.3 vs 93.0%,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
cefdinir 100 mg PO BID				respectively; P=0.539) and microbiologic (84.7 vs 79.7%, respectively; P=0.184) response rates. Secondary: Drug-related side effects were greater in patients treated with cefdinir compared to patients treated with cefaclor (20.2 vs 13.0%, respectively; P=0.025).
Christenson et al.[61] (1991) Cefaclor 250 mg PO TID vs cefprozil 500 mg PO QD	OL, RCT Patients ≥18 years of age with acute, uncomplicated urinary tract infection	N=98 10 days	Primary: Clinical efficacy, bacteriologic efficacy Secondary: Adverse events	Primary: Clinical efficacy was reported as 87 and 78% in patients treated with cefprozil and cefaclor, respectively (P=NS). Bacteriologic eradication was reported as 80 and 82% in patients treated with cefprozil and cefaclor, respectively (P=NS). Secondary: Leukopenia and nausea was more commonly reported by patients treated with cefprozil though the difference is not statistically significant (P=0.08 and P=0.07, respectively).
Bolding et al.[62] (1980) Cefadroxil 1,000 mg PO BID vs cephalexin 500 PO mg QID	DB, RCT Females 18 to 63 years of age with urinary tract infections	N=26 10 to 13 days	Primary: Clinical cure rate Secondary: Adverse event	Primary: Clinical cure rates were achieved in 100 and 92% of patients treated with cephalexin and cefadroxil, respectively, within five to nine days. One patient treated with cefadroxil was not cured due to an *Escherichia coli* urinary tract infection. Secondary: One patient taking cefadroxil reported side effects of nausea and vomiting which may be associated with concurrent therapy with propoxyphene-acetaminophen. Patients treated with cefadroxil reported less vaginal itching or irritation compared to patients treated with cephalexin.
Madsen et al.[63] (1981) Cefazolin 1,000 mg IM every eight hours vs	2 RCT Males aged 83 to 89 years with complicated urinary tract infections	N=91 7 to 10 days	Primary: Clinical cure rate Secondary: Adverse events	Primary: One week after treatment completion, clinical cure rates were reported as 71 and 60% in patients treated with cefotaxime and cefazolin, respectively. One week after treatment completion, clinical cure rates were reported as 64 and 59% in patients treated with cefotaxime 500 and 1,000 mg, respectively. No significant difference was found between the two groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
cefotaxime 500 mg IM every eight hours vs cefotaxime 1,000 mg IM every eight hours In study A, participants received one or two doses of cefotaxime; in study B, participants received cefotaxime 500 mg or cefazolin.				Secondary: Both treatments were well-tolerated by study participants.
Sanchez-Ramos et al.[64] (1995) Cefazolin 2 g IV every eight hours vs ceftriaxone 1 g IV QD and normal saline IV every eight hours from the ceftriaxone dose for two doses	DB, MC, RCT Pregnant patients with acute pyelo-nephritis confirmed by chill symptoms, costovertebral angle tenderness, urinalysis showing bacteria and white cells	N=178 48 hours to 10 days	Primary: Febrile morbidity, length of hospital stay, treatment failures Secondary: Not reported	Primary: There was no statistically significant difference between patients treated with ceftriaxone and cefazolin in terms of mean length of hospital stay (3.7 vs 4.0 days, respectively), temperature (101 vs 101.4 degrees F, respectively), length of fever (1.0 vs 1.3 days, respectively), or required IV doses (8.1 vs 8.8. doses, respectively; P=NS). Treatment failures were reported in 5.7 and 3.3% of patients treated with cefazolin and ceftriaxone, respectively (P=0.71). Secondary: Not reported
Iversen et al.[65] (1981)	PRO, RCT	N=58	Primary: Therapeutic	Primary: After one day of treatment, 97% of patients reported negative urine

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cefazolin 1 g IM every eight hours vs cefuroxime 0.75 g IM every eight hours	Males 38 to 91 years of age with urinary tract infections associated with benign hyperplasia of the prostate, carcinoma of the prostate or bladder, or urethral stricture	5 to 10 days	efficacy Secondary: Adverse events	cultures for both treatment groups; one week after treatment completion, 62 and 63% of cultures were negative for patients treated with cefuroxime and cefazolin, respectively; P=NS. Secondary: Minor pain at the injection site was the most common adverse event reported. Both treatments were well tolerated.
Newton et al.[66] (1993) Cefepime 2 g IM (or by a 30-minute IV infusion) BID vs cefotaxime 2 g IM (or by a 30-minute IV infusion) TID	MC, OL, RCT Female patients ≥18 years of age with acute obstetric and gynecological infections	N=131 2 to 10 days	Primary: Clinical response, microbiological eradication, overall response Secondary: Adverse events	Primary: Satisfactory clinical response was reported in 85 and 83% of patients treated with cefepime and cefotaxime, respectively (P=0.802); microbiological eradication was reported as 81 and 86%, respectively (P=0.379). Overall response of effective, partially effective, and ineffective was reported as 77, 13 and 11%, respectively, in patients treated with cefepime; for patients treated with cefotaxime, percentages of 75, 19, and 6%, respectively, were reported for overall response. Secondary: Drug-related adverse events were reported in 6 and 1% of patients treated with cefepime and cefotaxime, respectively (P=0.342). Drug-related discontinuation of therapy was reported in five and one patient(s) treated with cefepime and cefotaxime, respectively (P=0.476).
Gentry et al.[67] (1991) Cefepime 2 g IV BID vs ceftazidime 2 g IV every eight hours	OL, PRO, RCT Patients with skin or wound infections and complicated nosocomial urinary tract infections	N=112 4 to 28 days	Primary: Clinical efficacy, microbiologic eradication Secondary: Adverse events	Primary: Relative to skin/skin structure and wound infections, clinical efficacy was reported as 90 and 96% of patients treated with cefepime and ceftazidime, respectively (P=0.68); microbiologic eradication rate was reported as 94 and 95%, respectively. Relative to nosocomial urinary tract infections, clinical efficacy was reported as 84 and 88% of patients treated with cefepime and ceftazidime, respectively (P=1.0); microbiologic eradication was reported as 100 and 95%, respectively. Secondary: Both treatments were well tolerated. Increased serum creatinine and diarrhea were the only mild adverse events reported.
Arrieta et al.[68]	MA	N=521	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2001) Cefepime 50 mg/kg IV every eight hours vs cefepime 50 mg/kg IV every 12 hours vs ceftazidime 50 mg/kg IV every eight hours vs cefotaxime 30 mg/kg IV every six hours In studies A and B, participants received either cefepime or ceftazidime every eight hours. In study C, D, and E, participants received either cefepime every eight hours or cefepime every 12 hours or	Patients one month to 18 years of age with serious urinary tract infections, including pyelonephritis	(5 trials) 2 to 14 days	Clinical efficacy, microbiologic efficacy Secondary: Adverse events	In study A, clinical efficacy was reported as 98 and 96% for patients treated with cefepime and ceftazidime, respectively; at treatment completion, bacteriologic eradication was reported as 96 and 94%, respectively. In study B, clinical efficacy was reported as 97 and 100% for patients treated with cefepime and ceftazidime, respectively; bacteriologic eradication was reported as 95 and 92%, respectively. In studies C, D, and E, overall clinical efficacy was reported as 91 and 100% in patients treated with cefepime and cefotaxime, respectively; bacteriologic eradication was reported as 94 and 100%, respectively. Secondary: In study A, there was no statistically significant difference in drug-related adverse events between treatment groups (P=0.40). In studies D and E, both treatment regimens were well tolerated. The most commonly reported adverse events were gastrointestinal in nature.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
cefotaxime.				
Ho et al.[69] (2001) Cefixime 200 mg PO BID vs ceftibuten 200 mg PO BID	OL, PRO, RCT Patients ≥18 years of age with complicated urinary tract infections	N=45 10 to 14 days	Primary: Clinical efficacy rate, bacteriological eradication rate Secondary: Adverse events	Primary: There was no statistically significant difference in rates of clinical efficacy (78.3 vs, 77.3%; P=0.9) and bacteriological eradication (52.2 and 63.6%; P=0.08) for patients taking ceftibuten and cefixime, respectively. Secondary: Adverse events were minimal for both treatment groups. Patients treated with ceftibuten reported diarrhea and increased transaminase serum levels; patients treated with cefixime reported skin rash and increased transaminase serum levels.
Tripi et al.[70] (1985) Cefotaxime 0.5 to 1 g IV/IM BID vs ceftizoxime 0.5 to 1 g IV/IM BID	DB, PRO, RCT Patients with acute or chronic urinary tract infections	N=80 10 days	Primary: Therapeutic efficacy Secondary: Adverse events	Primary: For either the ceftizoxime and cefotaxime study groups, clinical responses classified as excellent, good, or fair were reported as 90, 7.5 and 2.5%, respectively. Secondary: Excellent tolerance rates to ceftizoxime and cefotaxime were reported as 100 and 97.5%, respectively.
Mårild et al.[71] (2009) SMX-TMP 3-15 mg/kg PO suspension BID for 10 days vs ceftibuten 9 mg/kg PO suspension QD for 10 days	MC, OL, RCT Patients 1 month to 12 years of age with a first-time febrile urinary tract infections	N=547 14 to 20 days	Primary: Bacteriological and clinical outcomes Secondary: Not reported	Primary: In the intention-to-treat population, the bacteriological elimination rates in the ceftibuten and SMX-TMP groups were 91 and 95%, respectively (P=NS). In the per protocol population, the bacteriological elimination rates in the ceftibuten and SMX-TMP groups were 91 and 97%, respectively (P<0.01). In the intention-to-treat population, the clinical cure rates among patients treated with ceftibuten and SMX-TMP were 93 and 83%, respectively (P=0.008). In the per protocol population, the clinical cure rates were 93 and 90%, respectively (P=NS).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Adverse events were reported by 3% of the patients in the ceftibuten group and by 5% in the SMX-TMP group (P=NS). Gastrointestinal symptoms were reported most frequently. There were no serious adverse events reported. Secondary: Not reported
Vazquez et al.[72] (2012) Ceftazidime–avibactam (500-125 mg) every eight hours vs imipenem–cilastatin (500 mg) every six hours Patients meeting pre-specified improvement criteria after four days could be switched to oral ciprofloxacin. Patients were treated for a total of seven to 14 days.	DB, MC, PRO, RCT Patients 18 to 90 years of age with complicated urinary tract infection due to Gram-negative pathogens	N=137 Microbiologi-cally evaluable patients=62 12 to 23 days	Primary: Favorable microbiological response at the test-of-cure visit five to nine days post-therapy in microbiologically evaluable patients Secondary: Microbiological response at the end of IV therapy and at the late follow-up visit, four to six weeks post-therapy in the microbiologically evaluable population; safety and tolerability	Primary: Favorable microbiological response in the microbiologically evaluable population at the test-of-cure visit was observed in 19/27 (70.4%) patients in the ceftazidime–avibactam arm and 25/35 (71.4%) in the imipenem–cilastatin arm (observed difference −1.1% [95% CI, −27.2 to 25.0%]). Secondary: Favorable microbiological response rates at the end of IV therapy were 25/26 (96.2%) and 34/34 (100%) in the ceftazidime–avibactam and imipenem–cilastatin arms, respectively, and 15/26 (57.7%) and 18/30 (60.0%) at the late follow-up visit. Over the course of the study, adverse events were reported in 46/68 (67.6%) patients in the ceftazidime–avibactam arm and 51/67 (76.1%) patients in the imipenem–cilastatin arm. The most common adverse events in both treatment arms included constipation, diarrhea, abdominal pain, headache, anxiety, and injection/infusion site reactions. Treatment-emergent serious adverse events were reported in 6/68 (8.8%) and 2/67 (3.0%) of patients in the ceftazidime–avibactam and imipenem–cilastatin arms, respectively, during the course of the study. Three of the serious adverse events in the ceftazidime–avibactam arm were considered to be drug-related: renal failure, diarrhea, and accidental overdose of ceftazidime–avibactam. Although the accidental overdose of ceftazidime–avibactam was recorded as a serious adverse event, there were no adverse events associated with this event. One patient in the imipenem–cilastatin arm developed a drug-related serious adverse event associated with an increase in serum creatinine level.
Goldstein et al.[73] (1991)	DB, PRO Adult heterosexual	N=204 1 day	Primary: Clinical cure	Primary: At seven to 10 days post-treatment, all patients in both treatment groups achieved cure (100%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ceftizoxime 250 mg IM for one dose vs ceftriaxone 250 mg IM for one dose	male inmates with documented uncomplicated urethral gonorrhea		Secondary: Adverse events	Secondary: No adverse events were reported.
Wagenlehner et al.[74] (2015) ASPECT-cUTI ceftolozane-tazobactam 1.5 g IV every eight hours for seven days vs levofloxacin 750 mg IV QD for seven days	DB, DD, NI, RCT Hospital inpatients ≥18 years of age who had pyuria and a diagnosis of a complicated lower-urinary-tract infection or pyelonephritis	N=800 12 to 16 days	Primary: Difference in composite cure rates at the test-of-cure visit in the microbiological modified intention to treat population Secondary: Difference in composite cure rates at the test-of-cure visit in the per-protocol population	Primary: Ceftolozane-tazobactam was non-inferior to levofloxacin for composite cure in the microbiological modified intention to treat population (ceftolozane-tazobactam, 306/398 [76.9%] vs levofloxacin, 275/402 [68.4%]; 95% CI, 8.5 [2.3 to 14.6]). Secondary: Ceftolozane-tazobactam was non-inferior to levofloxacin for composite cure in the per-protocol population (ceftolozane-tazobactam, 284/341 [83.3%] vs levofloxacin, 266/353 [75.4%]; 95% CI, 8.0 [2.0 to 14.0]).
Cooper et al.[75] (1992) Cefuroxime 125 mg PO BID vs cephradine 500 mg PO BID	PRO, RCT Patients ≥17 years of age with dysuria or frequency and diagnosed urinary tract infection	N=113 7 days	Primary: Clinical cure, bacteriological cure Secondary: Adverse events	Primary: At seven days post-treatment, clinical cure rates were reported as 56 and 81% in patients treated with cephradine and cefuroxime, respectively (P<0.05). Bacteriological cure at one week post-treatment and five weeks post-treatment were reported as 97 and 96%, respectively, for both study groups (P>0.05). Secondary: Fourteen percent and 6% of patients treated with cephradine and cefuroxime, respectively, reported adverse events; patients receiving cefuroxime reported a higher incidence of increased frequency of bowel movements (35.0 vs 17.5%, respectively; P<0.05).
Ziogos et al.[76]	RCT	N=176	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2010) Cefuroxime 1.5 g IV as a single dose vs ampicillin-sulbactam 3 g IV as a single dose	Women scheduled for cesarean delivery	30 days	Development of an infection Secondary: Not reported	Postoperative infections developed in 5.9% of patients receiving cefuroxime and 8.8% of patients receiving ampicillin-sulbactam (P=0.6). In univariate analyses six or more vaginal examinations prior to the operation (P=0.004), membrane rupture for more than six hours (P=0.08) and blood loss greater than 500 mL (P=0.018) were associated with developing a postoperative surgical site infection. In logistic regression having 6 or more vaginal examinations was the most significant risk factor for a postoperative surgical site infection (OR, 6.8; 95% CI, 1.4 to 33.4; P=0.019). Regular prenatal follow-up was associated with a protective effect (OR, 0.04; 95% CI, 0.005 to 0.36; P=0.004). Patients that developed an infection had a lengthier hospital stay (median of five vs four days; P<0.001). All patients with an infection responded well to subsequent antibiotics. No adverse drug reactions were reported. Secondary: Not reported
Friman et al.[77] (1989) Aztreonam 1 g IV every eight hours vs cefuroxime 1.5 g IV every eight hours	RCT Patients 18 to 99 years of age with symptoms of an upper urinary tract infection	N=171 1 month	Primary: Clinical response rates, bacteriologic response rates Secondary: Not reported	Primary: Clinical response rates were 89% in the aztreonam group and 87% in the cefuroxime group. Bacteriologic response rates at one week post-therapy were 70% in the aztreonam group and 73% in the cefuroxime group, while rates at one month were 43 and 40% respectively. Secondary: Not reported
Respiratory Infections—Upper Respiratory Tract				
Randolph et al.[78] (1988)	PRO, RCT Patients between	N=250 10 days	Primary: Clinical evaluation,	Primary: On day 14 (P=0.020) and days 21 to 28 (P=0.043), a greater number of patients treated with cefadroxil had good therapeutic response to therapy

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cefaclor 20 mg/kg PO TID vs cefadroxil 30 mg/kg PO QD	three and 21 years of age with clinical signs and symptoms of acute group A β-hemolytic streptococcal pharyngitis		microbiologic evaluations Secondary: Adverse event	compared to patients treated with cefaclor. Patients treated with cefadroxil had a lower failure or clinical recurrence compared to patients treated with cefaclor (4.6 vs 22.1%, respectively). Secondary: No significant drug-related adverse event reported.
Piippo et al.[79] (1991) Cefaclor 40 mg/kg/day PO divided BID vs cefixime 8 mg/kg/day PO divided BID	DB, PG, RCT Pediatric patients six months to 12 years of age with acute otitis media	N=345 7 days	Primary: Clinical cure Secondary: Adverse events	Primary: At days 10 to 12, clinical cure was reported in 93.5 and 90.5% of patients treated with cefixime and cefaclor, respectively (P=0.081). At days 28 to 35, clinical cure was reported in 90.1 and 86.6% of patients treated with cefixime and cefaclor, respectively (P=0.12). Secondary: Adverse events were reported in 17.9 and 10.6% of patients treated with cefixime and cefaclor, respectively.
Gehanno et al.[80] (1990) Cefaclor 500 mg PO TID vs cefpodoxime 200 mg PO BID	DB, MC, PC, PRO, RCT Adult outpatients with acute sinusitis	N=236 Mean days 9.9	Primary: Clinical cure, overall clinical efficacy (cure and improvement), bacteriological eradication Secondary: Adverse events	Primary: At the end of the treatment, clinical cure was reported as 84 and 68% of patients treated with cefpodoxime and cefaclor, respectively (P=0.01). Overall clinical efficacy was reported as 95 and 93% of patients treated with cefpodoxime and cefaclor, respectively (P=NS). Bacteriological eradication was reported as 95 and 91% in patients treated with cefpodoxime and cefaclor, respectively (P=NS). Secondary: Possible drug-related adverse events were reported in nine and 10 patients treated with cefpodoxime and cefaclor, respectively.
MacLoughlin et al.[81] (1996) Cefaclor suspension 40 mg/kg/day PO	MC, OL, RCT Pediatric patients one month to 11 years of age with acute otitis media	N=167 5 days	Primary: Clinical efficacy Secondary: Adverse events	Primary: Clinical success was reported as 93.6 and 91.6% of patients treated with cefpodoxime and cefaclor, respectively (P >0.05); at study day 30, clinical recurrence was reported as 99 and 94%, respectively (P>0.05). Secondary: Patients were able to tolerate both cefpodoxime and cefaclor (99 vs 94%,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
divided TID vs cefpodoxime suspension 10 mg/kg/day PO divided BID				respectively; P>0.05).
Blumer et al.[82] (1995) Cefaclor 40 mg/kg/day PO in three divided doses (maximum 1 g/day) vs ceftibuten 9 mg/kg/day PO for 1 dose (maximum 400 mg/day)	MC, RCT, SB Pediatric patients aged three months to 17 years with acute otitis media	N=154 10 days	Primary: Clinical cure Secondary: Adverse events	Primary: At one to three days post-treatment, clinical cure was reported in 89 and 88% of patients treated with ceftibuten and cefaclor, respectively (P=NS). At two to four weeks post-treatment, clinical cure was reported in 88 and 82% of patients treated with ceftibuten and cefaclor, respectively (P=NS). Secondary: Mild to moderate drug-related adverse events were reported in 8 and 14% of patients treated with ceftibuten and cefaclor, respectively.
Block et al.[83] (2000) Cefdinir 14 mg/kg/day PO divided BID (for five days) vs cefprozil 30 mg/kg/day PO divided BID (for 10 days)	DB, MC, PRO Pediatric patients six months to 12 years of age with acute otitis media	N=373 5 to 10 days	Primary: Clinical cure Secondary: Adverse events	Primary: At the end of therapy (study days nine to 11), clinical efficacy was reported as 80.0 and 82.5% in patients treated with cefdinir and cefprozil (P= NS). Secondary: Diarrhea and overall adverse events were reported in cefdinir-treated patients (7.8 and 13.0%, respectively) and cefprozil-treated patients (4.2 and 12.0%, respectively; P=0.116).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Asmar et al.[84] (1994) Cefixime oral suspension 8 mg/kg/day PO QD vs cefpodoxime oral suspension 10 mg/kg/day PO QD	DB, MC, PRO, RCT Patients two months to 17 years of age with acute suppurative otitis media	N=368 10 days	Primary: Clinical evaluations, microbiologic evaluations Secondary: Adverse events	Primary: On days 12 through 15, clinical cure or improvement was reported in 83 and 81% of patients treated with cefpodoxime and cefixime, respectively (P=0.541). On days 12 to 15, end-of-therapy response rates were reported as 53 and 51% in patients treated with cefpodoxime and cefixime, respectively (P=0.404). Overall microbiologic susceptibility was reported as 89 and 86% in patients treated with cefpodoxime and cefixime, respectively (P=0.70). Secondary: Drug-related adverse effects (e.g., diarrhea, diaper rash, vomiting, and rash) occurred in 23.3 and 17.9% of patients taking cefpodoxime and cefixime, respectively.
Respiratory Infections—Lower Respiratory Tract				
ZeLuff et al.[85] (1986) Cefaclor 500 mg PO every eight hours vs cefadroxil 1 g PO every 12 hours	PRO, RCT Black African gold miners 13 to 59 years of age with pneumococcal pneumonia confirmed by culture/serology	N=103 10 days	Primary: Clinical evaluations, microbiologic evaluations Secondary: Adverse events	Primary: Clinical cure was reported as 94% of patients treated with either cefadroxil or cefaclor. Microbiologic cure was reported in 98 and 96% of patients treated with cefadroxil and cefaclor, respectively. Secondary: One patient treated with cefaclor withdrew from the study due to severe diarrhea. Otherwise, minimal side effects were reported for both therapies.
Drehobl et al.[86] (1997) Cefaclor 500 mg PO TID vs cefdinir 300 mg	DB, MC, RCT Patients with community acquired-pneumonia	N=538 10 days	Primary: Clinical response, microbiological eradication Secondary: Adverse events	Primary: Satisfactory clinical response was reported as 89 and 86% of patients treated with cefdinir and cefaclor, respectively; microbiological eradication was reported as 92 and 93%, respectively. For all comparisons, P=NS. Secondary: Patients taking cefdinir reported a higher incidence of diarrhea compared to patients treated with cefaclor (13.7 vs 5.3%, respectively; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
PO BID				
Phillips et al.[87] (1993) Cefaclor 250 mg PO TID vs cefpodoxime 200 mg PO BID	DB, MC, RCT Patients with signs and symptoms of acute bacterial exacerbation of chronic obstructive pulmonary disease	N=301 10 days	Primary: Clinical evaluations, microbiologic evaluations Secondary: Adverse events	Primary: There were no statistically significant differences between cefpodoxime and cefaclor in the eradication of the original pathogen (91 vs 92%, respectively) or in clinical response at three to seven days post-treatment (99 vs 92%, respectively). More bacterial isolates were susceptible to cefpodoxime compared to cefaclor (91 vs 84%, respectively; P<0.001). Secondary: There were no significant differences between cefpodoxime and cefaclor in adverse events (11 vs 12%, respectively).
Chirurgi et al.[88] (1991) Cefaclor 250 mg PO every eight hours vs ceftibuten 400 mg PO QD	PRO, RCT Patients with acute bronchitis, not pneumonia	N=45 7 to 14 days	Primary: Clinical efficacy, bacteriologic efficacy Secondary: Adverse events	Primary: Clinical efficacy was reported as 87.5 and 92.3% of patients treated with ceftibuten and cefaclor, respectively. Bacteriologic efficacy was reported as 87.5 and 80.0% of patients treated with ceftibuten and cefaclor, respectively. Secondary: The rates of adverse events were reported as 7.9 and 5.6% in patients treated with ceftibuten and cefaclor, respectively.
Blaser et el.[89] (1983) Cefadroxil 500 mg PO BID vs cephalexin 250 mg PO QID	PRO, RCT Patients 19 to 92 years of age with community-acquired pneumonia of mild to moderate severity	N=34 10 days	Primary: Clinical evaluation, microbiologic evaluation Secondary: Adverse events	Primary: All 34 cases achieved clinical cure; no additional information in regards to differences in clinical cure rates were reported between cefadroxil and cephalexin. Clearing of chest exam findings were reported in 79 and 73% of patients treated with cefadroxil and cephalexin, respectively. Secondary: Drug-related adverse effects were minimal.
Fogarty et al.[90] (2000)	DB, MC, PRO, RCT	N=281 5 to 10 days	Primary: Clinical evaluations,	Primary: The observed clinical cure rate among cefdinir-treated patients was 80% compared to 72% of cefprozil-treated patients (95% CI, -1.6 to 18.3).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cefdinir 300 mg PO BID (for five days) vs cefprozil 500 mg PO BID (for 10 days)	Patients with acute exacerbations of chronic bronchitis		microbiologic evaluations Secondary: Adverse events	The overall rates of microbiological eradication of pathogens were 81% for cefdinir-treated patients and 84% for cefprozil-treated patients (95% CI, –10.0 to 5). Secondary: Safety of the drugs was analyzed for all patients who received study medication. Of these patients, 95 (34%) patients receiving cefdinir and 89 (33%) patients receiving cefprozil experienced at least one adverse event during treatment (P=0.90). The most frequent adverse events on therapy for both cefdinir- and cefprozil-treated patients were diarrhea and headache. Seventeen percent of cefdinir-treated patients and 6% of cefprozil-treated patients experienced diarrhea during treatment (P<0.01).
Alvarez-Sala et al.[91] (2006) Cefditoren 200 mg PO BID (for five days) vs cefuroxime 250 mg PO BID (for 10 days)	DB, DD, PG, RCT Patients ≥18 years of age with acute exacerbations of chronic bronchitis	N=541 5 to 10 days	Primary: Clinical evaluation, bacteriologic evaluation Secondary: Adverse events	Primary: On day 11, clinical success rate was reported as 79.9 and 82.7% for patients treated with cefditoren and cefuroxime, respectively (P=NS). On day 30, clinical success rate was reported as 81.0 and 85.5% for patients treated with cefditoren and cefuroxime, respectively (P=NS). On day 11, bacteriological response was reported as 72.8 and 67.0% for patients treated with cefditoren and cefuroxime, respectively (P=NS). Secondary: Drug-related adverse events were reported in 7.7 and 11.4% of patients treated with cefditoren and cefuroxime, respectively.
Leophonte et al.[92] (1993) Cefepime 1 g IV/IM BID vs ceftazidime 1 g	AC, MC, OL, RCT Adult patients with moderate to severe community-acquired lower respiratory tract infections	N=111 1 to 15 days	Primary: Clinical cure rate, pathogen eradication rate Secondary: Adverse events	Primary: Clinical cure was reported in 87 and 86% of patients treated with cefepime and ceftazidime, respectively (P=0.8); pathogen eradication rates were reported as 95% for both treatment groups (P=0.7). Secondary: Both treatments were well tolerated and a similar incidence of adverse events.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
IV/IM TID				
Grossman et al.[93] (1999) Cefepime 2 g every 12 hours vs ceftriaxone 1 g every 12 hours	DB, MC, PRO, RCT Patients ≥65 years of age who had been admitted to the hospital after being diagnosed with community-acquired pneumonia	N=151 3 to 14 days	Primary: Clinical response, bacteriologic eradication Secondary: Adverse events	Primary: Clinical response was reported as 79.1 and 75.4% in patients treated with cefepime and ceftriaxone, respectively (P=0.62). Relative to evaluable study participants, all but one patient treated with cefepime achieved bacteriologic eradication. Secondary: There was no statistically significant difference in the incidence of adverse events reported by patients treated with either cefepime or ceftriaxone (76.3 vs 84.0%, respectively; P=0.24). Diarrhea was the most common adverse event reported in patients treated with cefepime and ceftriaxone (five vs two patients, respectively).
Bradley et al.[94] (2001) Cefepime 50 mg/kg IV every eight hours (maximum 6 g/day) vs cefepime 50 mg/kg IV every 12 hours (maximum 4 g/day) vs cefotaxime 120 mg/kg/day IV in four divided doses (maximum 4.5 g/day)	4 trials MC, OL, RCT Pediatric patients two months to 18 years of age with serous lower respiratory tract infections	N=646 Up to 21 days	Primary: Clinical efficacy, bacteriologic efficacy Secondary: Adverse events	Primary: In study A, clinical efficacy was reported as 91% for patients treated with cefepime; bacteriologic eradication was 93%. In study B, clinical efficacy, at the end of treatment, was reported as 100% for patients treated with cefepime and cefuroxime; bacteriologic eradication was also reported as 100%. The study consisted of 10 evaluable study participants. In study C, clinical efficacy was 100% for patients treated with either cefepime or cefotaxime; bacteriologic eradication was reported in 75% and 100% of patients treated with cefepime and cefotaxime, respectively. The study consisted of 13 evaluable study participants. In study D, clinical efficacy was reported, at the end of treatment, as 93% and 95% of patients treated with cefepime and ceftazidime, respectively; bacteriologic eradication was reported as 95 and 100%, respectively. Secondary: Overall, adverse events reported by study participants were generally mild except for one case of rash and one case of vaginitis for patients treated with cefepime.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs ceftazidime 150 mg/kg/day IV in three divided doses (maximum 6 g/day) vs cefuroxime 100 mg/kg/day IV in three divided doses (maximum 4.5 g/day) vs placebo In study A, participants received either cefepime every eight or 12 hours. In studies B, C, and D, participants received either cefepime or a comparator (cefuroxime, cefotaxime, ceftazidime, respectively).				
Paladino et al.[95] (2007)	DB, RCT	N=69	Primary: Clinical success	Primary: Clinical success occurred in 78% of cefepime- and 66% of ceftriaxone-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cefepime 1 g IM every 24 hours vs ceftriaxone 1 g IM every 24 hours After three days, patients with objective evidence of improvement could be switched to oral antibiotics.	Patients 60 years of age and older with nursing home-acquired pneumonia who did not require hospitalization	10 to 14 days	(cure or improvement) and safety Secondary: Not reported	treated patients (P=0.39). Ninety-three percent of patients were switched to oral antibiotics after three days. Most patients experienced mild to no discomfort at the site of IM injection of ceftriaxone or cefepime; if present, it abated quickly. One patient with a history of diabetes mellitus had high blood glucose while receiving ceftriaxone. Other drug-related adverse events occurred rarely and only with the oral antibiotics. The overall mortality rate was 8%. Secondary: Not reported
Verghese et al.[96] (1990) Cefixime 400 mg PO for one dose vs cephalexin 250 mg PO QID	RCT Patients with purulent exacerbation of chronic bronchitis	N=86 1 to 14 days	Primary: Clinical cure, clinical improvement Secondary: Adverse events	Primary: Clinical cure was reported as 70.8 and 50.0% in patients treated with cefixime and cephalexin, respectively (P<0.05). Combined percentages for clinical cure and improvement were reported as 95.8 and 84.2% in patients treated with cefixime and cephalexin, respectively (P=0.06). Secondary: Both treatments were well tolerated. Diarrhea occurred more often in patients treated with cefixime compared to patients treated with cephalexin (P=0.013).
Sengupta et al.[97] (2004) Cefixime 4 mg/kg PO BID vs cefpodoxime 5 mg/kg PO BID	AC, MC, OL, PRO, RCT Pediatric patients six months to 12 years of age with community-acquired lower respiratory tract infections, including community-acquired pneumonia	N=776 10 to 14 days	Primary: Clinical cure, bacteriologic eradication Secondary: Adverse events	Primary: Clinical cure was reported as 97.0 and 86.8% for patients treated with cefpodoxime and cefixime, respectively; bacteriologic eradication was reported as 93.4 and 82.9%, respectively. Secondary: Both treatments were well tolerated.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	and acute exacer-bations of chronic bronchitis			
Zuck et al.[98] (1999) Cefixime 200 mg PO BID vs cefuroxime 250 mg PO BID	DB, MC, PG, RCT Hospitalized patients 30 to 75 years of age experiencing acute exacerbations of chronic bronchitis	N=58 8 days	Primary: Clinical cure, microbiological eradication Secondary: Adverse events	Primary: At two to four days post-treatment, clinical cure was reported in 94 and 71% of patients treated with cefuroxime and cefixime, respectively (P=NS); microbiological eradication occurred more quickly in patients treated with cefuroxime compared to cefixime (P=0.002 at two to four weeks post-treatment). Secondary: Both treatments were well tolerated. One patient treated with cefuroxime reported fever; one patient treated with cefixime reported buccal mycosis.
File et al.[99] (2011) Ceftaroline 600 mg IV every 12 hours for five to seven days vs ceftriaxone 1 g IV every 24 hours for five to seven days Patients also received two 500 mg doses of oral clarithromycin every 12 hours on day 1.	AC, DB, MC, RCT Patients hospitalized in a non-intensive care unit setting with community-acquired pneumonia of PORT risk class III or IV	N=613 Variable duration	Primary: Clinical cure rates at the test-of-cure visit (eight to 15 days post-therapy) in the clinically evaluable and modified intent-to-treat efficacy populations Secondary: Clinical cure in the microbiologically evaluable and microbiological modified intent-to-treat efficacy populations, overall success rate, clinical and microbiological response by pathogen, clinical	Primary: Clinical cure rates were 86.6% for ceftaroline and 78.2% for ceftriaxone in the clinically evaluable population (95% CI, 1.4 to 15.4). Clinical cure rates in the modified intent-to-treat efficacy population were 83.8% for ceftaroline and 77.7% for ceftriaxone (95% CI, -0.2 to 12.6). Secondary: Clinical cure was observed in 89.9 and 76.1% of patients in the ceftaroline and ceftriaxone groups, respectively, in the microbiologically evaluable population (95% CI, 1.3 to 26.4). In the microbiological modified intent-to-treat efficacy population, clinical cure was observed in 88.0 and 75.0% of patients in the ceftaroline and ceftriaxone groups, respectively (95% CI, 0.7 to 25.2). At the test-of-cure visit, overall (clinical and radiographic) success was observed in 86.6% of patients in the ceftaroline group and 78.2% of patients in the ceftriaxone group in the clinically evaluable population (95% CI, 1.4 to 15.4). In the modified intent-to-treat efficacy population, 83.5% of ceftaroline patients and 77.7% of ceftriaxone patients experienced overall success (95% CI, -0.6 to 12.2). At the late follow-up visit, clinical relapse was noted in 1.1% of patients in the ceftaroline group and 1.8% of patients in the ceftriaxone group (95% CI, -4.2 to 2.4) of the clinically evaluable population. In the modified

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			relapse at the late follow-up visit, and safety	intent-to-treat efficacy population, 1.2% of patients in the ceftaroline group and 1.3% of patients in the ceftriaxone group (95% CI, -2.6 to 2.4) were considered a clinical relapse. Per-patient favorable microbiological response rates in the microbiologically evaluable population were 89.9% in the ceftaroline group compared to 78.9% in the ceftriaxone group (95% CI, -1.2 to 23.3). Consistent results were observed in the microbiological modified intent-to-treat efficacy population; 88.0% in the ceftaroline group and 78.8% in the ceftriaxone group (95% CI, -2.7 to 21.1). The most common adverse events for ceftaroline-treated patients were diarrhea, headache, insomnia and nausea, compared to hypokalemia, hypertension, nausea and diarrhea for ceftriaxone-treated patients. The most common study drug-related treatment-emergent adverse events were diarrhea (4.4% for ceftaroline and 1.0% for ceftriaxone), sinus bradycardia (1.0% for ceftaroline and 1.0% for ceftriaxone), nausea (1.3% for ceftaroline and 0.6% for ceftriaxone) and phlebitis (1.3% for ceftaroline and 0.6% for ceftriaxone).
Low et al.[100] (2011) Ceftaroline 600 mg IV every 12 hours for up to seven days vs ceftriaxone 1 g IV every 24 hours for up to seven days	AC, DB, MC, RCT Patients hospitalized in a non-intensive care unit setting with community-acquired pneumonia of PORT risk class III or IV	N=627 Variable duration	Primary: Clinical cure rates at the test-of-cure visit (eight to 15 days post-therapy) in the clinically evaluable and modified intent-to-treat efficacy populations Secondary: Clinical cure in the microbiologically evaluable and microbiological modified intent-to-treat efficacy	Primary: Clinical cure rates were 82.1% for ceftaroline and 77.2% for ceftriaxone in the clinically evaluable population (95% CI, -2.5 to 12.5). Clinical cure rates in the modified intent-to-treat efficacy population were 81.3% for ceftaroline and 75.5% for ceftriaxone (95% CI, -1.0 to 12.7). Secondary: Clinical cure was observed in 81.2 and 75.0% of patients in the ceftaroline and ceftriaxone groups, respectively, in the microbiologically evaluable population (95% CI, -6.7 to 19.2). In the microbiological modified intent-to-treat efficacy population, clinical cure was observed in 80.0 and 75.0% of patients in the ceftaroline and ceftriaxone groups, respectively (95% CI, -7.4 to 17.4). Clinical cure rates at the end of treatment were 86.0% for ceftaroline and 80.0% for ceftriaxone in the clinically evaluable population (95% CI, -1.0 to 13.0). Clinical cure rates were 86.2% for ceftaroline and 78.8% for ceftriaxone in the modified intent-to-treat efficacy population at the end of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			populations, overall success rate, clinical and microbiological response by pathogen, clinical relapse at the late follow-up visit, and safety	treatment (95% CI, 1.1 to 13.8). At the test-of-cure visit, the overall (clinical and radiographic) success rates were 81.7% for ceftaroline and 77.2% ceftriaxone in the clinically evaluable population (95% CI, -3.0 to 12.1). Overall success rates were 81.0% with ceftaroline and 75.5% with ceftriaxone in the modified intent-to-treat efficacy population (95% CI, -1.3 to 12.4). Clinical relapse at the late follow-up visit was reported for 2.8% of patients in the ceftaroline group and 0.6% of patients in the ceftriaxone group of the clinically evaluable population (95% CI, -1.0 to 5.8). In the modified intent-to-treat efficacy population, clinical relapse was determined in 2.1% of patients in the ceftaroline group and 1.0% of patients in the ceftriaxone group (95% CI, -1.6 to 4.0). Favorable per-patient microbiological response rates were observed for 84.7% of patients in the ceftaroline group and 82.9% of patients in the ceftriaxone group in the microbiologically evaluable population (95% CI, -9.7 to 13.7). In the microbiological modified intent-to-treat efficacy population, 82.2% of patients in the ceftaroline group and 81.8% of patients in the ceftriaxone group had a favorable microbiological response rate (95% CI, -11.1 to 11.9). There were no occurrences of microbiological reinfection or recurrence at the late follow-up visit. The most common adverse events for ceftaroline-treated patients were diarrhea, headache, hypokalemia, insomnia and phlebitis, compared to diarrhea, hypertension, insomnia and phlebitis for ceftriaxone-treated patients. Similar incidence rates of serious adverse events were demonstrated across both treatment groups (13.0% for ceftaroline vs 12.7% for ceftriaxone).
File et al.[101] (2010) Ceftaroline 600 mg IV every 12 hours	Pooled analysis (2 trials) Patients hospitalized in a non-intensive	N=1,228 Variable duration	Primary: Clinical cure rates at the test-of-cure visit (eight to 15 days post-therapy)	Primary: Clinical cure rates were 6.7% (95% CI, 1.6 to 11.8) and 6.0% (95% CI, 1.4 to 10.7) higher for ceftaroline than for ceftriaxone in the clinically evaluable and modified intent-to-treat efficacy populations, respectively.

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for up to seven days vs ceftriaxone 1 g IV every 24 hours for up to seven days	care unit setting with community-acquired pneumonia of PORT risk class III or IV		in the clinically evaluable and modified intent-to-treat efficacy populations Secondary: Clinical cure in the microbiologically evaluable and microbiological modified intent-to-treat efficacy populations, clinical and microbiological clinical relapse at the late follow-up visit, and safety	Secondary: Clinical cure rates in the microbiologically evaluable and microbiological modified intent-to-treat efficacy populations were 85.1 and 83.6%, respectively, for ceftaroline, compared to 75.5 and 75.0%, respectively, for ceftriaxone. Clinical relapse rates at late follow-up were 1.9% for ceftaroline and 1.2% for ceftriaxone in the clinically evaluable population (95% CI, -1.4 to 2.9). Clinical relapse rates were 1.7% for ceftaroline and 1.1% for ceftriaxone in the modified intent-to-treat efficacy population (95% CI, -1.2 to 2.3). Favorable per-patient microbiological response rates in the microbiologically evaluable population were 87.0% for ceftaroline and 81.0% for ceftriaxone (95% CI, -2.3 to 14.6). In the modified intent-to-treat efficacy population, microbiological response rates were 84.8% for ceftaroline and 80.4% for ceftriaxone (95% CI, -3.7 to 12.8). The incidences of treatment-emergent adverse events were similar among the treatment groups. The most common adverse events were diarrhea, headache, and insomnia for patients receiving ceftaroline and diarrhea, hypertension, and hypokalemia for patients receiving ceftriaxone.
Lodise et al.[102] (2015) Ceftaroline 600 mg IV every 12 hours for up to seven days vs ceftriaxone 1 g IV every 24 hours for up to seven days	DB, MC, RCT (Pooled analysis of FOCUS 1 and FOCUS 2) Clinically evaluable patients hospitalized in a non-intensive care unit setting with community-acquired pneumonia of PORT risk class III or IV	N=908 Variable duration	Primary: Time to discharge readiness (clinical response), clinical stability, symptom improvement Secondary: Not reported	Primary: Time to a clinical response (i.e., discharge readiness) was shorter among patients treated with ceftaroline than among patients treated with ceftriaxone (P=0.0335). The time to clinical stability was also shorter among patients treated with ceftaroline (P=0.0190). Patients treated with ceftaroline had a nonsignificantly shorter time to the improvement of at least one clinical symptom without deterioration from the baseline. Secondary: Not reported
Friedland et al.[103] (2004)	DB, MC, RCT Patients 18 years of	N=857 7 to 14 days	Primary: Clinical response at the test-of-cure	Primary: At the test-of-cure visit, the combined response rates were 90% in patients with chronic obstructive pulmonary disease and 93% in patients without

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ertapenem 1 g IV daily vs ceftriaxone 1 g IV daily Patients with clinical improvement meeting pre-specified criteria could be switched to PO amoxicillin-clavulanate or other PO antimicrobial based on pathogen susceptibility for a total of 10 to 14 days.	age and older with typical community-acquired pneumonia admitted to the hospital for parenteral antimicrobial therapy	post-therapy	visit, clinical response at the completion of parenteral therapy Secondary: Not reported	chronic obstructive pulmonary disease. In the patients without chronic obstructive pulmonary disease, favorable results were seen in 93% of both ertapenem and ceftriaxone patients. There were no significant differences between treatment groups (P=0.94) or between patients with and without chronic obstructive pulmonary disease (P=0.17). Clinical response at the completion of parenteral therapy was seen in 95% of ertapenem patients and 94% of ceftriaxone patients. Secondary: Not reported
Miscellaneous Infections				
Nungu et al.[104] (1995) Cefadroxil 1 g/100 mL water PO two hours before surgery and 12 hours later vs cefuroxime 0.75 g IV 30 minutes prior to surgery	PRO, RCT Patients undergoing intra- or subtrochanteric femoral hip fracture surgery	N=559 1 to 2 days	Primary: Absence or presence of surgical wound infection Secondary: Not reported	Primary: One study participant treated with cefadroxil reported a case of superficial wound infection with methicillin-sensitive *Staphylococcus aureus*. Six study participants treated with cefuroxime reported infections post-surgery; the infections included both superficial and deep infections. The difference in efficacy for preventing infections between the two treatment groups was not statistically significant (P=0.07). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
and every eight hours for two additional doses				
Jones et al.[105] (1987) Cefazolin 1 g IV bolus prior to surgery and cefazolin 1 g every eight hours for 24 hours; cefazolin 1 g during surgery if surgery lasts longer than two hours vs cefotaxime 1 g IV bolus prior to surgery; cefotaxime 1 g during surgery if surgery lasts longer than two hours vs cefoxitin 2 g IV bolus prior to surgery and cefoxitin 2 g every six hours for 24 hours	PRO, RCT, SB Patients ≥18 years of age undergoing elective surgery	N=914 2 days	Primary: Absence or presence of surgical wound infection Secondary: Adverse events	Primary: The mean time to onset of infection was reported as 9.9, 15.8, and 11.8 days for patients treated with cefazolin, cefoxitin, and cefotaxime, respectively. There was no statistically significant difference in wound infection morbidity rate for all treatment groups (P>0.05). Secondary: Although not statistically significant, a greater number of adverse events were reported in patients treated with cefoxitin vs cefazolin and cefazolin vs cefotaxime. Allergic reactions were most commonly reported with cefoxitin.
Curtis et al.[106]	PRO, RCT	N=702	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1993) Cefazolin 1 g IV 1 hour prior to surgery and every eight hours (for 48 hours) plus cefazolin 1 g IV after four hours of surgery vs cefuroxime 1.5 g IV 1 hour prior to surgery plus cefuroxime 1.5 g every 12 hours for three additional doses	Patients undergoing open heart surgery	2 to 3 days	Absence or presence of surgical wound infection (draining wound with or without positive culture) Secondary: Not reported	There was no statistically significant difference in overall wound infection rate between treatment groups (P=0.68). Differences in infection rates for both treatment groups were reported as being not statistically significant for chest wound infections, true mediastinitis, and leg infections (P=0.79, P=0.84, P=0.83, respectively). Secondary: Not reported
Jewesson et al.[107] (1996) Cefazolin 1 g in 100 mL 0.9% NaCl IV 30 minutes prior to surgery and cefazolin 1 g every 12 hours for 24 hours vs ceftizoxime 1 g in 100 mL 0.9% NaCl IV 30	DB, PRO, RCT Patients ≥19 years of age undergoing elective biliary tract surgery	N=150 2 days	Primary: Absence or presence of surgical wound infection Secondary: Not reported	Primary: There was no clinical evidence of infection in 93 and 92% of patients treated with cefazolin and ceftizoxime, respectively (P=1.0). Clinical success of the treatments were not influenced by procedure type (P=0.48 to 0.59) nor the number of patients receiving less than two doses of the antibiotic (P=1.0). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
minutes prior to surgery and ceftizoxime 1 g every 12 hours for 24 hours				
Ozturk et al.[108] (2007) Cefazolin 1 g IV as a single dose vs cefuroxime 750 mg IV as a single dose vs ceftazidime 1 g IV as a single dose vs placebo	PC, RCT Patients who underwent transurethral resection of the prostate for symptomatic benign prostatic hyperplasia	N=120 10 days	Primary: Clinical outcomes Secondary: Not reported	Primary: The occurrence rates of fever were 10.3, 16.0, 13.7, and 23.3% in the cefazolin, cefuroxime, ceftazidime, and placebo groups, respectively (P>0.05). The urine culture on the second postoperative day was positive only in one patient in the cefazolin group (3.4%) and in two patients in the placebo group. The second day, postoperative bacteriuria rates were similar in all groups. On the 10th postoperative day, a positive urine culture was observed in 10 patients in the cefazolin group (34%), two patients in the cefuroxime group (6.6%), two patients in the ceftazidime group (6.8%), and in 12 patients in the placebo group (40.0%) On the 10th day, the incidence rates of bacteriuria in the placebo group and the cefazolin group were similar (P=0.661). In the cefuroxime group, the bacteriuria incidence rate was 6.6%, and when compared to the placebo group, the difference was considered significant (P=0.002). The difference between the cefuroxime and the ceftazidime groups was also significant (P=0.003). There were statistically significant differences between the cefazolin and cefuroxime group (P=0.008) as well as between the cefazolin and ceftazidime groups (P=0.01). All antibiotics were generally well tolerated in all patients, and there were no significant drug-related side effects. Secondary: Not reported
Huang et al.[109] (2002) Cefepime 2 g IV	OL, PRO, RCT Patients ≥18 years of age with severe	N=42 10 to 14 days	Primary: Clinical response rates, bacteriological	Primary: Clinical response rates of 71 and 61% were reported for patients treated with cefepime and ceftazidime, respectively. Bacteriological eradication rates were reported as 87.5 and 89.0% of patients treated with cefepime

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
every 12 hours vs ceftazidime 2 g IV every eight hours	infections including septicemia, urinary tract infection, bacterial bronchitis, bacterial pneumonia, intra-abdominal infection		eradication rates Secondary: Adverse events	and ceftazidime, respectively. Clinical response and bacteriological eradication rates were not statistically different between treatment groups. Secondary: Adverse events reported with both treatments were minimal. The most common adverse events were hyperkalemia (12%), impaired liver biochemistry (12%), diarrhea (10%), and hypoalbuminemia (10%).
Chandrasekar et al.[110] (2000) Cefepime 2 g IV every eight hours vs ceftazidime 2 g IV every eight hours	DB, MC, PRO, RCT Hospitalized patients ≥18 years of age with chemotherapy-induced neutropenia (absolute neutrophil count <500/mm^3) with fever	N=188 1 to 35 days	Primary: Presence or absence of febrile episodes, bacteremic clearance Secondary: Adverse events	Primary: Prevention of febrile episodes was reported in 57 and 60% of patients treated with cefepime and ceftazidime, respectively (P=0.77). Success rates in microbiologically documented infections were reported as 39 and 16% of patients treated with cefepime and ceftazidime, respectively (P=0.17). Bacteremic clearance was reported in 71 and 40% of patients treated with cefepime and ceftazidime, respectively (P=0.3). Treatment failure was reported in 43 and 40% of patients treated with cefepime and ceftazidime, respectively (P=NS). Of the treatment failures in microbiologically documented infections, 43 and 63% of patients treated with cefepime and ceftazidime, respectively, had resistant infections. Secondary: Overall non-drug-related mortality within 30 days of drug discontinuation of cefepime and ceftazidime was reported as 15 and 8%, respectively (P=0.06). The most common adverse effects of cefepime were rash, nausea and vomiting; for ceftazidime, rash and diarrhea.
Chuang et al.[111] (2002) Cefepime 50 mg/kg/dose IV BID to TID vs ceftazidime 50 mg/kg/dose IV BID to TID	OL, PRO, RCT Children aged two months to 15 years with chemotherapy-induced neutropenia (absolute neutrophil count <500/mm^3) with fever	N=96 3 to 20 days	Primary: Overall success rate of febrile prophylaxis, bacteremic clearances, new infection rate Secondary: Adverse events	Primary: After 72 hours of treatment, positive clinical response was reported as 82.8 and 87.9% in patients treated with cefepime and ceftazidime, respectively (P=0.94). Overall success rate of the empiric therapy was reported as 69 and 71% in patients treated with cefepime and ceftazidime, respectively (P=0.95). Bacteremic clearance was reported as 33 and 20% for patients treated with cefepime and ceftazidime, respectively (P=0.85). New infection rates were reported as 10.4 and 4.2% in patients treated with cefepime and ceftazidime, respectively (P=0.67). Secondary: Both treatments were well tolerated.
Gómez et al.[112]	OL, RCT	N=190	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2010) Cefepime 2 g IV every 12 hours plus amikacin 15 mg/kg/day as a single dose (C-A) vs piperacillin-tazobactam 4 g/500 mg IV every eight hours plus amikacin 15 mg/kg/day as a single dose (PT-A)	Patients >18 years of age with an episode of febrile neutropenia	(317 episodes) Variable duration	Clinical efficacy and toxicity Secondary: Not reported	The antibiotic success rate (no change or addition of antibiotics) was recorded in 59% of episodes in the C-A group and in 64% of episodes in the PT-A group (P=NS). Resolution of the febrile episode (with or without change in therapy) was observed in 92% of episodes in the C-A group and in 92% of episodes in the PT-A group. The 28-day mortality (all-cause) was similar in both groups: 9.9% in the C-A group and 10.5% in the PT-A group (P=NS). A microbiologically documented infection was present in 35% of episodes in the C-A group and 25% of episodes in the PT-A group (P=NS). A clinically documented infection was observed in 26% of episodes in the C-A group and 28% of episodes in the PT-A group. Toxicity was observed in 4% of episodes in the C-A group and in 3% of episodes in the PT-A group. Secondary: Not reported
Uygun et al.[113] (2009) Cefepime 50 mg/kg IV every eight hours (CEF) vs piperacillin-tazobactam 80 mg/kg-10 mg/kg IV every six hours (PIP/TAZO)	RCT, OL Patients ≤19 years of age who had been treated for hematological malignancies or solid tumors and had febrile neutropenia	N=70 (131 episodes) Variable duration	Primary: Success without modification Secondary: Not reported	Primary: Success without modification was similar between the two groups (60.0 vs 61.3% for PIP/TAZO and CEF, respectively; P>0.05). Success without modification was 84.8 and 92.1% for PIP/TAZO and CEF treatments, respectively, in patients with fever of unknown origin episodes. Success without modification was 29.2 and 12.5% in microbiologically documented infection episodes (P>0.05). Modifications were done with only glycopeptides in eight episodes, only antifungals in 20 episodes, only carbapenems in 11 episodes, and only antiprotozoals in two episodes. Duration of fever and neutropenia was similar in both groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was no significant difference in the duration of hospitalization between the treatment groups. No treatment changes were made because of potential side or adverse effect of PIP/TAZO or CEF. The most frequent adverse events were rash (7.7% in PIP/TAZO and 6.4% in CEF) and diarrhea (6.1% in PIP/TAZO and 6.4% in CEF). Secondary: Not reported
LeFrock et al.[114] (1982) Cefotaxime 2 to 6 g/day IV	PRO Patients 15 to 91 years of age with serious bone and joint infections including septic arthritis, bursitis, acute/chronic osteomyelitis	N=51 4 to 54 days	Primary: Clinical response Secondary: Adverse events	Primary: Satisfactory clinical response was reported in 39 of 51 patients; clinical failure was reported in six patients. Secondary: Cefotaxime therapy was well tolerated with transient adverse events.
Mauceri et al.[115] (1994) Cefotaxime 1 g (moderate infections) to 2 g (severe infections) IV TID using an ambulatory delivery system	MC, OL, PRO Patients ≥18 years of age with bone and joint infections using an ambulatory delivery system for medication	N=18 30.5±17.52 days	Primary: Clinical response, bacteriological response Secondary: Adverse events	Primary: Satisfactory clinical response was reported in 83.8% of patients; satisfactory bacteriological response was reported in 78.6% of patients. All patients were eventually maintained on outpatient therapy. Secondary: Both the medication and delivery system were well tolerated. Two patients reported drug-related rash and one patient reported drug-related diarrhea.
Segev et al.[116] (1988) Cefotaxime 1 to 2 g IV TID vs	MC, PRO, RCT Patients ≥17 years of age with moderate to severe infections	N=96 4 to 21 days	Primary: Clinical efficacy, bacteriological eradication Secondary: Adverse events	Primary: For both treatment groups, clinical efficacy and bacteriological eradication were reported as 90 and 95%, respectively. Secondary: Adverse events were more commonly reported by patients treated with cefotaxime compared to ceftizoxime (13.5 vs 6.8%, respectively);

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ceftizoxime 1 to 2 g IV TID				superinfection was more common with ceftizoxime therapy compared to cefotaxime therapy (25 vs 19%, respectively).
Hemsell et al.[117] (1995) Cefotetan 1 g IV as a single dose vs cefazolin 1 g IV as a single dose	DB, PRO, RCT Women undergoing elective abdominal hysterectomy	N=511 Single dose study	Primary: Prevention of major operative site infections Secondary: Not reported	Primary: A major operative site infection requiring parenteral antimicrobial therapy developed in 9.0% of evaluable women: 11.6% of women given cefazolin prophylaxis and 6.3% of women given cefotetan prophylaxis (RR, 1.84; 95% CI, 1.03 to 3.29; P<0.05). Risk factors for major operative site infection were younger age, lower postoperative hemoglobin concentration, and a proliferative endometrium. Of the women given cefazolin prophylaxis, 3.9%had a postoperative pelvic abscess compared to 0.8% of women given cefotetan prophylaxis (RR, 4.9; 95% CI, 1.09 to 22.16; P =0.04). A greater number of infections and more serious infections occurred following cefazolin prophylaxis; this treatment resulted in 234 additional hospital days for administration of IV antimicrobial therapy. Secondary: Not reported
Kobayashi et al.[118] (2009) Aztreonam 150 mg/kg/day plus ampicillin-sulbactam 150 mg/kg/day divided into four doses vs ceftazidime 100 mg/kg/day plus piperacillin-	RCT Pediatric patients with hematologic disease and solid tumor with febrile neutropenia	N=54 (177 episodes) 120 hours	Primary: Treatment success Secondary: Not reported	Primary: Success rates were 57.1 and 62.5% in the piperacillin-tazobactam plus ceftazidime and ampicillin-sulbactam plus aztreonam groups, respectively (P≥0.05). There were two deaths in the piperacillin-tazobactam plus ceftazidime group. The patients died within 48 hours from onset of the febrile episode. The success rates in episodes with absolute neutrophil counts <0.5×10^9/L at the end of treatment were 70.0 and 74.1% in the piperacillin-tazobactam plus ceftazidime and ampicillin-sulbactam plus aztreonam groups, respectively, and the success rates in bacteremia episodes were 50% in both groups. The percentages of episodes with new infections were 25.7 and 20.3%,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
tazobactam 125 mg/kg/day divided into four doses Treatment was continued until completion of the appropriate course of therapy for a defined clinical or microbiologic infection.				respectively. Duration of fever and antibiotic therapy did not differ between the groups, and no major adverse effects occurred in the study. Secondary: Not reported
Lucasti et al.[119] (2013) Ceftazidime-avibactam (2000-500 mg) plus metronidazole (500 mg) IV every eight hours for five to 14 days vs meropenem 1000 mg plus placebo IV every 8 hours for 5 to 14 days	AC, DB, RCT Hospitalized patients 18 to 90 years of age with complicated intra-abdominal infection requiring surgical intervention and antibiotics	N=144 Test-of-cure: 2 weeks after last dose Late follow-up: 4 to 6 weeks post-therapy	Primary: Clinical response in microbiologically evaluable patients at the test-of-cure visit two weeks after the last dose of study therapy Secondary: Safety	Primary: A favorable clinical response in the microbiologically evaluable population at the test-of-cure visit was observed in 91.2% (62/68) and 93.4% (71/76) of ceftazidime-avibactam plus metronidazole and meropenem patients, respectively. The estimated difference in response rates was –2.2% (95% CI, –20.4 to 12.2%). Secondary: Adverse events were observed in 64.4% (65/101) and 57.8% (59/102) of patients in the ceftazidime-avibactam plus metronidazole and meropenem groups, respectively. Overall, the types and frequencies of adverse events were similar in the two treatment groups, but there were more cases of nausea and vomiting and abdominal pain in the ceftazidime-avibactam plus metronidazole group and more cases of liver enzyme elevations in the meropenem group. In the majority of cases, adverse events were mild or moderate in intensity.
Solomkin et al.[120] (2015) ASPECT-cIAI Ceftolozane-tazobactam 1.5 g plus metronidazole 500 mg every eight	DB, PC, RCT Patients ≥18 years of age with complicated intra-abdominal infections	N=806 24 to 32 days	Primary: Difference in clinical cure rates at the test-of-cure visit in the microbiological modified intention to treat population	Primary: Clinical cure rates were 83.0% (323/389) with ceftolozane-tazobactam plus metronidazole and 87.3% (364/417) with meropenem in the modified intention to treat population at the test-of-cure visit. The weighted difference in clinical cure rates (ceftolozane-tazobactam plus metronidazole minus meropenem) was −4.2% with a 2-sided 95% CI of −8.91% to 0.54%, thus meeting the statistical criteria for noninferiority.

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hours IV for four to 14 days vs meropenem 1 g every eight hours IV for four to 14 days			Secondary: Difference in clinical cure rates at the test-of-cure visit in the intention to treat and clinically evaluable populations	Secondary: Clinical cure rates in the intention to treat population at test-of-cure were 83.6% for ceftolozane-tazobactam plus metronidazole and 86.2% for meropenem (difference, −2.6; 95% CI, −7.08 to 1.87), similar to those observed in the modified intention to treat population. In the clinically evaluable population, cure rates were 94.1% and 94.0%, respectively (difference, 0.1; 95% CI, −3.30 to 3.55). Clinical outcomes in the subgroup analyses were generally consistent with the primary and secondary analyses, with no meaningful differences recorded between treatments.
Kaplinsky et al.[121] (1994) Ceftriaxone 50 mg/kg IV over 20 minutes	OL, non-RCT, PRO Pediatric outpatients with fever and neutropenia while being treated with various myelosuppressive agents for different malignancies	N=41 7 days	Primary: Clinical response, medication adherence Secondary: Not reported	Primary: Patients treated with ceftriaxone reported normalization of temperature within two to four days of treatment and resolution of neutropenia after about 10 days. Medication adherence to ceftriaxone regimens, by both patients and patients' parents, was rated excellent. Secondary: Not reported
Metallidis et al.[122] (2008) Ceftriaxone 4 g IV every 24 hours plus ciprofloxacin 400 mg IV BID vs ceftazidime 2 g IV every eight hours plus amikacin 500 mg IV every eight hours or 20 mg/kg divided in three doses	RCT Patients with febrile neutropenia	N=95 ≥3 days	Primary: Microbiologically and clinically documented infections and adverse events Secondary: Not reported	Primary: The overall incidence of microbiologically and clinically documented infections was 81.3% (80.85% in the ceftriaxone/ciprofloxacin group and 82.14% in the ceftazidime/amikacin group). There was no significant difference between the groups. The overall incidence of documented infections was 45.9% (51.1% in the ceftriaxone/ciprofloxacin group and 37% in the ceftazidime/amikacin group; P=0.011). The ceftriaxone/ciprofloxacin group had an overall incidence of resolution and improvement of 95.7% in comparison to 75% in the ceftazidime/amikacin group. Thirty-nine organisms were isolated, 66.67% gram-negative and 33.33% gram-positive.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There was a low incidence of adverse events in both groups. Secondary: Not reported
Bradley et al.[123] (1988) Ceftriaxone 50 mg/kg IV/IM QD (for non central nervous system infections) or ceftriaxone 100 mg/kg IV for day 1, then 80 mg/kg IV QD or BID (for meningitis)	PRO Pediatric outpatients one week to 15 years of age with serious bacterial soft tissue infections (egg cellulitis, arthritis, pyelonephritis) or meningitis using home therapy	N=101 1 to 6 days	Primary: Clinical failure, microbiologic failure Secondary: Adverse events	Primary: No clinical or microbiologic failures were reported in treatment groups. Pediatric patients with meningitis who were treated as outpatients did not report any neurologic dysfunction, cardiovascular instability, or relapse. Secondary: Diarrhea was reported in 13 and 6% of patients treated for meningitis and soft tissue infections, respectively. There were no discontinuations of therapy.
Dagan et al.[124] (1987) Ceftriaxone 75 mg/kg IM QD, then 50 mg/kg (maximum 1.5 g/day)	PRO Pediatric outpatients eight days to 17 years of age with serious community-acquired infection, including periorbital/buccal cellulitis, other cellulitis, urinary tract infection, pneumonia, osteomyelitis, mastoiditis, suppurative	N=74 3 to 21 days	Primary: Clinical response Secondary: Adverse events	Primary: A 24-hour cure rate was reported for 72 patients (97%) treated with ceftriaxone in the outpatient setting. Three cases of new infection were reported within two months post ceftriaxone therapy. Secondary: No serious adverse events were reported. The most commonly reported side effect was mild diarrhea which occurred in 10% of patients.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	arthritis, orbital cellulitis			
Arguedas et al.[125] (2009) Ertapenem 1 g IV as a single daily dose (children aged 13 to 17 years) or 30 mg/kg/day divided BID (children aged 3 months to 12 years) vs ceftriaxone 50 mg/kg/day as a single dose (children aged 13 to 17 years) or 50 mg/kg/day divided BID (children aged 3 months to 12 years)	AC, DB, RCT Patients ≥3 months and <18 years with complicated urinary tract infection, skin and skin structure infection and community-acquired pneumonia requiring initial parenteral antibiotic therapy	N=404 14 days	Primary: Incidence of clinical and laboratory drug-related serious adverse events Secondary: Incidence of any drug-related adverse events and any moderate-to-severe reactions at the parenteral infusion site	Primary: In each group, the mean duration of therapy (parenteral and oral antibiotic therapy) was 11 days and the median duration of parenteral therapy (ertapenem or ceftriaxone) was four days. Overall, 46.7% of the children had one or more clinical adverse events during parenteral therapy. During the parenteral therapy period, 26.7% of ertapenem-treated children and 24.0% of ceftriaxone-treated children reported a drug-related clinical and/or laboratory adverse event (P=0.69). Secondary: The most common drug-related clinical adverse events during parenteral therapy were diarrhea, infusion site pain, infusion site erythema and vomiting. Eighteen patients (5.9%) receiving ertapenem and 10 patients (10%) receiving ceftriaxone experienced diarrhea. Fifteen patients (5%) and one patient (1%) receiving ertapenem and ceftriaxone, respectively, experienced infusion site pain. Nine patients (3%) receiving ertapenem and two patients (2%) receiving ceftriaxone experienced infusion site erythema. Six patients (2%) receiving ertapenem and two patients (2%) receiving ceftriaxone experienced vomiting. The most common laboratory adverse event in both groups was a decrease in the neutrophil count (5.7% in the ertapenem group and 2.2% in the ceftriaxone group). In the ertapenem group, 18.8% of patients experienced more than one symptom at the site of drug administration during parenteral therapy of any intensity. The rates of moderate-to-severe local symptoms were comparable between the treatment groups (5.3% in the ertapenem group and 5.0% in the ceftriaxone group; P=1.000). The most common infusion/injection-related events were local erythema and pain. A total of 4.6% of children in the ertapenem group and 3.0% of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				children in the ceftriaxone group experienced erythema. A total of 6.6% of children in the ertapenem group and 4.0% of children in the ceftriaxone group experienced administration site pain.
Gupta et al.[126] (2009) Ceftriaxone 75 mg/kg/day IV and amikacin 15 mg/kg QD as outpatient therapy vs ofloxacin 7.5 mg/kg orally every 12 hours and amoxicillin-clavulanate 12.5 mg/kg orally every eight hours as outpatient therapy	OL, RCT, SC Pediatric patients two to 15 years of age with low-risk febrile neutropenia	N=88 (123 episodes) Variable duration	Primary: Treatment success Secondary: Not reported	Primary: In the per protocol analysis, treatment was successful in 90.16% of episodes in the oral group and in 93.10% of episodes in the IV group. In the intention-to-treat analysis, the success rate was 88.7% in the oral group and 88.5% in the IV group (P=0.97). There were three hospitalizations (all in the oral group) and no mortality. Secondary: Not reported
Solomkin et al.[127] (2009) Ceftriaxone 2 g IV QD plus metronidazole 500 mg IV BID for three to 14 days vs moxifloxacin 400 mg IV QD for three 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-therapy;	Primary: At the test-of-cure visit, cure rates were 90.2% for moxifloxacin and 96.5% for ceftriaxone plus metronidazole (95% CI, −11.7 to −1.7). In the intention-to-treat population, the clinical cure rates were 87.2% for moxifloxacin and 91.2% for ceftriaxone plus metronidazole (95% CI, −10.7 to 1.9). Moxifloxacin was found to be non-inferior to ceftriaxone plus metronidazole in the per protocol and intention-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 plus metronidazole group (28.1%). In the intention-to-treat population, clinical improvement occurred in 30.6% of patients receiving moxifloxacin and 27.1% of patients receiving ceftriaxone plus metronidazole.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			bacteriological 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	In the per protocol population, clinical resolution at end-of-therapy occurred in 92.5% of patients receiving moxifloxacin and in 97.1% of patients receiving ceftriaxone plus metronidazole (95% CI, −9.8 to −0.2). In the intention-to-treat population, clinical resolution at end-of-therapy occurred in 91.1% of patients receiving moxifloxacin and in 94.5% of patients receiving ceftriaxone plus metronidazole. The overall incidence of treatment-emergent adverse events was similar between the two treatment groups (31.7% with moxifloxacin vs 24.3% with ceftriaxone plus metronidazole; P=0.129).
Towfigh et al.[128] (2010) Ceftriaxone 2 g IV QD plus metronidazole 1 to 2 g IV daily in divided doses for four to 14 days (CTX/MET) vs tigecycline 100 mg IV as an initial dose, followed by 50 mg IV every 12 hours for four to 14 days (TGC)	MC, OL, RCT, Patients ≥18 years of age with community-origin 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 TGC and in 74% of patients in the CTX/MET group (-4.0; 95% CI, -13.1 to 5.1; P=0.009). TCG was found to be non-inferior to CTX/MET. Secondary: Clinical cure rates for the microbiologically evaluable population were 66% with TGC and 70% with CTX/MET (-3.4; 95% CI, -14.5 to 7.8; P=0.020. TCG was found to be non-inferior to CTX/MET. In the c-mITT population, clinical cure was reported in 64% of patients receiving TGC and in 71% of patients receiving CTX/MET (-7.0; 95% CI, -15.8 to 1.08; P=0.038. TGC was found to be non-inferior to CTX/MET. *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 population, infections were cured in 68.0 and 67.0% of all monomicrobial and polymicrobial infections, respectively, in the TGC-treated patients, and 71.5 and 68.3% of all monomicrobial and polymicrobial infections, respectively, in the CTX/MET-treated patients. Adverse events were similar with TGC and CTX/MET. There were no

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				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%).
Song et al.[129] (1998) Gentamicin plus metronidazole vs cefuroxime plus metronidazole vs first generation or second generation cephalosporin vs third generation cephalosporin vs other antibiotic agents as monotherapy or combination therapy	MA Patients scheduled to undergo elective surgery of the colon	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 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
Chen et al.[130] (2011)	RCT Patients six months	N=200 3 months	Primary: Clinical improvement at 48	Primary: A total of 94% of patients in the cephalexin group and 97% of patients in the clindamycin group showed improvement or resolution in their

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Cephalexin 40 mg/kg/day orally in divided doses TID for seven days vs clindamycin 20 mg/kg/day orally in divided doses TID for seven days	to 18 years of age with uncomplicated skin and soft tissue infections not requiring hospitalization		to 72 hours from the initiation of treatment Secondary: Resolution of disease at seven days	infection at 48 to 72 hours from the initial of treatment (P=0.50). The primary infection had worsened in 6% of patients in the cephalexin group and in 3% of patients in the clindamycin group. Secondary: A total of 97% of patients in the cephalexin group and 94% of patients in the clindamycin group had clinical resolution by seven days (P=0.33). Only one patient developed a new skin and soft tissue infection while on therapy. Compliance with taking medications as directed was 88% in the cephalexin group and 85% in the clindamycin group (P=0.66). According to data obtained from telephone contact (73%) and chart review (100%) at the three-month follow-up, 18% of patients had a recurrent skin and soft tissue infection. The risk of new skin and soft tissue infection did not differ according to isolation of methicillin-resistant *Staphylococcus aureus* vs methicillin-susceptible *Staphylococcus aureus* from initial wound culture (21% methicillin-resistant *Staphylococcus aureus* vs 16% methicillin-susceptible *Staphylococcus aureus*; P=0.51) or by cephalexin or clindamycin assignment (20 vs 16%; P=0.46). There were no serious adverse events related to study treatment.
Phoolcharoen et al.[131] (2012) Ceftriaxone 1 g IV single dose before surgery vs cefazolin 1 g IV single dose before surgery	DB, RCT Patients undergoing elective total abdominal hysterectomy	N=320 4 weeks	Primary: Postoperative fever and infection Secondary: Not reported	Primary: Infectious events occurred in 23 (14.4%) patients who received ceftriaxone and in 21 (13.1%) patients who received cefazolin (P=0.74). Febrile morbidity occurred in 11.2% of patients in the ceftriaxone group and 9.4% of patients in the cefazolin group (P=0.55). Wound and vaginal cuff infection occurred in six (3.8%) and three (1.9%) patients in the ceftriaxone and cefazolin groups, respectively (P=0.32). Urinary tract infection occurred in three patients in each group (1.9%). Adverse clinical events were rare in both groups. Secondary: Not reported
Wu et al.[132]	RETRO	N=102	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2013) Cefazolin IV 1 g every eight hours for two to seven days vs ceftriaxone IV 1 g every 12 hours for two to seven days	Patients with acute variceal bleeding who had received endoscopic procedures from a university-affiliated tertiary care center and were enrolled in two groups based on severity of liver cirrhosis: group A (Child's A patients) and group B (Child's B and C patients)	34 months	Incidence of infections, time of rebleeding, death (during hospitalization) Secondary: Not reported	Infection prevention between patients who received prophylactic IV cefazolin and those who received IV ceftriaxone among all cirrhotic patients (85.7 vs 89.1%; P=0.319), for subgroup analysis for Child's A patients (93.1 vs 90.9%; P=0.641), and for subgroup analysis for Child's B and C patients (77.8 vs 87.5%; P=0.072) was similar. There was no significant difference in the actuarial probability of remaining free of overall rebleeding between patients prescribed cefazolin and those prescribed ceftriaxone (P=0.220). More rebleeding occurred in patients with Child's B and C who had received cefazolin compared to ceftriaxone (66.7 vs 25.0%; P=0.011); there was no difference between the two medications for patients with Child's A (P=0.376). The independent risk factors were thrombocytopenia (HR, 0.992; 95% CI, 0.985 to 0.999; P=0.029) and history of bleeding (HR, 2.674; 95% CI, 1.348 to 5.305; P=0.005). Death during hospitalization occurred in six patients (5.8%). Sepsis was the most frequent non-bleeding-related cause of death in three patients, followed by two patients with multiple organ failure. Secondary: Not reported
Winans et al.[133] (2012) Cefazolin IV (various dosing regimens) vs ceftriaxone IV (various dosing regimens)	RETRO Patients 18 years of age or older and discharged home on parenteral antibiotic therapy for a documented methicillin-susceptible *Staphylococcus aureus* infection	N=122 5 years	Primary: Clinical outcomes Secondary: Adverse events, complications, cost of therapy to the hospital	Primary: Sixty-eight percent of the patients in the cefazolin group and 79.5% patients in the ceftriaxone group had favorable clinical outcomes (P=0.17). Secondary: Adverse events were similar between the two groups (5.1% in the cefazolin group vs 2.3% in the ceftriaxone group; P=0.65). The most common adverse event reported in the cefazolin and ceftriaxone group was nausea/vomiting/diarrhea (2.6 vs 0%), followed by elevated blood urea nitrogen and serum creatinine (1.9 vs 0%), anemia (1.9 vs 0%), and rash (0 vs 2.3%). Complications occurred in 26.9% patients in the cefazolin group and 18.2% patients in the ceftriaxone group (P=0.38).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Readmissions or emergency department visits due to the lack of improvement of the infectious process were similar in each group (P=0.68).
Nathan et al.[134] (2005) Chloramphenicol 100 mg/kg IM as a single dose vs ceftriaxone 100 mg/kg IM as a single dose	MC, OL, RCT Patients >2 months of age with meningitis	N=510 1 month	Primary: Treatment failure at 72 hours Secondary: Mortality within 72 hours, clinical sequelae at 72 hours, clinical failure between 24 and 48 hours requiring a second injection	Primary: Both treatment groups exhibited a treatment failure rate of 9% (90% CI, -3.8 to 4.5). Secondary: There was no significant difference in the mortality rate at 72 hours between the chloramphenicol and ceftriaxone groups (5 vs 6%, respectively; 90% CI, -2.3 to 3.8). Clinical failure took place in 4% of the chloramphenicol-group survivors and 3% of the ceftriaxone-treated patients (90% CI, -3.3 to 2.8). There was no significant difference in the re-injection rate between the chloramphenicol and ceftriaxone groups (8 vs 7%, respectively; 90% CI, -4.7 to 3.0). Neurologic sequelae occurred in 5% of patients on chloramphenicol and 7% of patients on ceftriaxone therapy (90% CI, -2.1 to 5.1).
Peltola et al.[135] (1989) Chloramphenicol 100 mg/kg/day in four divided doses vs ampicillin 250 mg/kg/day in four divided doses plus chloramphenicol (administered until bacterial strain was shown to be	MC, RCT Children three months to 15 years of age with bacterial meningitis	N=220 7 days	Primary: Cerebrospinal fluid culture pathogens, time to sterile cerebrospinal fluid culture Secondary: Not reported	Primary: The cerebrospinal fluid became sterile significantly earlier in meningococcal meningitis compared to patients presenting with *H. influenzae* type b (P<0.01). At 24 hours, positive cultures were found only in patients receiving chloramphenicol. At 24 hours, the cerebrospinal fluid was sterile in a greater proportion of patients treated with cephalosporins compared to those treated with ampicillin-chloramphenicol or chloramphenicol (P<0.05). On day four, cerebrospinal fluid culture was positive in only one patient, who was treated with chloramphenicol. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
susceptible to ampicillin alone) vs cefotaxime 150 mg/kg/day in four divided doses vs ceftriaxone 100 mg/kg QD				Not reported
Girgis et al.[136] (1988) Chloramphenicol 100 mg/kg/day plus ampicillin 160 mg/kg/day every six hours (AMCL) vs ceftriaxone 100 mg/kg QD	RCT Patients with bacterial meningitis	N=100 6 days	Primary: Cerebrospinal fluid leukocyte count, glucose, protein content, disappearance of meningeal irritation, fever defervescence, patient alertness, mortality rate Secondary: Not reported	Primary: There was no significant difference between the two groups in the disappearance of meningeal irritation, fever defervescence, and patient alertness. There was no significant difference between the two groups in the cerebrospinal fluid leukocyte count, glucose or protein content at baseline, as well as the final evaluation. There was no significant difference between the two groups in mortality. While 20% of patients treated with AMCL died, the mortality in the ceftriaxone group was 7%. Secondary: Not reported
Girgis et al.[137] (1987) Chloramphenicol 100 mg/kg/day IV plus ampicillin 160 mg/kg/day IV every six hours (group 1)	RCT Patients 16 to 30 years of age with bacterial meningitis	N=30 6 days	Primary: Mortality, time taken for defervescence, time for patients to regain full consciousness Secondary:	Primary: One patient in each group died within 24 hours of initiation of therapy. Both had meningitis due to *Streptococcus pneumoniae*. The mean number of days to become afebrile were 3.4 and 3.5 for group 1 and group 2, respectively. The mean number of days to regain full consciousness was 3.9 and 2.5 for group 1 and group 2, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs ceftriaxone 100 mg/kg IV QD (group 2)			Not reported	Secondary: Not reported
Jacobs et al.[138] (1985) Chloramphenicol 25 mg/kg/dose IV plus ampicillin 50 to 100 mg/kg/dose IV every six hours vs cefotaxime 50 mg/kg/dose IV every six hours	PRO, RCT Patients one week to 16 years of age with meningitis	N=50 3 months	Primary: Clinical cure rate, survival without sequelae, duration of therapy Secondary: Not reported	Primary: There was no significant difference in the clinical cure rate between the chloramphenicol-ampicillin and cefotaxime groups (96 vs 100%, respectively; P>0.5). There was no significant difference in survival without detectable sequelae between the chloramphenicol-ampicillin and cefotaxime groups (77 vs 78%, respectively). Mean duration of therapy was similar in the chloramphenicol-ampicillin and cefotaxime groups (11.9 and 11.1 days, respectively). Secondary: Not reported
Rodriguez et al.[139] (1986) Chloramphenicol 75 to 100 mg/kg/day IV in four divided doses plus ampicillin 400 mg/kg/day IV in six divided doses vs ceftazidime 150 mg/kg/day IV divided into three doses,	OL, RCT Patients one month to 15 years of age with meningitis	N=100 Up to 6 months	Primary: Clinical cure rate, clinical improvement, mortality rate, neurological sequelae, mean duration of therapy Secondary: Not reported	Primary: After the first 24 hours of therapy, 10% of the patients died, 2% clinically improved, and 88% were cured in the ceftazidime group. In the chloramphenicol-ampicillin group, 10% of patients died, 1% clinically improved, and 81% were cured in the ceftazidime. Seizures occurred in 54% of patients treated with ceftazidime and 51% of patients treated with chloramphenicol-ampicillin therapy. Mean duration of therapy was 10.2 and 10.4 days in the ceftazidime and chloramphenicol-ampicillin groups, respectively. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
administered every eight hours				
Marks et al.[140] (1986) Chloramphenicol 75 to 100 mg/kg/day IV in four divided doses plus ampicillin 300 to 400 mg/kg/day IV every six hours vs cefuroxime 225 mg/kg/day IV divided into three doses, administered every eight hours	MC, RCT Patients 3 months to 16 years of age with bacterial meningitis	N=107 Up to 6 months	Primary: Clinical cure rate, cerebrospinal fluid sterilization rate Secondary: Not reported	Primary: Clinical cure rate was 95% in both treatment groups. There was no significant difference in the cerebrospinal fluid sterilization rates between the cefuroxime and chloramphenicol-ampicillin groups (90 vs 100%, respectively). Secondary: Not reported
Johansson et al.[141] (1982) Chloramphenicol and ampicillin IV every six hours for at least five days (A+C) vs cefuroxime IV every eight hours for at least five days (CXM)	MC, RCT Patients with bacterial meningitis	N=67 ≥5 days	Primary: Efficacy and safety Secondary: Not reported	Primary: Complete resolution of symptoms was recorded in 18 of the 21 patients in the CXM group and in 14 of the 19 patients in the A+C group. Two patients died in each group. Adverse events were reported on eight occasions in seven patients in the CXM group and in four patients in the A+C group. Rashes developed in two CXM patients and three A+C patients. Fever was noted in two CXM patients. Moderately severe diarrhea which required symptomatic treatment developed in one patient in each group, and one CXM patient had repeated thrombophlebitis. Secondary: Not reported
Sexton et al.[142]	MC, OL, RCT	N=51	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1998) Gentamicin 3 mg/kg QD plus ceftriaxone 2 g IV QD for two weeks vs ceftriaxone 2 g IV QD for four weeks	Patients ≥18 years of age with endocarditis who had received <72 hours of parenteral antibiotic therapy	4 years	Clinical cure Secondary: Not reported	Clinical cure was observed for patients both at termination of therapy and at the three-month follow-up: 25 (96.2%) of the monotherapy patients and 24 (96%) of combination therapy patients were considered clinically cured. Ceftriaxone 2 g QD for four weeks and ceftriaxone 2 g QD plus gentamicin 3 mg/kg QD for two weeks were both judged effective for treatment of streptococcal endocarditis. Secondary: Not reported
Klugman et al.[143] (1995) Meropenem 40 mg/kg every eight hours for 7 to 14 days vs cefotaxime 75 to 100 mg/kg every eight hours for 7 to 14 days	PRO, RCT Children with a diagnosis of bacterial meningitis	N=190 6 weeks post-treatment	Primary: Clinical response (cure, cure with audiologic sequelae, cure with neurologic sequelae, cure with both audiologic and neurologic sequelae, death), bacteriologic response Secondary: Not reported	Primary: In patients with pre-existing neurologic abnormalities, cure was achieved in 47% of meropenem patients compared to 60% of cefotaxime patients, cure with audiologic sequelae was reported in 6% of meropenem patients and 20% of cefotaxime patients, cure with neurologic sequelae was reported in 35% of meropenem patients and 0% of cefotaxime patients, cure with both audiologic and neurologic sequelae was reported in 12% of meropenem patients and 20% of cefotaxime patients, and death was not reported in any patients in either group. In patients without pre-existing neurological abnormalities, cure was achieved in 79% of meropenem patients compared to 83% of cefotaxime patients, cure with audiologic sequelae was reported in 16% of meropenem patients and 12% of cefotaxime patients, cure with neurologic sequelae was reported in 3% of meropenem patients and 2% of cefotaxime patients, cure with both audiologic and neurologic sequelae was reported in 2% of meropenem patients and 0% of cefotaxime patients, and death was reported in no patients in the meropenem group and 3% of cefotaxime patients. Bacteriologic eradication rates were 100% in both groups. Secondary: Not reported
Odio et al.[144] (1999)	MC, PRO, RCT	N=266	Primary: Clinical response	Primary: At the five to seven week follow-up, no significant differences between

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Meropenem 40 mg/kg every eight hours vs cefotaxime 45 mg/kg every six hours Treatment duration for both groups was 7 to 14 days depending on infection.	Patients 2 months to 12 years of age with a diagnosis of bacterial meningitis	5 to 7 months post-treatment	(cure, survival with mild neurological sequelae, survival with severe neurological sequelae, death), microbiologic efficacy Secondary: Not reported	the meropenem group and the cefotaxime group were observed with respect to cure, survival with sequelae, or death (P=0.624). Severe sequelae were present in 30% of meropenem patients and in 17% of cefotaxime patients, and this difference was NS (P=0.056). At the five to seven week visit, severe sequelae in the form of audiology were present in 25% of children in the meropenem group and 15% in the cefotaxime group. By the five to seven month visit, the percentages had decreased to 18% in the meropenem group and 14% in the cefotaxime group. No significant differences were seen in any group at any time. At the end of treatment, bacterial eradication was observed in 95% of patients in the meropenem group and 96% in the cefotaxime group. Secondary: Not reported
Smyth et al. [145] (2005) Tobramycin 10 mg/kg/day IV administered TID for 14 days plus ceftazidime vs tobramycin 10 mg/kg/day IV QD for 14 days plus ceftazidime IV	DB, RCT Patients older than five years of age with cystic fibrosis who had a pulmonary exacerbation	N=244 14 days	Primary: Change in forced expiratory volume in one second over 14 days of treatment, mean change in baseline forced expiratory volume in one second Secondary: Change in serum creatinine	Primary: The mean change in forced expiratory volume in one second (percent predicted) over 14 days was similar between the two regimens (10.4% [QD] vs 10.0% [TID] (adjusted mean difference, 0.4%; 95% CI, –3.3 to 4.1). Mean % change in forced expiratory volume in one second from baseline was also similar in both treatments (21.9 vs 22.1%; –0.1%; –8.0 to 7.9). Secondary: There was no significant difference in percent change in creatinine from baseline (–1.5% [QD] vs 1.7% [TID]). In children, once-daily treatment was significantly less nephrotoxic than TID treatment (mean percent change in creatine, –4.5% [QD] vs 3.7% [TID] (adjusted mean difference, –8.0%; 95% CI, –15.7 to –0.4; P=0.04).

Drug regimen abbreviations: BID=twice daily, IM=intramuscularly, IV=intravenously, PO=by mouth, QD=once daily, QID=four times daily, TID=three times daily
Study abbreviations: AC=active-controlled, DB=double-blind, DD=double-dummy, MA=meta-analysis, MC=multicenter, NI=non-inferiority, OL=open-label, OS=observational study, PC=placebo-controlled, PG=parallel- group, PRO=prospective, RETRO=retrospective, RCT=randomized controlled trial, SB=single-blind, XO=crossover
Other abbreviations: CI=confidence interval, HR=hazard ratio, IV=intravenous, NaCl=sodium chloride, NS=non-significant, OR=odds ratio, RR=relative risk, SMX-TMP=sulfamethoxazole-trimethoprim

Additional Evidence

Dose Simplification:
Frequency of dosing is identified as a major factor in compliance for antibiotic treatment.[146] Average compliance is reduced as dosing frequency is increased. Acceptable compliance was observed most frequently with once or twice daily antibiotic regimens.[146] In a study of medication adherence, Ballantyne reported no significant difference in clinical efficacy for patients treated with once daily cefadroxil compared to cefaclor administered three times daily (91 vs 95%, respectively; P=0.41). However, medication adherence was greater in patients treated with cefadroxil once daily compared to patients treated with cefaclor three times daily (2 vs 77%, respectively).[45]

A study comparing intramuscular ceftriaxone (for up to two doses) and oral amoxicillin-clavulanate (three times daily for 10 days) in patients with acute otitis media demonstrated similar treatment failure rates in both groups (4.6 and 4.7%, respectively).[147] However, recurrence rates of acute otitis media between days 31 and 90 were observed significantly more frequently in children treated with amoxicillin-clavulanate than with ceftriaxone (29.4 vs 13.6%; P=0.012). Seventy-five percent of study participants took amoxicillin-clavulanate as prescribed or in excess; 25% of study participants took amoxicillin-clavulanate in a quantity less than that prescribed. More parents preferred the intramuscular route over oral therapy (68 vs 32%, respectively; P=0.0001).

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 15. Relative Cost of the Cephalosporins

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Cefaclor	capsule, extended-release tablet, suspension	N/A	N/A	$$$$
Cefadroxil	capsule, suspension, tablet	N/A	N/A	$
Cefazolin	injection	N/A	N/A	$$
Cefdinir	capsule, suspension	N/A	N/A	$$

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Cefepime	injection	Maxipime®*	$$$$-$$$$$	$$$$
Cefixime	capsule, chewable tablet, suspension	Suprax®*	$$$$$	$$$$$
Cefotaxime	injection	Claforan®*	$$-$$$$$	$$$
Cefpodoxime	suspension, tablet	N/A	N/A	$$$$
Cefprozil	suspension, tablet	N/A	N/A	$$
Ceftaroline	injection	Teflaro®	$$$$$	N/A
Ceftazidime	injection	Fortaz®*, Fortaz in Iso-Osmotic Dextrose®, Tazicef®*	$$$-$$$$$	$$$$
Ceftibuten	capsule, suspension	Cedax®*	$$$$$	$$$$$
Ceftriaxone	injection	N/A	N/A	$$
Cefuroxime	injection, suspension, tablet	Ceftin®*, Zinacef®*	$$$$$	$$
Cephalexin	capsule, suspension, tablet	Keflex®*	$$$$	$
Combination Products				
Ceftazidime and Avibactam	injection	Avycaz®	$$$$$	N/A
Ceftolozane and Tazobactam	injection	Zerbaxa®	$$$$$	N/A

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

X. Conclusions

The cephalosporins are approved to treat a variety of infections, including central nervous system, dermatologic, genitourinary, respiratory, as well as several miscellaneous infections.[1-13] They are often grouped into generations according to their spectrum of activity. The majority of the cephalosporins are available in a generic formulation. All of the cephalosporins are available in a generic formulation with the exception of ceftaroline and the combination products.

There are many guidelines that define the appropriate place in therapy for the cephalosporins. The agent that is recommended is dependent upon the infectious organism being treated and the corresponding spectrum of activity of the cephalosporin. The cephalosporins are recommended as specific therapy for the treatment of susceptible pathogens causing endocarditis, encephalitis, meningitis, skin and soft-tissue infections, infectious diarrhea, sexually transmitted diseases, infectious exacerbations of chronic obstructive pulmonary disease, nosocomial pneumonia, febrile neutropenia, intra-abdominal infections, Lyme disease, and for surgical prophylaxis.[15,16,18-23,26,27,35,38,39,41,43,44] They are recommended as an alternative treatment option for urinary tract infections, otitis media, group A streptococcal pharyngitis, community-acquired pneumonia, and sinusitis, especially in situations where the patient is allergic to penicillin.[28-31,33,36,37]

Numerous studies have demonstrated comparable efficacy among the cephalosporins for the treatment of skin and soft-tissue infections, urinary tract infections, upper/lower respiratory tract infections, febrile neutropenia, and for surgical prophylaxis.[45,46,50,51,53,60-69,79,81-95,104-111] There are relatively few studies which demonstrate greater clinical cure or microbiological eradication rates with one cephalosporin over another.[47,48,75,78,80,96,98,122] Data from published studies supports similar safety profiles among the cephalosporins, particularly within each generation.

Ceftaroline is approved for the treatment of skin and skin-structure infections, as well as community-acquired pneumonia.[6] Two studies compared ceftaroline to the combination of vancomycin and aztreonam in patients with complicated skin and skin-structure infections.[54-56] Clinical cure rates were similar among the treatment groups in the clinically evaluable and modified intent-to-treat populations, as well as in patients infected with methicillin-resistant *Staphylococcus aureus*. Two studies compared ceftaroline to ceftriaxone in patients with community-acquired pneumonia.[99-101] Ceftaroline was found to be non-inferior to ceftriaxone in the clinically evaluable population.

Both ceftazidime-avibactam and ceftolozane-tazobactam are indicated for the treatment of complicated intra-abdominal infections when used in combination with metronidazole and complicated urinary tract infections including pyelonephritis.[12,13] Clinical trials have suggested ceftolozane-tazobactam and ceftazidime-avibactam have similar efficacy to imipenem–cilastatin and levofloxacin, respectively in the treatment of complicated urinary-tract infections.[72,74] Both combination products, each in combination with metronidazole, have also demonstrated similar efficacy to meropenem in the treatment of complicated intra-abdominal infections.[119,120]

There is insufficient evidence to support that one brand cephalosporin 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 cephalosporins 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 cephalosporin 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 Miscellaneous β-Lactam Antibiotics
AHFS Class 081207
November 9, 2016

I. Overview

The miscellaneous β-lactam antibiotics are approved to treat a variety of infections, including central nervous system, dermatologic, genitourinary, respiratory, as well as several miscellaneous infections.[1-10] With the exception of aztreonam inhalation solution, the miscellaneous β-lactam antibiotics are only available in an injectable formulation and are primarily administered in the inpatient setting. Aztreonam inhalation solution is approved to improve respiratory symptoms in cystic fibrosis patients colonized with *Pseudomonas aeruginosa*.[4]

The β-lactam antibiotics exert their antibacterial activity by binding to penicillin-binding proteins, which inactivate the enzymes responsible for cell-wall synthesis in susceptible microorganisms. Aztreonam belongs to the monobactam class of antibiotics and has strong activity against susceptible gram-negative bacteria; however, it has no useful activity against gram-positive bacteria or anaerobes. Aztreonam is resistant to some β-lactamases, but is inactivated by extended-spectrum β-lactamases. Cefotetan and cefoxitin are considered cephamycins and demonstrate a spectrum of activity similar to the second generation cephalosporins. The carbapenems include doripenem, ertapenem, imipenem-cilastatin, and meropenem. These agents have a broad spectrum of activity and their chemical structure renders them highly resistant to β-lactamases.[1-10]

The miscellaneous β-lactam antibiotics that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All of the injectable products are available in a generic formulation, with the exception of doripenem and ertapenem. This class was last reviewed in August 2014.

Table 1. Miscellaneous β-Lactam Antibiotics Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Aztreonam	inhalation solution, injection	Azactam®*, Cayston®	aztreonam
Cefotetan	injection	Cefotan®*	cefotetan
Cefoxitin	injection	Mefoxin®*	cefoxitin
Doripenem	injection	Doribax®	none
Ertapenem	injection	Invanz®	none
Meropenem	injection	Merrem®*	meropenem
Combination Products			
Imipenem and cilastatin	injection	Primaxin®*	imipenem and cilastatin

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

The miscellaneous β-lactam antibiotics 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 β-lactam antibiotics 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 Miscellaneous β-Lactam Antibiotics[1-10]

Organism	Single Entity Agents						Combination Products
	Aztreonam†	Cefotetan	Cefoxitin	Doripenem	Ertapenem	Meropenem	Imipenem and Cilastatin
Gram-Positive Aerobes							
Enterococcus faecalis						✔	✔ §‡
Staphylococcus aureus		✔	✔		✔	✔	✔ §‡
Staphylococcus epidermidis		✔	✔				✔ ‡
Streptococcus species		✔	✔				
Streptococcus agalactiae		✔	✔		✔	✔	✔ ‡
Streptococcus constellatus				✔			
Streptococcus intermedius				✔			
Streptococcus pneumoniae		✔	✔		✔	✔	✔ §‡
Streptococcus pyogenes		✔	✔		✔	✔	✔ §‡
Streptococcus viridans group						✔	✔ §
Gram-Negative Aerobes							
Acinetobacter species							✔ §‡
Acinetobacter baumannii				✔			
Acinetobacter calcoaceticus							✔ §
Citrobacter species	✔						✔ §‡
Citrobacter freundii	✔						
Enterobacter species	✔						✔ §‡
Enterobacter cloacae	✔						✔ §
Escherichia coli	✔	✔	✔	✔	✔	✔	✔ §‡
Gardnerella vaginalis							✔ ‡
Haemophilus influenzae	✔	✔	✔		✔	✔	✔ §‡
Haemophilus parainfluenzae							✔ ‡
Klebsiella species	✔	✔	✔		✔		✔ §‡
Klebsiella oxytoca	✔						
Klebsiella pneumoniae	✔	✔	✔	✔	✔	✔	✔ §
Moraxella catarrhalis					✔		
Morganella morganii		✔	✔				✔ ‡
Neisseria gonorrhoeae		✔	✔				
Neisseria meningitidis						✔	
Proteus species		✔					
Proteus mirabilis	✔	✔	✔	✔	✔	✔	
Proteus vulgaris		✔	✔				✔ ‡

Organism	Single Entity Agents						Combination Products
	Aztreonam†	Cefotetan	Cefoxitin	Doripenem	Ertapenem	Meropenem	Imipenem and Cilastatin
Providencia species			✔				
Providencia rettgeri		✔	✔				✔ ‡
Pseudomonas aeruginosa	✔			✔		✔	✔ §‡
Serratia species	✔						✔ ‡
Serratia marcescens	✔	✔					✔ ‡
Gram-Positive Anaerobes							
Clostridium species		✔	✔				✔ ‡
Clostridium clostridioforme					✔		
Eubacterium species							✔ ‡
Eubacterium lentum					✔		
Peptococcus species							✔ ‡
Peptococcus niger		✔	✔				
Peptostreptococcus species		✔	✔		✔	✔	✔ §‡
Peptostreptococcus micros				✔			
Porphyromonas asaccharolytica					✔		
Prevotella bivia		✔			✔		
Prevotella disiens		✔					
Prevotella melaninogenica		✔					
Propionibacterium species							✔ ‡
Gram-Negative Anaerobes							
Bacteroides species			✔				✔ §‡
Bacteroides caccae				✔			
Bacteroides distasonis			✔		✔		✔ §
Bacteroides fragilis		✔	✔	✔	✔	✔	✔ §‡
Bacteroides intermedius							✔ §
Bacteroides ovatus			✔		✔		
Bacteroides thetaiotaomicron			✔	✔	✔	✔	✔ §
Bacteroides uniformis				✔	✔		
Bacteroides vulgatus		✔		✔			
Bifidobacterium species							✔ ‡
Fusobacterium species		✔					✔ §‡

†Injection formulation.
‡Intramuscular formulation.
§Intravenous formulation.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the miscellaneous β-lactam antibiotics are summarized in Table 3.

Table 3. Treatment Guidelines Using the Miscellaneous β-Lactam Antibiotics

Clinical Guideline	Recommendation(s)
American Heart Association: **Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications (2015)**[11]	• Therapy for native valve endocarditis caused by viridans group streptococci and *Streptococcus gallolyticus* (Formerly Known as *Streptococcus bovis)*: o Highly penicillin-susceptible strains: ▪ Penicillin G or ceftriaxone for four weeks. ▪ Penicillin G or ceftriaxone plus gentamicin for two weeks (in patients with uncomplicated infective endocarditis, rapid response to therapy, and no underlying renal disease). ▪ Vancomycin for four weeks (recommended only for patients unable to tolerate penicillin or ceftriaxone therapy). o Relatively penicillin-resistant strains: ▪ Penicillin for four weeks plus gentamicin for the first two weeks. ▪ If the isolate is ceftriaxone susceptible, then ceftriaxone alone may be considered. ▪ Vancomycin for four weeks (recommended only for patients unable to tolerate beta-lactam therapy). • Therapy for native valve endocarditis caused by *A defectiva* and *Granulicatella* Species and viridans group streptococci: o For patients with infective endocarditis caused by *A defectiva*, *Granulicatella* species, and viridans group streptococci with a penicillin MIC ≥0.5 µg/mL, treat with a combination of ampicillin or penicillin plus gentamicin as done for enterococcal infective endocarditis with infectious diseases consultation. o If vancomycin is used in patients intolerant of ampicillin or penicillin, then the addition of gentamicin is not needed. o Ceftriaxone combined with gentamicin may be a reasonable alternative treatment option for isolates that are susceptible to ceftriaxone. • Therapy for endocarditis of prosthetic valves or other prosthetic material caused by viridans group streptococci and *Streptococcus gallolyticus* (Formerly Known as *Streptococcus bovis)*: o Penicillin for six weeks plus gentamicin for the first two weeks. o Extend gentamicin to six weeks if the MIC is >0.12 µg/mL for the infecting strain. o Vancomycin can be used in patients intolerant of penicillin, ceftriaxone, or gentamicin. • Therapy for endocarditis of prosthetic valves or other prosthetic material caused by *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and Groups B, C, F, and G β-Hemolytic Streptococci: o Penicillin, cefazolin, or ceftriaxone for four weeks is reasonable for infective endocarditis caused by *S pneumoniae*; vancomycin can be useful for patients intolerant of β-lactam therapy. o Six weeks of therapy is reasonable for prosthetic valve endocarditis caused by *S pneumoniae*. o High-dose penicillin or a third-generation cephalosporin is reasonable in patients with infective endocarditis caused by penicillin-resistant *S pneumoniae* without meningitis; if meningitis is present, then high doses of cefotaxime (or ceftriaxone) are reasonable. o The addition of vancomycin and rifampin to cefotaxime (or ceftriaxone) may be considered in patients with infective endocarditis caused by *S pneumoniae* that are resistant to cefotaxime.

Clinical Guideline	Recommendation(s)
	o Because of the complexities of infective endocarditis caused by *S pneumoniae*, consultation with an infectious diseases specialist is recommended. o For infective endocarditis caused by *S pyogenes*, four to six weeks of therapy with aqueous crystalline penicillin G or ceftriaxone is reasonable; vancomycin is reasonable only in patients intolerant of β-lactam therapy. o For infective endocarditis caused by group B, C, or G streptococci, the addition of gentamicin to penicillin G or ceftriaxone for at least the first two weeks of a four to six week treatment course may be considered. o Consultation with an infectious diseases specialist to guide treatment is recommended in patients with infective endocarditis caused by β-hemolytic streptococci. • Therapy for endocarditis caused by staphylococci in the absence of prosthetic valves or other prosthetic material: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin for six weeks. ▪ For penicillin-allergic individuals: cefazolin for six weeks. o Oxacillin-resistant strains ▪ Vancomycin for six weeks. ▪ Daptomycin for six weeks. • Therapy for prosthetic valve endocarditis caused by staphylococci: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin plus rifampin (for at least six weeks) and gentamicin (for two weeks). o Oxacillin-resistant strains: ▪ Vancomycin plus rifampin (for at least six weeks) and gentamicin (for two weeks). • Therapy for native valve or prosthetic valve enterococcal endocarditis: o Strains susceptible to penicillin and gentamicin: ▪ Ampicillin or penicillin G plus gentamicin for four to six weeks. ▪ Double β-lactam ampicillin plus ceftriaxone for six. o Strains susceptible to penicillin and resistant to aminoglycosides or streptomycin-susceptible gentamicin-resistant in patients able to tolerate β-Lactam therapy: ▪ Ampicillin plus ceftriaxone for six weeks. ▪ Ampicillin or penicillin G plus streptomycin for four to six weeks. o Vancomycin and aminoglycoside-susceptible penicillin-resistant enterococcus species in patients unable to tolerate β-lactam : ▪ Unable to tolerate β-lactams: • Vancomycin plus gentamicin for six weeks (vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone therapy). ▪ Intrinsic penicillin resistance: • Vancomycin plus gentamicin for six weeks. o Strains Resistant to Penicillin, Aminoglycosides, and Vancomycin: ▪ Linezolid or daptomycin for at least six weeks. • Therapy for both native and prosthetic valve endocarditis caused by *Haemophilus* species *(Haemophilus parainfluenzae, Haemophilus aphrophilus, Haemophilus paraphrophilus), Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* species microorganisms: o Ceftriaxone (cefotaxime or another third- or fourth-generation cephalosporin may be substituted) or ampicillin or ciprofloxacin for four weeks. Fluoroquinolone therapy recommended only for patients unable to tolerate cephalosporin and ampicillin therapy; levofloxacin or moxifloxacin may be substituted.

Clinical Guideline	Recommendation(s)
	• Therapy for culture-negative endocarditis including *Bartonella* endocarditis: o For patients with acute (days) clinical presentations of native valve infection, coverage for *S aureus*, β-hemolytic streptococci, and aerobic Gram-negative bacilli is reasonable. o For patients with a subacute (weeks) presentation of native valve endocarditis, coverage of *S aureus*, viridans group streptococci, HACEK, and enterococci is reasonable. o For patients with culture-negative prosthetic valve endocarditis, coverage for staphylococci, enterococci, and aerobic Gram-negative bacilli is reasonable if onset of symptoms is within one year of prosthetic valve placement. o If symptom onset is >1 year after valve placement, then infective endocarditis is more likely to be caused by staphylococci, viridans group streptococci, and enterococci, and antibiotic therapy for these potential pathogens is reasonable.
American College of Cardiology/American Heart Association: **2008 Focused Update Incorporated Into the American College of Cardiology/ American Heart Association 2006 Guidelines for the Management of Patients With Valvular Heart Disease (2008)**[12] American College of Cardiology/American Heart Association: **Guideline for the Management of Patients With Valvular Heart Disease (2014)**[13] **(although a more current guideline more detailed information was included as part of the 2008 Focused update; as such both are summarized together)**	<u>Rheumatic fever prophylaxis</u> • Primary prevention of rheumatic heart disease: o Penicillin G benzathine intramuscular once or penicillin V orally for 10 days. o Erythromycin estolate or erythromycin ethylsuccinate orally for 10 days, or azithromycin orally for five days in patients who are allergic to penicillin. • Secondary prevention of rheumatic fever: o Penicillin G benzathine intramuscular every four weeks, or penicillin V orally twice daily, or sulfadiazine orally once daily. o Erythromycin orally twice daily for patients who are allergic to penicillin. <u>Endocarditis prophylaxis</u> • Prophylaxis against infective endocarditis is reasonable for the following patients at highest risk for adverse outcomes from infective endocarditis who undergo dental procedures that involve manipulation of either gingival tissue or the periapical region of teeth or perforation of the oral mucosa: o Patients with prosthetic cardiac valve or prosthetic material used for cardiac valve repair. o Patients with previous infective endocarditis. o Patients with congenital heart disease. o Cardiac transplant recipients with valve regurgitation due to a structurally abnormal valve. • Prophylaxis against infective endocarditis is not recommended for non-dental procedures (such as transesophageal echocardiogram, esophagogastroduodenoscopy, or colonoscopy) in the absence of active infection. • Regimens for dental procedures (single dose 30 to 60 minutes before procedure): o Oral: amoxicillin. o Unable to take oral medications: ampicillin, cefazolin or ceftriaxone. o Allergic to penicillin or ampicillin (oral): cephalexin, clindamycin, or azithromycin. o Allergic to penicillins or ampicillin and unable to take oral medication: cefazolin, ceftriaxone, or clindamycin. • Therapy of native valve endocarditis caused by highly penicillin-susceptible viridans group streptococci and *Streptococcus bovis:* o Penicillin G or ceftriaxone for four weeks. o Ceftriaxone plus gentamicin for two weeks. o Vancomycin for four weeks in patients allergic to penicillin. • Therapy of native valve endocarditis caused by strains of viridans group streptococci and *Streptococcus bovis* relatively resistant to penicillin:

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	o Penicillin G or ceftriaxone for four weeks plus gentamicin for two weeks. o Vancomycin for four weeks in patients allergic to penicillin. • Therapy for native valve or prosthetic valve enterococcal endocarditis caused by strains susceptible to penicillin, gentamicin, and vancomycin: o Ampicillin for four to six weeks or penicillin G plus gentamicin for four to six weeks. o Vancomycin plus gentamicin for six weeks in patients allergic to penicillin. • Therapy for endocarditis caused by staphylococci in the absence of prosthetic materials: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin for six weeks plus the optional addition of gentamicin for three to five days. ▪ Cefazolin for six weeks with the optional addition of gentamicin in patients allergic to penicillin. o Oxacillin-resistant strains: ▪ Vancomycin for six weeks. • Therapy for prosthetic valve endocarditis caused by staphylococci: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin, rifampin, and gentamicin for ≥6 weeks. o Oxacillin-resistant strains: ▪ Vancomycin, rifampin, and gentamicin for ≥6 weeks. • Therapy for both native and prosthetic valve endocarditis caused by *Haemophilus* species *(Haemophilus parainfluenzae, Haemophilus aphrophilus, Haemophilus paraphrophilus), Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* species microorganisms: o Ceftriaxone for four weeks. o Ampicillin-sulbactam for four weeks. o Ciprofloxacin for four weeks. • Therapy for culture-negative endocarditis including *Bartonella* endocarditis: o Native valve: ▪ Ampicillin-sulbactam plus gentamicin (or vancomycin for patients allergic to penicillin) plus ciprofloxacin for four to six weeks. o Prosthetic valve (early; ≤1 year): ▪ Vancomycin for six weeks, plus gentamicin for two weeks, plus cefepime for six weeks, plus rifampin for six weeks. o Prosthetic valve (late; >1 year): ▪ Suspected *Bartonella*, culture negative: • Ceftriaxone for six weeks plus gentamicin with/without doxycycline for six weeks. ▪ Documented *Bartonella*, culture positive: • Doxycycline for six weeks plus gentamicin for two weeks.
European Society of Cardiology: **Guidelines for the Management of Infective Endocarditis (2015)**[14]	Main principles of prevention if infective endocarditis • The principle of antibiotic prophylaxis when performing procedures at risk of infective endocarditis (IE) in patients with predisposing cardiac conditions is maintained. • Antibiotic prophylaxis must be limited to patients with the highest risk of IE undergoing the highest risk dental procedures (dental procedures requiring manipulation of the gingival or periapical region of the teeth or perforation of the oral mucosa). o Patients with a prosthetic valve, including transcatheter valve, or a prosthetic material used for cardiac valve repair. o Patients with previous IE. o Patients with congenital heart disease.

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	• Good oral hygiene and regular dental review are more important than antibiotic prophylaxis to reduce the risk of IE.
	• Aseptic measures are mandatory during venous catheter manipulation and during any invasive procedures in order to reduce the rate of health care-associated IE.
	• Recommended prophylaxis for dental procedures at high-risk:
	  o Single-dose amoxicillin or penicillin 30 to 60 minutes before procedure.
	  o If allergy to penicillin or ampicillin, single-dose clindamycin 30 to 60 minutes before procedure.
	
	<u>Antimicrobial therapy: principles</u>
	• The treatment of infective endocarditis relies on the combination of prolonged antimicrobial therapy and - in about half of patients - surgical eradication of the infected tissues.
	• Prolonged therapy with a combination of bactericidal drugs is the basis of IE treatment. Drug treatment of prosthetic valve endocarditis (PVE) should last longer (at least six weeks) than that of native valve endocarditis (NVE) (two to six weeks).
	• In both NVE and PVE, the duration of treatment is based on the first day of effective antibiotic therapy, not on the day of surgery. A new full course of treatment should only start if valve cultures are positive, the choice of antibiotic being based on the susceptibility of the latest recovered bacterial isolate.
	• The indications and pattern of use of aminoglycosides have changed. They are no longer recommended in staphylococcal NVE because their clinical benefits have not been demonstrated but they can increase renal toxicity; and, when they are indicated in other conditions, aminoglycosides should be given in a single daily dose in order to reduce nephrotoxicity.
	• New antibiotic regimens have emerged in the treatment of staphylococcal IE, including daptomycin and the combination of high-doses of cotrimoxazole plus clindamycin, but additional investigations are necessary in large series before they can be recommended in all patients.
	
	<u>Antimicrobial therapy: regimens</u>
	• Antibiotic treatment of infective endocarditis due to oral streptococci and *Streptococcus* bovis group:
	  o Penicillin-susceptible strains:
	  ▪ Penicillin G, amoxicillin, or ceftriaxone for four weeks.
	  ▪ Penicillin G, amoxicillin, or ceftriaxone plus gentamicin or netilmicin for two weeks.
	  ▪ Vancomycin for four weeks (in beta-lactam allergic patients).
	  o Penicillin-resistant strains:
	  ▪ Penicillin G, amoxicillin, or ceftriaxone for four weeks plus gentamicin for two weeks.
	  ▪ Vancomycin for four weeks plus gentamicin for two weeks (in beta-lactam allergic patients).
	• Antibiotic treatment of infective endocarditis due to *Staphylococcus* species:
	  o Methicillin-susceptible strains (native valves):
	  ▪ Flucloxacillin or oxacillin for four to six weeks.
	  ▪ Cotrimoxazole intravenous for one week and oral for five weeks plus clindamycin for one week (for *Staphylococcus aureus*).
	  o Penicillin-allergic patients or methicillin-resistant staphylococci (native valves):
	  ▪ Vancomycin for four to six weeks.
	  ▪ Alternative: Daptomycin for four to six weeks.
	  ▪ Cotrimoxazole intravenous for one week and oral for five weeks plus clindamycin for one week (for *Staphylococcus aureus*).
	  o Methicillin-susceptible strains (prosthetic valves):

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	▪ Flucloxacillin or oxacillin for at least six weeks, rifampin for at least six weeks, and gentamicin for two weeks. o Penicillin-allergic patients or methicillin-resistant staphylococci (prosthetic valves): ▪ Vancomycin for at least six weeks, rifampin for at least six weeks, and gentamicin for two weeks. • Antibiotic treatment of infective endocarditis due to *Enterococcus* species: o Beta-lactam and gentamicin susceptible strains: ▪ Amoxicillin for four to six weeks plus gentamicin for two to six weeks. ▪ Ampicillin plus gentamicin for six weeks. ▪ Vancomycin plus gentamicin for six weeks. • Antibiotic treatment of blood culture-negative infective endocarditis: o *Brucella* species: ▪ Doxycycline, cotrimoxazole, and rifampin for ≥3 months. o *Coxiella burnetii* (agent of Q fever): ▪ Doxycycline plus hydroxychloroquine for >18 months. ▪ o *Bartonella* species: ▪ Doxycycline orally for four weeks plus gentamicin for two weeks. o *Legionella* species: ▪ Levofloxacin intravenous for ≥6 weeks or clarithromycin intravenous for two weeks then orally for four weeks plus rifampin. o *Mycoplasma* species: ▪ Levofloxacin for ≥6 months. o *Tropheryma whipplei* (agent of Whipple's disease): ▪ Doxycycline plus hydroxychloroquine orally for ≥18 months. • Proposed antibiotic regimens for initial empirical treatment of infective endocarditis in acute severely ill patients (before pathogen identification): o Community-acquired native valves or late prosthetic valves (≥12 months post surgery) endocarditis: ▪ Ampicillin intravenous plus flucloxacillin or oxacillin intravenous plus gentamicin intravenous for once dose. ▪ Vancomycin intravenous plus gentamicin intravenous (for penicillin allergic patients). o Early PVE (<12 months post surgery) or nosocomial and non-nosocomial healthcare associated endocarditis: ▪ Vancomycin intravenous, gentamicin intravenous, and rifampin orally.
European Federation of Neurological Societies: **Guideline on the Management of Community-acquired Bacterial Meningitis (2008)**[15]	Empirical therapy • Ceftriaxone 2 g every 12 to 24 hours or cefotaxime 2 g every six to eight hours. • Alternative therapy: meropenem 2 g every eight hours or chloramphenicol 1 g every six hours. • If penicillin or cephalosporin-resistant pneumococcus is suspected, use ceftriaxone or cefotaxime plus vancomycin 60 mg/kg every 24 hours after a loading dose of 15 mg/kg. • Ampicillin-amoxicillin 2 g every four hours if *Listeria* is suspected. Pathogen specific therapy • Penicillin-sensitive pneumococcal meningitis: o Benzyl penicillin 250,000 U/kg/day, ampicillin-amoxicillin 2 g every four hours, ceftriaxone 2 g every 12 hours or cefotaxime 2 g every six to eight hours. o Alternative therapy: meropenem 2 g every eight hours or vancomycin 60

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	mg/kg every 24 hours as a continuous infusion after a 15 mg/kg loading dose plus rifampicin 600 mg every 12 hours, or moxifloxacin 400 mg daily. • Pneumococcus with reduced susceptibility to penicillin or cephalosporins: o Ceftriaxone or cefotaxime plus vancomycin±rifampicin. o Alternative therapy: moxifloxacin, meropenem or linezolid 600 mg combined with rifampicin. • Meningococcal meningitis: o Benzyl penicillin, ceftriaxone, or cefotaxime. o Alternative therapy: meropenem, chloramphenicol, or moxifloxacin. • *Haemophilus influenzae* type B: o Ceftriaxone or cefotaxime. o Alternative therapy: chloramphenicol–ampicillin-amoxicillin. • Listerial meningitis: o Ampicillin or amoxicillin 2 g every four hours±gentamicin 1 to 2 mg every eight hours for the first seven to 10 days. o Alternative therapy: sulfamethoxazole-trimethoprim 10 to 20 mg/kg every six to 12 hours or meropenem. • *Staphylococcal* species: o Flucloxacillin 2 g every four hours or vancomycin if penicillin allergy is suspected. o Rifampicin should also be considered in addition to either agent. Linezolid should be considered for methicillin-resistant staphylococcal meningitis. • Gram-negative *Enterobacteriaceae*: o Ceftriaxone, cefotaxime or meropenem. • Pseudomonal meningitis: o Meropenem±gentamicin.
Infectious Diseases Society of America: **Practice Guidelines for the Management of Bacterial Meningitis (2004)**[16]	Empiric therapy • Empirical antimicrobial therapy is initiated either when the lumbar puncture is delayed or for patients with purulent meningitis and a negative cerebrospinal fluid gram stain result: o Age <1 month: ampicillin plus cefotaxime or ampicillin plus an aminoglycoside. o Age one to 23 months: vancomycin plus a third-generation cephalosporin. o Age two to 50 years: vancomycin plus a third-generation cephalosporin. o Age >50 years: vancomycin plus ampicillin plus a third-generation cephalosporin. o Basilar skull fracture: vancomycin plus a third-generation cephalosporin. o Penetrating head trauma: vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem. o Post neurosurgery: vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem. o Cerebrospinal fluid shunt: vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem. Specific therapy • Recommendations for specific antimicrobial therapy in bacterial meningitis are based on isolated pathogens and susceptibility. • *Streptococcus pneumoniae* o Penicillin minimum inhibitory concentrations <0.1 µg/mL: standard therapy includes penicillin G or ampicillin; alternative therapies include ceftriaxone, cefotaxime, or chloramphenicol. o Penicillin minimum inhibitory concentrations 0.1 to 1.0 µg/mL: standard therapy includes ceftriaxone or cefotaxime; alternative therapies include

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	cefepime or meropenem. o Penicillin minimum inhibitory concentrations ≥2 µg/mL: standard therapies include vancomycin plus ceftriaxone or cefotaxime; alternative therapies include gatifloxacin or moxifloxacin. o Cefotaxime or ceftriaxone minimum inhibitory concentrations ≥1.0 µg/mL: standard therapies include vancomycin plus ceftriaxone or cefotaxime (consider addition of rifampin if minimum inhibitory concentrations of ceftriaxone is >2 µg/mL); alternative therapies include gatifloxacin or moxifloxacin. • *Neisseria meningitides* o Penicillin minimum inhibitory concentrations <0.1 µg/mL: standard therapy includes penicillin G or ampicillin; alternative therapy includes ceftriaxone, cefotaxime or chloramphenicol. o Penicillin minimum inhibitory concentrations 0.1 to 1.0 µg/mL: standard therapy includes ceftriaxone or cefotaxime; alternative therapies include chloramphenicol, a fluoroquinolone or meropenem. • *Listeria monocytogenes* o Standard therapy includes ampicillin or penicillin G; alternative therapies include sulfamethoxazole-trimethoprim or meropenem. • *Streptococcus agalactiae* o Standard therapy includes ampicillin or penicillin G; alternative therapies include ceftriaxone or cefotaxime. • *Escherichia coli* and other Enterobacteriaceae o Standard therapy includes a third-generation cephalosporin; alternative therapies include aztreonam, fluoroquinolone, meropenem, sulfamethoxazole-trimethoprim or ampicillin. • *Pseudomonas aeruginosa* o Standard therapies include cefepime or ceftazidime; alternative therapies include aztreonam, ciprofloxacin, or meropenem (addition of an aminoglycoside should be considered). • *Haemophilus influenzae* β-lactamase negative strains o Standard therapy includes ampicillin; alternative therapies include ceftriaxone, cefotaxime, cefepime, chloramphenicol or a fluoroquinolone. • *Haemophilus influenzae* β-lactamase positive strains o Standard therapy includes a third-generation cephalosporin; alternative therapies include cefepime, chloramphenicol or a fluoroquinolone. • *Staphylococcus aureus* methicillin susceptible o Standard therapy includes nafcillin or ofloxacin; alternative therapies include vancomycin or meropenem. • *Staphylococcus aureus* methicillin resistant o Standard therapy includes vancomycin (consider addition of rifampin); alternative therapies include sulfamethoxazole-trimethoprim or linezolid. • *Staphylococcus epidermidis* o Standard therapy includes vancomycin (consider addition of rifampin); alternative therapy includes linezolid. • *Enterococcus* species ampicillin susceptible o Standard therapy includes ampicillin plus gentamicin. • *Enterococcus* species ampicillin resistant o Standard therapy includes vancomycin plus gentamicin. • *Enterococcus* species ampicillin and vancomycin resistant o Standard therapy includes linezolid.
Infectious Diseases Society of America: **Practice Guidelines**	Impetigo and ecthyma • Gram stain and culture of the pus or exudates from skin lesions of impetigo and ecthyma are recommended to help identify whether *Staphylococcus*

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for the Diagnosis and Management of Skin and Soft-Tissue Infections (2014)[17]	*aureus* and/or a β-hemolytic *Streptococcus* is the cause (strong, moderate), but treatment without these studies is reasonable in typical cases.
	• Bullous and nonbullous impetigo can be treated with oral or topical antimicrobials, but oral therapy is recommended for patients with numerous lesions or in outbreaks affecting several people to help decrease transmission of infection. Treatment for ecthyma should be an oral antimicrobial.
	  o Treatment of bullous and nonbullous impetigo should be with either mupirocin or retapamulin twice daily for five days.
	  o Oral therapy for ecthyma or impetigo should be a seven-day regimen with an agent active against *S. aureus* unless cultures yield streptococci alone (when oral penicillin is the recommended agent). Because *S. aureus* isolates from impetigo and ecthyma are usually methicillin susceptible, dicloxacillin or cephalexin is recommended. When MRSA is suspected or confirmed, doxycycline, clindamycin, or sulfamethoxazole-trimethoprim is recommended.
	
	<u>Purulent skin and soft-tissue infections (cutaneous abscesses, furuncles, carbuncles, and inflamed epidermoid cysts)</u>
	• Gram stain and culture of pus from carbuncles and abscesses are recommended, but treatment without these studies is reasonable in typical cases. Gram stain and culture of pus from inflamed epidermoid cysts are not recommended.
	• Incision and drainage is the recommended treatment for inflamed epidermoid cysts, carbuncles, abscesses, and large furuncles.
	• The decision to administer antibiotics directed against *S. aureus* as an adjunct to incision and drainage should be made based upon presence or absence of systemic inflammatory response syndrome (SIRS), such as temperature >38°C or <36°C, tachypnea >24 breaths per minute, tachycardia >90 beats per minute, or white blood cell count >12 000 or <400 cells/µL. An antibiotic active against MRSA is recommended for patients with carbuncles or abscesses who have failed initial antibiotic treatment or have markedly impaired host defenses or in patients with SIRS and hypotension.
	
	<u>Recurrent skin abscesses</u>
	• A recurrent abscess at a site of previous infection should prompt a search for local causes such as a pilonidal cyst, hidradenitis suppurativa, or foreign material.
	• Recurrent abscesses should be drained and cultured early in the course of infection.
	• After obtaining cultures of recurrent abscess, treat with a five to ten day course of an antibiotic active against the pathogen isolated.
	• Consider a five-day decolonization regimen twice daily of intranasal mupirocin, daily chlorhexidine washes, and daily decontamination of personal items such as towels, sheets, and clothes for recurrent *S. aureus* infection.
	• Adult patients should be evaluated for neutrophil disorders if recurrent abscesses began in early childhood.
	
	<u>Erysipelas and cellulitis</u>
	• Cultures of blood or cutaneous aspirates, biopsies, or swabs are not routinely recommended except in patients with malignancy on chemotherapy, neutropenia, severe cell-mediated immunodeficiency, immersion injuries, and animal bites.
	• Typical cases of cellulitis without systemic signs of infection should receive an antimicrobial agent that is active against streptococci. For cellulitis with systemic signs of infection (moderate nonpurulent), systemic antibiotics are

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	indicated. Many clinicians could include coverage against methicillin-susceptible *S. aureus* (MSSA). For patients whose cellulitis is associated with penetrating trauma, evidence of MRSA infection elsewhere, nasal colonization with MRSA, injection drug use, or SIRS (severe nonpurulent), vancomycin or another antimicrobial effective against both MRSA and streptococci is recommended. In severely compromised patients, broad-spectrum antimicrobial coverage may be considered. Vancomycin plus either piperacillin-tazobactam or imipenem/meropenem is recommended as a reasonable empiric regimen for severe infections. • The recommended duration of antimicrobial therapy is five days, but treatment should be extended if the infection has not improved within this time period. Surgical site infections • Suture removal plus incision and drainage should be performed for surgical site infections. • Adjunctive systemic antimicrobial therapy is not routinely indicated, but in conjunction with incision and drainage may be beneficial for surgical site infections associated with a significant systemic response. • A brief course of systemic antimicrobial therapy is indicated in patients with surgical site infections following clean operations on the trunk, head and neck, or extremities that also have systemic signs of infection. • A first-generation cephalosporin or an antistaphylococcal penicillin for MSSA, or vancomycin, linezolid, daptomycin, telavancin, or ceftaroline where risk factors for MRSA are high (nasal colonization, prior MRSA infection, recent hospitalization, recent antibiotics), is recommended. • Agents active against gram-negative bacteria and anaerobes, such as a cephalosporin or fluoroquinolone in combination with metronidazole, are recommended for infections following operations on the axilla, gastrointestinal tract, perineum, or female genital tract. Necrotizing fasciitis • Empiric antibiotic treatment should be broad (e.g., vancomycin or linezolid plus piperacillin-tazobactam or a carbapenem; or plus ceftriaxone and metronidazole), as the etiology can be polymicrobial (mixed aerobic–anaerobic microbes) or monomicrobial (group A streptococci, community-acquired MRSA). • Penicillin plus clindamycin is recommended for treatment of documented group A streptococcal necrotizing fasciitis. Pyomyositis • Cultures of blood and abscess material should be obtained. • Vancomycin is recommended for initial empirical therapy. An agent active against enteric gram-negative bacilli should be added for infection in immunocompromised patients or following open trauma to the muscles. • Cefazolin or antistaphylococcal penicillin (e.g., nafcillin or oxacillin) is recommended for treatment of pyomyositis caused by MSSA. • Antibiotics should be administered intravenously initially, but once the patient is clinically improved, oral antibiotics are appropriate for patients in whom bacteremia cleared promptly and there is no evidence of endocarditis or metastatic abscess. Two to three weeks of therapy is recommended. Clostridial gas gangrene or myonecrosis • Urgent surgical exploration of the suspected gas gangrene site and surgical debridement of involved tissue should be performed.

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	• In the absence of a definitive etiologic diagnosis, broad-spectrum treatment with vancomycin plus either piperacillin-tazobactam, ampicillin-sulbactam, or a carbapenem antimicrobial is recommended. Definitive antimicrobial therapy with penicillin and clindamycin is recommended for treatment of clostridial myonecrosis. Animal bites • Preemptive early antimicrobial therapy for three to five days is recommended for patients who: o are immunocompromised; o are asplenic; o have advanced liver disease; o have preexisting or resultant edema of the affected area; o have moderate to severe injuries, especially to the hand or face; or o have injuries that may have penetrated the periosteum or joint capsule. • 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 o β-lactam-β-lactamase combinations, piperacillin-tazobactam, second-generation cephalosporins, and carbapenems. • Tetanus toxoid should be administered to patients without toxoid vaccination within 10 years. Tetanus, diphtheria, and tetanus (Tdap) is preferred over Tetanus and diphtheria (Td) if the former has not been previously given. Cutaneous anthrax • Oral penicillin V 500 mg four times daily for seven to 10 days is the recommended treatment for naturally acquired cutaneous anthrax. • Ciprofloxacin 500 mg by mouth twice daily or levofloxacin 500 mg intravenously/orally every 24 hours for 60 days is recommended for bioterrorism cases because of presumed aerosol exposure. Bacillary angiomatosis and cat scratch disease • Azithromycin is recommended for cat scratch disease (strong, moderate) according to the following dosing protocol: o Patients >45 kg: 500 mg on day one followed by 250 mg for four additional days. o Patients <45 kg: 10 mg/kg on day one and 5 mg/kg for four more days. • Erythromycin 500 mg four times daily or doxycycline 100 mg bid for two weeks to two months is recommended for treatment of bacillary angiomatosis. Erysipeloid • Penicillin (500 mg four times daily) or amoxicillin (500 mg three times daily) for seven to 10 days is recommended for treatment of erysipeloid. Glanders • Ceftazidime, gentamicin, imipenem, doxycycline, or ciprofloxacin is recommended based on in vitro susceptibility.

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	Bubonic plague • Bubonic plague should be diagnosed by Gram stain and culture of aspirated material from a suppurative lymph node. Streptomycin (15 mg/kg intramuscularly every 12 hours) or doxycycline (100 mg twice daily by mouth) is recommended for treatment of bubonic plague. Gentamicin could be substituted for streptomycin. Tularemia • Streptomycin (15 mg/kg every 12 hours intramuscularly) or gentamicin (1.5 mg/kg every 8 hours intravenously) is recommended for treatment of severe cases of tularemia. • Tetracycline (500 mg four times daily) or doxycycline (100 mg twice daily by mouth) is recommended for treatment of mild cases of tularemia.
Infectious Diseases Society of America: **Diagnosis and Treatment of Diabetic Foot Infections (2012)**[18]	• Empirical antibiotic regimens should be based on the clinical severity of the infection. • Current clinical data does not allow for the recommendation of any specific antibiotic regimen for diabetic foot infections. • Suggested agents are derived from available published clinical trials and expert experience. • Definitive regimens should consider results of culture and susceptibility tests, as well as the clinical response to the empirical regimen. Similar agents of the same drug class may be substituted. Some of these regimens may not have Food and Drug Administration approval for complicated skin and skin-structure infections, and only linezolid, ertapenem and piperacillin-tazobactam are currently specifically approved for diabetic foot infections. • Suggested empirical antibiotic regimens for mild infections: dicloxacillin, clindamycin, cephalexin, sulfamethoxazole-trimethoprim, amoxicillin-clavulanate, levofloxacin and doxycycline. • Suggested empirical antibiotic regimens for moderate infections: levofloxacin, cefoxitin, ceftriaxone, ampicillin-sulbactam, moxifloxacin, tigecycline, linezolid, daptomycin, ertapenem, ticarcillin-clavulanate, piperacillin-tazobactam, levofloxacin or ciprofloxacin with clindamycin, imipenem-cilastatin, vancomycin, ceftazidime, cefepime, aztreonam. • Suggested empirical antibiotic regimens for severe infections: piperacillin-tazobactam, vancomycin, ceftazidime, cefepime, aztreonam or a carbapenem.

Centers for Disease Control and Prevention: **Sexually Transmitted Diseases Treatment Guidelines (2015)**[19]	Arthritis and arthritis-dermatitis syndrome
	• Recommended regimen:
	  o Ceftriaxone 1 g intramuscular or intravenous every 24 hours plus azithromycin 1 g orally in a single dose.
	• Alternative regimen:
	  o Cefotaxime 1 g intravenous every eight hours or ceftizoxime 1 g intravenous every eight hours plus azithromycin 1 g orally in a single dose.
	
	Bacterial vaginosis
	• Recommended regimens:
	  o Metronidazole 500 mg orally twice a day for seven days.
	  o Metronidazole gel 0.75%, one full applicator (5 g) intravaginally, once a day for five days.
	  o Clindamycin cream 2%, one full applicator (5 g) intravaginally at bedtime for seven days.
	• Alternative regimens:
	  o Tinidazole 2 g orally once daily for two days.
	  o Tinidazole 1 g orally once daily for five days.
	  o Clindamycin 300 mg orally twice daily for seven days.

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	o Clindamycin ovules 100 mg intravaginally once at bedtime for three days. Cervicitis • Recommended regimens for presumptive treatment: o Azithromycin 1 g orally in a single dose. o Doxycycline 100 mg orally twice a day for seven days. Chancroid • Recommended regimens: o Azithromycin 1 g 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. Chlamydial infections • Recommended regimens: o Azithromycin 1 g 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. Chlamydial infections among children • 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 g orally in a single dose. • Recommended regimens for children ≥8 years of age: o Azithromycin 1 g orally in a single dose. o Doxycycline 100 mg orally twice a day for seven days. Disseminated gonococcal infection • Recommended regimen: o Ceftriaxone 1 g intramuscular or intravenous every 24 hours. • Alternative regimens: o Cefotaxime 1 g intravenous every eight hours. o Ceftizoxime 1 g intravenous every eight hours. Epididymitis • 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. Granuloma inguinale (Donovanosis) • Recommended regimen: o Azithromycin 1 g orally once per week or 500 mg daily for at least three weeks and until all lesions have completely healed.

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	• Alternative regimens:
	  o Doxycycline 100 mg orally twice a day 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 g intramuscular in a single dose plus azithromycin 1 g orally 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 25 to 50 mg/kg intravenous or intramuscular in a single dose, not to exceed 125 mg.
	• Recommended regimen for children who weigh ≤45 kg and who have bacteremia or arthritis:
	  o Ceftriaxone 50 mg/kg (maximum dose: 1 g) 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 g intravenous every 12 hours plus azithromycin 1 g orally in a single dose.
	
	<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 g 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.

Clinical Guideline	Recommendation(s)
	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. • Alternative regimen: o Azithromycin suspension, 20 mg/kg/day orally, one dose daily for three days. Pelvic inflammatory disease • Recommended parenteral regimen A: o Cefotetan 2 g intravenous every 12 hours. o Cefoxitin 2 g 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 g 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 g intramuscular in a single dose and probenecid, 1 g 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. Proctitis, proctocolitis, and enteritis • Recommended regimen: o Ceftriaxone 250 mg intramuscular plus doxycycline 100 mg orally twice a day for seven days. Recurrent and persistent urethritis • Recommended regimens: o Metronidazole 2 g orally in a single dose. o Tinidazole 2 g orally in a single dose plus azithromycin 1 g orally in a single dose (if not used for initial episode). Primary and secondary syphilis • 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. Early latent syphilis • Recommended regimens for adults: o Benzathine penicillin G 2.4 million units intramuscular in a single dose.

Clinical Guideline	Recommendation(s)

	• 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.
	
	Late latent syphilis or latent syphilis of unknown duration
	• 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.
	
	Tertiary syphilis
	• 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.
	
	Trichomoniasis
	• Recommended regimen:
	  o Metronidazole 2 g orally in a single dose.
	  o Tinidazole 2 g orally in a single dose.
	• Alternative regimen:
	  o Metronidazole 500 mg orally twice a day for seven days.
	
	Neurosyphilis
	• 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.
	
	Uncomplicated gonococcal infections of the cervix, urethra, and rectum
	• 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 1g orally in a single dose or doxycycline 100 mg orally twice a day for seven days.
	
	Uncomplicated gonococcal infections of the pharynx
	• Recommended regimens:
	  o Ceftriaxone 250 mg intermuscular in a single dose plus azithromycin 1g orally in a single dose or doxycycline 100 mg orally twice a day for seven days.

Infectious Diseases Society of America/European Society for Microbiology and Infectious Diseases: **International Clinical Practice Guidelines for the**	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.

Clinical Guideline	Recommendation(s)
Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women (2010)[20] Reviewed and deemed current as of 07/2013	• Fosfomycin (3 g 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 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 g 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 g 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 g 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 g 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.

American College of Obstetricians and Gynecologists: **Treatment of Urinary Tract Infections in Nonpregnant Women**	• 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.

Clinical Guideline	Recommendation(s)
(2008)[21]	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 g dose (powder) single dose.
Global Initiative for Chronic Obstructive Lung Disease: **Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2016)**[22]	• Prophylactic, continuous use of antibiotics has been shown to have no effect on the frequency of exacerbations in chronic obstructive pulmonary disease. • The use of antibiotics, other than for treating infectious exacerbations of chronic obstructive pulmonary disease and other bacterial infections, is currently not indicated. • Based on current available evidence, antibiotics should be given to: o Patients with exacerbations of chronic obstructive pulmonary disease with the following three cardinal symptoms: dyspnea, sputum volume, and sputum purulence. o Patients with exacerbations of chronic obstructive pulmonary disease with two of the cardinal symptoms, if the increased purulence of sputum is one of the two symptoms. o Patients with a severe exacerbation of chronic obstructive pulmonary disease that requires mechanical ventilation (invasive or noninvasive). • The recommended length of antibiotic therapy is usually five to 10 days. • The choice of antibiotic should be based on local bacterial resistance patterns. • Initial empiric treatment may include an aminopenicillin with or without clavulanic acid, macrolide, or tetracycline. In patients with frequent exacerbations, severe airflow limitation, and/or exacerbations requiring mechanical ventilation, sputum cultures or cultures from other materials from the lung should be performed, as gram-negative bacteria or resistant pathogens that may not be sensitive to the afore-mentioned antibiotics may be present.
Cystic Fibrosis Foundation: **Cystic Fibrosis Pulmonary Guidelines (2013)**[23]	Aerosolized antibiotics • For patients with cystic fibrosis, six years of age and older, who have moderate to severe lung disease with *Pseudomonas aeruginosa* persistently present in cultures of the airways, the chronic use of inhaled tobramycin to improve lung function, improve quality of life, and reduce exacerbations is strongly recommended. • For patients with cystic fibrosis, six years of age or older, who have mild lung disease, and with *Pseudomonas aeruginosa* persistently present in cultures of the airways, chronic use of inhaled tobramycin to reduce exacerbations is recommended. • For patients with cystic fibrosis, six years of age and older, who have moderate to severe lung disease with *Pseudomonas aeruginosa* persistently present in cultures of the airways, the chronic use of inhaled aztreonam to improve lung function and quality of life is strongly recommended. • For patients with cystic fibrosis, six years of age or older, who have mild lung disease, and with *Pseudomonas aeruginosa* persistently present in cultures of the airways, chronic use of inhaled aztreonam to improve lung function and quality of life is recommended. • For patients with cystic fibrosis, six years of age or older, with *Pseudomonas aeruginosa* persistently present in cultures of the airways, there is insufficient evidence to recommend for or against routinely providing other chronically inhaled antibiotics (i.e., carbenicillin, ceftazidime, colistin, gentamicin) to improve lung function, improve quality of life, or reduce exacerbations. Anti-inflammatory agents • For patients with cystic fibrosis, six years of age or older, without asthma or allergic bronchopulmonary aspergillosis, routine use of inhaled corticosteroids to improve lung function, quality of life and reduce pulmonary exacerbations is not recommended. • For patients with cystic fibrosis, six years of age or older, without asthma or allergic bronchopulmonary aspergillosis, chronic use of oral corticosteroids to

Clinical Guideline	Recommendation(s)
	improve lung function, quality of life or reduce exacerbations is not recommended. • For patients with cystic fibrosis, between six and 17 years of age, with an forced expiratory volume in one second greater than or equal to 60% predicted, the chronic use of oral ibuprofen, at a peak plasma concentration of 50 to 100 µg/mL, to slow the loss of lung function is recommended. • For patients with cystic fibrosis, 18 years of age and older, the evidence is insufficient to recommend for or against the chronic use of oral ibuprofen to slow the loss of lung function or reduce exacerbations. • For patients with cystic fibrosis, six years of age or older, there is insufficient evidence to recommend for or against routinely providing the chronic use of leukotriene modifiers to improve lung function, quality of life, or reduce exacerbations. <u>Antipseudomonal antibiotics</u> • For patients with cystic fibrosis, six years of age and older, with *Pseudomonas aeruginosa* persistently present in cultures of the airways, there is insufficient evidence to recommend for or against routinely providing the chronic use of oral antipseudomonal antibiotics to improve lung function, quality of life, or reduce exacerbations. <u>Antistaphylococcal antibiotics</u> • For patients with cystic fibrosis, six years of age or older, with *Staphylococcus aureus* persistently present in cultures of the airways, there is insufficient evidence to recommend for or against the chronic use of oral antistaphylococcal antibiotics to improve lung function and quality of life or reduce exacerbations. • For patients with cystic fibrosis, prophylactic use of oral antistaphylococcal antibiotics to improve lung function and quality of life or to reduce exacerbations is not recommended. <u>Bronchodilators</u> • For patients with cystic fibrosis, six years of age or older, there is insufficient evidence to recommend for or against chronic use of inhaled β_2-adrenergic receptor agonists to improve lung function and quality of life or reduce exacerbations. • For patients with cystic fibrosis, six years of age or older, there is insufficient evidence to recommend for or against routinely providing the chronic use of inhaled anticholinergic bronchodilators to improve lung function and quality of life or reduce exacerbations. • For patients with cystic fibrosis, six years of age or older, there is insufficient evidence to recommend for or against routinely providing chronic use of inhaled or oral N-acetylcysteine or inhaled glutathione to improve lung function, quality of life or reduce exacerbations. <u>Hypertonic saline</u> • For patients with cystic fibrosis, six years of age or older, chronic use of inhaled hypertonic saline to improve lung function, improve quality of life, and to reduce exacerbations is recommended. <u>Ivacaftor</u> • For patients with cystic fibrosis, six years of age or older, with at least one G551D CFTR mutation, the chronic use of ivacaftor to improve lung function, quality of life, and to reduce exacerbations is strongly recommended. <u>Macrolide antibiotics</u>

Clinical Guideline	Recommendation(s)
	• For patients with cystic fibrosis, six years of age or older, and with *Pseudomonas aeruginosa* persistently present in cultures of the airways, chronic use of azithromycin to improve lung function and to reduce exacerbations is recommended. • For patients with cystic fibrosis, six years of age or older, without *Pseudomonas aeruginosa* persistently present in cultures of the airways, chronic use of azithromycin to reduce exacerbations is recommended. <u>Recombinant human DNase</u> • For patients with cystic fibrosis, six years of age or older, with moderate to severe lung disease, chronic use of dornase alfa to improve lung function, improve quality of life, and reduce exacerbations is strongly recommended. • For patients with cystic fibrosis, six years of age or older, and asymptomatic or with mild lung disease, chronic use of dornase alfa to improve lung function and reduce exacerbations is recommended.

Infectious Diseases Society of America: **Management of Community-Acquired Pneumonia in Infants and Children Older Than 3 Months of Age (2011)**[24]
 	
Reviewed and deemed current as of 04/2013
	<u>Outpatient treatment</u>
	• Antimicrobial therapy is not routinely required for preschool-aged children with community-acquired pneumonia, because viral pathogens are responsible for the great majority of clinical disease.
	• Amoxicillin should be used as first-line therapy for previously healthy, appropriately immunized infants and preschool children with mild to moderate community-acquired pneumonia suspected to be of bacterial origin. Amoxicillin provides appropriate coverage for *Streptococcus pneumoniae*.
	• For patients allergic to amoxicillin, the following agents are considered alternative treatment options:
	  o Second- or third-generation cephalosporin (cefpodoxime, cefuroxime, cefprozil).
	  o Levofloxacin (oral therapy).
	  o Linezolid (oral therapy).
	• Macrolide antibiotics should be prescribed for treatment of children (primarily school-aged children and adolescents) evaluated in an outpatient setting with findings compatible with community-acquired pneumonia caused by atypical pathogens.
	
	<u>Inpatient treatment</u>
	• Ampicillin or penicillin G should be administered to the fully immunized infant or school-aged child admitted to a hospital ward with community-acquired pneumonia when local epidemiologic data document lack of substantial high-level penicillin resistance for invasive *Streptococcus pneumoniae*.
	• Empiric therapy with a third-generation parenteral cephalosporin (ceftriaxone or cefotaxime) should be prescribed for hospitalized infants and children who are not fully immunized, in regions where local epidemiology of invasive pneumococcal strains documents high-level penicillin resistance, or for infants and children with life-threatening infection, including those with empyema.
	• Non–β-lactam agents, such as vancomycin, have not been shown to be more effective than third-generation cephalosporins in the treatment of pneumococcal pneumonia for the degree of resistance noted currently in North America.
	• Empiric combination therapy with a macrolide (oral or parenteral), in addition to a β-lactam antibiotic, should be prescribed for the hospitalized child for whom *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* are significant considerations.
	• Vancomycin or clindamycin (based on local susceptibility data) should be provided in addition to β-lactam therapy if clinical, laboratory, or imaging characteristics are consistent with infection caused by *Staphylococcus aureus*.

Infectious Diseases	<u>Empirical antimicrobial therapy</u>

Clinical Guideline	Recommendation(s)

Society of America/American Thoracic Society: **Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults (2007)**[25]	• Recommendations are generally for a class of antibiotics rather than for a specific drug, unless outcome data clearly favor one drug.
	• Because overall efficacy remains good for many classes of agents, the more potent drugs are given preference because of their benefit in decreasing the risk of selection for antibiotic resistance.
	• Outpatient treatment
	  o Previously healthy and no risk factors for drug-resistant *Streptococcus pneumoniae* infection:
	  ▪ Macrolide (azithromycin, clarithromycin, or erythromycin).
	  ▪ Doxycycline.
	  o Presence of comorbidities, such as chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressing conditions or use of immunosuppressing drugs; use of antimicrobials within the previous three months (in which case an alternative from a different class should be selected); or other risks for drug-resistant Streptococcus pneumoniae infection:
	  ▪ Respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin).
	  ▪ β-lactam plus a macrolide (high-dose amoxicillin or amoxicillin-clavulanate is preferred; alternatives include ceftriaxone, cefpodoxime, and cefuroxime; doxycycline is an alternative to the macrolide).
	  o In regions with a high rate of infection with high-level macrolide-resistant *Streptococcus pneumoniae,* consider the use of alternative agents listed above for any patient, including those without comorbidities.
	• Inpatient, non-intensive care unit treatment
	  o Respiratory fluoroquinolone.
	  o β-lactam plus a macrolide (preferred β-lactam agents include cefotaxime, ceftriaxone, and ampicillin; ertapenem for selected patients; with doxycycline as an alternative to the macrolide. A respiratory fluoroquinolone should be used for penicillin-allergic patients).
	• Inpatient, intensive care unit treatment
	  o β-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) plus either azithromycin or a fluoroquinolone (for penicillin-allergic patients, a respiratory fluoroquinolone and aztreonam are recommended).
	  o For *Pseudomonas* infection, use an antipneumococcal, antipseudomonal β-lactam (piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin; OR
	  o Antipneumococcal, antipseudomonal β-lactam (listed above) plus an aminoglycoside and azithromycin; OR
	  o Antipneumococcal, antipseudomonal β-lactam (listed above) plus an aminoglycoside and an antipneumococcal fluoroquinolone (for penicillin-allergic patients, substitute aztreonam for the above β-lactam).
	  o For community-acquired methicillin-resistant *Staphylococcus aureus* infection, add vancomycin or linezolid.

American Thoracic Society/ Infectious Diseases Society of America: **Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and**	• Select an initial empiric therapy based on the absence or presence of risk factors for multidrug-resistant pathogens. These risk factors include prolonged duration of hospitalization (five days or more), admission from a healthcare-related facility, and recent prolonged antibiotic therapy. • Patients with healthcare-related pneumonia should be treated for potentially drug-resistant organisms, regardless of when during the hospital stay the pneumonia begins. • In selecting empiric therapy for patients who have recently received an antibiotic, an effort should be made to use an agent from a different antibiotic class, because recent therapy increases the probability of inappropriate therapy and can

Clinical Guideline	Recommendation(s)

Healthcare-associated Pneumonia (2005)[26]	predispose to resistance to that same class of antibiotics.
	• Initial empiric antibiotic therapy for hospital-acquired pneumonia or ventilator-associated pneumonia in patients with no known risk factors for multidrug-resistant pathogens, early onset, and any disease severity:
	  o Ceftriaxone; OR
	  o Levofloxacin, moxifloxacin, ciprofloxacin; OR
	  o Ampicillin-sulbactam; OR
	  o Ertapenem.
	• Initial empiric antibiotic therapy for hospital-acquired pneumonia, ventilator-associated pneumonia, and healthcare-associated pneumonia in patients with late-onset disease or risk factors for multidrug-resistant pathogens and all disease severity–combination antibiotic therapy is recommended as follows:
	  o Antipseudomonal cephalosporin (cefepime, ceftazidime) or antipseudomonal carbapenem (imipenem or meropenem) or β-lactam-β-lactamase inhibitor (piperacillin-tazobactam) plus antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) or aminoglycoside (amikacin, gentamicin, or tobramycin) plus linezolid or vancomycin if methicillin-resistant *Staphylococcus aureus* risk factors are present or there is a high incidence locally.

Infectious Diseases Society of America: **Diagnosis and Management of Complicated Intra-abdominal Infection in Adults and Children (2010)[27]**	<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.

Clinical Guideline	Recommendation(s)
	• 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 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. <u>Health care-associated infection:</u> • 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. <u>Cholecystitis and cholangitis:</u> • 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: **Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer (2010)**[28]
 	
Reviewed and deemed current as of 04/2013
	<u>Initial antibiotic therapy</u>
	• Oral route:
	  o For low-risk adults only; use ciprofloxacin plus amoxicillin-clavulanate.
	• Monotherapy with vancomycin not indicated:
	  o Choose therapy with one of the following agents: cefepime or ceftazidime, or imipenem or meropenem.
	• Two drugs without vancomycin:
	  o Choose an aminoglycoside plus antipseudomonal penicillin, cephalosporin (cefepime or ceftazidime), or carbapenem.
	• Vancomycin plus one or two antibiotics:
	  o Choose cefepime or ceftazidime plus vancomycin, with or without an aminoglycoside; carbapenem plus vancomycin, with or without an aminoglycoside; or antipseudomonal penicillin plus an aminoglycoside and vancomycin.
	
	<u>Modification of therapy during the first week of treatment</u>

Clinical Guideline	Recommendation(s)

	• Patient becomes afebrile in three to five days:
	  o Adjust therapy to the most appropriate drug(s). If no etiologic agent is identified and if the patient is at low risk initially, and oral antibiotic treatment was begun with no subsequent complications, continue use of the same drugs.
	  o If the patient was at low risk initially and therapy with intravenous drugs was begun with no subsequent complications, the regimen may be changed after 48 hours to oral ciprofloxacin plus amoxicillin-clavulanate for adults or cefixime for children.
	  o If the patient is at high risk initially with no subsequent complications, continue use of the same intravenous drugs.
	• Persistent fever throughout the first three to five days:
	  o Reassess therapy on day three. If there is no clinical worsening, continue use of the same antibiotics; stop vancomycin use if cultures do not yield organisms.
	  o If there is progressive disease, change antibiotics.
	  o If the patient is febrile after five days, consider adding an antifungal drug.
	
	Antibiotic prophylaxis for afebrile neutropenic patients
	• Use of antibiotic prophylaxis is not routine because of emerging antibiotic resistance, except for the use of sulfamethoxazole-trimethoprim to prevent *Pneumocystis carinii* pneumonitis.

National Comprehensive Cancer Network: **Prevention and Treatment of Cancer-Related Infections (2016)**[29]	Low infection risk prophylaxis • Antimicrobial prophylaxis is not recommended in patients with low infection risk. Intermediate infection risk prophylaxis • Consider using fluoroquinolone prophylaxis. High infection risk prophylaxis • Consider using fluoroquinolone prophylaxis. • Additional prophylaxis may be necessary. *Pneumocystis jirovecii* prophylaxis • Sulfamethoxazole-trimethoprim is the preferred treatment. Sulfamethoxazole-trimethoprim has the additional benefit of activity against other pathogens including Nocardia, Toxoplasma, and Listeria. • Atovaquone, dapsone, and pentamidine are potential alternatives as prophylaxis for patients intolerant to sulfamethoxazole-trimethoprim. • Consider sulfamethoxazole-trimethoprim desensitization or atovaquone, dapsone, or pentamidine when *Pneumocystis* prophylaxis is required in patients who are sulfamethoxazole-trimethoprim intolerant. For patients receiving dapsone, consider assessing G6PD levels. Pneumococcal infection prophylaxis • Prophylaxis for pneumococcal infection should begin three months after patients undergo hematopoietic stem cell transplantation with penicillin, and prophylaxis should continue for at least one year after the transplant. • In regions that have pneumococcal isolates with intermediate or high-level resistance to penicillin, sulfamethoxazole-trimethoprim will likely be adequate for pneumococcal prophylaxis. Initial empiric antibiotic therapy • Patients with neutropenia should begin empiric treatment with broad spectrum

Clinical Guideline	Recommendation(s)
	antibiotics at the first sign of infection. • Intravenous antibiotic monotherapy for uncomplicated infections (choose one): o Cefepime. o Imipenem-cilastatin. o Meropenem. o Piperacillin-tazobactam. o Ceftazidime. • Oral antibiotic combination therapy for low-risk patients with uncomplicated infections: o Ciprofloxacin plus amoxicillin-clavulanate. o Moxifloxacin. o Oral antibiotic regimen recommended should not be used if quinolone prophylaxis was used. • Complicated infections (choose based on local antibiotic susceptibility patterns): o Intravenous antibiotic monotherapy is preferred. o Intravenous combination therapy could be considered especially in cases of resistance. <u>Antibacterial agents: empiric gram-positive activity</u> • Vancomycin o Gram-positive organisms with the exception of VRE and a number of rare organisms. o Should not be considered as routine therapy for neutropenia and fever unless certain risk factors present. o Dosing individualized with monitoring of levels; loading dose may be considered. • Daptomycin o Has in vitro activity against VRE but is not FDA-approved for this indication. o Weekly creatine phosphokinase (CPK) to monitor for rhabdomyolysis. o Not indicated for pneumonia due to inactivation by pulmonary surfactant. • Linezolid o Gram-positive organisms including VRE. o Hematologic toxicity (typically with prolonged cases over two weeks) may occur. o Not routinely use in fever and neutropenia, although may impair neutrophil and platelet recovery for extended use. o Treatment option for VRE and MRSA. o Peripheral/optic neuropathy with long-term use. <u>Antibacterial agents: anti-pseudomonal</u> • Cefepime o Broad-spectrum activity against most gram-positive and negative organisms (not active against most anaerobes and *Enterococcus* species). o Use for suspected/proven CNS infection with susceptible organism. o Empiric therapy for neutropenic fever. • Ceftazidime o Relatively poor gram-positive activity (not active against most anaerobes and *Enterococcus* species). o Use for suspected/proven CNS infection with susceptible organism. o Empiric therapy for neutropenic fever (resistance among gram-negative rods at some centers). • Imipenem-cilastatin/ meropenem/ doripenem o Broad spectrum activity against most gram-positive, gram-negative, and anaerobic organisms. o Preferred against extended spectrum beta-lactamase and serious

Clinical Guideline	Recommendation(s)
	Enterobacter infections. o Carbapenem-resistant gram-negative rod infections are an increasing problem at a number of centers. o Use for suspected intra-abdominal source. o Meropenem is preferred over imipenem for suspected/proven CNS infection. o Effective in nosocomial pneumonia and intra-abdominal infections. • Piperacillin-tazobactam o Broad spectrum activity against most gram-positive, gram-negative, and anaerobic organisms. o Use for suspected intra-abdominal source. Antibacterial agents: other • Aminoglycosides o Activity primarily against gram-negative organisms. o Often used as empiric therapy in seriously ill or hemodynamically unstable patients. • Ciprofloxacin in combination with amoxicillin-clavulanate o Good activity against gram-negative and atypical organisms. Less active than "respiratory" fluoroquinolones against gram-positive organisms. o Ciprofloxacin alone has no activity against anaerobes. o Avoid for empiric therapy if patient recently treated with fluoroquinolone prophylaxis. • Levofloxacin/ moxifloxacin o Good activity against gram-negative and atypical organisms. o Levofloxacin has no activity against anaerobes. Moxifloxacin has limited activity against Pseudomonas. o Prophylaxis may increase bacterial resistance and superinfection. • Metronidazole o Good activity against anaerobic organisms. • Sulfamethoxazole-trimethoprim o Highly effective as prophylaxis against *Pneumocystis jiroveci* in high-risk patients. o Monitor for myelosuppression, hepatotoxicity, and hyperkalemia.
American Society of Health-System Pharmacists/ Infectious Diseases Society of America/ Surgical Infection Society/ Society for Healthcare Epidemiology of America: **Clinical practice guidelines for antimicrobial prophylaxis in surgery (2013)**[30]	Common principles • The optimal time for administration of preoperative doses is within 60 minutes before surgical incision. Some agents, such as fluoroquinolones and vancomycin, require administration over one to two hours; therefore, the administration of these agents should begin within 120 minutes before surgical incision. • The selection of an appropriate antimicrobial agent for a specific patient should take into account the characteristics of the ideal agent, the comparative efficacy of the antimicrobial agent for the procedure, the safety profile, and the patient's medication allergies. • For most procedures, cefazolin is the drug of choice for prophylaxis because it is the most widely studied antimicrobial agent, with proven efficacy. It has a desirable duration of action, spectrum of activity against organisms commonly encountered in surgery, reasonable safety, and low cost. • There is little evidence to suggest that broad-spectrum antimicrobial agents (i.e., agents with broad in vitro antibacterial activity) result in lower rates of postoperative SSI compared with older antimicrobial agents with a narrower spectrum of activity. However, comparative studies are limited by small sample sizes, resulting in difficulty detecting a significant difference between antimicrobial agents. Cardiac procedures

Clinical Guideline	Recommendation(s)
	• For patients undergoing cardiac procedures, the recommended regimen is a single preincision dose of cefazolin or cefuroxime with appropriate intraoperative redosing. • For patients with serious allergy or adverse reaction to β-lactams, vancomycin or clindamycin may be an acceptable alternative. • Vancomycin should be used for prophylaxis in patients known to be colonized with MRSA. • Mupirocin should be given intranasally to all patients with documented *S. aureus* colonization. Thoracic procedures • In patients undergoing thoracic procedures, a single dose of cefazolin or ampicillin–sulbactam is recommended. • For patients with serious allergy or adverse reaction to β-lactams, vancomycin or clindamycin may be an acceptable alternative. • Vancomycin should be used for prophylaxis in patients known to be colonized with MRSA. Gastroduodenal procedures • Antimicrobial prophylaxis in gastroduodenal procedures should be considered for patients at highest risk for postoperative infections, including risk factors such as increased gastric pH (e.g., patients receiving acid-suppression therapy), gastroduodenal perforation, decreased gastric motility, gastric outlet obstruction, gastric bleeding, morbid obesity, ASA classification of ≥3, and cancer. • A single dose of cefazolin is recommended in procedures during which the lumen of the intestinal tract is entered. A single dose of cefazolin is recommended in clean procedures, such as highly selective vagotomy, and antireflux procedures only in patients at high risk of postoperative infection due to the presence of the above risk factors. • Alternative regimens for patients with β -lactam allergy include clindamycin or vancomycin plus gentamicin, aztreonam, or a fluoroquinolone. • Higher doses of antimicrobials are uniformly recommended in morbidly obese patients undergoing bariatric procedures. Higher doses of antimicrobials should be considered in significantly overweight patients undergoing gastroduodenal and endoscopic procedures. Biliary tract procedures • A single dose of cefazolin should be administered in patients undergoing open biliary tract procedures. • Alternatives include ampicillin–sulbactam and other cephalosporins (cefotetan, cefoxitin, and ceftriaxone). Alternative regimens for patients with β -lactam allergy include clindamycin or vancomycin plus gentamicin, aztreonam, or a fluoroquinolone; or metronidazole plus gentamicin or a fluoroquinolone. Appendectomy procedures • For uncomplicated appendicitis, the recommended regimen is a single dose of a cephalosporin with anaerobic activity (cefoxitin or cefotetan) or a single dose of a first-generation cephalosporin (cefazolin) plus metronidazole. • For β -lactam-allergic patients, alternative regimens include clindamycin plus gentamicin, aztreonam, or a fluoroquinolone; and metronidazole plus gentamicin or a fluoroquinolone (ciprofloxacin or levofloxacin). Small intestine procedures • For small bowel surgery without obstruction, the recommended regimen is a first generation cephalosporin (cefazolin). For small bowel surgery with intestinal

Clinical Guideline	Recommendation(s)

	obstruction, the recommended regimen is a cephalosporin with anaerobic activity (cefoxitin or cefotetan) or the combination of a first-generation cephalosporin (cefazolin) plus metronidazole.
	• For β -lactam-allergic patients, alternative regimens include clindamycin plus gentamicin, aztreonam, or a fluoroquinolone; and metronidazole plus gentamicin or a fluoroquinolone (ciprofloxacin or levofloxacin).
	
	Hernia repair procedures
	• For hernioplasty and herniorrhaphy, the recommended regimen is a single dose of a first-generation cephalosporin (cefazolin). For patients known to be colonized with MRSA, it is reasonable to add a single preoperative dose of vancomycin to the recommended agent. For β –lactam-allergic patients, alternative regimens include clindamycin and vancomycin.
	
	Colorectal procedures
	• A single dose of second-generation cephalosporin with both aerobic and anaerobic activities (cefoxitin or cefotetan) or cefazolin plus metronidazole is recommended for colon procedures.
	• In institutions where there is increasing resistance to first- and second-generation cephalosporins among gram-negative isolates from SSIs, a single dose of ceftriaxone plus metronidazole is recommended over routine use of carbapenems. An alternative regimen is ampicillin–sulbactam.
	• In most patients, mechanical bowel preparation combined with a combination of oral neomycin sulfate plus oral erythromycin base or oral neomycin sulfate plus oral metronidazole should be given in addition to intravenous prophylaxis. The oral antimicrobial should be given as three doses over approximately 10 hours the afternoon and evening before the operation and after the mechanical bowel preparation.
	• Alternative regimens for patients with β–lactam allergies include (1) clindamycin plus an aminoglycoside, aztreonam, or a fluoroquinolone and (2) metronidazole plus an aminoglycoside or a fluoroquinolone. Metronidazole plus aztreonam is not recommended as an alternative because this combination has no aerobic gram-positive activity.
	
	Head and neck procedures
	• Clean procedures:
	  o Antimicrobial prophylaxis is not required.
	• Clean-contaminated procedures:
	  o Antimicrobial prophylaxis has not been shown to benefit patients undergoing tonsillectomy or functional endoscopic sinus procedures.
	  o The preferred regimens for patients undergoing other clean-contaminated head and neck procedures are (1) cefazolin or cefuroxime plus metronidazole and (2) ampicillin–sulbactam.
	  o Clindamycin is a reasonable alternative in patients with a documented β-lactam allergy. The addition of an aminoglycoside to clindamycin may be appropriate when there is an increased likelihood of gram-negative contamination of the surgical site.
	
	Neurosurgery procedures
	• A single dose of cefazolin is recommended for patients undergoing clean neurosurgical procedures, CSF-shunting procedures, or intrathecal pump placement. Clindamycin or vancomycin should be reserved as an alternative agent for patients with a documented β-lactam allergy (vancomycin for MRSA-colonized patients).
	
	Cesarean delivery procedures

Clinical Guideline	Recommendation(s)
	• The recommended regimen for all women undergoing cesarean delivery is a single dose of cefazolin administered before surgical incision. For patients with β-lactam allergies, an alternative regimen is clindamycin plus gentamicin. Hysterectomy procedures • The recommended regimen for women undergoing vaginal or abdominal hysterectomy, using an open or laparoscopic approach, is a single dose of cefazolin. • Cefoxitin, cefotetan, or ampicillin–sulbactam may also be used. Alternative agents for patients with a b-lactam allergy include (1) either clindamycin or vancomycin plus an aminoglycoside, aztreonam, or a fluoroquinolone and (2) metronidazole plus an aminoglycoside or a fluoroquinolone. Ophthalmic procedures • Due to the lack of robust data from trials, specific recommendations cannot be made regarding choice, route, or duration of prophylaxis. • As a general principle, the antimicrobial prophylaxis regimens used in ophthalmic procedures should provide coverage against common ocular pathogens, including *Staphylococcus* species and gram-negative organisms, particularly *Pseudomonas* species. Orthopedic procedures • Antimicrobial prophylaxis is not recommended for patients undergoing clean orthopedic procedures, including knee, hand, and foot procedures, arthroscopy, and other procedures without instrumentation or implantation of foreign materials. • Antimicrobial prophylaxis is recommended for orthopedic spinal procedures with and without instrumentation. The recommended regimen is cefazolin. • The recommended regimen in hip fracture repair or other orthopedic procedures involving internal fixation is cefazolin. Clindamycin and vancomycin should be reserved as alternative agents. • The recommended regimen for patients undergoing total hip, elbow, knee, ankle, or shoulder replacement is cefazolin. Clindamycin and vancomycin should be reserved as alternative agents. Urologic procedures • No antimicrobial prophylaxis is recommended for clean urologic procedures in patients without risk factors for postoperative infections. • Patients with preoperative bacteriuria or UTI should be treated before the procedure, when possible, to reduce the risk of postoperative infection. • For patients undergoing lower urinary tract instrumentation with risk factors for infection, the use of a fluoroquinolone or trimethoprim– sulfamethoxazole (oral or intravenous) or cefazolin (intravenous or intramuscular) is recommended. Vascular procedures • The recommended regimen for patients undergoing vascular procedures associated with a higher risk of infection, including implantation of prosthetic material, is cefazolin. Heart, lung, heart-lung, liver, pancreas, and kidney transplantation • Antimicrobial prophylaxis is indicated for all patients undergoing heart transplantation. The recommended regimen is a single dose of cefazolin. Alternatives include vancomycin or clindamycin with or without gentamicin, aztreonam, or a single fluoroquinolone dose. • Adult patients undergoing lung transplantation should receive antimicrobial prophylaxis, because of the high risk of infection. Patients with negative

Clinical Guideline	Recommendation(s)
	pretransplantation cultures should receive antimicrobial prophylaxis as appropriate for other types of cardiothoracic procedures. The recommended regimen is a single dose of cefazolin. • The recommended agents for patients undergoing liver transplantation are (1) piperacillin–tazobactam and (2) cefotaxime plus ampicillin. The duration of prophylaxis should be restricted to 24 hours or less. • The recommended regimen for patients undergoing pancreas or SPK transplantation is cefazolin. • The recommended agent for patients undergoing kidney transplantation is cefazolin. <u>Plastic surgery and breast procedures</u> • Antimicrobial prophylaxis is not recommended for most clean procedures in patients without additional postoperative infection risk factors. • Although no studies have demonstrated antimicrobial efficacy in these procedures, expert opinion recommends that patients with risk factors undergoing clean plastic procedures receive antimicrobial prophylaxis. The recommendation for clean-contaminated procedures, breast cancer procedures, and clean procedures with other risk factors is a single dose of cefazolin or ampicillin–sulbactam.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the miscellaneous β-lactam antibiotics 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 Miscellaneous β-Lactam Antibiotics[1-10]

Indication	Single Entity Agents						Combination Products
	Aztreonam	Cefotetan	Cefoxitin	Doripenem	Ertapenem	Mero-penem	Imipenem and Cilastatin
Central Nervous System Infections							
Meningitis						✔	
Dermatological Infections							
Abscesses							✔ §
Burns	✔ ‡						
Cellulitis							✔ §
Cutaneous infections (adjunctive therapy to surgery)	✔ ‡						
Diabetic foot infections without osteomyelitis					✔		
Infected skin ulcers	✔ ‡						✔ §
Postoperative wounds	✔ ‡						
Skin and skin-structure infections	✔ ‡	✔	✔		✔	✔	✔ § ‖
Wounds infections							✔ §
Genitourinary Infections							
Cystitis	✔ ‡						
Endometritis	✔ ‡		✔				
Gynecologic infections	✔ ‡	✔	✔				✔ § ‖
Pelvic cellulitis	✔ ‡		✔				
Pelvic infections, acute					✔		
Pelvic inflammatory disease			✔				
Postpartum endomyometritis					✔		✔ §
Postsurgical gynecologic infections					✔		
Pyelonephritis	✔ ‡			✔	✔		
Septic abortion					✔		
Urinary tract infections	✔ ‡	✔	✔	✔	✔		✔ ‖
Respiratory Infections							
Bronchitis	✔ ‡						✔ §

Indication	Single Entity Agents						Combination Products
	Aztreonam	Cefotetan	Cefoxitin	Doripenem	Ertapenem	Mero-penem	Imipenem and Cilastatin
Improve respiratory symptoms in cystic fibrosis patients with *Pseudomonas aeruginosa*	✔ †						
Lung abscess			✔				
Pneumonia	✔ ‡		✔				✔ §
Pneumonia (community acquired)					✔		
Respiratory tract infections (lower)	✔ ‡	✔	✔				✔ § ‖
Miscellaneous Infections							
Abscesses (adjunctive therapy to surgery)	✔ ‡						
Appendicitis						✔	✔ §
Appendicitis with peritonitis							✔ §
Bone and/or joint infections		✔	✔				✔ ‖
Endocarditis							✔ ‖
Infections complicating hollow viscus perforations (adjunctive therapy to surgery)	✔ ‡						
Infections of serous surfaces (adjunctive therapy to surgery)	✔ ‡						
Intra-abdominal infections	✔ ‡	✔	✔	✔	✔	✔	✔ § ‖
Peritonitis	✔ ‡		✔			✔	
Polymicrobic infections							✔ ‖
Perioperative prophylaxis		✔	✔		✔		
Septicemia	✔ ‡		✔				✔ ‖

†Inhalation solution formulation.
‡Injection formulation.
§Intramuscular formulation.
‖Intravenous formulation.

IV. Pharmacokinetics

The pharmacokinetic parameters of the miscellaneous β-lactam antibiotics are listed in Table 5.

Table 5. Pharmacokinetic Parameters of the Miscellaneous β-Lactam Antibiotics[1-10]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents					
Aztreonam	INH: low IM: 100	INH: 56	Liver (7)	INH: Renal (10) IM/IV: Renal (60 to 70) Feces (12)	INH: 2.1 IM/IV: 1.6 to 2.9
Cefotetan	N/A	78 to 91	Not reported	Renal (51 to 81) Bile (12)	3.0 to 4.6
Cefoxitin	N/A	65 to 79	Liver (<2)	Renal (85) Bile (<1)	0.8 to 1.0
Doripenem	N/A	8	Not reported	Renal (71) Feces (<1)	1
Ertapenem	IM: 90	85 to 95	Renal	Renal (>80) Feces (10)	4
Meropenem	N/A	2	Extrarenal (20 to 25)	Renal (70) Fecal (2)	1.0 to 1.5
Combination Products					
Imipenem and cilastatin	Imipenem: 75 Cilastatin: 95	Imipenem: 20 Cilastatin: 40	Renal	Imipenem: Renal (50 to 70) Cilastatin: Renal (70 to 75)	Cilastatin: 2 to 3 Imipenem: 1

IM=intramuscular, INH=inhalation, IV=intravenous

V. Drug Interactions

Major drug interactions with the miscellaneous β-lactam antibiotics are listed in Table 6.

Table 6. Major Drug Interactions with the Miscellaneous β-Lactam Antibiotics[1]

Generic Name(s)	Interaction	Mechanism
Doripenem, ertapenem, imipenem-cilastatin, meropenem	Valproic acid	Plasma concentrations and pharmacologic effects of valproic acid may be decreased by carbapenems.
Doripenem	Probenecid	Plasma concentrations of carbapenems may increase as a result of decreased active tubular secretion with co-administration of probenecid.
Imipenem-cilastatin	Valganciclovir	Concurrent use may result in increased central nervous system toxicity (e.g., seizures).
Imipenem-cilastatin	Theophylline	Concurrent use of imipenem and theophylline may result in theophylline toxicity (nausea, vomiting, palpitations, seizures).

VI. Adverse Drug Events

The most common adverse drug events reported with the miscellaneous β-lactam antibiotics are listed in Table 7.

Table 7. Adverse Drug Events (%) Reported with the Miscellaneous β-Lactam Antibiotics[1-10]

Adverse Events	Single Entity Agents						Combination Products
	Aztreonam	Cefotetan	Cefoxitin	Doripenem	Ertapenem	Meropenem	Imipenem and Cilastatin
Cardiovascular							
Arrhythmia	-	-	-	-	<1	-	-
Asystole	-	-	-	-	<1	-	-
Atrial fibrillation	-	-	-	-	<1	-	-
Bradycardia	-	-	-	-	<1	<1	-
Cardiac arrest	-	-	-	-	<1	<1	-
Chest pain	<1†, 8‡	-	-	-	1 to 2	<1	-
Edema	-	-	-	-	3	-	-
Heart failure	-	-	-	-	<1	<1	-
Heart murmur	-	-	-	-	<1	-	-
Hypertension	-	-	-	-	1 to 2	<1	-
Hypotension	<1†	-	<1	-	1 to 2	<1	<1
Myocardial infarction	-	-	-	-	-	<1	-
Palpitations	-	-	-	-	-	-	<1
Shock	-	-	-	-	-	1	-
Syncope	-	-	-	-	<1	<1	-
Tachycardia	-	-	-	-	1 to 2	<1	≤2
Ventricular tachycardia	-	-	-	-	<1	-	-
Central Nervous System							
Agitation/delirium	-	-	-	-	-	<1	-
Anxiety	-	-	-	-	1	<1	-
Confusion	<1†	-	-	-	-	<1	<1
Delirium	-	-	-	-	<1	-	-
Depression	-	-	-	-	-	<1	-
Dizziness	<1†	-	-	-	2	<1	<1
Encephalopathy	-	-	-	-	-	-	<1
Fatigue	-	-	-	-	1	-	-
Fever	<1†, 13‡	<1	<1	-	2 to 5	<1	<1
Hallucinations	-	-	-	-	-	<1	<1
Headache	<1†	-	-	3 to 16	6 to 7	2 to 8	-
Insomnia	<1†	-	-	-	3	<1	-

Adverse Events	Single Entity Agents						Combination Products
	Aztreonam	Cefotetan	Cefoxitin	Doripenem	Ertapenem	Meropenem	Imipenem and Cilastatin
Mental status changes	-	-	-	-	3 to 5	-	-
Myasthenia gravis exacerbation	-	-	<1	-	-	-	-
Myoclonus	-	-	-	-	<1	-	<1
Nervousness	-	-	-	-	-	<1	-
Paresthesia	<1†	-	-	-	-	<1	<1
Psychic disturbances	-	-	-	-	-	-	<1
Seizures	<1†	✔	✔	✔	✔	<1	≤1
Somnolence	-	-	-	-	-	<1	<1
Tremor	-	-	-	-	-	-	<1
Vertigo	<1†	-	-	-	-	-	<1
Dermatological							
Angioedema	<1†	✔	<1	-	-	<1	-
Angioneurotic edema	-	-	-	-	-	-	<1
Dermatitis	-	-	-	1 to 5	-	-	-
Diaphoresis	<1†	-	-	-	-	<1	-
Erythema	-	-	-	1 to 5	1 to 2	-	-
Erythema multiforme	<1†	-	✔	1 to 5	-	<1	<1
Exfoliative dermatitis	<1†	-	<1	-	-	-	-
Flushing	<1†	-	-	-	-	-	<1
Hyperhidrosis	-	-	-	-	-	-	<1
Macular/papular eruptions	-	-	-	1 to 5	-	-	-
Petechiae	<1†	-	-	-	-	-	-
Pruritus	<1†	<1	<1	≤3	1 to 2	1	<1
Rash	1 to 10†, 2‡	<1	<1	1 to 5	2 to 3	2 to 3	≤2
Skin ulcer	-	-	-	-	-	<1	-
Stevens-Johnson syndrome	-	✔	✔	✔	-	<1	<1
Toxic epidermal necrolysis	<1†	✔	<1	✔	-	<1	<1
Urticaria	<1†	<1	<1	1 to 5	-	<1	<1
Gastrointestinal							
Abdominal cramps	<1†	-	-	-	-	-	-
Abdominal enlargement	-	-	-	-	-	<1	-
Abdominal pain	7‡	-	-	-	4 to 5	<1	<1
Abnormal taste	<1†	-	-	-	-	-	-
Acid regurgitation	-	-	-	-	1 to 2	-	-
Anorexia	-	-	-	-	-	<1	-
Aphthous ulcer	<1†	-	-	-	-	-	-

Adverse Events	Single Entity Agents						Combination Products
	Aztreonam	Cefotetan	Cefoxitin	Doripenem	Ertapenem	Meropenem	Imipenem and Cilastatin
Clostridium difficile -associated colitis	✔	-	-	<1	-	-	-
Clostridium difficile-associated diarrhea	<1†	-	-	-	<1	✔	-
Cholelithiasis	-	-	-	-	<1	-	-
Constipation	-	-	-	-	2 to 4	1 to 7	-
Diarrhea	1 to 10†	1	1 to 10	6 to 14	9 to 12	4 to 7	1 to 2
Dyspepsia	-	-	-	-	1	<1	-
Dysphagia	-	-	-	-	<1	-	-
Flatulence	-	-	-	-	-	<1	-
Gastritis	-	-	-	-	<1	-	-
Gastroenteritis	-	-	-	-	-	-	<1
Gastrointestinal hemorrhage	✔	-	-	-	<1	<1	-
Glossitis	-	-	-	-	-	1	<1
Halitosis	<1†	-	-	-	-	-	-
Hemoperitoneum, nontraumatic	-	-	-	-	-	<1	-
Hemorrhagic colitis	-	-	-	-	-	-	<1
Ileus	-	-	-	-	<1	<1	-
Intestinal obstruction	-	-	-	-	-	<1	-
Melena	-	-	-	-	-	<1	-
Nausea	1 to 10†	<1	<1	4 to 12	2 to 9	1 to 8	2
Numb tongue	<1†	-	-	-	-	-	-
Oral candidiasis	-	-	-	1	≤1	≤2	-
Pancreatitis	-	-	-	-	<1	-	-
Pseudomembranous colitis	<1†	<1	<1	-	-	-	<1
Tongue papillar hypertrophy	-	-	-	-	-	-	<1
Vomiting	1 to 10†, 6‡	<1	<1	-	4 to 10	1 to 8	≤2
Genitourinary							
Abnormal urinalysis	-	-	-	-	-	-	<1
Dysuria	-	-	-	-	-	<1	-
Hematuria	-	-	-	-	1 to 3	<1	-
Interstitial nephritis	-	-	<1	-	-	-	-
Nephrotoxicity	✔	<1	<1	-	-	-	-
Oliguria/anuria	-	-	-	-	<1	-	≤2
Pelvic pain	-	-	-	-	-	<1	-
Polyuria	-	-	-	-	-	-	<1

Adverse Events	Single Entity Agents						Combination Products
	Aztreonam	Cefotetan	Cefoxitin	Doripenem	Ertapenem	Meropenem	Imipenem and Cilastatin
Pyuria	-	-	-	-	2 to 3	-	-
Renal impairment/failure	-	-	-	≤1	<1	<1	<1
Urinary incontinence	-	-	-	-	-	<1	-
Vaginal candidiasis	-	-	-	-	-	<1	-
Vaginitis	<1†	-	-	-	1.4	-	-
Vulvomycotic infection	-	-	-	1 to 2	-	-	-
Hematologic							
Agranulocytosis	-	<1	-	-	-	<1	<1
Anemia	<1†	-	-	2 to 10	-	≤6	<1
Bleeding	-	-	-	-	-	1	-
Bone marrow depression	-	-	<1	-	-	-	<1
Eosinophilia	<1†	<1	<1	-	1 to 2	<1	<1
Hematocrit decreased	-	-	-	-	3 to 5	-	-
Hemoglobin decreased	-	-	-	-	3 to 5	-	-
Hemolytic anemia	-	<1	<1	-	-	<1	<1
Leukocytosis	-	-	-	-	-	<1	<1
Leukopenia	<1†	<1	<1	✔	1 to 2	<1	<1
Neutropenia	<1†	-	-	✔	1 to 2	<1	<1
Pancytopenia	<1†	-	-	-	-	-	<1
Prothrombin time decreased	-	-	-	-	-	<1	-
Prothrombin time increased	-	-	-	-	≤1	-	-
Partial thromboplastin time decreased	-	-	-	-	-	<1	-
Thrombocythemia	-	-	-	-	-	-	<1
Thrombocytopenia	<1†	<1	-	-	1	<1	<1
Thrombocytosis	-	<1	-	-	4 to 7	<1	-
Hepatic							
Hepatic failure	-	-	-	-	-	<1	<1
Hepatitis	<1†	-	-	-	-	-	<1
Jaundice	<1†	-	<1	-	<1	<1	<1
Laboratory Test Abnormalities							
Albumin decreased	-	-	-	-	1 to 2	-	-
Alkaline phosphatase increased	✔	-	-	-	4 to 7	<1	<1
Alanine aminotransferase increased	<1†	1	<1	1 to 2	7 to 9	<1	<1
Aspartate aminotransferase increased	<1†	1	<1	1 to 2	7 to 9	<1	<1
Blood urea nitrogen increased	-	<1	<1	-	-	<1	<1

Adverse Events	Single Entity Agents						Combination Products
	Aztreonam	Cefotetan	Cefoxitin	Doripenem	Ertapenem	Meropenem	Imipenem and Cilastatin
Hematocrit decreased	-	-	-	-	-	<1	<1
Hemoglobin decreased	-	-	-	-	-	<1	<1
Hyperbilirubinemia	-	-	-	-	<1	<1	-
Hyperchloremia	-	-	-	-	-	-	<1
Hyperglycemia	-	-	-	-	1 to 2	-	-
Hyperkalemia	-	-	-	-	≤1	-	<1
Hypoglycemia	-	-	-	-	-	✔	-
Hypokalemia	-	-	-	-	2	<1	-
Hyponatremia	-	-	-	-	-	-	<1
Lactic acid dehydrogenase increased	-	-	-	-	-	<1	<1
Positive Coombs' test	-	-	-	-	-	<1	<1
Prothrombin time prolonged	-	<1	<1	-	-	-	<1
Serum creatinine increased	✔	<1	<1	-	1	<1	<1
Musculoskeletal							
Asthenia	-	-	-	-	-	-	<1
Back pain	-	-	-	-	-	<1	-
Dyskinesia	-	-	-	-	<1	-	-
Leg pain	-	-	-	-	≤1	-	-
Myalgia	<1†	-	-	-	-	-	-
Polyarthralgia	-	-	-	-	-	-	<1
Weakness	<1†	-	-	-	1	<1	-
Respiratory							
Apnea	-	-	-	-	-	1	-
Asthma	-	-	-	-	<1	<1	-
Bronchoconstriction	-	-	-	-	<1	-	-
Bronchospasm	<1†, 3‡	-	-	-	-	-	-
Cough	54‡	-	-	-	1 to 2	<1	-
Cyanosis	-	-	-	-	-	-	<1
Dyspnea	<1†	-	<1	-	1 to 3	<1	<1
Hemoptysis	-	-	-	-	<1	-	-
Hypoxemia	-	-	-	-	<1	-	-
Hypoxia	-	-	-	-	-	<1	-
Hyperventilation	-	-	-	-	-	-	<1
Interstitial pneumonia	-	-	-	✔	-	-	-
Nasal congestion	16‡	-	-	-	-	-	-
Pharyngeal pain	12‡	-	-	-	-	-	<1

Adverse Events	Single Entity Agents						Combination Products
	Aztreonam	Cefotetan	Cefoxitin	Doripenem	Ertapenem	Meropenem	Imipenem and Cilastatin
Pharyngitis	-	-	-	-	1	✔	-
Pleural effusion	-	-	-	-	<1	<1	-
Pneumonia	-	-	-	-	-	✔	-
Pulmonary edema	-	-	-	-	-	<1	-
Pulmonary embolus	-	-	-	-	-	<1	-
Rales/rhonchi	-	-	-	-	1	-	-
Respiratory disorder	-	-	-	-	-	<1	-
Respiratory distress	-	-	-	-	≤1	-	-
Sneezing	<1†	-	-	-	-	-	-
Wheezing	<1†, 16‡	-	-	-	-	-	-
Other							
Anaphylactoid reactions	-	-	-	-	<1	-	-
Anaphylaxis	<1†	<1	<1	✔	<1	-	<1
Bleeding	-	<1	-	-	-	-	-
Breast tenderness	<1†	-	-	-	-	-	-
Chills	-	-	-	-	-	<1	-
Diplopia	<1†	-	-	-	-	-	-
Drug fever	-	-	-	-	-	-	<1
Epistaxis	-	-	-	-	-	<1	-
Extravasation	-	-	-	-	1 to 2	-	-
Facial edema	<1‡	-	-	-	<1	-	-
Gout	-	-	-	-	<1	-	-
Hearing loss	-	-	-	-	-	-	<1
Hemoperitoneum	-	-	-	-	-	<1	-
Hypersensitivity	<1‡	1	-	<1	-	-	<1
Hypervolemia	-	-	-	-	-	<1	-
Inflammation at injection site	-	-	-	-	-	2	-
Infused vein complication	-	-	-	-	5 to 7	-	-
Injection site edema	-	-	-	-	-	<1	-
Injection site pain	1 to 10†	-	-	-	-	<1	1
Injection site reaction	-	-	✔	-	✔	1	-
Ototoxicity	✔	-	-	-	-	-	-
Pain	-	-	-	-	-	≤5	-
Peripheral edema	-	-	-	-	-	<1	-
Purpura	<1†	-	-	-	-	-	-
Septicemia	-	-	-	-	<1	2	-

Adverse Events	Single Entity Agents						Combination Products
	Aztreonam	Cefotetan	Cefoxitin	Doripenem	Ertapenem	Meropenem	Imipenem and Cilastatin
Subdural hemorrhage	-	-	-	-	<1	-	-
Thoracic spine pain	-	-	-	-	-	-	<1
Throat tightness	<1‡	-	-	-	-	-	-
Thrombophlebitis/phlebitis	1 to 10†	<1	<1	4 to 8	2	1	3
Tinnitus	<1†	-	-	-	-	-	<1

✓ Percent not specified.
- Event not reported or incidence <1%.
‡Inhalation formulation.
†Injection formulation.

VII. Dosing and Administration

The usual dosing regimens for the miscellaneous β-lactam antibiotics are listed in Table 8.

Table 8. Usual Dosing Regimens for the Miscellaneous β-Lactam Antibiotics[1-10]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Aztreonam	Improve respiratory symptoms in cystic fibrosis patients with *Pseudomonas aeruginosa*: Inhalation solution: 75 mg inhaled three times daily for 28 days followed by 28 days off of therapy Moderately severe systemic infections: Injection: 1 to 2 g IM/IV every eight to 12 hours Severe systemic or life-threatening infections: Injection: 2 g IM/IV every six or eight hours Urinary tract infections: Injection: 500 mg to 1 g IM/IV every eight to 12 hours	Improve respiratory symptoms in cystic fibrosis patients with *Pseudomonas aeruginosa* in patients ≥7 years of age: Inhalation: 75 mg inhaled three times daily for 28 days followed by 28 days off of therapy Mild to moderate infections in patients ≥9 months of age: Injection: 30 mg/kg IV every eight hours Moderate to severe infections in patients ≥9 months of age: Injection: 30 mg/kg IV every six to eight hours	Inhalation solution: 75 mg/ml Injection: 1 g 2 g
Cefotetan	Life-threatening infections: Injection: 3 g IV every 12 hours Prophylaxis of postoperative infections: Injection: 1 to 2 g IV administered 30 to 60 minutes prior to surgery; in patients undergoing cesarean section, the dose should be administered as soon as the umbilical cord is clamped Severe infections: Injection: 2 g IV every 12 hours Skin and skin-structure infections (mild to moderate): Injection: 2 g IV every 24 hours or 1 g IM/IV every 12 hours Unspecified infections: Injection: 1 to 2 g IM/IV every 12 hours Urinary tract infections: Injection: 500 mg IM/IV every 12 hours, 1 or 2 g IM/IV every 24 hours, or 1 or 2 g IM/IV	Safety and efficacy in children have not been established.	Injection: 1 g 2 g 10 g

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	every 12 hours		
Cefoxitin	Infections needing antibiotics in higher doses: Injection: 2 g IV every four hours or 3 g IV every six hours Moderately severe or severe infections: Injection: 1 g IV every four hours or 2 g IV every six to eight hours Prophylaxis of infections (uncontaminated gastrointestinal surgery, vaginal hysterectomy, abdominal hysterectomy, or cesarean section): Injection: 2 g IV administered 30 to 60 minutes prior to surgery, followed by 2 g IV every six hours after the first dose for no more than 24 hours; for patients undergoing cesarean section, either a single 2 g dose administered IV as soon as the umbilical cord is clamped or a three-dose regimen consisting of 2 g given IV as soon as the umbilical cord is clamped, followed by 2 g IV four and eight hours after the initial dose Uncomplicated infections (pneumonia, urinary tract infection, cutaneous infection): Injection: 1 g IV every six to eight hours	Prophylaxis of infections (uncontaminated gastrointestinal surgery, vaginal hysterectomy, abdominal hysterectomy in patients ≥3 months of age: Injection: 30 to 40 mg/kg administered 30 to 60 minutes prior to surgery, followed by 30 to 40 mg/kg every six hours after the first dose for no more than 24 hours Unspecified infections in patients ≥3 months of age: Injection: 80 to 160 mg/kg of body weight per day divided into four to six equal doses	Injection: 1 g 2 g 10 g
Doripenem	Complicated intra-abdominal infections: Injection: 500 mg IV every eight hours Unspecified infections: Injection: 500 mg IV every eight hours Urinary tract infections (complicated): Injection: 500 mg IV every eight hours	Safety and efficacy in children have not been established.	Injection: 250 mg 500 mg
Ertapenem	Acute pelvic infections (postpartum endomyometritis, septic abortion, postsurgical gynecologic infections): Injection: 1 g IM/IV once daily	Acute pelvic infections (postpartum endomyometritis, septic abortion, postsurgical gynecologic infections) in patients three months to 12 years of age:	Injection: 1 g

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Community-acquired pneumonia: Injection: 1 g IM/IV once daily Intra-abdominal infections (complicated): Injection: 1 g IM/IV once daily Prophylaxis of surgical site infections (colorectal surgery): Injection: single 1 g dose IV administered one hour prior to surgical incision Skin and skin-structure infections (complicated): Injection: 1 g IM/IV once daily Urinary tract infections (complicated): Injection: 1 g IM/IV once daily	Injection: 15 mg/kg IM/IV twice daily Acute pelvic infections (postpartum endomyometritis, septic abortion, postsurgical gynecologic infections) in patients ≥13 years of age: Injection: 1 g IM/IV once daily Community-acquired pneumonia in patients three months to 12 years of age: Injection: 15 mg/kg IM/IV twice daily Community-acquired pneumonia in patients ≥13 years of age: Injection: 1 g IM/IV once daily Intra-abdominal infections (complicated) in patients three months to 12 years of age: Injection: 15 mg/kg IM/IV twice daily Intra-abdominal infections (complicated) in patients ≥13 years of age: Injection: 1 g IM/IV once daily Skin and skin-structure infections (complicated) in patients three months to 12 years of age: Injection: 15 mg/kg IM/IV twice daily Skin and skin-structure infections (complicated) in patients ≥13 years of age: Injection: 1 g IM/IV once daily Urinary tract infections (complicated) in patients three months to 12 years of age: Injection: 15 mg/kg IM/IV twice daily Urinary tract infections (complicated) in patients ≥13 years of age: Injection: 1 g IM/IV once daily	
Meropenem	Intra-abdominal infections: Injection: 1 g IV every eight	Intra-abdominal infections in patients ≥3 months of age:	Injection: 500 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	hours Skin and skin-structure infections (caused by *P. aeruginosa*): Injection: 1 g IV every eight hours Skin and skin-structure infections (not caused by *P. aeruginosa*): Injection: 500 mg IV every eight hours	Injection: ≤50 kg, 20 mg/kg IV every eight hours; >50 kg, 1 g IV every eight hours Meningitis in patients ≥3 months of age: Injection: ≤50 kg, 40 mg/kg IV every eight hours; >50 kg, 2 g IV every eight hours Skin and skin-structure infections (complicated) in patients ≥3 months of age: Injection: ≤50 kg, 10 mg/kg IV every eight hours; >50 kg, 500 mg IV every eight hours	1 g
Combination Products			
Imipenem and cilastatin	Gynecologic infections (mild to moderate): Injection: 500 to 750 mg IM every 12 hours Intra-abdominal infections (mild to moderate): Injection: 250 to 500 mg IV every six hours Intra-abdominal infections (severe): Injection: 500 mg IV every six hours or 1 g IV every eight hours Lower respiratory tract infections (mild to moderate): Injection: 500 to 750 mg IM every 12 hours Mild infections (fully susceptible organisms): Injection: 250 mg IV every six hours Mild infection (moderately susceptible organisms): Injection: 500 mg IV every six hours Moderate infections (fully susceptible organisms): Injection: 500 mg IV every six to eight hours Moderate infections (moderately susceptible organisms): Injection: 500 mg IV every six hours or 1 g IV every eight hours	Gynecologic infections (mild to moderate) in patients ≥12 years of age: Injection: 500 to 750 mg IM every 12 hours Intra-abdominal infections (mild to moderate) in patients ≥12 years of age: Injection: 750 mg IM every 12 hours Lower respiratory tract infections (mild to moderate) in patients ≥12 years of age: Injection: 500 to 750 mg IM every 12 hours Non-central nervous system infections in patients <1 week of age: Injection: 25 mg/kg IV every 12 hours Non-central nervous system infections in patients one to four weeks of age: Injection: 25 mg/kg IV every eight hours Non-central nervous system infections in patients four weeks to three months of age: Injection: 25 mg/kg IV every six hours Non-central nervous system infections in patients ≥3 months of age:	Injection: 250 mg 500 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Severe or life-threatening infections (fully susceptible organisms): Injection: 500 mg IV every six hours Severe or life-threatening infections (moderately susceptible organisms): Injection: 1 g IV every six to eight hours Skin and skin-structure infections (mild to moderate): Injection: 500 to 750 mg IM every 12 hours Urinary tract infections (complicated): Injection: 500 mg IV every six hours Urinary tract infections (uncomplicated): Injection: 250 mg IV every six hours	Injection: 15 to 25 mg/kg/dose IV every six hours Skin and skin-structure infections (mild to moderate) in patients ≥12 years of age: Injection: 500 to 750 mg IM every 12 hours	

IM=intramuscular, IV=intravenous

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the miscellaneous β-lactam antibiotics are summarized in Table 9.

Table 9. Comparative Clinical Trials with the Miscellaneous β-Lactam Antibiotics

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Dermatological Infections				
Corey et al.[31] (2010) Aztreonam 1 g plus vancomycin 1 g every 12 hours for 5 to 14 days vs ceftaroline 600 mg every 12 hours for 5 to 14 days	AC, DB, MC, RCT Patients ≥18 years of age with complicated skin and cSSSIs who required ≥5 days of parenteral antibacterial therapy	N=702 Variable duration	Primary: Clinical cure rate at the test-of-cure visit (eight to 15 days after administration of the last dose of study medication) in the clinically evaluable and modified intent-to-treat populations Secondary: Microbiological success rate, safety	Primary: Clinical cure rates were similar for ceftaroline and vancomycin plus aztreonam in the clinically evaluable (91.1 vs 93.3%; 95% CI, -6.6 to 2.1) and modified intent-to-treat (86.6 vs 85.6%; 95% CI, -4.2 to 6.2) populations, respectively. Secondary: The clinical cure rate for MRSA cSSSIs was 95.1% for ceftaroline and 95.2% for vancomycin plus aztreonam. Similar cure rates were found in patients with MSSA (91.3 and 94.6%), as well as in the patients from whom Gram-negative pathogens were isolated. The microbiological success rate was similar for ceftaroline and vancomycin overall, and for MRSA. Among the microbiologically evaluable patients, the baseline pathogen(s) was eradicated or presumed eradicated at similar rates in both the microbiologically evaluable and modified intent-to-treat populations (91.8 and 86.3% for ceftaroline; 92.5 and 83.7% for vancomycin plus aztreonam; 95% CI, -5.7 to 4.4 and 95% CI, -3.4 to 8.9, respectively). The incidence of adverse events was similar in both study groups. The majority of adverse events were mild in severity and similar in type among study groups. Diarrhea occurred in 3.4 vs 3.2% of patients in the ceftaroline and vancomycin plus aztreonam treatment groups, respectively.
Wilcox et al.[32] (2010) Aztreonam 1 g plus vancomycin 1 g every 12 hours	AC, DB, MC, RCT Patients ≥18 years of age with cSSSIs who required ≥5 days of parenteral	N=694 Variable duration	Primary: Clinical cure rate at the test-of-cure visit (eight to 15 days after administration of	Primary: Cure rates at test-of-cure were comparable in both treatment groups across all study populations. In the clinically evaluable population, cure rates were 92.2 and 92.1% for ceftaroline and vancomycin plus aztreonam, respectively (95% CI, -4.4 to 4.5). In the modified intent-to-treat population, clinical cure rates for ceftaroline and vancomycin plus

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
for 5 to 14 days vs ceftaroline 600 mg every 12 hours for 5 to 14 days	antibacterial therapy		the last dose of study medication) in the clinically evaluable and modified intent-to-treat populations Secondary: Microbiological success rate, safety	aztreonam were similar (85.1 vs 85.5%, respectively; 95% CI, -5.8 to 5.0). Secondary: In patients with MRSA isolated at baseline, cure rates were 91.4 and 93.3% for ceftaroline and vancomycin plus aztreonam, respectively. Similar cure rates were found in patients with MSSA (94.4% in both groups) as well as in the patients from whom a Gram-negative pathogen was isolated. Baseline pathogens were eradicated or presumed eradicated at similar rates in both the microbiologically evaluable and modified intent-to-treat populations among Gram-positive and a limited number of Gram-negative pathogens (92.9 and 86.6% for ceftaroline; 95.0 and 88.4% for vancomycin plus aztreonam; 95% CI, -6.9 to 2.5 and 95% CI, -7.5 to 3.9, respectively). There were no microbiological reinfections or recurrences at the late follow-up visit in either treatment group. The incidence of adverse events was similar in both study groups. The majority of adverse events were mild in severity and similar in type among study groups. Diarrhea occurred in 6.5 vs 4.4% in the ceftaroline and vancomycin plus aztreonam treatment groups, respectively. Adverse events considered related to the study drug and occurring in ≥3% of patients were diarrhea and pruritus.
Corey et al.[33] (2010) Aztreonam 1 g plus vancomycin 1 g every 12 hours for 5 to 14 days vs ceftaroline 600 mg every 12 hours for	Pooled analysis (2 trials) Patients ≥18 years of age with cSSSIs who required ≥5 days of parenteral antibacterial therapy	N=1,378 Variable duration	Primary: Clinical cure rate at the test-of-cure visit (eight to 15 days after administration of the last dose of study medication) in the clinically evaluable and modified intent-to-treat populations	Primary: Clinical cure rates were similar for ceftaroline and vancomycin plus aztreonam in the clinically evaluable (91.6 vs 92.7%) and modified intent-to-treat (85.9 vs 85.5%) populations, respectively. Secondary: Clinical cure rates were similar for ceftaroline and vancomycin plus aztreonam in patients infected with MRSA (93.4 vs 94.3%). The efficacy of ceftaroline and vancomycin plus aztreonam against polymicrobial and monomicrobial infections was similar.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
5 to 14 days			Secondary: Microbiological success rate, safety	Clinical relapse at the late follow-up visit was noted in 1.1% of patients in the ceftaroline group compared to 0.9% of patients in the vancomycin plus aztreonam group (clinically evaluable). Favorable microbiological response (microbiologically evaluable) was observed in 92.3% of patients in the ceftaroline group compared to 93.7% of patients in the vancomycin plus aztreonam group (95% CI, -4.8 to 2.0). Incidences of treatment-emergent adverse events were similar among the treatment groups. Diarrhea occurred in 4.9% of patients in the ceftaroline group and in 3.8% of patients in the vancomycin plus aztreonam group (modified intent-to-treat population). Adverse events considered to be related to study drug in ≥3% of patients were pruritus, nausea, and diarrhea.
Chuang et al.[34] (2011) Aztreonam 2 g IV every 12 hours plus vancomycin 1 g IV vs tigecycline 100 mg IV as an initial dose, followed by 50 mg IV every 12 hours	DB, MC, RCT Hospitalized patients ≥18 years of age with cSSSIs	N=127 5 to 14 days	Primary: Clinical response in clinically evaluable and clinical modified intent-to-treat populations Secondary: Clinical response (cure or failure) by baseline isolate and type of infection	Primary: In India, the clinical response rates in the clinically evaluable and clinically evaluable-modified intent-to-treat populations were higher in the tigecycline group than in the vancomycin-aztreonam group. Clinically evaluable rates were 83.3% in patients treated with tigecycline and 75.8% in patients treated with vancomycin-aztreonam. The clinically evaluable-modified intent-to-treat cure rates for tigecycline vs vancomycin-aztreonam were 78.6 vs 66.7%, respectively. Small sample size prevented non-inferiority analysis. In Taiwan, the clinical response rates in the clinically evaluable populations were lower in the tigecycline group than in the vancomycin-aztreonam group. Clinically evaluable rates were 78.6% in patients treated with tigecycline and 90.0% in patients treated with vancomycin-aztreonam. The clinically evaluable-modified intent-to-treat cure rates for tigecycline vs vancomycin-aztreonam were 73.3 and 75%, respectively. Small sample size prevented any meaningful statistical analysis. Secondary: In India, the number of isolates was small and no definitive inferences are possible. However, tigecycline demonstrated antimicrobial efficacy against isolates commonly linked to cSSSIs. No MRSA isolates were noted among Indian patients.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				In Taiwan, few isolates were available. They included one patient with MRSA, which responded to tigecycline.
Gesser et al.[35] (2004) Ertapenem 1 g IV daily vs piperacillin-tazobactam 13.5 grams IV divided every six hours Study medications were given as outpatient parenteral antimicrobial therapy or as inpatient therapy.	DB, MC, PRO, RCT Patients 18 years of age and older with SSSI requiring parenteral therapy	N=146 10 to 21 days post-therapy	Primary: Clinical response, adverse events Secondary: Not reported	Primary: For patients receiving outpatient parenteral antimicrobial therapy, 83.3% in the ertapenem group and 82.0% in the piperacillin-tazobactam group had a clinical response to therapy and were considered cured (P=0.78). The only significant difference in adverse event between the two treatment groups was that 10.5% of patients in the piperacillin-tazobactam group experienced moderate-severe tenderness compared to 0% in the ertapenem group; P=0.006). Secondary: Not reported
Lipsky et al.[36] (2005) Ertapenem 1 g IV daily vs piperacillin-tazobactam 3.375 g every six hours Investigators switched patients	DB, MC, RCT Adult patients with type 2 diabetes mellitus with a foot infection not extending above the knees	N=445 10 days after completion of antibiotic therapy	Primary: Proportion of patients with a favorable clinical response at the discontinuation of IV therapy Secondary: Proportion of patients with a favorable clinical response at follow-up assessment	Primary: At the discontinuation of IV therapy visit, 94% of patients in the ertapenem group and 92% in the piperacillin-tazobactam group had a favorable clinical response. Secondary: At the follow-up assessment visit, 87% of patients in the ertapenem group and 83% in the piperacillin-tazobactam group had a favorable clinical response.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
to PO therapy if appropriate after five days of IV therapy.				
Lauf et al.[37] (2014) Ertapenem 1 g IV every 24 hours, with or without adjunctive IV vancomycin for up to 28 days vs tigecycline 150 mg IV every 24 hours, with or without placebo for up to 28 days Patients with osteomyelitis were treated for up to 42 days.	DB, RCT Hospitalized men and women ≥18 years of age with diabetes mellitus who had a foot infection that did not extend above the knee, with or without osteomyelitis. The infection had to be of acute onset or a worsening within 14 days prior to the screening visit.	N=955 (without osteomyelitis) N=118 (with osteomyelitis) 12 to 92 days after the last dose for patients without osteomyelitis and 25 to 27 weeks for patients with osteomyelitis	Primary: Clinical response within the clinically evaluable and the clinically modified intent-to-treat populations at the test-of-cure visit Secondary: Microbiologic efficacy of tigecycline, in vitro susceptibility data on tigecycline	Primary: At the test-of-cure assessment in the patients without osteomyelitis, 77.5% of tigecycline-treated subjects and 82.5% of ertapenem ± vancomycin-treated subjects in the clinically evaluable population were considered cured, and 71.4% of those treated with tigecycline subjects and 77.9% of those who received ertapenem ± vancomycin in the clinically modified intent-to-treat population were considered cured. The tigecycline regimen did not meet the primary study endpoint of noninferiority to the ertapenem ± vancomycin regimen for the clinically evaluable population (true difference in efficacy of tigecycline minus ertapenem ± vancomycin regimen, −5.5%; 95% CI, −11.0 to 0.1) or clinically modified intent-to-treat population (true difference in efficacy of tigecycline minus ertapenem ± vancomycin regimen, −6.7; 95% CI, −12.3 to −1.1). Secondary: In the population without osteomyelitis, the cure rates for most baseline isolates were either slightly higher or similar for ertapenem ± vancomycin as compared with tigecycline-treated subjects. However, participants in the tigecycline regimen with *Escherichia coli* (21/28; 75.0%), MRSA (29/44; 65.9%), and *S. agalactiae* infections (35/40; 87.5%) had higher cure rates compared to subjects receiving ertapenem ± vancomycin (28/38, 73.7%; 17/26, 65.4%; and 40/48, 83.3%; respectively). The cure rates for tigecycline-treated participants with methicillin-susceptible *S. aureus* (MSSA) or *Klebsiella pneumoniae* infections were lower than expected compared with those treated with ertapenem ± vancomycin. For subjects with baseline bacteremia, excluding contaminants, in the primary study, the clinical cure rate at the test-of-cure visit was 6/7 (86%) for tigecycline-treated subjects and 14/14 (100%) for ertapenem-treated subjects.
Saltoglu et al.[38] (2010)	OL, RCT, SC Patients ≥18 years	N=64 2 months	Primary: Clinical response	Primary: A successful clinical response was seen in 46.7% of patients in the piperacillin-tazobactam group and in 28.1% of patients in the imipenem

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Imipenem-cilastatin 0.5 g IV every six hours for 14 to 28 days vs piperacillin-tazobactam 4.5 g IV every eight hours for 14 to 28 days	of age with a diagnosis of moderate to severe diabetic lower extremity foot infection	post-treatment	Secondary: Relapse rate after two months	group (RR, 1.6; 95% CI, 0.84 to 3.25; P=0.130). Secondary: During two months follow-up, two patients in the imipenem group and none in the piperacillin-tazobactam group relapsed (RR, 2; 95% CI, 0.94 to 4.24; P=0.058). Sixty-four percent of patients had amputations. There was no significant difference in amputation rates between the piperacillin-tazobactam and imipenem groups (60 vs 68.8%; P=0.739).
Nichols et al.[39] (1995) Meropenem 500 mg IV every eight hours vs imipenem-cilastatin 500 mg IV every six hours	MC, OL, PRO, RCT Hospitalized patients, 18 years of age or older, who required parenteral antibiotics for the treatment of SSSI	N=377 6 to 7 days	Primary: Clinical response (a response of cured or improved were considered satisfactory) Secondary: Bacteriologic Response	Primary: Satisfactory clinical responses were achieved in 98% of meropenem treated patients and in 95% of imipenem-cilastatin treated patients, a difference that was NS (95% CI, -2.29 to 6.93). Secondary: Satisfactory bacteriologic response rates were 94% with meropenem and 91% with imipenem-cilastatin, a difference that was NS (95% CI, -2.73 to 10.39).
Fabian et al.[40] (2005) Meropenem 500 mg IV every eight hours vs imipenem-cilastatin 500 mg IV every eight	DB, MC, RCT Hospitalized patients with cSSSI	N=1,076 14 days	Primary: Clinical response at the post-treatment followup visit in the clinically evaluable and modified intent-to-treat populations Secondary:	Primary: The proportion of patients assessed as cured in the clinically evaluable population at the post-treatment follow-up evaluation was 86.2% for the meropenem and 82.9% for the imipenem-cilastatin treatment groups (95% CI, -2.8 to 9.3). In the modified intent-to-treat population, the clinical cure rates at the follow-up assessment were 73.1% (meropenem) and 74.9% (imipenem-cilastatin; 95% CI, -8.4 to 4.7). Secondary: The clinical response rates at the end of treatment were 93.5 vs 92.3%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
hours			Clinical response at the post-treatment follow-up visit in the intent-to-treat population and at the end-of-treatment visit in the clinically evaluable, modified intent-to-treat, and intent-to-treat populations	(clinically evaluable), 91.0 vs 91.1% (modified intent-to-treat), and 81.0 vs 83.5% (intent-to-treat) for meropenem and imipenem-cilastatin, respectively. The 95% CI for the difference between treatment groups in all three analysis demonstrated non-inferiority of meropenem to imipenem-cilastatin.
Genitourinary Infections				
Friman et al.[41] (1989) Aztreonam 1 g IV every eight hours vs cefuroxime 1.5 g IV every eight hours	RCT Patients 18 to 99 years of age with symptoms of an upper urinary tract infection	N=171 1 month	Primary: Clinical response rates, bacteriologic response rates Secondary: Not reported	Primary: Clinical response rates were 89% in the aztreonam group and 87% in the cefuroxime group. Bacteriologic response rates at one week post-therapy were 70% in the aztreonam group and 73% in the cefuroxime group, while rates at one month were 43 and 40% respectively. Secondary: Not reported
MacGregor et al.[42] (1992) Cefoxitin 2 g IV every six hours vs cefotetan 2 g IV every 12 hours	DB, RCT Patients with post-cesarean section endometritis	N=140 Duration varied	Primary: Clinical response, duration of therapy, length of hospital stay Secondary: Not reported	Primary: Cure rates were 83% in the cefotetan group compared to 79% in the cefoxitin group (P=0.56). The duration of therapy and length of hospital stay were similar in both groups. Secondary: Not reported
Naber et al.[43] (2009)	DB, MC, RCT	N=753	Primary: Microbiological	Primary: The microbiologically evaluable population achieved microbiological cure

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Doripenem 500 mg IV every eight hours vs levofloxacin 250 mg IV QD Patients in both treatment arms were eligible to switch to PO levofloxacin after three days of IV therapy to complete a 10-day treatment course if they demonstrated significant clinical and microbiological improvements.	Patients ≥18 years of age with cUTI or pyelonephritis who required initial treatment with a parenterally administered antibacterial agent	Up to 14 days	cure rate in the microbiologically evaluable and microbiologically evaluable-modified intent-to-treat population Secondary: Clinical cure rate at the test-of-cure visit for the clinically evaluable population and the microbiological cure rate for the microbiologically evaluable patients infected with *Escherichia coli*	rates of 82.1 and 83.4% with doripenem and levofloxacin, respectively. Patients in the microbiologically evaluable-modified intent-to-treat population achieved microbiological cure rates of 79.2 and 78.2%, respectively. Doripenem was not therapeutically inferior to levofloxacin for the treatment of cUTI or pyelonephritis. In the microbiologically evaluable population, the microbiological cure rates at the end-of-treatment were 100% for the doripenem-treated patients and 88% for the levofloxacin-treated patients (P<0.001). The non-inferior response demonstrated for the doripenem-treated patients at the test-of-cure visit could be attributed to the IV portion of the therapeutic regimen, independently of a switch to PO levofloxacin. Secondary: In the clinically evaluable population, the clinical cure rates at end-of-treatment were 98.3 and 93.2% in the doripenem and levofloxacin arms, respectively. At the test-of-cure visit, the clinical cure rates were 95.1 and 90.2%, respectively (95% CI, 0.2 to 9.6). Clinical cure rates at the late follow-up visit of 90.8% for the doripenem-treated patients and 95.2% for the levofloxacin-treated patients who were clinically evaluable were sustained. For the patients who received the IV study drug only, the clinical cure rates at the test-of-cure visit were 78.1% with doripenem and 52.3% with levofloxacin. The microbiological cure rates for *Escherichia coli* infections of microbiologically evaluable patients at the test-of-cure visit were 84.4% for the doripenem arm and 87.2% for the levofloxacin arm (P=0.83).
Redman et al.[44] (2010) <u>Study 1</u> Doripenem 500 mg IV every eight hours	DB, RCT Patients ≥18 years of age with cUTI and pyelonephritis	N=1,179 42 days after the last dose	Primary: Microbiological response at the test-of-cure visit (five to 11 days after the last dose); clinical cure rates	Primary: Microbiological eradication rates in the microbiologically evaluable patient population at the test-of-cure visit were 82.1% with doripenem and 83.4% with levofloxacin in study 1, and 83.6% with doripenem in study 2. The combined analysis demonstrated that doripenem was non-inferior to levofloxacin.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs levofloxacin 250 mg IV QD Study 2 Doripenem 500 mg IV every eight hours After a minimum of three days of IV therapy, investigators could switch patients from IV therapy to PO levofloxacin 250 mg daily.			Secondary: Not reported	Microbiological eradication rates in the microbiologically evaluable-modified intent-to-treat population at the test-of-cure visit were 79.2% with doripenem and 78.2% with levofloxacin in study 1, and 82.5% with doripenem in study 2.The combined analysis in the evaluable-modified intent-to-treat population demonstrated that doripenem was non-inferior to levofloxacin. The pooled microbiological eradication rates in the microbiologically evaluable populations at the test-of-cure and end-of-treatment visits from both studies were 99.8% with doripenem and 88.4% with levofloxacin (95% CI, 7.2 to 15.6). These results suggest that the eradication preceded a switch from IV to PO levofloxacin therapy. Clinical cure rates for the combined clinically evaluable population at the test-of-cure visit were 95.1% with doripenem and 90.2% with levofloxacin in study 1, and 93.0% with doripenem in study 2. The pooled clinical cure rates in the clinically evaluable populations at the test-of-cure and end-of-treatment visits showed that clinical improvement preceded a switch to PO levofloxacin; 98.9% with doripenem and 93.2% with levofloxacin in study 1, and 99.6% with doripenem in study 2. Secondary: Not reported
Vazquez et al.[45] (2012) Imipenem–cilastatin (500 mg) every six hours vs ceftazidime–avibactam (500-125 mg) every eight hours	DB, MC, PRO, RCT Patients 18 to 90 years of age with complicated urinary tract infection due to Gram-negative pathogens	N=137 Microbiologi-cally evaluable patients=62 12 to 23 days	Primary: Favorable microbiological response at the test-of-cure visit five to nine days post-therapy in microbiologically evaluable patients Secondary: Microbiological response at the end	Primary: Favorable microbiological response in the microbiologically evaluable population at the test-of-cure visit was observed in 19/27 (70.4%) patients in the ceftazidime–avibactam arm and 25/35 (71.4%) in the imipenem–cilastatin arm (observed difference −1.1% [95% CI, −27.2 to 25.0%]). Secondary: Favorable microbiological response rates at the end of IV therapy were 25/26 (96.2%) and 34/34 (100%) in the ceftazidime–avibactam and imipenem–cilastatin arms, respectively, and 15/26 (57.7%) and 18/30 (60.0%) at the late follow-up visit. Over the course of the study, adverse events were reported in 46/68

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Patients meeting pre-specified improvement criteria after four days could be switched to oral ciprofloxacin. Patients were treated for a total of seven to 14 days.			of IV therapy and at the late follow-up visit, four to six weeks post-therapy in the microbiologically evaluable population; safety and tolerability	(67.6%) patients in the ceftazidime–avibactam arm and 51/67 (76.1%) patients in the imipenem–cilastatin arm. The most common adverse events in both treatment arms included constipation, diarrhea, abdominal pain, headache, anxiety, and injection/infusion site reactions. Treatment-emergent serious adverse events were reported in 6/68 (8.8%) and 2/67 (3.0%) of patients in the ceftazidime–avibactam and imipenem–cilastatin arms, respectively, during the course of the study. Three of the serious adverse events in the ceftazidime–avibactam arm were considered to be drug-related: renal failure, diarrhea, and accidental overdose of ceftazidime–avibactam. Although the accidental overdose of ceftazidime–avibactam was recorded as a serious adverse event, there were no adverse events associated with this event. One patient in the imipenem–cilastatin arm developed a drug-related serious adverse event associated with an increase in serum creatinine level.
Cox et al.[46] (1995) Imipenem-cilastatin 500 mg IV QID vs meropenem 500 mg IV TID	MC, OL, PG, PRO, RCT Hospitalized patients ≥18 years of age, with cUTI requiring IV antibiotic treatment	N=235 21 days after final dose	Primary: Clinical response (complete resolution or improvement in signs and symptoms of infection), bacteriological response rate (negative urine culture), superinfection, relapse, reinfection Secondary: Not reported	Primary: There was no significant difference in clinical response between the groups (99% for each group) at the end of treatment. At follow-up 83% of the imipenem-cilastatin group and 87% of the meropenem group, reported a satisfactory clinical response. A satisfactory bacterial response was reported in 81% of the patients receiving imipenem-cilastatin and 90% of patients receiving meropenem (95% CI, -1.58 to 19.55; P=0.075). Response at follow-up was observed in 70% in those treated with imipenem-cilastatin and 79% in meropenem recipients. There were few incidences of superinfection or relapse. The same number of patients in each group experienced reinfection. Adverse events were reported in 52% of imipenem-cilastatin recipients and 32% of meropenem patients. There were three patients from the imipenem-cilastatin group and no patients from the meropenem group who withdrew from the study secondary to adverse events. Secondary: Not reported
Ryo et al.[47] (2005)	RETRO Pregnant women	N=140 1 year	Primary: Time from preterm premature rupture	Primary: The mean time from preterm premature rupture of membranes to delivery was 11 days in the imipenem-cilastatin group and 6 days in the control

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Imipenem-cilastatin 500 mg IV BID for three days plus betamethasone 12 mg SC vs penicillin or a cephalosporin or no antibiotic treatment	admitted to hospital with preterm premature rupture of membranes at 24 weeks and 0 days to 31 weeks and 6 days gestation		of membranes to delivery, prognosis of infants (death within one year, alive with or without handicap) Secondary: Sensitivity of imipenem-cilastatin to cultured bacteria obtained at admission compared to ampicillin	group (P=0.016). Also 53% of women treated with imipenem-cilastatin were able to continue pregnancy for greater than one week after preterm premature rupture of membranes as opposed to 25% in the control group (P=0.0048). There were no infant deaths in the imipenem-cilastatin group but 12.5% of the infants died in the control group (P=0.002). There was no difference in the incidence of infants with handicaps between each group (P=0.3277). Secondary: All cultured bacteria specimens in 94% of the women in the study group were sensitive to imipenem-cilastatin while all specimens found in 25% of those in the control group were sensitive to ampicillin (P<0.0001).
Respiratory Tract Infections				
McCoy et al.[48] (2008) AIR-CF2 Aztreonam inhalation solution 75 mg BID or TID for 28 days vs placebo	DB, MC, PC, RCT Patients ≥6 years of age with cystic fibrosis with FEV_1 >25 and <75% who were on maintenance therapy for *Pseudomonas aeruginosa* and who had completed a 28-day course of tobramycin inhalation solution	N=211 84 days	Primary: Time to need for additional inhaled or IV antipseudomonal antibiotics to treat symptoms indicative of pulmonary exacerbation Secondary: Changes in clinical symptoms, pulmonary function, *Pseudomonas aeruginosa* density, time to hospitalization,	Primary: The median time to need for additional inhaled or IV antipseudomonal antibiotics to treat symptoms indicative of pulmonary exacerbation was 21 days longer for the aztreonam inhalation solution-pooled group than for the placebo group (92 vs 71 days; P=0.007). The median time to antibiotic need was also longer in the aztreonam inhalation solution-BID (>92 days; P=0.002) and aztreonam inhalation solution-TID (87 days; P=0.182) groups, compared to placebo (71 days). Secondary: Adjusted mean CFQ-R respiratory scores increased 5.01 points in the aztreonam inhalation solution-pooled group compared to placebo (day 28; 95% CI, 0.81 to 9.21; P=0.020). Significant improvements were observed for both aztreonam inhalation solution-BID and aztreonam inhalation solution-TID groups compared to placebo and the responses of the aztreonam inhalation solution-BID and aztreonam inhalation solution-TID groups were comparable. Adjusted mean FEV_1 improved 6.3% in the aztreonam inhalation solution-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			hospitalizations, and weight	pooled group compared to placebo (day 28; 95% CI, 2.5 to 10.1; P=0.001). Significant improvements were observed for both aztreonam inhalation solution-BID and aztreonam inhalation solution-TID groups compared to placebo. Responses of the aztreonam inhalation solution-BID and aztreonam inhalation solution-TID groups were comparable. FEV_1 decreased during the follow-up period for all groups. Adjusted mean relative FEV_1 percent predicted improved in the aztreonam inhalation solution-pooled group compared to placebo (day 28; adjusted means; aztreonam inhalation solution-pooled, 4.1%; placebo, 22.5%; 95% CI, 2.8 to 10.4; P<0.001). Adjusted mean *Pseudomonas aeruginosa* sputum density decreased 0.66 $\log_{10}$ *Pseudomonas aeruginosa* cfu/g sputum in the aztreonam inhalation solution-pooled group compared to the placebo group (day 28: 95% CI, 21.13 to 20.19; P=0.006). Significant decreases were observed for both aztreonam inhalation solution-BID and aztreonam inhalation solution-TID compared to placebo groups. Time to first hospitalization and median days per number of patients hospitalized did not differ significantly between the treatment groups (days 0 to 84). Weight increased 0.77% for the aztreonam inhalation solution-pooled group compared to placebo (day 28: 95% CI, 0.00 to 1.55; P=0.051).
Retsch-Bogart et al.[49] (2009) AIR-CF1 Aztreonam inhalation solution 75 mg TID for 28 days vs	DB, MC, PC, RCT Patients ≥6 years of age with cystic fibrosis, FEV_1 >25 and <75%, *Pseudomonas aeruginosa* airway infection, and no recent use of antipseudomonal antibiotics or	N=164 42 days	Primary: Change in symptoms Secondary: Changes in pulmonary function, hospitalizations, nonrespiratory CFQ-R scales, sputum	Primary: The adjusted mean CFQ-R-Respiratory scores increased for aztreonam inhalation solution-treated patients and decreased for placebo-treated patients (day 28 treatment difference, 9.7 points; 95% CI, 4.3 to 15.1; P<0.001). Two weeks after treatment, CFQ-R-Respiratory scores had declined but remained above baseline values for aztreonam inhalation solution-treated patients, and had continued to decline for placebo-treated patients (day 42 treatment difference, 6.3 points; 95% CI, 1.2 to 11.4; P<0.015). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	azithromycin		*Pseudomonas aeruginosa* density	The adjusted mean FEV_1 increased for aztreonam inhalation solution-treated patients and decreased for placebo-treated patients (day 28 treatment difference, 10.3%; 95% CI, 6.3 to 14.3; P<0.001). Two weeks after treatment, the mean FEV_1 had declined but remained above baseline for aztreonam inhalation solution-treated patients, and had continued to decline for placebo-treated patients (day 42 treatment difference, 5.7%; 95% CI, 2.1 to 9.4; P<0.002). The adjusted mean relative change in FEV% predicted values also increased for aztreonam inhalation solution-treated patients and decreased for placebo-treated patients (day 28 treatment difference, 10.2%; 95% CI, 6.2 to 14.2; P<0.001) and declined for both groups after treatment (day 42 treatment difference, 5.7%; 95% CI, 2.0 to 9.4; P=0.003). The adjusted mean sputum *Pseudomonas aeruginosa* density decreased for aztreonam inhalation solution-treated patients and remained near baseline for placebo-treated patients (day 28 treatment difference, -1.453 log_{10} cfu/g; 95% CI, -2.1 to -0.8; P<0.001). Two weeks after treatment (day 42), values were near baseline values for both treatment groups (P=0.822). There was a trend toward fewer hospitalized patients in the aztreonam inhalation solution group (5%) than in the placebo group (14%; days 0 to 42; P=0.064) and toward fewer mean hospitalization days (aztreonam inhalation solution group, 0.5 days; placebo group, 1.5 days; P=0.049). Weight increased 1.1% for the aztreonam inhalation solution-treated group and 0.1% for the placebo-treated group (day 28: 95% CI, 0.33 to 1.69; P=0.004). The responses of aztreonam inhalation solution-treated patients were significantly larger than those of placebo-treated patients for 6 of the 11 nonrespiratory CFQ-R scales; these scales included Eating, Emotional Functioning, Health Perceptions, Physical Functioning, Role Limitation/School Performance, and Vitality.
Oermann et al.[50] (2010)	OL	N=274	Primary: Disease-related	Primary: For treatment courses one through nine, percent change in FEV_1 (L) was

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
AIR-CF3 Aztreonam inhalation solution 75 mg BID to TID for 28 days Patients received up to nine courses (28 days on/28 days off) of 75mg aztreonam inhalation solution BID or TID based on randomization in the previous trials.	Patients ≥6 years of age with cystic fibrosis and *Pseudomonas aeruginosa* airway infection, who previously participated in one of two Phase 3 studies (AIR-CF1 or AIR-CF2)	18 months	endpoints (change from baseline FEV_1 percent predicted, FEV_1 absolute volume, CFQ-R-Respiratory scores, and density of *Pseudomonas aeruginosa* in sputum Secondary: Not reported	positive at the end of each on-drug course. A greater response was observed for the TID regimen in general. The mean change in FVC from baseline ranged from -1.40 to 5.39% (BID) and from 0.97 to 6.18% (TID). The mean change in $FEF_{25–75}$ from baseline ranged from -4.20 to 16.05% (BID) and from -5.02 to 14.14% (TID). For the on-treatment months, the mean increase in CFQ-R-Respiratory score was >4. Changes on other symptom scales of the CFQ-R were consistent with treatment benefit. There was a greater improvement in the TID group than in the BID group. In the TID group, mean improvements from baseline for the Physical Functioning, Vitality and Health Perceptions domains tended to be greater during each of the intervals when the patient was on treatment and less during each of the intervals when the patient was off treatment. For the TID group, mean scores for the Weight domain tended to be above baseline throughout the nine treatment courses. Absolute changes from baseline for the remaining domains (emotional functioning, social functioning, body image, eating disturbances, role limitations/school performance and digestion) were variable and showed no apparent dose response. A total of 47.8% of patients were hospitalized at least once during the study. The median time to the first hospitalization for a respiratory event was 449 days, with median times of 431 and 449 days for the BID- and TID-treated groups, respectively. Median time to IV antipseudomonal antibiotics was 247 days (95% CI, 210 to 287), with similar times between the two regimen groups: 276 days for the BID-treated group (95% CI, 217 to 316) and 232 days for the TID group (95% CI, 179 to 288). Repeated courses of aztreonam inhalation solution resulted in consistent weight gain, which were sustained over the 18-month period. Improvement was greater among patients receiving TID compared to BID

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				treatment. Mean adherence was 92.0% in the BID group and 88.0% in the TID group. Secondary: Not reported
Wainwright et al.[51] (2011) Aztreonam inhalation solution 75 mg TID for 28 days vs placebo	DB, MC, PC, RCT Patients ≥6 years of age with cystic fibrosis with an FEV_1 >75%, *Pseudomonas aeruginosa* airway infection, and who did not require immediate antipseudomonal antibiotic treatment of an impending exacerbation	N=157 42 days	Primary: Change from baseline at Day 28 on the CFQ-R RSS Secondary: Change from baseline at Days 14 and 42 on the CFQ-R RSS, change from baseline at Day 28 on the CFQ-R Physical Functioning Scale, use of additional antipseudomonal antibiotics, proportion of patients hospitalized, and change from baseline at Day 28 for log_{10} *Pseudomonas aeruginosa* CFUs in sputum and FEV_1 percent predicted	Primary: Adjusted mean change at Day 28 from baseline CFQ-R RSS scores was 3.22 for aztreonam inhalation solution-treated and 1.41 for placebo-treated patients (treatment effect 1.80; 95% CI, −2.83to 6.44; P=0.443). Secondary: Significant treatment effects favoring aztreonam inhalation solution were observed for several secondary efficacy endpoints: change from baseline at day 28 for adjusted mean log_{10} *Pseudomonas aeruginosa* CFUs in sputum (aztreonam inhalation solution, −1.4; placebo, −0.14; P=0.016) and adjusted mean relative change in FEV_1 percent predicted (aztreonam inhalation solution, 0.29%; placebo, −2.5%; P=0.021). Amongst other efficacy endpoints, significant treatment effects favoring aztreonam inhalation solution were observed for relative mean change from baseline FEV_1 (L) at day 28 and CFQ-R Social Functioning scores. Use of PO, IV, or additional inhaled antibiotics was similar for the aztreonam inhalation solution and placebo groups during the entire study, with most use occurring during the follow-up period for both treatment groups.
Tiddens et al.[52] (2015)	MC, OL	N=105	Primary: Proportion of	Primary: Of 79 patients in the primary efficacy evaluable set, 46 patients (58.2%;

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ALPINE Aztreonam for inhalation solution 75 mg three times daily for 28 days	Newly acquired *Pseudomonas aeruginosa* infection in cystic fibrosis patients three months to <18 years of age	24 weeks	patients with cultures negative for *Pseudomonas aeruginosa* at all visits throughout the 24-week follow-up period Secondary: Proportion of patients with cultures negative for *Pseudomonas aeruginosa* at each follow-up visit, additional anti-pseudomonal antibiotic use, and for patients ≥6 years, changes from baseline in FEV1 % predicted and Cystic Fibrosis Questionnaire-Revised Respiratory Symptoms Scale (CFQ-R-RSS) scores	95% CI, 47.4 to 69.1%) remained culture-negative for *Pseudomonas aeruginosa* throughout the 24-week follow-up period. Secondary: Of the 101 patients who completed four weeks of aztreonam treatment, 89.1% had cultures negative for *Pseudomonas aeruginosa* at week 4, and 75.2, 63.4, and 47.5% were culture-negative at weeks eight, 16, and 28, respectively. Patients ≥ 6 years of age in the sensitivity analysis set who met the primary endpoint (n=25), had FEV1% predicted remain near baseline until week 16, with a 2.5% mean actual decrease from baseline at week 28. For patients not meeting the primary endpoint (n=27), corresponding decreases in observed values were 4.2, 5.1, and 8.9%, at weeks eight, 16, and 28, respectively. Mean changes in CFQ-R RSS for the patients in the sensitivity analysis set who met the primary eradication endpoint (n=25) were numerically higher or similar to patients who did not meet the endpoint (n=31), with mean changes above the minimum important difference score for stable patients (4.0 points [28]) at all but one time point (week 16 for patients who did not meet the primary endpoint).
Réa-Neto et al.[53] (2008) Doripenem 500 mg IV every eight hours vs	MC, OL, PRO, RCT Patients aged 18 years or older with signs and symptoms of nosocomial pneumonia,	N=448 7 to 14 days	Primary: Clinical cure rate in the clinically evaluable population and in the clinically evaluable-modified intent-to-treat	Primary: The clinical cure rates in clinically evaluable patients at the test-of-cure visit were 81.3% in the doripenem arm and 79.8% in the piperacillin-tazobactam arm (95% CI, -9.1 to 12.1). In the clinically evaluable-modified intent-to-treat population, the clinical cure rates in the doripenem and piperacillin-tazobactam arms were 69.5 and 64.1%, respectively (95% CI, -4.1 to 14.8).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
piperacillin-tazobactam 4.5 grams IV every six hours	including non-ventilated patients and those with early-onset ventilator-associated pneumonia		population Secondary: Clinical cure rate at the end of IV therapy and at the late follow-up visit, clinical and microbiological cure rates in the microbiologically evaluable patients at the test-of-cure visit and in the microbiologically evaluable-modified intent-to-treat population, clinical and microbiological cure rates at the test-of-cure visit in microbiologically evaluable patients with early-onset ventilator-associated pneumonia, and all-cause mortality at day 28 in the clinically evaluable-modified intent-to-treat population.	Secondary: Clinical response rates at the end of IV study drug therapy in clinically evaluable patients were 87% in both treatment arms (95% CI, -9.2 to 9.2%). Clinical relapse rates at the late follow-up visits were low for both the doripenem (3%) and piperacillin-tazobactam (4%) treatment arms. The clinical cure rates in microbiologically evaluable patients at the test-of-cure visit were 82.1 and 78.3% (95% CI, -9.4 to 17.1) in the doripenem and piperacillin-tazobactam arms, respectively. In the microbiologically evaluable-modified intent-to-treat population, clinical cure rates were 67.6 and 67.4%, respectively (95% CI, -11.4 to 11.9). Microbiological responses in the microbiologically evaluable patients at the test-of-cure visit were achieved in 84.5% of patients in the doripenem arm and 80.7% of patients in the piperacillin-tazobactam arm (95% CI, -8.9 to 16.5). The all-cause mortality at day 28 in the clinically evaluable-modified intent-to-treat population was 13.8% with doripenem and 14.6% with piperacillin-tazobactam (95% CI, -7.9 to 6.3). A Kaplan-Meier analysis found no difference in cumulative mortality rate between the two treatment arms.
Chastre et al.[54] (2008)	AC, MC, OL, RCT Adults meeting	N=531 7 to 14 days	Primary: Clinical cure rates in the clinically	Primary: Clinical cure rates were 68.3% (doripenem) and 64.2% (imipenem) in the clinically evaluable (95% CI, -7.9% to 10.3%) and 59.0% (doripenem) and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Doripenem 500 mg IV every eight hours vs imipenem 500 mg IV every six hours or 1,000 mg every eight hours	clinical and radiologic criteria for ventilator-associated pneumonia		evaluable and clinically evaluable-modified intent-to-treat populations Secondary: Clinical cure rates in the microbiologically evaluable-modified intent-to-treat, microbiological cure rates in the microbiologically evaluable population; clinical relapse rates at the late follow-up visit; per-pathogen clinical/ microbiological cure rates; emergence of *Pseudomonas aeruginosa* strains acquiring decreased susceptibility to study drug; emergent infection rate; all-cause mortality	57.8% (imipenem) in the clinically evaluable-modified intent-to-treat populations (95% CI, -9.1 to 16.1). Secondary: In the microbiologically evaluable patients, favorable microbiological response rates were 73.3% with doripenem and 67.3% with imipenem (95% CI, -6.8 to 18.8). In patients with *Pseudomonas aeruginosa*, clinical cure was 80.0% (doripenem) and 42.9% (imipenem) (P=NS); microbiological cure was 65.0% (doripenem) and 37.5% (imipenem). The all-cause mortality at day 28 in the clinically evaluable-modified intent-to-treat population was 10.8% with doripenem and 9.5% with imipenem (95% CI, -4.4 to 7.0). The incidence and types of all adverse events and those considered drug-related by the investigators were similar in both treatment groups.
Friedland et al.[55] (2004) Ertapenem 1 g IV	DB, MC, RCT Patients 18 years of age and older with	N=857 7 to 14 days post-therapy	Primary: Clinical response at the test-of-cure visit, clinical	Primary: At the test-of-cure visit, the combined response rates were 90% in patients with COPD and 93% in patients without COPD.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
daily vs ceftriaxone 1 g IV daily Patients with clinical improvement meeting pre-specified criteria could be switched to PO amoxicillin-clavulanate or other PO antimicrobial based on pathogen susceptibility for a total of 10 to 14 days.	typical community-acquired pneumonia admitted to the hospital for parenteral antimicrobial therapy		response at the completion of parenteral therapy Secondary: Not reported	In the patients without COPD, favorable results were seen in 93% of both ertapenem and ceftriaxone patients. There were no significant differences between treatment groups (P=0.94) or between patients with and without COPD (P=0.17). Clinical response at the completion of parenteral therapy was seen in 95% of ertapenem patients and 94% of ceftriaxone patients. Secondary: Not reported
Yanagihara et al.[56] (2006) Imipenem-cilastatin 0.5 g BID vs ampicillin-sulbactam 3 g BID	PRO, RCT Elderly patients >65 years of age with moderate-to-severe community-acquired pneumonia	N=67 7 to 14 days	Primary: Clinical efficacy Secondary: Bacteriological efficacy, adverse events	Primary: Overall clinical efficacy of ampicillin-sulbactam therapy was 91.4% compared to 87.5% for imipenem-cilastatin therapy (P=NS). Secondary: The eradication rate was 100% in both treatment arms (P=NS). The overall eradication rate for the pathogenic microorganism was 84% in the ampicillin-sulbactam group and 80%in the imipenem-cilastatin group (P=NS). All adverse reactions were mild or moderate and transient in both treatment groups.
Bartoloni et al.[57] (1999)	MC, RCT Individuals aged 18	N=144 9 to 10 days	Primary: Clinical efficacy (cure or	Primary: At the end of therapy, clinical response was observed in 90.9% of the patients receiving imipenem-cilastatin and 89.1% of meropenem-treated

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Imipenem-cilastatin 2 g IV QD vs meropenem 1.5 g IV QD	to 94 years of age with community-acquired pneumonia		improvement in signs and symptoms) Secondary: Bacteriological response (either presumed or confirmed eradication of all pathogens) and safety assessment	patients. In patients who were followed up for two to four weeks, the response was satisfactory (100%) for both treatments. Secondary Response was considered satisfactory in 100% of the meropenem group and 92.9% in the imipenem-cilastatin group and at follow-up; it was 100% for both treatments. Drug-related adverse events were reported in 4.2% of the meropenem-treated patients and in 11.0% of the imipenem-cilastatin-treated patients.
Schmitt et al.[58] (2006) Imipenem-cilastatin 4 g-500 mg every eight hours vs piperacillin-tazobactam 1 g-1 g every eight hours Additional aminoglycoside therapy was mandatory if *Pseudomonas aeruginosa* was present.	DB, MC, RCT Hospitalized patients with nosocomial pneumonia	N=221 5 to 21 days	Primary: Clinical response at the end of the treatment period Secondary: Clinical responses on the last day of treatment or on day 21 and on day 14±7 days after treatment, bacteriological responses, safety	Primary: Therapeutic response was seen in 66% [95% CI, 56.5 to 75] of patients receiving piperacillin-tazobactam and in 70% [95% CI, 60.4 to 78.2] of patients receiving imipenem-cilastatin. Failure rates were similar at 18.7 and 18.2%, respectively. On the last day of treatment or on day 21, therapeutic responses were higher and seen in 71% [95% CI, 61.3 to 79.2] and 77.3% [95% CI, 68.1 to 84.5] of patients receiving piperacillin-tazobactam and imipenem-cilastatin respectively. Failure rates were 17.8 and 16.4% respectively. Secondary: At the second follow-up (14±4 days after the end of treatment) clinical responses were 59.8% [95% CI, 49.9 to 69] and 66.4% [95% CI, 56.6 to 74.9] and failure rates were 19.6 and 15%, in patients receiving piperacillin-tazobactam and imipenem-cilastatin respectively. The majority of patients in both groups responded to treatment and the overall response rate was similar for the two agents. Failure rates were also similar for the two treatment groups at each of the observation periods. Eradication immediately after treatment with piperacillin-tazobactam or imipenem-cilastatin was 45.7 and 52.7%, respectively compared to 40.3 and 50% at the first follow-up and 34.6 and 42.2% at the second follow-up, respectively. Overall, 74.5 and 64.9% of patients receiving piperacillin-tazobactam and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				imipenem-cilastatin, respectively reported adverse events, the majority of which were of mild intensity. The most common related adverse events were diarrhea and fever in the piperacillin-tazobactam group and increased alkaline phosphatase, nausea and vomiting in the imipenem-cilastatin group.
Joshi et al.[59] (2006) Imipenem-cilastatin 500 mg IV every six hours vs piperacillin-tazobactam 4.5 grams IV every six hours Patients also received aminoglycoside therapy.	DB, MC, RCT Hospitalized patients with acute nosocomial pneumonia	N=437 21 days	Primary: Clinical cure and microbiological response rates; pathogen eradication rates; length of hospital stay; hospital readmissions; adverse events Secondary: Not reported	Primary: The overall clinical cure rate was 68% in piperacillin-tazobactam patients and 61% in imipenem patients in the efficacy evaluable population (P=0.256). Microbiological response rates were comparable among efficacy evaluable patients treated with piperacillin-tazobactam and those treated with imipenem. Microbiological responses for piperacillin-tazobactam and imipenem patients were: eradication, 64 vs 59%; persistence, 29 vs 21%; relapse, 0 vs 5%; and superinfection, 7 vs 15%, respectively. Gram-positive isolates were eradicated in 83% of piperacillin-tazobactam patients and 75% of imipenem patients; Gram-negative pathogens were eradicated in 72% of piperacillin-tazobactam patients and 77% of imipenem patients. Piperacillin-tazobactam and imipenem patients had similar hospital and intensive care unit length of stay. Hospital readmission rates in both groups were small and were not significantly different. There were no significant differences in adverse events between the two treatment groups. Secondary: Not reported
Ito et al.[60] (2010) Imipenem-cilastatin 1 g IV every 12 hours for 7 to 14 days	OL, RCT, SC Patients aged ≥15 years of age with a risk for aspiration who had been hospitalized after	N=469 30 days	Primary: Clinical response rate at the end of treatment in validated per protocol population	Primary: At the end-of-treatment visit, the clinical effective rate for the validated per protocol population was 83% for piperacillin-tazobactam and 82% for imipenem-cilastatin (P=0.92). Secondary: There were no significant differences between the groups in any of the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs piperacillin-tazobactam 5 g IV every 12 hours for 7 to 14 days	developing moderate-to-severe pneumonia in the community or nursing home		Secondary: Clinical response during treatment (days four and seven) and at the end of study in validated per protocol population, and survival at day 30 in modified intention-to-treat population	secondary outcome measures. Mortality rate within 30 days of admission in modified intention-to-treat population was 15% in the piperacillin-tazobactam group and 24% in the imipenem-cilastatin group (P=0.12). The most frequent adverse event was diarrhea in both groups, affecting 28% of patients receiving piperacillin-tazobactam and 31% of patients receiving imipenem-cilastatin.
Miscellaneous Infections				
Kobayashi et al.[61] (2009) Aztreonam 150 mg/kg/day plus ampicillin-sulbactam 150 mg/kg/day divided into four doses vs ceftazidime 100 mg/kg/day plus piperacillin-tazobactam 125 mg/kg/day divided into four doses Treatment was continued until completion of the	RCT Pediatric patients with hematologic disease and solid tumor with febrile neutropenia	N=54 (177 episodes) 120 hours	Primary: Treatment success Secondary: Not reported	Primary: Success rates were 57.1 and 62.5% in the piperacillin-tazobactam plus ceftazidime and ampicillin-sulbactam plus aztreonam groups, respectively (P≥0.05). There were two deaths in the piperacillin-tazobactam plus ceftazidime group. The patients died within 48 hours from onset of the febrile episode. The success rates in episodes with absolute neutrophil counts $<0.5 \times 10^9$/L at the end of treatment were 70.0 and 74.1% in the piperacillin-tazobactam plus ceftazidime and ampicillin-sulbactam plus aztreonam groups, respectively, and the success rates in bacteremia episodes were 50% in both groups. The percentages of episodes with new infections were 25.7 and 20.3%, respectively. Duration of fever and antibiotic therapy did not differ between the groups, and no major adverse effects occurred in the study. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
appropriate course of therapy for a defined clinical or microbiologic infection.				
Liberman et al.[62] (1995) Cefotetan 2 g IV as a single dose preoperatively (group one) vs cefoxitin 2 g IV as a single dose preoperatively (group two) vs cefoxitin 2 g IV as a single dose preoperatively followed by three doses postoperatively (group three)	DB, RCT Patients with nonperforated acute appendicitis undergoing appendectomy	N=136 Single dose study	Primary: Wound infection rates Secondary: Not reported	Primary: The overall wound infection rate was 4.4%. No post-operative infections were found in group one, 11.1% occurred in group two, and 1.9% occurred in group three. There was no significant difference between groups one and three; however, there were significant differences in infections rates between groups one and two (P=0.04) and groups two and three (P=0.05). Secondary: Not reported
Hemsell et al.[63] (1995) Cefotetan 1 g IV as a single dose vs	DB, PRO, RCT Women undergoing elective abdominal hysterectomy	N=511 Single dose study	Primary: Prevention of major operative site infections Secondary: Not reported	Primary: A major operative site infection requiring parenteral antimicrobial therapy developed in 9.0% of evaluable women: 11.6% of women given cefazolin prophylaxis and 6.3% of women given cefotetan prophylaxis (RR, 1.84; 95% CI, 1.03 to 3.29; P<0.05). Risk factors for major operative site infection were younger age, lower postoperative hemoglobin concentration, and a proliferative endometrium.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
cefazolin 1 g IV as a single dose				Of the women given cefazolin prophylaxis, 3.9%had a postoperative pelvic abscess compared to 0.8% of women given cefotetan prophylaxis (RR, 4.9; 95% CI, 1.09 to 22.16; P =0.04). A greater number of infections and more serious infections occurred following cefazolin prophylaxis; this treatment resulted in 234 additional hospital days for administration of IV antimicrobial therapy. Secondary: Not reported
Lucasti et al.[64] (2008) Doripenem 500 mg IV every eight hours vs meropenem 1 gram IV every eight hours Patients could be switched to PO amoxicillin-clavulanate after a minimum of nine doses and adequate clinical improvement.	DB, MC, RCT Hospitalized adult patients with cIAIs	N=476 21 to 60 days	Primary: Clinical cure rate at the test-of-cure visit (21 to 60 days after the last dose of study drug) and the clinical cure rate in the microbiological modified intent-to-treat population Secondary: Clinical cure rates at the end of IV treatment, early follow-up, and test-of-cure visits	Primary: Doripenem and meropenem were associated with clinical cure rates at the test-of-cure visit of 85.9 and 85.3%, respectively (95% CI, -7.7 to 9.0). In the microbiological modified intent-to-treat population, the clinical cure rates were 77.9 and 78.9%, respectively (95% CI, -9.7 to 7.7). Secondary: Clinical cures assessed in the clinically evaluable and microbiologically evaluable population at the end of IV treatment, early follow-up, and test-of-cure visits were not significantly different within or between populations of doripenem and meropenem. The proportions of patients experiencing adverse events were not significantly different between the two treatment arms (83.0 vs 78.0%).
Tazuma et al.[65] (2015) Doripenem 0.5 g IV three times	OL, RCT Patients ≥20 years of age with moderate or severe	N=127 Mean duration of treatment was 7 days	Primary: Clinical response rate Secondary:	Primary: The clinical response rate was not significantly different between the doripenem group (93.1%, 54/58 patients) and the imipenem-cilastatin group (93.8%, 60/64). There was no significant between-group difference (P=1.000). Non-inferiority assessment using confidence intervals

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
daily vs imipenem-cilastatin 0.5 mg IV three times daily	biliary tract infection (acute cholangitis or cholecystitis) who were hospitalized		Bacteriological efficacy, safety	demonstrated the non-inferiority in the clinical response rate between the two groups. The response rates in the doripenem and imipenem-cilastatin groups were, respectively, 100.0 and 94.6% for patients with cholangitis, 90.9 and 90.9% for those with cholecystitis, and 66.7 and 100.0% for those with both cholangitis and cholecystitis. For any of the diseases, the between-group difference was not significant (P=0.498, 1.000, and 0.455, respectively). Secondary: The bacteriological response rate was 69.0% (29/42 patients) in the doripenem group and 78.3% (36/46 patients) in the imipenem-cilastatin group (P=0.344). Two patients each in the two groups (3.3 and 3.1%, respectively) presented with adverse drug reactions, including one patient with watery diarrhea and one patient with drug eruption in the doripenem group, and one patient with vomiting and one patient with pseudomembranous colitis in the imipenem-cilastatin group.
Namias et al.[66] (2007) Ertapenem 1 gram IV QD vs piperacillin-tazobactam 3.375 grams IV every six hours	DB, MC, RCT Patients 18 to 90 years of age with presumptive (pre-operative) or confirmed cIAI	N=500 4 to 14 days	Primary: Clinical response rates Secondary: Microbiological efficacy, clinical failure, mortality	Primary: Favorable clinical responses were demonstrated for 82.1% of the patients in the ertapenem group and 81.7% of the patients in the piperacillin-tazobactam group (95% CI, -9.6 to 10.5). At the end of therapy, 89.6 and 86.2%, and at late follow-up assessment, 78.9 and 79.3%, of the microbiologically evaluable patients had favorable clinical responses in the ertapenem and piperacillin-tazobactam treatment groups, respectively. Clinical response rates of 63.2% for ertapenem and 60.9% were similar for piperacillin-tazobactam-treated patients in the modified intent-to-treat population at early follow-up assessment (95% CI, -7.5 to 12.0). Secondary: There were no clinically important differences in the response rates of gram-positive, gram-negative, or anaerobic pathogens in the ertapenem

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				and piperacillin-tazobactam treatment groups. Favorable overall microbiological responses were demonstrated in 82.2% in the ertapenem group and 82.5% in the piperacillin-tazobactam group (95% CI, -10.1 to 9.8) at early follow-up assessment. The pathogens isolated most frequently were *Escherichia coli, Bacteroides fragilis*, and *Bacteroides thetaiotaomicron*. At the early follow-up assessment, there were 22 clinical failures (17.9%) in the ertapenem group and 20 (18.5%) in the piperacillin-tazobactam group. The incidence of adverse events and study discontinuations because of adverse events was similar in the two groups. During the study and post-treatment follow-up period, clinical adverse events resulted in 21 deaths, nine of which occurred in the ertapenem group (3.6%) and 12 in the piperacillin-tazobactam group (4.9%; RR, 0.75; 95% CI, 0.30 to 1.77; risk difference, -1.21; 95% CI, -5.08 to 2.53).
Yellin et al.[67] (2007) Ertapenem 1 g IV QD (13 to 17 years of age) or 15 mg/kg (2 to 12 years of age) vs ticarcillin-clavulanate 50 mg/kg four to six times daily (<60 kg) or 3.1 grams four to six times daily (≥60 kg)	MC, OL, RCT Children aged 3 months to 17 years of age with cIAI or acute pelvic infections	N=105 3 to 9 days	Primary: Incidence of any serious drug-related clinical and/or laboratory adverse experiences Secondary: Overall response rates, drug-related clinical and/or laboratory adverse experiences, incidence of moderate-to-severe administration site reactions	Primary: Forty-six percent of patients had one or more clinical adverse event as assessed by the investigator: 39% in the ertapenem group and 67% in the comparator group. Eleven patients (14%; 95% CI, 7.0 to 23.0) in the ertapenem group and eight patients (33%; 95% CI, 15.6 to 55.3) in the comparator group reported drug-related clinical and/or laboratory adverse experiences. Infusion site pain was the most common drug-related adverse event in both groups. Secondary: Overall response rates were 89% for ertapenem and 73% for the comparator. Comparable rates were seen across each of the age groups studied. In the modified intent-to-treat analysis, the age-adjusted posttreatment

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				clinical response rates were 87 and 100% in the cIAI and acute pelvic infection patients, respectively, for ertapenem and 73and 100%, respectively, for ticarcillin-clavulanate. Overall age-adjusted response rates were 91% for ertapenem and 83% for the comparator. Eleven percent (95% CI, 5.2 to 20.0) in the ertapenem group and 25% (95% CI, 9.8 to 46.7) in the comparator group experienced ≥1 local reactions of any intensity at the infusion/injection site.
Falagas et al.[68] (2008) Ertapenem vs piperacillin-tazobactam, ceftriaxone plus metronidazole, or ticarcillin-clavulanic acid	MA Patients with cIAI infections or acute pelvic infections	7 trials 4 to 14 days	Primary: Clinical success Secondary: Mortality, laboratory adverse events, patient withdrawals because of adverse events	Primary: No difference was found regarding clinical success in patients treated with ertapenem, compared to those treated with other antibiotics (OR, 1.11; 95% CI, 0.89 to 1.39). There was no difference in microbiological success of adult patients with cIAIs treated with ertapenem compared to those treated with comparator antibiotics (OR, 1.19, 95% CI, 0.83 to 1.71). Microbiological or clinical success did not differ between compared treatments for the subsets of patients infected with either *Pseudomonas aeruginosa* (OR, 1.00; 95% CI, 0.41 to 2.45) or *Enterococcus* spp. (OR, 1.19; 95% CI, 0.60 to 2.39). Secondary: There was no difference in mortality between adult patients with cIAIs treated with ertapenem or comparator antibiotics (OR, 1.14; 95% CI, 0.72 to 1.83). No difference was found regarding clinical adverse events between adult patients with cIAIs treated with ertapenem compared to those treated with other antibiotics (OR, 0.86; 95% CI, 0.61 to 1.20). Significantly more laboratory adverse events were noted in patients with cIAIs, treated with ertapenem compared to patients treated with other antibiotics (OR, 1.73; 95% CI, 1.14 to 2.61).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				No difference was found regarding withdrawals from the included studies because of adverse events, between patients with cIAIs treated with ertapenem compared to those treated with other antibiotics (OR, 0.94; 95% CI, 0.47 to 1.87).
Itani et al.[69] (2006) Ertapenem vs cefotetan	DB, RCT Patients undergoing elective colorectal surgery	N=1,002 4 weeks	Primary: Absence of surgical-site infection, anastomotic leakage, or antibiotic use four weeks postoperatively Secondary: Not reported	Primary: The rate of overall prophylactic failure was 40.2% in the ertapenem group and 50.9% in the cefotetan group in the intent-to-treat analysis (95% CI, -17.1 to -4.2). The rate of overall prophylactic failure was 28.0% in the ertapenem group and 42.8% in the cefotetan group in the per-protocol analysis (95% CI, -21.9 to -7.5). The most common reason for failure of prophylaxis in both groups was surgical-site infection: 17.1% in the ertapenem group and 26.2% in the cefotetan group (95% CI, -14.4 to -3.7). In the treated population, the overall incidence of *Clostridium difficile* infection was 1.7% in the ertapenem group and 0.6% in the cefotetan group (P=0.22). Secondary: Not reported
Arguedas et al.[70] (2009) Ertapenem 1 g IV as a single daily dose (children aged 13 to 17 years) or 30 mg/kg/day divided BID (children aged 3 months to 12 years) vs	AC, DB, RCT Patients ≥3 months and <18 years with cUTI, SSI and community-acquired pneumonia requiring initial parenteral antibiotic therapy	N=404 14 days	Primary: Incidence of clinical and laboratory drug-related serious adverse events Secondary: Incidence of any drug-related adverse events and any moderate-to-severe reactions at the parenteral	Primary: In each group, the mean duration of therapy (parenteral and PO antibiotic therapy) was 11 days and the median duration of parenteral therapy (ertapenem or ceftriaxone) was four days. Overall, 46.7% of the children had one or more clinical adverse events during parenteral therapy. During the parenteral therapy period, 26.7% of ertapenem-treated children and 24.0% of ceftriaxone-treated children reported a drug-related clinical and/or laboratory adverse event (P=0.69). Secondary: The most common drug-related clinical adverse events during parenteral

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ceftriaxone 50 mg/kg/day as a single dose (children aged 13 to 17 years) or 50 mg/kg/day divided BID (children aged 3 months to 12 years)			infusion site	therapy were diarrhea, infusion site pain, infusion site erythema and vomiting. Eighteen patients (5.9%) receiving ertapenem and 10 patients (10%) receiving ceftriaxone experienced diarrhea. Fifteen patients (5%) and one patient (1%) receiving ertapenem and ceftriaxone, respectively, experienced infusion site pain. Nine patients (3%) receiving ertapenem and two patients (2%) receiving ceftriaxone experienced infusion site erythema. Six patients (2%) receiving ertapenem and two patients (2%) receiving ceftriaxone experienced vomiting. The most common laboratory adverse event in both groups was a decrease in the neutrophil count (5.7% in the ertapenem group and 2.2% in the ceftriaxone group). In the ertapenem group, 18.8% of patients experienced more than one symptom at the site of drug administration during parenteral therapy of any intensity. The rates of moderate-to-severe local symptoms were comparable between the treatment groups (5.3% in the ertapenem group and 5.0% in the ceftriaxone group; P=1.000). The most common infusion/injection-related events were local erythema and pain. A total of 4.6% of children in the ertapenem group and 3.0% of children in the ceftriaxone group experienced erythema. A total of 6.6% of children in the ertapenem group and 4.0% of children in the ceftriaxone group experienced administration site pain.
Hou et al.[71] (2001) Imipenem-cilastatin 500 mg IV BID (or 1 g IV BID) vs meropenem 500 mg IV BID (or 1 g IV BID)	OL, RCT Hospitalized patients ≥16 years of age with lower respiratory infections, urinary tract infections and other acute infections	N=140 7 to 14 days	Primary: Cure rate, overall efficacy rate (the proportion of patients cured and markedly improved), clinical efficacy, and adverse events Secondary: Not reported	Primary: The cure rate was 57% in the imipenem-cilastatin group and 66% in the meropenem group (P=0.298). The overall efficacy rate was 87% for the imipenem-cilastatin group and 90% for the meropenem group (P=0.595). The bacterial eradication rates were 86% in both groups. There were 72 cases of adverse drug reactions in the meropenem group and 70 cases in the imipenem-cilastatin group that were evaluated resulting in an adverse drug reaction rate of 9.7 and 8.6%, respectively (P>0.05). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Nelson et al.[72] (2002) Imipenem-cilastatin 20 mg/kg IV QID in addition to cytotoxic chemotherapy and total body irradiation vs meropenem 20 mg/kg IV TID in addition to cytotoxic chemotherapy and total body irradiation	RCT Pre-engrafted pediatric bone marrow transplant patients	N=32 3 to 31 days	Primary: Evidence of bacterial infection, need for concurrent antibiotics, incidence of vomiting and duration of concurrent total parenteral nutrition Secondary: Not reported	Primary: There was no detectable difference in the evidence of bacterial infection between the two treatment groups. Concurrent antibiotics were required for 7.1±2.0 days in the imipenem-cilastatin group compared to 7.2±1.7 days in the meropenem treatment group (P=0.944). There were 30.38±5.08 episodes of vomiting per course of imipenem-cilastatin, vs 9.75±3.53 episodes per course of meropenem, a difference that was statistically significant (P=0.0021). There was no significant difference in the duration of total parenteral nutrition support required between the imipenem-cilastatin group (19.2±2.9 days) and the meropenem group (13.9±2.4 days; P=0.1662). Secondary: Not reported
Vural et al.[73] (2010) Imipenem-cilastatin 60 mg/kg/day IV in four divided doses vs piperacillin-tazobactam 360 mg/kg/day IV in four divided doses	RCT Patients with acute leukemia, lymphoma and solid tumors who were hospitalized with febrile neutropenia	N=63 (99 episodes) Variable duration	Primary: Success and failure rate Secondary: Not reported	Primary: The overall success rate was 67% and the failure rate was 33% in both treatment groups. The success and failure rates in the piperacillin–tazobactam group were 71 and 29%, respectively. The success and failure rates in the imipenem–cilastatin group were 62 and 38%, respectively (P>0.05 vs piperacillin-tazobactam). There were no deaths in the study and no major adverse effects were seen in either group. Mild adverse effects included nausea, vomiting, transient increase in liver function tests and rash. No patient required discontinuation of the therapy due to adverse effects. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Chen et al.[74] (2010) Imipenem-cilastatin 500-500 mg every six hours vs tigecycline 100 mg IV as an initial dose, followed by 50 mg IV every 12 hours	OL, MC, RCT Patients ≥18 years of age with cIAI	N=191 ≤2 weeks	Primary: Clinical response at the test-of-cure visit (12 to 37 days after therapy) for the microbiologically evaluable and microbiologic modified intent-to-treat populations Secondary: Not reported	Primary: In the microbiologically evaluable population, 86.5% of patients receiving tigecycline and 97.9% of patients receiving imipenem-cilastatin were cured at the test-of-cure visit (95% CI, -23.05 to 0.7). In the microbiologic modified intent-to-treat population, 81.7% of patients receiving tigecycline and 90.9% of patients receiving imipenem-cilastatin were cured at the test-of-cure visit (95% CI, -23.4 to 4.9). In the clinically evaluable population, 87.0% of patients receiving tigecycline and 95.4% of patients receiving imipenem-cilastatin were cured at the test-of-cure visit (95% CI, -18.3 to 1.5). In the clinical microbiologic modified intent-to-treat population (those with complicated appendicitis), 80.4% of patients receiving tigecycline and 89.8% of patients receiving imipenem-cilastatin were cured at the test-of-cure visit (95% CI, -20.3 to 1.6). The overall incidence of treatment-emergent adverse events was 80.4% for tigecycline compared to 53.9% for imipenem-cilastatin (P<0.001). Adverse events were primarily gastrointestinal in nature, especially nausea (21.6 vs 3.9%; P<0.001) and vomiting (12.4 vs 2.0%; P=0.005). Secondary: Not reported
Klugman et al.[75] (1995) Meropenem 40 mg/kg every eight hours for 7 to 14 days vs cefotaxime 75 to 100 mg/kg every	PRO, RCT Children with a diagnosis of bacterial meningitis	N=190 6 weeks posttreatment	Primary: Clinical response (cure, cure with audiologic sequelae, cure with neurologic sequelae, cure with both audiologic and neurologic sequelae, death), bacteriologic response	Primary: In patients with pre-existing neurologic abnormalities, cure was achieved in 47% of meropenem patients compared to 60% of cefotaxime patients, cure with audiologic sequelae was reported in 6% of meropenem patients and 20% of cefotaxime patients, cure with neurologic sequelae was reported in 35% of meropenem patients and 0% of cefotaxime patients, cure with both audiologic and neurologic sequelae was reported in 12% of meropenem patients and 20% of cefotaxime patients, and death was not reported in any patients in either group. In patients without pre-existing neurological abnormalities, cure was achieved in 79% of meropenem patients compared to 83% of cefotaxime

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
eight hours for 7 to 14 days			Secondary: Not reported	patients, cure with audiologic sequelae was reported in 16% of meropenem patients and 12% of cefotaxime patients, cure with neurologic sequelae was reported in 3% of meropenem patients and 2% of cefotaxime patients, cure with both audiologic and neurologic sequelae was reported in 2% of meropenem patients and 0% of cefotaxime patients, and death was reported in no patients in the meropenem group and 3% of cefotaxime patients. Bacteriologic eradication rates were 100% in both groups. Secondary: Not reported
Odio et al.[76] (1999) Meropenem 40 mg/kg every eight hours vs cefotaxime 45 mg/kg every six hours Treatment duration for both groups was 7 to 14 days depending on infection.	MC, PRO, RCT Patients 2 months to 12 years of age with a diagnosis of bacterial meningitis	N=266 5 to 7 months posttreatment	Primary: Clinical response (cure, survival with mild neurological sequelae, survival with severe neurological sequelae, death), microbiologic efficacy Secondary: Not reported	Primary: At the five to seven week follow-up, no significant differences between the meropenem group and the cefotaxime group were observed with respect to cure, survival with sequelae, or death (P=0.624). Severe sequelae were present in 30% of meropenem patients and in 17% of cefotaxime patients, and this difference was NS (P=0.056). At the five to seven week visit, severe sequelae in the form of audiology were present in 25% of children in the meropenem group and 15% in the cefotaxime group. By the five to seven month visit, the percentages had decreased to 18% in the meropenem group and 14% in the cefotaxime group. No significant differences were seen in any group at any time. At the end of treatment, bacterial eradication was observed in 95% of patients in the meropenem group and 96% in the cefotaxime group. Secondary: Not reported
Lucasti et al.[77] (2013) Meropenem 1000 mg plus placebo IV every eight	AC, DB, RCT Hospitalized patients 18 to 90 years of age with cIAI requiring	N=144 Test-of-cure: 2 weeks after last dose	Primary: Clinical response in microbiologically evaluable patients at the test-of-cure	Primary: A favorable clinical response in the microbiologically evaluable population at the test-of-cure visit was observed in 91.2% (62/68) and 93.4% (71/76) of ceftazidime-avibactam plus metronidazole and meropenem patients, respectively. The estimated difference in response rates was –2.2% (95% CI, –20.4 to 12.2%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
hours for 5 to 14 days vs ceftazidime-avibactam (2000-500 mg) plus metronidazole (500 mg) IV every eight hours for five to 14 days	surgical intervention and antibiotics	Late follow-up: 4 to 6 weeks post-therapy	visit two weeks after the last dose of study therapy Secondary: Safety	Secondary: Adverse events were observed in 64.4% (65/101) and 57.8% (59/102) of patients in the ceftazidime-avibactam plus metronidazole and meropenem groups, respectively. Overall, the types and frequencies of adverse events were similar in the two treatment groups, but there were more cases of nausea and vomiting and abdominal pain in the ceftazidime-avibactam plus metronidazole group and more cases of liver enzyme elevations in the meropenem group. In the majority of cases, adverse events were mild or moderate in intensity.
Solomkin et al.[78] (2015) ASPECT-cIAI Meropenem 1 g every eight hours IV for four to 14 days vs ceftolozane-tazobactam 1.5 g plus metronidazole 500 mg every eight hours IV for four to 14 days	DB, PC, RCT Patients ≥18 years of age with cIAI	N=806 24 to 32 days	Primary: Difference in clinical cure rates at the test-of-cure visit in the microbiological modified intention to treat population Secondary: Difference in clinical cure rates at the test-of-cure visit in the intention to treat and clinically evaluable populations	Primary: Clinical cure rates were 83.0% (323/389) with ceftolozane-tazobactam plus metronidazole and 87.3% (364/417) with meropenem in the modified intention to treat population at the test-of-cure visit. The weighted difference in clinical cure rates (ceftolozane-tazobactam plus metronidazole minus meropenem) was −4.2% with a 2-sided 95% CI of −8.91% to 0.54%, thus meeting the statistical criteria for noninferiority. Secondary: Clinical cure rates in the intention to treat population at test-of-cure were 83.6% for ceftolozane-tazobactam plus metronidazole and 86.2% for meropenem (difference, −2.6; 95% CI, −7.08 to 1.87), similar to those observed in the modified intention to treat population. In the clinically evaluable population, cure rates were 94.1% and 94.0%, respectively (difference, 0.1; 95% CI, −3.30 to 3.55). Clinical outcomes in the subgroup analyses were generally consistent with the primary and secondary analyses, with no meaningful differences recorded between treatments.

Drug regimen abbreviations: BID=twice daily, IM=intramuscular, IV=intravenous, PO=oral, QD=once daily, QID=four times daily, TID=three times daily
Study abbreviations: AC=active control, CI=confidence interval, DB=double blind, MA=meta-analysis, MC=multicenter, NS=not significant, OL=open-label, OR=odds ratio, PC=placebo controlled, PG=parallel group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, SC=single center
Other abbreviations: CFQ-R=cystic fibrosis questionnaire-revised, CFU=colony formulating unit, COPD=chronic obstructive pulmonary disease, cIAI=complicated intra-abdominal infection, cSSSI=complicated skin and skin structure infection, cUTI=complicated urinary tract infection, FEF_{25-75}=forced expiratory flow at 25 to 75%, FEV_1=forced expiratory volume in one second, FVC=forced vital capacity, MRSA=Methicillin-resistant *Staphylococcus aureus*, MSSA=methicillin-susceptible *Staphylococcus aureus*, RSS=respiratory symptom scale, SSSI=skin and skin structure infection

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 Miscellaneous β-Lactam Antibiotics

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Aztreonam	inhalation solution, injection	Azactam®*, Cayston®	$$$$$	$$$$$
Cefotetan	injection	Cefotan®*	$$$$-$$$$$	$$$$-$$$$$
Cefoxitin	injection	Mefoxin®*	$$$$$	$$$$-$$$$$
Doripenem	injection	Doribax®	$$$$$	N/A
Ertapenem	injection	Invanz®	$$$$$	N/A
Meropenem	injection	Merrem®*	$$$$$	$$$$$
Combination Products				
Imipenem and cilastatin	injection	Primaxin®*	$$$$$	$$$$$

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

X. Conclusions

The miscellaneous β-lactam antibiotics are approved to treat a variety of infections, including central nervous system, dermatologic, genitourinary, respiratory, as well as several miscellaneous infections.[1-10] All of the injectable products are available in a generic formulation, with the exception of doripenem and ertapenem.

There are many guidelines that define the appropriate place in therapy for the miscellaneous β-lactam antibiotics. The agent that is recommended is dependent upon the infectious organism being treated and the corresponding spectrum of activity of the β-lactam. The miscellaneous β-lactam antibiotics are recommended as specific therapy for the treatment of susceptible pathogens causing endocarditis, meningitis, skin and soft-tissue infections, pelvic inflammatory disease, infectious exacerbations of chronic obstructive pulmonary disease, community-acquired pneumonia, nosocomial pneumonia, intra-abdominal infections, febrile neutropenia, and for surgical prophylaxis.[11,15-17,19,22,25,26-28,30]

Studies have demonstrated comparable efficacy among the miscellaneous β-lactam antibiotics for the treatment of skin and soft-tissue infections, urinary tract infections, endometritis, pneumonia, intra-abdominal infections, and for surgical prophylaxis.[39,40,42,46,54,57,64,65,71,72] Few studies have demonstrated greater efficacy with one agent over another.[70] The miscellaneous β-lactam antibiotics have also been shown to be comparable in efficacy to antibacterial agents in other classes. [31-33,35,36,38,41,43,44,53,55,56,58-61,66-68,73-78] Clinical data from published studies supports similar safety profiles among the miscellaneous β-lactam antibiotics.

Aztreonam inhalation solution is approved to improve respiratory symptoms in cystic fibrosis patients colonized with *Pseudomonas aeruginosa*. Treatment with aztreonam has been associated with improvements in pulmonary function, improved quality of life, and decreased requirement for inhaled or intravenous anti-pseudomonal antibiotics compared to placebo.[48,49,51] An open-label study following patients for 18 months demonstrated continued benefit over time.[50]

There is insufficient evidence to support that one brand miscellaneous β-lactam is safer or more efficacious than another within its given indication. With the exception of aztreonam inhalation solution, the miscellaneous β-lactam antibiotics are only available in an injectable formulation and are primarily administered in the inpatient setting. 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 miscellaneous β-lactam antibiotics 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. Aztreonam inhalation solution has been shown to improve lung function and reduce exacerbations in cystic fibrosis patients colonized with *Pseudomonas aeruginosa*.[23] Therefore, these patients should be allowed approval for aztreonam inhalation solution through the medical justification portion of the prior authorization process.

XI. Recommendations

No brand miscellaneous β-lactam antibiotics 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.

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Chloramphenicol
AHFS Class 081208
November 9, 2016

I. Overview

Chloramphenicol is approved for the treatment of serious infections caused by susceptible microorganisms, acute infections caused by *Salmonella typhi*, and as part of a cystic fibrosis regimen.[1-3] However, it should only be used when less potentially dangerous drugs are ineffective or contraindicated. Chloramphenicol exhibits its antibacterial effect by interfering with the ribosomal transfer of activated amino acids from ribonucleic acid and thus inhibiting bacterial protein synthesis.[3]

Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) have occurred following treatment with chloramphenicol.[1-3] There have also been reports of aplastic anemia progressing to leukemia that were attributed to chloramphenicol. Blood dyscrasias have occurred after both short- and long-term therapy.

The chloramphenicol products that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Chloramphenicol is available in a generic formulation. This class was last reviewed in August 2014.

Table 1. Chloramphenicol Products Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Chloramphenicol	injection	N/A	chloramphenicol

PDL=Preferred Drug List
N/A=Not available

Chloramphenicol has 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 chloramphenicol that are noted in Table 4. This agent may also have been found to show activity to other microorganisms in vitro; however, the clinical significance of this is unknown since its 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 Chloramphenicol[1-3]

Organism	Chloramphenicol
Gram-Negative Aerobes	
Haemophilus influenzae	✔
Salmonella species, including *Salmonella typhi*	✔
Miscellaneous Organisms	
Lymphogranuloma-psittacosis group	✔
Rickettsia	✔

II. Evidence-Based Medicine and Current Treatment Guidelines

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

Table 3. Treatment Guidelines Using Chloramphenicol

Clinical Guideline	Recommendation(s)
Infectious Diseases Society of America: **Clinical Practice**	Empirical therapy • Acyclovir should be initiated in all patients with suspected encephalitis, pending

Clinical Guideline	Recommendation(s)
Guidelines: Management of Encephalitis (2008)[4] **(Was reviewed and deemed current as of July 2011)**	results of diagnostic studies. • Other empirical antimicrobial agents should be initiated on the basis of specific epidemiologic or clinical factors, including appropriate therapy for presumed bacterial meningitis, if clinically indicated. • In patients with clinical clues suggestive of rickettsial or ehrlichial infection during the appropriate season, doxycycline should be added to empirical treatment regimens. <u>Bacteria</u> • *Bartonella bacilliformis:* chloramphenicol, ciprofloxacin, doxycycline, ampicillin, or sulfamethoxazole-trimethoprim is recommended. • *Bartonella henselae:* doxycycline or azithromycin, with or without rifampin, can be considered. • *Listeria monocytogenes:* ampicillin plus gentamicin is recommended; sulfamethoxazole-trimethoprim is an alternative in the penicillin-allergic patient. • *Mycoplasma pneumoniae:* antimicrobial therapy (azithromycin, doxycycline, or a fluoroquinolone) can be considered. • *Tropheryma whipplei:* ceftriaxone, followed by either sulfamethoxazole-trimethoprim or cefixime, is recommended. <u>Helminths</u> • *Baylisascaris procyonis:* albendazole plus diethylcarbamazine can be considered; adjunctive corticosteroids should also be considered. • *Gnathostoma* species: albendazole or ivermectin is recommended. • *Taenia solium:* need for treatment should be individualized; albendazole and corticosteroids are recommended; praziquantel can be considered as an alternative. <u>Rickettsioses and ehrlichiosis</u> • *Anaplasma phagocytophilum:* doxycycline is recommended. • *Ehrlichia chaffeensis:* doxycycline is recommended. • *Rickettsia rickettsii:* doxycycline is recommended; chloramphenicol can be considered an alternative in selected clinical scenarios, such as pregnancy. • *Coxiella burnetii:* doxycycline plus a fluoroquinolone plus rifampin is recommended. <u>Spirochetes</u> • *Borrelia burgdorferi:* ceftriaxone, cefotaxime, or penicillin G is recommended. • *Treponema pallidum:* penicillin G is recommended; ceftriaxone is an alternative. <u>Protozoa</u> • *Acanthamoeba:* sulfamethoxazole-trimethoprim plus rifampin plus ketoconazole or fluconazole plus sulfadiazine plus pyrimethamine can be considered. • *Balamuthia mandrillaris:* pentamidine, combined with a macrolide (azithromycin or clarithromycin), fluconazole, sulfadiazine, flucytosine, and a phenothiazine can be considered. • *Naegleria fowleri:* amphotericin B (intravenous and intrathecal) and rifampin, combined with other agents, can be considered. • *Plasmodium falciparum:* quinine, quinidine, or artemether is recommended; atovaquone-proguanil is an alternative; exchange transfusion is recommended for patients with 110% parasitemia or cerebral malaria; corticosteroids are not recommended. • *Toxoplasma gondii:* pyrimethamine plus either sulfadiazine or clindamycin is recommended; sulfamethoxazole-trimethoprim alone and pyrimethamine plus atovaquone, clarithromycin, azithromycin, or dapsone are alternatives. • *Trypanosoma brucei gambiense:* eflornithine is recommended; melarsoprol is an

Clinical Guideline	Recommendation(s)
	alternative. • *Trypanosoma brucei rhodesiense:* melarsoprol is recommended.
European Federation of Neurological Societies: **Guideline on the Management of Community-acquired Bacterial Meningitis (2008)**[5]	Empirical therapy • Ceftriaxone 2 g every 12 to 24 hours or cefotaxime 2 g every six to eight hours. • Alternative therapy: meropenem 2 g every eight hours or chloramphenicol 1 g every six hours. • If penicillin or cephalosporin-resistant pneumococcus is suspected, use ceftriaxone or cefotaxime plus vancomycin 60 mg/kg every 24 hours after a loading dose of 15 mg/kg. • Ampicillin-amoxicillin 2 g every four hours if *Listeria* is suspected. Pathogen specific therapy • Penicillin-sensitive pneumococcal meningitis: o Benzyl penicillin 250,000 U/kg/day, ampicillin-amoxicillin 2 g every four hours, ceftriaxone 2 g every 12 hours or cefotaxime 2 g every six to eight hours. o Alternative therapy: meropenem 2 g every eight hours or vancomycin 60 mg/kg every 24 hours as a continuous infusion after a 15 mg/kg loading dose plus rifampicin 600 mg every 12 hours, or moxifloxacin 400 mg daily. • Pneumococcus with reduced susceptibility to penicillin or cephalosporins: o Ceftriaxone or cefotaxime plus vancomycin±rifampicin. o Alternative therapy: moxifloxacin, meropenem or linezolid 600 mg combined with rifampicin. • Meningococcal meningitis: o Benzyl penicillin, ceftriaxone, or cefotaxime. o Alternative therapy: meropenem, chloramphenicol, or moxifloxacin. • *Haemophilus influenzae* type B: o Ceftriaxone or cefotaxime. o Alternative therapy: chloramphenicol–ampicillin-amoxicillin. • Listerial meningitis: o Ampicillin or amoxicillin 2 g every four hours±gentamicin 1 to 2 mg every eight hours for the first seven to 10 days. o Alternative therapy: sulfamethoxazole-trimethoprim 10 to 20 mg/kg every six to 12 hours or meropenem. • *Staphylococcal* species: o Flucloxacillin 2 g every four hours or vancomycin if penicillin allergy is suspected. o Rifampicin should also be considered in addition to either agent. Linezolid should be considered for methicillin-resistant staphylococcal meningitis. • Gram-negative *Enterobacteriaceae*: o Ceftriaxone, cefotaxime or meropenem. • Pseudomonal meningitis: o Meropenem±gentamicin.
Infectious Diseases Society of America: **Practice Guidelines for the Management of Bacterial Meningitis (2004)**[6]	Empiric therapy • Empirical antimicrobial therapy is initiated either when the lumbar puncture is delayed or for patients with purulent meningitis and a negative cerebrospinal fluid gram stain result: o Age <1 month: ampicillin plus cefotaxime or ampicillin plus an aminoglycoside. o Age one to 23 months: vancomycin plus a third-generation cephalosporin. o Age two to 50 years: vancomycin plus a third-generation cephalosporin. o Age >50 years: vancomycin plus ampicillin plus a third-generation cephalosporin. o Basilar skull fracture: vancomycin plus a third-generation cephalosporin.

Clinical Guideline	Recommendation(s)
	o Penetrating head trauma: vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem. o Post neurosurgery: vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem. o Cerebrospinal fluid shunt: vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem. <u>Specific therapy</u> • Recommendations for specific antimicrobial therapy in bacterial meningitis are based on isolated pathogens and susceptibility. • *Streptococcus pneumoniae* o Penicillin minimum inhibitory concentrations <0.1 µg/mL: standard therapy includes penicillin G or ampicillin; alternative therapies include ceftriaxone, cefotaxime, or chloramphenicol. o Penicillin minimum inhibitory concentrations 0.1 to 1.0 µg/mL: standard therapy includes ceftriaxone or cefotaxime; alternative therapies include cefepime or meropenem. o Penicillin minimum inhibitory concentrations ≥2 µg/mL: standard therapies include vancomycin plus ceftriaxone or cefotaxime; alternative therapies include gatifloxacin or moxifloxacin. o Cefotaxime or ceftriaxone minimum inhibitory concentrations ≥1.0 µg/mL: standard therapies include vancomycin plus ceftriaxone or cefotaxime (consider addition of rifampin if minimum inhibitory concentrations of ceftriaxone is >2 µg/mL); alternative therapies include gatifloxacin or moxifloxacin. • *Neisseria meningitides* o Penicillin minimum inhibitory concentrations <0.1 µg/mL: standard therapy includes penicillin G or ampicillin; alternative therapy includes ceftriaxone, cefotaxime or chloramphenicol. o Penicillin minimum inhibitory concentrations 0.1 to 1.0 µg/mL: standard therapy includes ceftriaxone or cefotaxime; alternative therapies include chloramphenicol, a fluoroquinolone or meropenem. • *Listeria monocytogenes* o Standard therapy includes ampicillin or penicillin G; alternative therapies include sulfamethoxazole-trimethoprim or meropenem. • *Streptococcus agalactiae* o Standard therapy includes ampicillin or penicillin G; alternative therapies include ceftriaxone or cefotaxime. • *Escherichia coli* and other Enterobacteriaceae o Standard therapy includes a third-generation cephalosporin; alternative therapies include aztreonam, fluoroquinolone, meropenem, sulfamethoxazole-trimethoprim or ampicillin. • *Pseudomonas aeruginosa* o Standard therapies include cefepime or ceftazidime; alternative therapies include aztreonam, ciprofloxacin, or meropenem (addition of an aminoglycoside should be considered). • *Haemophilus influenzae* β-lactamase negative strains o Standard therapy includes ampicillin; alternative therapies include ceftriaxone, cefotaxime, cefepime, chloramphenicol or a fluoroquinolone. • *Haemophilus influenzae* β-lactamase positive strains o Standard therapy includes a third-generation cephalosporin; alternative therapies include cefepime, chloramphenicol or a fluoroquinolone. • *Staphylococcus aureus* methicillin susceptible o Standard therapy includes nafcillin or ofloxacin; alternative therapies include vancomycin or meropenem. • *Staphylococcus aureus* methicillin resistant

Clinical Guideline	Recommendation(s)
	o Standard therapy includes vancomycin (consider addition of rifampin); alternative therapies include sulfamethoxazole-trimethoprim or linezolid. • *Staphylococcus epidermidis* o Standard therapy includes vancomycin (consider addition of rifampin); alternative therapy includes linezolid. • *Enterococcus* species ampicillin susceptible o Standard therapy includes ampicillin plus gentamicin. • *Enterococcus* species ampicillin resistant o Standard therapy includes vancomycin plus gentamicin. • *Enterococcus* species ampicillin and vancomycin resistant o Standard therapy includes linezolid.
Working Group on Civilian Biodefense: **Plague as a Biological Weapon: Medical and Public Health Management Consensus Statement (2000)**[7]	• For adults with pneumonic plague in the contained casualty settings, the preferred choice is streptomycin or gentamicin and alternative choices include doxycycline, ciprofloxacin, or chloramphenicol. • For children with pneumonic plague in the contained casualty settings, the preferred choice is streptomycin or gentamicin and alternative choices include doxycycline, ciprofloxacin, or chloramphenicol. • For pregnant women with pneumonic plague in the contained casualty settings, the preferred choice is gentamicin and an alternative choice is doxycycline. • For adults with pneumonic plague in the mass casualty setting and postexposure prophylaxis, the preferred choice is doxycycline, or ciprofloxacin and the alternative choice is chloramphenicol. • For children with pneumonic plague in the mass casualty setting and postexposure prophylaxis, the preferred choice is doxycycline or ciprofloxacin and an alternative choice is chloramphenicol. • For pregnant women with pneumonic plague in the mass casualty setting and postexposure prophylaxis, the preferred choice is doxycycline or ciprofloxacin and an alternative choice is chloramphenicol.
Centers for Disease Control and Prevention: **Diagnosis and Management of Tickborne Rickettsial Diseases: Rocky Mountain Spotted Fever, Ehrlichiosis, and Anaplasmosis—United States (2016)**[8]	• The Centers for Disease Control and Prevention recommends doxycycline as the treatment of choice for all tickborne rickettsial diseases in patients of all ages, including children aged <8 years, and should be initiated immediately in persons with signs and symptoms suggestive of rickettsial disease. • Chloramphenicol is an alternative drug that has been used to treat Rocky Mountain Spotted Fever; however, epidemiologic studies in which Centers for Disease Control and Prevention case report data have been used suggested that patients with Rocky Mountain Spotted Fever treated with chloramphenicol have a higher risk of dying than persons who received a tetracycline. • Chloramphenicol is associated with adverse hematologic effects, which have resulted in its limited use in the United States, and monitoring of blood indices is required if this drug is used. • If chloramphenicol is substituted for doxycycline in the empiric treatment of tickborne rickettsial diseases, ehrlichiosis and anaplasmosis will not be covered and Rocky Mountain Spotted Fever treatment might be suboptimal. • Rifampin could be an alternative for the treatment of mild illness due to anaplasmosis in the case of pregnancy or documented allergy to tetracycline-class drugs.

III. Indications

The Food and Drug Administration (FDA)-approved indications for chloramphenicol 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 Chloramphenicol[1-3]

Indications	Chloramphenicol
Serious infections caused by susceptible strains, including *Salmonella* species, *Haemophilus influenzae* (specifically meningeal infections), *Rickettsia*, Lymphogranuloma-psittacosis group, Various gram-negative bacteria causing bacteremia, meningitis, or other serious gram-negative infections, or other susceptible organisms which have been demonstrated to be resistant to all other appropriate antimicrobial agents*	✔
Acute infections caused by *Salmonella typhi*†	✔
Cystic fibrosis regimens	✔

* In accord with the concepts in chloramphenicols Black Box Warning, chloramphenicol must be used only in those serious infections for which less potentially dangerous drugs are ineffective or contraindicated. However, chloramphenicol may be chosen to initiate antibiotic therapy on the clinical impression that one of the conditions listed is believed to be present; in vitro sensitivity tests should be performed concurrently so that the drug may be discontinued as soon as possible if less potentially dangerous agents are indicated by such tests. The decision to continue use of chloramphenicol rather than another antibiotic when both are suggested by in vitro studies to be effective against a specific pathogen should be based upon severity of the infection, susceptibility of the pathogen to the various antimicrobial drugs, efficacy of the various drugs in the infection, and the important additional concepts contained in chloramphenicols Black Box Warning.
† It is not recommended for the routine treatment of the typhoid carrier state. In treatment of typhoid fever some authorities recommend that chloramphenicol be administered at therapeutic levels for eight to 10 days after the patient has become afebrile to lessen the possibility of relapse.

IV. Pharmacokinetics

The pharmacokinetic parameters for chloramphenicol are listed in Table 5.

Table 5. Pharmacokinetic Parameters for Chloramphenicol[2]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Chloramphenicol	50 (intramuscular)	50 to 80	Liver (90)	Renal (5 to 15)	1.6 to 3.3 (highly variable in infants)

V. Drug Interactions

Major drug interactions with chloramphenicol are listed in Table 6.

Table 6. Major Drug Interactions with Chloramphenicol[2]

Generic Name(s)	Interaction	Mechanism
Chloramphenicol	Voriconazole	Concurrent use of chloramphenicol and voriconazole may result in increased voriconazole exposure and plasma concentrations.
Chloramphenicol	Citalopram	Concurrent use of chloramphenicol and citalopram may result in increased citalopram exposure and risk of QT interval prolongation.

VI. Adverse Drug Events

The most common adverse drug events reported with chloramphenicol are listed in Table 7. The boxed warning for chloramphenicol is listed in Table 8.

Table 7. Adverse Drug Events (%) Reported with Chloramphenicol[1-3]

Adverse Events	Chloramphenicol
Central Nervous System	
Confusion	✔
Delirium	✔
Depression	✔

Adverse Events	Chloramphenicol
Fever	✔
Headache	✔
Optic neuritis	✔
Peripheral neuritis	✔
Gastrointestinal	
Diarrhea	✔
Enterocolitis	✔
Glossitis	✔
Nausea	✔
Stomatitis	✔
Vomiting	✔
Hematologic	
Aplastic anemia	✔
Granulocytopenia	✔
Hypoplastic anemia	✔
Leukemia	✔
Leukopenia	✔
Pancytopenia	✔
Thrombocytopenia	✔
Other	
Anaphylaxis	✔
Angioedema	✔
Hypersensitivity reactions	✔
Gray Syndrome	✔
Rash	✔

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

Table 8. Boxed Warning for Chloramphenicol[1]

WARNING
Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after the administration of chloramphenicol. In addition, there have been reports of aplastic anemia attributed to chloramphenicol which later terminated in leukemia. Blood dyscrasias have occurred after both short-term and prolonged therapy with this drug. Chloramphenicol must not be used when less potentially dangerous agents will be effective. *It must not be used in the treatment of trivial infections or where it is not indicated, as in colds, influenza, infections of the throat; or as a prophylactic agent to prevent bacterial infections.* It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes, such as leukopenia, reticulocytopenia, or granulocytopenia, before they become irreversible, such studies cannot be relied on to detect bone marrow depression prior to development of aplastic anemia. To facilitate appropriate studies and observation during therapy, it is desirable that patients be hospitalized.

VII. Dosing and Administration

The usual dosing regimens for chloramphenicol are listed in Table 9.

Table 9. Usual Dosing Regimens for Chloramphenicol[1-3]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Chloramphenicol	Serious infections caused by susceptible strains,	Serious infections caused by susceptible strains, including *Salmonella* species,	Injection: 1 g

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	including *Salmonella* species, *Haemophilus influenzae* (specifically meningeal infections), *Rickettsia*, Lymphogranuloma-psittacosis group, Various gram-negative bacteria causing bacteremia, meningitis, or other serious gram-negative infections, or other susceptible organisms which have been demonstrated to be resistant to all other appropriate antimicrobial agents; acute infections caused by *Salmonella typhi*; Cystic fibrosis regimens: Injection: 50 mg/kg/day intravenous in divided doses every six hours; patients with infections due to moderately resistant organisms may require increased dosage up to 100 mg/kg/day to achieve blood levels inhibiting the pathogen, but these high doses should be decreased as soon as possible	*Haemophilus influenzae* (specifically meningeal infections), *Rickettsia*, Lymphogranuloma-psittacosis group, Various gram-negative bacteria causing bacteremia, meningitis, or other serious gram-negative infections, or other susceptible organisms which have been demonstrated to be resistant to all other appropriate antimicrobial agents; acute infections caused by *Salmonella typhi*; Cystic fibrosis regimens for infants and children: Injection: 50 mg/kg/day in divided doses every six hours; severe infections may require dosage up to 100 mg/kg/day; however, it is recommended that dosage be reduced to 50 mg/kg/day as soon as possible Serious infections caused by susceptible strains, including Salmonella species, Haemophilus influenzae (specifically meningeal infections), Rickettsia, Lymphogranuloma-psittacosis group, Various gram-negative bacteria causing bacteremia, meningitis, or other serious gram-negative infections, or other susceptible organisms which have been demonstrated to be resistant to all other appropriate antimicrobial agents; acute infections caused by Salmonella typhi; Cystic fibrosis regimens for neonates: Injection: 25 mg/kg/day in divided doses every six hours; after the first two full weeks of life, 50 mg/kg/day in divided doses every six hours may be administered	

VIII. Effectiveness

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

Table 10. Comparative Clinical Trials with Chloramphenicol

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Bacterial Meningitis				
Shann et al.[9] (1985) Chloramphenicol 25 mg/kg IM every 6 hours vs chloramphenicol 25 mg/kg IV every 6 hours plus penicillin Once clinical improvement was observed patients received oral chloramphenicol palmitate 25 mg/kg every 6 hours for a total of 14 days.	MC, PRO, RCT Children with bacterial meningitis	N=367 14 days	Primary: Cumulative endpoint of mortality, brain damage, and persistent illness; death Secondary: Not reported	Primary: The cumulative outcome measure was poor (death, discharged with brain damage) in 38% of the patients receiving chloramphenicol alone compared to 40% of those receiving combination therapy. There was no significant difference in mortality between the chloramphenicol and the combination treatment groups (26 vs 27%). Secondary: Not reported
Nathan et al.[10] (2005) Chloramphenicol 100 mg/kg IM as a single dose vs ceftriaxone 100	MC, OL, RCT Patients >2 months of age with meningitis	N=510 1 month	Primary: Treatment failure at 72 hours Secondary: Mortality within 72 hours, clinical sequelae at 72 hours, clinical failure between 24	Primary: Both treatment groups exhibited a treatment failure rate of 9% (90% CI, -3.8 to 4.5). Secondary: There was no significant difference in the mortality rate at 72 hours between the chloramphenicol and ceftriaxone groups (5 vs 6%, respectively; 90% CI, -2.3 to 3.8). Clinical failure took place in 4% of the chloramphenicol-group survivors

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/kg IM as a single dose			and 48 hours requiring a second injection	and 3% of the ceftriaxone-treated patients (90% CI, -3.3 to 2.8). There was no significant difference in the re-injection rate between the chloramphenicol and ceftriaxone groups (8 vs 7%, respectively; 90% CI, -4.7 to 3.0). Neurologic sequelae occurred in 5% of patients on chloramphenicol and 7% of patients on ceftriaxone therapy (90% CI, -2.1 to 5.1).
Rodriguez et al.[11] (1986) Chloramphenicol 100 mg/kg/day IV in 4 divided doses plus ampicillin 400 mg/kg/day IV in 4-6 divided doses vs ampicillin 400 mg/kg/day IV in 4-6 divided doses plus sulbactam 50 mg/kg/day	MC, PRO, RCT Hospitalized patients 1 month to 14 years of age with meningitis	N=81 10 days	Primary: Mortality rate, resolution of symptoms, complications, adverse effects Secondary: Not reported	Primary: Of the patients with assessable CSF pathogens, the mortality rate was 3% in the ampicillin-sulbactam group and 18% in the chloramphenicol-ampicillin group. Neurologic sequelae occurred in 12% of patients on ampicillin-sulbactam and 18% of patients on chloramphenicol-ampicillin therapy. The mean time to resolution of symptoms was 4.4 days in the ampicillin-sulbactam group and 4.8 days in the chloramphenicol-ampicillin. Abnormal laboratory findings were found in 20% of the ampicillin-sulbactam group and 35% in the chloramphenicol-ampicillin group. Secondary: Not reported
Girgis et al.[12] (1988) Chloramphenicol 100 mg/kg/day plus ampicillin 160 mg/kg/day every 6 hours (AMCL) vs ceftriaxone 100	RCT Patients with bacterial meningitis	N=100 6 days	Primary: CSF leukocyte count, glucose, protein content, disappearance of meningeal irritation, fever defervescence, patient alertness, mortality rate Secondary:	Primary: There was no significant difference between the two groups in the disappearance of meningeal irritation, fever defervescence, and patient alertness. There was no significant difference between the two groups in the CSF leukocyte count, glucose or protein content at baseline, as well as the final evaluation. There was no significant difference between the two groups in mortality. While 20% of patients treated with AMCL died, the mortality in the ceftriaxone group was 7%.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/kg once daily			Not reported	Secondary: Not reported
Girgis et al.[13] (1987) Chloramphenicol 100 mg/kg/day IV plus ampicillin 160 mg/kg/day IV every 6 hours (group 1) vs ceftriaxone 100 mg/kg IV once daily (group 2)	RCT Patients 16 to 30 years of age with bacterial meningitis	N=30 6 days	Primary: Mortality, time taken for defervescence, time for patients to regain full consciousness Secondary: Not reported	Primary: One patient in each group died within 24 hours of initiation of therapy. Both had meningitis due to *S. pneumoniae*. The mean number of days to become afebrile were 3.4 and 3.5 for group 1 and group 2, respectively. The mean number of days to regain full consciousness was 3.9 and 2.5 for group 1 and group 2, respectively. Secondary: Not reported
Jacobs et al.[14] (1985) Chloramphenicol 25 mg/kg/dose IV plus ampicillin 50-100 mg/kg/dose IV every 6 hours vs cefotaxime 50 mg/kg/dose IV every 6 hours	PRO, RCT Patients 1 week to 16 years of age with meningitis	N=50 3 months	Primary: Clinical cure rate, survival without sequelae, duration of therapy Secondary: Not reported	Primary: There was no significant difference in the clinical cure rate between the chloramphenicol-ampicillin and cefotaxime groups (96 vs 100%, respectively; P>0.5). There was no significant difference in survival without detectable sequelae between the chloramphenicol-ampicillin and cefotaxime groups (77 vs 78%, respectively). Mean duration of therapy was similar in the chloramphenicol-ampicillin and cefotaxime groups (11.9 and 11.1 days, respectively). Secondary: Not reported
Rodriguez et al.[15] (1986) Chloramphenicol 75 to 100 mg/kg/day IV in 4 divided	OL, RCT Patients 1 month to 15 years of age with meningitis	N=100 Up to 6 months	Primary: Clinical cure rate, clinical improvement, mortality rate, neurological	Primary: After the first 24 hours of therapy, 10% of the patients died, 2% clinically improved, and 88% were cured in the ceftazidime group. In the chloramphenicol-ampicillin group, 10% of patients died, 1% clinically improved, and 81% were cured in the ceftazidime.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
doses plus ampicillin 400 mg/kg/day IV in 6 divided doses vs ceftazidime 150 mg/kg/day IV divided into 3 doses, administered every 8 hours			sequelae, mean duration of therapy Secondary: Not reported	Seizures occurred in 54% of patients treated with ceftazidime and 51% of patients treated with chloramphenicol-ampicillin therapy. Mean duration of therapy was 10.2 and 10.4 days in the ceftazidime and chloramphenicol-ampicillin groups, respectively. Secondary: Not reported
Marks et al.[16] (1986) Chloramphenicol 75 to 100 mg/kg/day IV in 4 divided doses plus ampicillin 300 to 400 mg/kg/day IV every 6 hours vs cefuroxime 225 mg/kg/day IV divided into 3 doses, administered every 8 hours	MC, RCT Patients 3 months to 16 years of age with bacterial meningitis	N=107 Up to 6 months	Primary: Clinical cure rate, CSF sterilization rate Secondary: Not reported	Primary: Clinical cure rate was 95% in both treatment groups. There was no significant difference in the CSF sterilization rates between the cefuroxime and chloramphenicol-ampicillin groups (90 vs 100%, respectively). Secondary: Not reported
Johansson et al.[17] (1982) Chloramphenicol and ampicillin IV every 6 hours for at least 5 days (A+C)	MC, RCT Patients with bacterial meningitis	N=67 ≥5 days	Primary: Efficacy and safety Secondary: Not reported	Primary: Complete resolution of symptoms was recorded in 18 of the 21 patients in the CXM group and in 14 of the 19 patients in the A+C group. Two patients died in each group. Adverse events were reported on eight occasions in seven patients in the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs cefuroxime IV every 8 hours for at least 5 days (CXM)				CXM group and in four patients in the A+C group. Rashes developed in two CXM patients and three A+C patients. Fever was noted in two CXM patients. Moderately severe diarrhea which required symptomatic treatment developed in one patient in each group, and one CXM patient had repeated thrombophlebitis. Secondary: Not reported
Peltola et al.[18] (1989) Chloramphenicol 100 mg/kg/day in 4 divided doses vs ampicillin 250 mg/kg/day in 4 divided doses plus chloramphenicol (administered until bacterial strain was shown to be susceptible to ampicillin alone) vs cefotaxime 150 mg/kg/day in 4 divided doses vs ceftriaxone 100 mg/kg once daily	MC, RCT Children 3 months to 15 years of age with bacterial meningitis	N=220 7 days	Primary: CSF culture pathogens, time to sterile CSF culture Secondary: Not reported	Primary: The CSF became sterile significantly earlier in meningococcal meningitis compared to patients presenting with *H. influenzae* type b (P<0.01). At 24 hours, positive cultures were found only in patients receiving chloramphenicol. At 24 hours, the CSF was sterile in a greater proportion of patients treated with cephalosporins compared to those treated with ampicillin-chloramphenicol or chloramphenicol (P<0.05). On day four, CSF culture was positive in only one patient, who was treated with chloramphenicol. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Typhoid and Enteric Fever				
Tanaka-Kido et al.[19] (1990) Chloramphenicol 100 mg/kg/day in 4 divided doses, which was continued for 8 days after the last fever day vs aztreonam 150 mg/kg/day IV in 3 divided doses, which was continued for 8 days after the last fever day	RCT Patients 2 to 6 years of age with typhoid fever	N=36 1 month	Primary: Clinical cure rate, fever duration, relapse rate, adverse effects Secondary: Not reported	Primary: There was no significant difference between the chloramphenicol and aztreonam groups in clinical cure rate (94 vs 100%). There was no significant difference between the chloramphenicol and aztreonam groups in fever duration (4.1 vs 5.9 days, respectively; P>0.05). There were no relapses in either of the two groups. While there was no incidence of anemia in the aztreonam group, there were five cases of anemia in the chloramphenicol group (P<0.05). There was no difference in the incidence of leukopenia and neutropenia between the two treatment groups (P>0.05). The approximate mean duration of antibiotic therapy was 15 days in the aztreonam group and 13 days in the chloramphenicol group. Secondary: Not reported
Gotuzzo et al.[20] (1994) Chloramphenicol 50 mg/kg/day oral/IV in 4 divided doses for 14 days vs aztreonam 2 g IV every 8 hours for 10 days	MC, RCT Patients >14 years of age with typhoid fever	N=44 10 weeks	Primary: Clinical cure rate, fever duration, bacteremia Secondary: Not reported	Primary: There was a significant difference between the chloramphenicol and aztreonam groups in terms of clinical cure rates (100 vs 68%, respectively; P<0.01). Defervescence occurred more quickly in patients receiving chloramphenicol compared to patients on aztreonam therapy (4.5 vs 6.6 days, respectively; P<0.03). There were no relapses in either of the two groups. While 24-hour positive blood cultures occurred in 32% of patients on chloramphenicol therapy, none of the patients in the aztreonam group had positive blood cultures (P<0.05). Adverse reactions experienced by patients in each treatment group deemed

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				unusual or mild with no statistical difference found between the two groups. Secondary: Not reported
Arjyal et al.[21] (2011) Chloramphenicol 75 mg/kg/day in four divided doses for 14 days vs gatifloxacin 10 mg/kg once daily for 7 days	OL, RCT Patients with uncomplicated enteric fever	N=853 6 months	Primary: Treatment failure Secondary: Fever clearance time, late relapse, and fecal carriage	Primary: There were 14 treatment failures in the chloramphenicol group and 12 treatment failures in the gatifloxacin group (HR, 0.86; 95% CI, 0.40 to 1.86; P=0.70). Secondary: The median time to fever clearance was 3.95 days in the chloramphenicol group and 3.90 in the gatifloxacin group (P=0.64). There was no significant difference between the treatment groups in relapses until day 31 (P=0.35) or day 62 (P=0.77). Only three of 148 patients receiving chloramphenicol and none of 154 patients receiving gatifloxacin were stool-culture-positive at the end of one month (P=0.12). At the end of three months, only one patient in the chloramphenicol group had a positive stool culture, and at six months no patients had a positive stool culture. In the chloramphenicol group, 25% of culture-positive patients experienced at least one adverse event. In the gatifloxacin group, 16.9% of culture-positive patients experienced at least one adverse event.

Drug regimen abbreviations: IM=intramuscular, IV=intravenous
Study abbreviations: CI=confidence interval, CSF=cerebrospinal fluid, MC=multicenter OL=open-label, PRO=prospective, RCT=randomized 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 11. Relative Cost of Chloramphenicol

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Chloramphenicol	injection	N/A	N/A	$$$$

N/A=Not available

X. Conclusions

Chloramphenicol is approved for the treatment of serious infections caused by susceptible microorganisms, acute infections caused by *Salmonella typhi*, and as part of a cystic fibrosis regimen.[1-3] It is available in a generic formulation.

Guidelines recommend chloramphenicol as an alternative treatment option in patients with bacterial meningitis and Rocky Mountain spotted fever.[4-8] Clinical trials have demonstrated similar efficacy with chloramphenicol (as monotherapy or in combination with ampicillin) compared to broad-spectrum cephalosporins in patients with bacterial meningitis.[10-18]

Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after both short-term and prolonged therapy with chloramphenicol. It should only be used when less potentially dangerous drugs are ineffective or contraindicated.[1-3] To facilitate appropriate studies and observation during therapy, it is desirable that patients receiving chloramphenicol be hospitalized.

There is insufficient evidence to support that one brand chloramphenicol product 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 chloramphenicol products 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 chloramphenicol 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.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Macrolides
AHFS Class 081212
November 9, 2016

I. Overview

The macrolides are approved to treat a variety of infections, including dermatologic, gastrointestinal, genitourinary, respiratory, as well as several miscellaneous infections.[1-12] Most of the agents bind to the 50S subunit of bacterial ribosomes, which inhibits bacterial protein synthesis.[13-14] Fidaxomicin has a unique mechanism of action; it inhibits ribonucleic acid synthesis by ribonucleic acid polymerases.[11]

Erythromycin is available in several different pharmaceutical preparations, which were developed to improve the absorption of erythromycin base. Azithromycin and clarithromycin are structural derivatives of erythromycin. They have a broader spectrum of activity, improved oral absorption, fewer gastrointestinal adverse events, and a more favorable pharmacokinetic profile than erythromycin.[13-14] Resistance to the macrolides is increasing and cross-resistance among the various agents has been documented. Telithromycin is a structural derivative of erythromycin and was designed to treat macrolide-resistant pathogens. The mechanism of action is similar to that of erythromycin and other macrolide antibacterials. However, telithromycin may also inhibit the formation of the 30S ribosomal subunit at high concentrations, in addition to the 50S subunit.[14] Fidaxomicin is a newer macrolide that is approved to treat *Clostridium difficile*-associated diarrhea. It is minimally absorbed after oral administration and has little or no activity against organisms other than clostridia.[11,13]

The macrolides that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Several of the macrolides are available in a generic formulation, with the exception of erythromycin lactobionate, erythromycin stearate, fidaxomicin, and telithromycin. This class was last reviewed in August 2014.

Table 1. Macrolides Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Azithromycin	extended-release suspension, injection, powder for suspension, suspension, tablet	Zithromax®*, Zithromax Tri-Pak®*, Zmax®	azithromycin
Clarithromycin	extended-release tablet, suspension, tablet	Biaxin®*	clarithromycin, clarithromycin ER
Erythromycin base	coated-particle tablet, delayed-release capsule, delayed-release tablet, tablet	PCE®	erythromycin base
Erythromycin ethylsuccinate	suspension, tablet	E.E.S. 200®, E.E.S. 400®*, EryPed 200®, EryPed 400®	erythromycin ethylsuccinate
Erythromycin lactobionate	injection	Erythrocin Lactobionate®	none
Erythromycin stearate	tablet	Erythrocin Stearate®	none
Fidaxomicin	tablet	Dificid®	none
Telithromycin	tablet	Ketek®	none

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

The macrolides 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 macrolides 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 Macrolides[1-12]

Organism	Azithromycin	Clarithromycin	Erythromycin	Fidaxomicin	Telithromycin
Gram-Positive Aerobes					
Listeria monocytogenes			✔		
Staphylococcus aureus	✔	✔	✔		
Streptococcus agalactiae	✔				
Streptococcus pneumoniae	✔	✔	✔		✔
Streptococcus pyogenes	✔	✔	✔		
Gram-Negative Aerobes					
Bordetella pertussis			✔		
Haemophilus ducreyi	✔				
Haemophilus influenzae	✔	✔	✔		✔
Haemophilus parainfluenzae		✔			
Helicobacter pylori		✔			
Legionella pneumophila	✔		✔		
Moraxella catarrhalis	✔	✔			✔
Neisseria gonorrhoeae	✔		✔		
Anaerobes					
Clostridium difficile				✔	
Corynebacterium diphtheriae			✔		
Corynebacterium minutissimum			✔		
Miscellaneous Organisms					
Entamoeba histolytica			✔		
Chlamydia trachomatis	✔		✔		
Chlamydophila pneumoniae	✔	✔			✔
Mycobacterium avium	✔	✔			
Mycobacterium intracellulare	✔	✔			
Mycoplasma hominis	✔				
Mycoplasma pneumoniae	✔	✔	✔		✔
Treponema pallidum			✔		
Ureaplasma urealyticum			✔		

II. Evidence-Based Medicine and Current Treatment Guidelines

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

Table 3. Treatment Guidelines Using the Macrolides

Clinical Guideline	Recommendation(s)

European Society of Cardiology: **Guidelines for the Management of Infective Endocarditis (2015)**[15]	Main principles of prevention if infective endocarditis
	• The principle of antibiotic prophylaxis when performing procedures at risk of infective endocarditis (IE) in patients with predisposing cardiac conditions is maintained.
	• Antibiotic prophylaxis must be limited to patients with the highest risk of IE undergoing the highest risk dental procedures (dental procedures requiring manipulation of the gingival or periapical region of the teeth or perforation of the oral mucosa).
	  o Patients with a prosthetic valve, including transcatheter valve, or a prosthetic material used for cardiac valve repair.
	  o Patients with previous IE.
	  o Patients with congenital heart disease.
	• Good oral hygiene and regular dental review are more important than antibiotic prophylaxis to reduce the risk of IE.
	• Aseptic measures are mandatory during venous catheter manipulation and during any invasive procedures in order to reduce the rate of health care-associated IE.
	• Recommended prophylaxis for dental procedures at high-risk:
	  o Single-dose amoxicillin or penicillin 30 to 60 minutes before procedure.
	  o If allergy to penicillin or ampicillin, single-dose clindamycin 30 to 60 minutes before procedure.
	
	Antimicrobial therapy: principles
	• The treatment of infective endocarditis relies on the combination of prolonged antimicrobial therapy and - in about half of patients - surgical eradication of the infected tissues.
	• Prolonged therapy with a combination of bactericidal drugs is the basis of IE treatment. Drug treatment of prosthetic valve endocarditis (PVE) should last longer (at least six weeks) than that of native valve endocarditis (NVE) (two to six weeks).
	• In both NVE and PVE, the duration of treatment is based on the first day of effective antibiotic therapy, not on the day of surgery. A new full course of treatment should only start if valve cultures are positive, the choice of antibiotic being based on the susceptibility of the latest recovered bacterial isolate.
	• The indications and pattern of use of aminoglycosides have changed. They are no longer recommended in staphylococcal NVE because their clinical benefits have not been demonstrated but they can increase renal toxicity; and, when they are indicated in other conditions, aminoglycosides should be given in a single daily dose in order to reduce nephrotoxicity.
	• New antibiotic regimens have emerged in the treatment of staphylococcal IE, including daptomycin and the combination of high-doses of cotrimoxazole plus clindamycin, but additional investigations are necessary in large series before they can be recommended in all patients.
	
	Antimicrobial therapy: regimens
	• Antibiotic treatment of infective endocarditis due to oral streptococci and *Streptococcus* bovis group:
	  o Penicillin-susceptible strains:
	  ▪ Penicillin G, amoxicillin, or ceftriaxone for four weeks.
	  ▪ Penicillin G, amoxicillin, or ceftriaxone plus gentamicin or netilmicin for two weeks.

Clinical Guideline	Recommendation(s)
	▪ Vancomycin for four weeks (in beta-lactam allergic patients). o Penicillin-resistant strains: ▪ Penicillin G, amoxicillin, or ceftriaxone for four weeks plus gentamicin for two weeks. ▪ Vancomycin for four weeks plus gentamicin for two weeks (in beta-lactam allergic patients). • Antibiotic treatment of infective endocarditis due to *Staphylococcus* species: o Methicillin-susceptible strains (native valves): ▪ Flucloxacillin or oxacillin for four to six weeks. ▪ Cotrimoxazole intravenous for one week and oral for five weeks plus clindamycin for one week (for *Staphylococcus aureus*). o Penicillin-allergic patients or methicillin-resistant staphylococci (native valves): ▪ Vancomycin for four to six weeks. ▪ Alternative: Daptomycin for four to six weeks. ▪ Cotrimoxazole intravenous for one week and oral for five weeks plus clindamycin for one week (for *Staphylococcus aureus*). o Methicillin-susceptible strains (prosthetic valves): ▪ Flucloxacillin or oxacillin for at least six weeks, rifampin for at least six weeks, and gentamicin for two weeks. o Penicillin-allergic patients or methicillin-resistant staphylococci (prosthetic valves): ▪ Vancomycin for at least six weeks, rifampin for at least six weeks, and gentamicin for two weeks. • Antibiotic treatment of infective endocarditis due to *Enterococcus* species: o Beta-lactam and gentamicin susceptible strains: ▪ Amoxicillin for four to six weeks plus gentamicin for two to six weeks. ▪ Ampicillin plus gentamicin for six weeks. ▪ Vancomycin plus gentamicin for six weeks. • Antibiotic treatment of blood culture-negative infective endocarditis: o *Brucella* species: ▪ Doxycycline, cotrimoxazole, and rifampin for ≥3 months. o *Coxiella burnetii* (agent of Q fever): ▪ Doxycycline plus hydroxychloroquine for >18 months. ▪ o *Bartonella* species: ▪ Doxycycline orally for four weeks plus gentamicin for two weeks. o *Legionella* species: ▪ Levofloxacin intravenous for ≥6 weeks or clarithromycin intravenous for two weeks then orally for four weeks plus rifampin. o *Mycoplasma* species: ▪ Levofloxacin for ≥6 months. o *Tropheryma whipplei* (agent of Whipple's disease): ▪ Doxycycline plus hydroxychloroquine orally for ≥18 months. • Proposed antibiotic regimens for initial empirical treatment of infective endocarditis in acute severely ill patients (before pathogen identification): o Community-acquired native valves or late prosthetic valves (≥12 months post surgery) endocarditis: ▪ Ampicillin intravenous plus flucloxacillin or oxacillin intravenous plus gentamicin intravenous for once dose. ▪ Vancomycin intravenous plus gentamicin intravenous (for penicillin allergic patients). o Early PVE (<12 months post surgery) or nosocomial and non-nosocomial

Clinical Guideline	Recommendation(s)
	healthcare associated endocarditis: ▪ Vancomycin intravenous, gentamicin intravenous, and rifampin orally.
American College of Cardiology/American Heart Association: **2008 Focused Update Incorporated Into the American College of Cardiology/American Heart Association 2006 Guidelines for the Management of Patients With Valvular Heart Disease (2008)[16]** American College of Cardiology/American Heart Association: **Guideline for the Management of Patients With Valvular Heart Disease (2014)[17] (although a more current guideline more detailed information was included as part of the 2008 Focused update; as such both are summarized together)**	<u>Rheumatic fever prophylaxis</u> • Primary prevention of rheumatic heart disease: o Penicillin G benzathine intramuscular once or penicillin V orally for 10 days. o Erythromycin estolate or erythromycin ethylsuccinate orally for 10 days, or azithromycin orally for five days in patients who are allergic to penicillin. • Secondary prevention of rheumatic fever: o Penicillin G benzathine intramuscular every four weeks, or penicillin V orally twice daily, or sulfadiazine orally once daily. o Erythromycin orally twice daily for patients who are allergic to penicillin. <u>Endocarditis prophylaxis</u> • Prophylaxis against infective endocarditis is reasonable for the following patients at highest risk for adverse outcomes from infective endocarditis who undergo dental procedures that involve manipulation of either gingival tissue or the periapical region of teeth or perforation of the oral mucosa: o Patients with prosthetic cardiac valve or prosthetic material used for cardiac valve repair. o Patients with previous infective endocarditis. o Patients with congenital heart disease. o Cardiac transplant recipients with valve regurgitation due to a structurally abnormal valve. • Prophylaxis against infective endocarditis is not recommended for non-dental procedures (such as transesophageal echocardiogram, esophagogastroduodenoscopy, or colonoscopy) in the absence of active infection. • Regimens for dental procedures (single dose 30 to 60 minutes before procedure): o Oral: amoxicillin. o Unable to take oral medications: ampicillin, cefazolin or ceftriaxone. o Allergic to penicillin or ampicillin (oral): cephalexin, clindamycin, or azithromycin. o Allergic to penicillins or ampicillin and unable to take oral medication: cefazolin, ceftriaxone, or clindamycin. • Therapy of native valve endocarditis caused by highly penicillin-susceptible viridans group streptococci and *Streptococcus bovis:* o Penicillin G or ceftriaxone for four weeks. o Ceftriaxone plus gentamicin for two weeks. o Vancomycin for four weeks in patients allergic to penicillin. • Therapy of native valve endocarditis caused by strains of viridans group streptococci and *Streptococcus bovis* relatively resistant to penicillin: o Penicillin G or ceftriaxone for four weeks plus gentamicin for two weeks. o Vancomycin for four weeks in patients allergic to penicillin. • Therapy for native valve or prosthetic valve enterococcal endocarditis caused by strains susceptible to penicillin, gentamicin, and vancomycin: o Ampicillin for four to six weeks or penicillin G plus gentamicin for four to six weeks. o Vancomycin plus gentamicin for six weeks in patients allergic to penicillin. • Therapy for endocarditis caused by staphylococci in the absence of prosthetic materials: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin for six weeks plus the optional addition of gentamicin for three to five days.

Clinical Guideline	Recommendation(s)
	▪ Cefazolin for six weeks with the optional addition of gentamicin in patients allergic to penicillin. o Oxacillin-resistant strains: ▪ Vancomycin for six weeks. • Therapy for prosthetic valve endocarditis caused by staphylococci: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin, rifampin, and gentamicin for ≥6 weeks. o Oxacillin-resistant strains: ▪ Vancomycin, rifampin, and gentamicin for ≥6 weeks. • Therapy for both native and prosthetic valve endocarditis caused by *Haemophilus* species *(Haemophilus parainfluenzae, Haemophilus aphrophilus, Haemophilus paraphrophilus), Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* species microorganisms: o Ceftriaxone for four weeks. o Ampicillin-sulbactam for four weeks. o Ciprofloxacin for four weeks. • Therapy for culture-negative endocarditis including *Bartonella* endocarditis: o Native valve: ▪ Ampicillin-sulbactam plus gentamicin (or vancomycin for patients allergic to penicillin) plus ciprofloxacin for four to six weeks. o Prosthetic valve (early; ≤1 year): ▪ Vancomycin for six weeks, plus gentamicin for two weeks, plus cefepime for six weeks, plus rifampin for six weeks. o Prosthetic valve (late; >1 year): ▪ Suspected *Bartonella*, culture negative: • Ceftriaxone for six weeks plus gentamicin with/without doxycycline for six weeks. ▪ Documented *Bartonella*, culture positive: • Doxycycline for six weeks plus gentamicin for two weeks.
American Heart Association: **Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications (2015)**[18]	• Therapy for native valve endocarditis caused by viridans group streptococci and *Streptococcus gallolyticus* (Formerly Known as *Streptococcus bovis)*: o Highly penicillin-susceptible strains: ▪ Penicillin G or ceftriaxone for four weeks. ▪ Penicillin G or ceftriaxone plus gentamicin for two weeks (in patients with uncomplicated infective endocarditis, rapid response to therapy, and no underlying renal disease). ▪ Vancomycin for four weeks (recommended only for patients unable to tolerate penicillin or ceftriaxone therapy). o Relatively penicillin-resistant strains: ▪ Penicillin for four weeks plus gentamicin for the first two weeks. ▪ If the isolate is ceftriaxone susceptible, then ceftriaxone alone may be considered. ▪ Vancomycin for four weeks (recommended only for patients unable to tolerate beta-lactam therapy). • Therapy for native valve endocarditis caused by *A defectiva* and *Granulicatella* Species and viridans group streptococci: o For patients with infective endocarditis caused by *A defectiva*, *Granulicatella* species, and viridans group streptococci with a penicillin MIC ≥0.5 µg/mL, treat with a combination of ampicillin or penicillin plus gentamicin as done for enterococcal infective endocarditis with infectious diseases consultation. o If vancomycin is used in patients intolerant of ampicillin or penicillin, then the addition of gentamicin is not needed.

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	o Ceftriaxone combined with gentamicin may be a reasonable alternative treatment option for isolates that are susceptible to ceftriaxone. • Therapy for endocarditis of prosthetic valves or other prosthetic material caused by viridans group streptococci and *Streptococcus gallolyticus* (Formerly Known as *Streptococcus bovis)*: o Penicillin for six weeks plus gentamicin for the first two weeks. o Extend gentamicin to six weeks if the MIC is >0.12 µg/mL for the infecting strain. o Vancomycin can be used in patients intolerant of penicillin, ceftriaxone, or gentamicin. • Therapy for endocarditis of prosthetic valves or other prosthetic material caused by *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and Groups B, C, F, and G β-Hemolytic Streptococci: o Penicillin, cefazolin, or ceftriaxone for four weeks is reasonable for infective endocarditis caused by *S pneumoniae*; vancomycin can be useful for patients intolerant of β-lactam therapy. o Six weeks of therapy is reasonable for prosthetic valve endocarditis caused by *S pneumoniae*. o High-dose penicillin or a third-generation cephalosporin is reasonable in patients with infective endocarditis caused by penicillin-resistant *S pneumoniae* without meningitis; if meningitis is present, then high doses of cefotaxime (or ceftriaxone) are reasonable. o The addition of vancomycin and rifampin to cefotaxime (or ceftriaxone) may be considered in patients with infective endocarditis caused by *S pneumoniae* that are resistant to cefotaxime. o Because of the complexities of infective endocarditis caused by *S pneumoniae*, consultation with an infectious diseases specialist is recommended. o For infective endocarditis caused by *S pyogenes*, four to six weeks of therapy with aqueous crystalline penicillin G or ceftriaxone is reasonable; vancomycin is reasonable only in patients intolerant of β-lactam therapy. o For infective endocarditis caused by group B, C, or G streptococci, the addition of gentamicin to penicillin G or ceftriaxone for at least the first two weeks of a four to six week treatment course may be considered. o Consultation with an infectious diseases specialist to guide treatment is recommended in patients with infective endocarditis caused by β-hemolytic streptococci. • Therapy for endocarditis caused by staphylococci in the absence of prosthetic valves or other prosthetic material: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin for six weeks. ▪ For penicillin-allergic individuals: cefazolin for six weeks. o Oxacillin-resistant strains ▪ Vancomycin for six weeks. ▪ Daptomycin for six weeks. • Therapy for prosthetic valve endocarditis caused by staphylococci: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin plus rifampin (for at least six weeks) and gentamicin (for two weeks). o Oxacillin-resistant strains: ▪ Vancomycin plus rifampin (for at least six weeks) and gentamicin (for two weeks). • Therapy for native valve or prosthetic valve enterococcal endocarditis: o Strains susceptible to penicillin and gentamicin: ▪ Ampicillin or penicillin G plus gentamicin for four to six weeks. ▪ Double β-lactam ampicillin plus ceftriaxone for six.

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	o Strains susceptible to penicillin and resistant to aminoglycosides or streptomycin-susceptible gentamicin-resistant in patients able to tolerate β-Lactam therapy: ▪ Ampicillin plus ceftriaxone for six weeks. ▪ Ampicillin or penicillin G plus streptomycin for four to six weeks. o Vancomycin and aminoglycoside-susceptible penicillin-resistant enterococcus species in patients unable to tolerate β-lactam : ▪ Unable to tolerate β-lactams: • Vancomycin plus gentamicin for six weeks (vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone therapy). ▪ Intrinsic penicillin resistance: • Vancomycin plus gentamicin for six weeks. o Strains Resistant to Penicillin, Aminoglycosides, and Vancomycin: ▪ Linezolid or daptomycin for at least six weeks. • Therapy for both native and prosthetic valve endocarditis caused by *Haemophilus* species *(Haemophilus parainfluenzae, Haemophilus aphrophilus, Haemophilus paraphrophilus), Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* species microorganisms: o Ceftriaxone (cefotaxime or another third- or fourth-generation cephalosporin may be substituted) or ampicillin or ciprofloxacin for four weeks. Fluoroquinolone therapy recommended only for patients unable to tolerate cephalosporin and ampicillin therapy; levofloxacin or moxifloxacin may be substituted. • Therapy for culture-negative endocarditis including *Bartonella* endocarditis: o For patients with acute (days) clinical presentations of native valve infection, coverage for *S aureus*, β-hemolytic streptococci, and aerobic Gram-negative bacilli is reasonable. o For patients with a subacute (weeks) presentation of native valve endocarditis, coverage of *S aureus*, viridans group streptococci, HACEK, and enterococci is reasonable. o For patients with culture-negative prosthetic valve endocarditis, coverage for staphylococci, enterococci, and aerobic Gram-negative bacilli is reasonable if onset of symptoms is within one year of prosthetic valve placement. o If symptom onset is >1 year after valve placement, then infective endocarditis is more likely to be caused by staphylococci, viridans group streptococci, and enterococci, and antibiotic therapy for these potential pathogens is reasonable.
Infectious Diseases Society of America: **Clinical Practice Guidelines: Management of Encephalitis (2008)**[19] **(Was reviewed and deemed current as of July 2011)**	Empirical therapy • Acyclovir should be initiated in all patients with suspected encephalitis, pending results of diagnostic studies. • Other empirical antimicrobial agents should be initiated on the basis of specific epidemiologic or clinical factors, including appropriate therapy for presumed bacterial meningitis, if clinically indicated. • In patients with clinical clues suggestive of rickettsial or ehrlichial infection during the appropriate season, doxycycline should be added to empirical treatment regimens. Bacteria • *Bartonella bacilliformis:* chloramphenicol, ciprofloxacin, doxycycline, ampicillin, or sulfamethoxazole-trimethoprim is recommended. • *Bartonella henselae:* doxycycline or azithromycin, with or without rifampin, can be considered. • *Listeria monocytogenes:* ampicillin plus gentamicin is recommended;

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	sulfamethoxazole-trimethoprim is an alternative in the penicillin-allergic patient. • *Mycoplasma pneumoniae:* antimicrobial therapy (azithromycin, doxycycline, or a fluoroquinolone) can be considered. • *Tropheryma whipplei:* ceftriaxone, followed by either sulfamethoxazole-trimethoprim or cefixime, is recommended. Helminths • *Baylisascaris procyonis:* albendazole plus diethylcarbamazine can be considered; adjunctive corticosteroids should also be considered. • *Gnathostoma* species: albendazole or ivermectin is recommended. • *Taenia solium:* need for treatment should be individualized; albendazole and corticosteroids are recommended; praziquantel can be considered as an alternative. Rickettsioses and ehrlichiosis • *Anaplasma phagocytophilum:* doxycycline is recommended. • *Ehrlichia chaffeensis:* doxycycline is recommended. • *Rickettsia rickettsii:* doxycycline is recommended; chloramphenicol can be considered an alternative in selected clinical scenarios, such as pregnancy. • *Coxiella burnetii:* doxycycline plus a fluoroquinolone plus rifampin is recommended. Spirochetes • *Borrelia burgdorferi:* ceftriaxone, cefotaxime, or penicillin G is recommended. • *Treponema pallidum:* penicillin G is recommended; ceftriaxone is an alternative. Protozoa • *Acanthamoeba:* sulfamethoxazole-trimethoprim plus rifampin plus ketoconazole or fluconazole plus sulfadiazine plus pyrimethamine can be considered. • *Balamuthia mandrillaris:* pentamidine, combined with a macrolide (azithromycin or clarithromycin), fluconazole, sulfadiazine, flucytosine, and a phenothiazine can be considered. • *Naegleria fowleri:* amphotericin B (intravenous and intrathecal) and rifampin, combined with other agents, can be considered. • *Plasmodium falciparum:* quinine, quinidine, or artemether is recommended; atovaquone-proguanil is an alternative; exchange transfusion is recommended for patients with 110% parasitemia or cerebral malaria; corticosteroids are not recommended. • *Toxoplasma gondii:* pyrimethamine plus either sulfadiazine or clindamycin is recommended; sulfamethoxazole-trimethoprim alone and pyrimethamine plus atovaquone, clarithromycin, azithromycin, or dapsone are alternatives. • *Trypanosoma brucei gambiense:* eflornithine is recommended; melarsoprol is an alternative. • *Trypanosoma brucei rhodesiense:* melarsoprol is recommended.

Infectious Diseases Society of America: **Practice Guidelines for the Diagnosis and Management of Skin and Soft-Tissue Infections (2014)**[20]	Impetigo and ecthyma
	• Gram stain and culture of the pus or exudates from skin lesions of impetigo and ecthyma are recommended to help identify whether *Staphylococcus aureus* and/or a β-hemolytic *Streptococcus* is the cause (strong, moderate), but treatment without these studies is reasonable in typical cases.
	• Bullous and nonbullous impetigo can be treated with oral or topical antimicrobials, but oral therapy is recommended for patients with numerous lesions or in outbreaks affecting several people to help decrease transmission of infection. Treatment for ecthyma should be an oral antimicrobial.
	  o Treatment of bullous and nonbullous impetigo should be with either mupirocin or retapamulin twice daily for five days.
	  o Oral therapy for ecthyma or impetigo should be a seven-day regimen

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	with an agent active against *S. aureus* unless cultures yield streptococci alone (when oral penicillin is the recommended agent). Because *S. aureus* isolates from impetigo and ecthyma are usually methicillin susceptible, dicloxacillin or cephalexin is recommended. When MRSA is suspected or confirmed, doxycycline, clindamycin, or sulfamethoxazole-trimethoprim is recommended. Purulent skin and soft-tissue infections (cutaneous abscesses, furuncles, carbuncles, and inflamed epidermoid cysts) • Gram stain and culture of pus from carbuncles and abscesses are recommended, but treatment without these studies is reasonable in typical cases. Gram stain and culture of pus from inflamed epidermoid cysts are not recommended. • Incision and drainage is the recommended treatment for inflamed epidermoid cysts, carbuncles, abscesses, and large furuncles. • The decision to administer antibiotics directed against *S. aureus* as an adjunct to incision and drainage should be made based upon presence or absence of systemic inflammatory response syndrome (SIRS), such as temperature >38°C or <36°C, tachypnea >24 breaths per minute, tachycardia >90 beats per minute, or white blood cell count >12 000 or <400 cells/µL. An antibiotic active against MRSA is recommended for patients with carbuncles or abscesses who have failed initial antibiotic treatment or have markedly impaired host defenses or in patients with SIRS and hypotension. Recurrent skin abscesses • A recurrent abscess at a site of previous infection should prompt a search for local causes such as a pilonidal cyst, hidradenitis suppurativa, or foreign material. • Recurrent abscesses should be drained and cultured early in the course of infection. • After obtaining cultures of recurrent abscess, treat with a five to ten day course of an antibiotic active against the pathogen isolated. • Consider a five-day decolonization regimen twice daily of intranasal mupirocin, daily chlorhexidine washes, and daily decontamination of personal items such as towels, sheets, and clothes for recurrent *S. aureus* infection. • Adult patients should be evaluated for neutrophil disorders if recurrent abscesses began in early childhood. Erysipelas and cellulitis • Cultures of blood or cutaneous aspirates, biopsies, or swabs are not routinely recommended except in patients with malignancy on chemotherapy, neutropenia, severe cell-mediated immunodeficiency, immersion injuries, and animal bites. • Typical cases of cellulitis without systemic signs of infection should receive an antimicrobial agent that is active against streptococci. For cellulitis with systemic signs of infection (moderate nonpurulent), systemic antibiotics are indicated. Many clinicians could include coverage against methicillin-susceptible *S. aureus* (MSSA). For patients whose cellulitis is associated with penetrating trauma, evidence of MRSA infection elsewhere, nasal colonization with MRSA, injection drug use, or SIRS (severe nonpurulent), vancomycin or another antimicrobial effective against both MRSA and streptococci is recommended. In severely compromised patients, broad-spectrum antimicrobial coverage may be considered. Vancomycin plus either piperacillin-tazobactam or imipenem/meropenem is recommended as a reasonable empiric regimen for severe infections.

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	• The recommended duration of antimicrobial therapy is five days, but treatment should be extended if the infection has not improved within this time period. Surgical site infections • Suture removal plus incision and drainage should be performed for surgical site infections. • Adjunctive systemic antimicrobial therapy is not routinely indicated, but in conjunction with incision and drainage may be beneficial for surgical site infections associated with a significant systemic response. • A brief course of systemic antimicrobial therapy is indicated in patients with surgical site infections following clean operations on the trunk, head and neck, or extremities that also have systemic signs of infection. • A first-generation cephalosporin or an antistaphylococcal penicillin for MSSA, or vancomycin, linezolid, daptomycin, telavancin, or ceftaroline where risk factors for MRSA are high (nasal colonization, prior MRSA infection, recent hospitalization, recent antibiotics), is recommended. • Agents active against gram-negative bacteria and anaerobes, such as a cephalosporin or fluoroquinolone in combination with metronidazole, are recommended for infections following operations on the axilla, gastrointestinal tract, perineum, or female genital tract. Necrotizing fasciitis • Empiric antibiotic treatment should be broad (e.g., vancomycin or linezolid plus piperacillin-tazobactam or a carbapenem; or plus ceftriaxone and metronidazole), as the etiology can be polymicrobial (mixed aerobic–anaerobic microbes) or monomicrobial (group A streptococci, community-acquired MRSA). • Penicillin plus clindamycin is recommended for treatment of documented group A streptococcal necrotizing fasciitis. Pyomyositis • Cultures of blood and abscess material should be obtained. • Vancomycin is recommended for initial empirical therapy. An agent active against enteric gram-negative bacilli should be added for infection in immunocompromised patients or following open trauma to the muscles. • Cefazolin or antistaphylococcal penicillin (e.g., nafcillin or oxacillin) is recommended for treatment of pyomyositis caused by MSSA. • Antibiotics should be administered intravenously initially, but once the patient is clinically improved, oral antibiotics are appropriate for patients in whom bacteremia cleared promptly and there is no evidence of endocarditis or metastatic abscess. Two to three weeks of therapy is recommended. Clostridial gas gangrene or myonecrosis • Urgent surgical exploration of the suspected gas gangrene site and surgical debridement of involved tissue should be performed. • In the absence of a definitive etiologic diagnosis, broad-spectrum treatment with vancomycin plus either piperacillin-tazobactam, ampicillin-sulbactam, or a carbapenem antimicrobial is recommended. Definitive antimicrobial therapy with penicillin and clindamycin is recommended for treatment of clostridial myonecrosis. Animal bites • Preemptive early antimicrobial therapy for three to five days is recommended for patients who:

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	o are immunocompromised; o are asplenic; o have advanced liver disease; o have preexisting or resultant edema of the affected area; o have moderate to severe injuries, especially to the hand or face; or o have injuries that may have penetrated the periosteum or joint capsule. • 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 o β-lactam-β-lactamase combinations, piperacillin-tazobactam, second-generation cephalosporins, and carbapenems. • Tetanus toxoid should be administered to patients without toxoid vaccination within 10 years. Tetanus, diphtheria, and tetanus (Tdap) is preferred over Tetanus and diphtheria (Td) if the former has not been previously given. Cutaneous anthrax • Oral penicillin V 500 mg four times daily for seven to 10 days is the recommended treatment for naturally acquired cutaneous anthrax. • Ciprofloxacin 500 mg by mouth twice daily or levofloxacin 500 mg intravenously/orally every 24 hours for 60 days is recommended for bioterrorism cases because of presumed aerosol exposure. Bacillary angiomatosis and cat scratch disease • Azithromycin is recommended for cat scratch disease (strong, moderate) according to the following dosing protocol: o Patients >45 kg: 500 mg on day one followed by 250 mg for four additional days. o Patients <45 kg: 10 mg/kg on day one and 5 mg/kg for four more days. • Erythromycin 500 mg four times daily or doxycycline 100 mg bid for two weeks to two months is recommended for treatment of bacillary angiomatosis. Erysipeloid • Penicillin (500 mg four times daily) or amoxicillin (500 mg three times daily [tid]) for seven to 10 days is recommended for treatment of erysipeloid. Glanders • Ceftazidime, gentamicin, imipenem, doxycycline, or ciprofloxacin is recommended based on in vitro susceptibility. Bubonic plague • Bubonic plague should be diagnosed by Gram stain and culture of aspirated material from a suppurative lymph node. Streptomycin (15 mg/kg intramuscularly [IM] every 12 hours) or doxycycline (100 mg twice daily by mouth) is recommended for treatment of bubonic plague. Gentamicin could be substituted for streptomycin. Tularemia • Streptomycin (15 mg/kg every 12 hours intramuscularly) or gentamicin (1.5

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	mg/kg every 8 hours intravenously) is recommended for treatment of severe cases of tularemia. • Tetracycline (500 mg four times daily) or doxycycline (100 mg twice daily by mouth) is recommended for treatment of mild cases of tularemia.
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 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 • 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

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	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 (2012)**[23]	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. • 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. Antimicrobial agents for the treatment of specific causes of diarrhea • 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]	Chemoprophylaxis • 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

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	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. • 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>
	• *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.
	• *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:*

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	o Metronidazole. • *Isospora* species: o Sulfamethoxazole-trimethoprim. • *Cyclospora* species: o Sulfamethoxazole-trimethoprim.
American College of Gastroenterology: **Guideline on the Management of *Helicobacter pylori* Infection (2007)**[26]	• The recommended primary therapies for *Helicobacter pylori* infection include: a proton pump inhibitor, clarithromycin, and amoxicillin, or metronidazole (clarithromycin-based triple therapy) for 14 days or a proton pump inhibitor or histamine 2 receptor antagonist, bismuth, metronidazole, and tetracycline (bismuth quadruple therapy) for 10 to 14 days.
Canadian Helicobacter Study Group: **The Toronto Consensus for the Treatment of *Helicobacter pylori* Infection in Adults (2016)**[27]	• A quadruple combination of a proton pump inhibitor, bismuth, tetracycline, and metronidazole or a proton pump inhibitor, amoxicillin, metronidazole, and clarithromycin for 14 days can be considered first-line therapy for the eradication of *Helicobacter pylori*. • Proton pump inhibitor-based triple therapy is restricted to areas with known low clarithromycin resistance or high eradication success with these regimens. • Recommended rescue therapies include bismuth quadruple therapy and levofloxacin-containing therapy. • Rifabutin regimens should be restricted to patients who have failed to respond to at least three prior regimens.
European *Helicobacter pylori* Study Group: **Management of *Helicobacter pylori* Infection–The Maastricht IV Consensus Report (2012)**[28]	• First-line therapy should be with triple therapy using a proton pump inhibitor or ranitidine bismuth citrate, combined with clarithromycin and amoxicillin or metronidazole. • Second-line therapy should include bismuth-containing quadruple therapy or proton pump inhibitor, levofloxacin and amoxicillin.
Centers for Disease Control and Prevention: **Sexually Transmitted Diseases Treatment Guidelines (2015)**[29]	<u>Arthritis and arthritis-dermatitis syndrome</u> • Recommended regimen: o Ceftriaxone 1 g intramuscular or intravenous every 24 hours plus azithromycin 1 g orally in a single dose. • Alternative regimen: o Cefotaxime 1 g intravenous every eight hours or ceftizoxime 1 g intravenous every eight hours plus azithromycin 1 g orally in a single dose. <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 g) intravaginally, once a day for five days. o Clindamycin cream 2%, one full applicator (5 g) intravaginally at bedtime for seven days. • Alternative regimens: o Tinidazole 2 g orally once daily for two days. o Tinidazole 1 g 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>

Clinical Guideline	Recommendation(s)
	• Recommended regimens for presumptive treatment: o Azithromycin 1 g orally in a single dose. o Doxycycline 100 mg orally twice a day for seven days. Chancroid • Recommended regimens: o Azithromycin 1 g 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. Chlamydial infections • Recommended regimens: o Azithromycin 1 g 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. Chlamydial infections among children • 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 g orally in a single dose. • Recommended regimens for children ≥8 years of age: o Azithromycin 1 g orally in a single dose. o Doxycycline 100 mg orally twice a day for seven days. Disseminated gonococcal infection • Recommended regimen: o Ceftriaxone 1 g intramuscular or intravenous every 24 hours. • Alternative regimens: o Cefotaxime 1 g intravenous every eight hours. o Ceftizoxime 1 g intravenous every eight hours. Epididymitis • 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. Granuloma inguinale (Donovanosis) • Recommended regimen: o Azithromycin 1 g orally once per week or 500 mg daily for at least three weeks and until all lesions have completely healed. • Alternative regimens: o Doxycycline 100 mg orally twice a day 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

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	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 g intramuscular in a single dose plus azithromycin 1 g orally 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 25 to 50 mg/kg intravenous or intramuscular in a single dose, not to exceed 125 mg. • Recommended regimen for children who weigh ≤45 kg and who have bacteremia or arthritis: o Ceftriaxone 50 mg/kg (maximum dose: 1 g) 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 g intravenous every 12 hours plus azithromycin 1 g orally in a single dose. 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 g 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:

Clinical Guideline	Recommendation(s)
	o Erythromycin base or ethylsuccinate 50 mg/kg/day orally divided into four doses daily for 14 days. • Alternative regimen: o Azithromycin suspension, 20 mg/kg/day orally, one dose daily for three days. Pelvic inflammatory disease • Recommended parenteral regimen A: o Cefotetan 2 g intravenous every 12 hours. o Cefoxitin 2 g 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 g 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 g intramuscular in a single dose and probenecid, 1 g 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. Proctitis, proctocolitis, and enteritis • Recommended regimen: o Ceftriaxone 250 mg intramuscular plus doxycycline 100 mg orally twice a day for seven days. Recurrent and persistent urethritis • Recommended regimens: o Metronidazole 2 g orally in a single dose. o Tinidazole 2 g orally in a single dose plus azithromycin 1 g orally in a single dose (if not used for initial episode). Primary and secondary syphilis • 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. Early latent syphilis • 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.

Clinical Guideline	Recommendation(s)
	Late latent syphilis or latent syphilis of unknown duration • 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. Tertiary syphilis • 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. Trichomoniasis • Recommended regimen: o Metronidazole 2 g orally in a single dose. o Tinidazole 2 g orally in a single dose. • Alternative regimen: o Metronidazole 500 mg orally twice a day for seven days. Neurosyphilis • 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. Uncomplicated gonococcal infections of the cervix, urethra, and rectum • 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 1g orally in a single dose or doxycycline 100 mg orally twice a day for seven days. Uncomplicated gonococcal infections of the pharynx • Recommended regimens: o Ceftriaxone 250 mg intermuscular in a single dose plus azithromycin 1g orally in a single dose or doxycycline 100 mg orally twice a day for seven days.
American Academy of Pediatrics/ American Academy of Family Physicians: **Diagnosis and Management of Acute Otitis Media (2013)**[30]	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.

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	• 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: **Practice Guidelines for the Diagnosis and Management of Group A Streptococcal Pharyngitis (2012)**[31] Reviewed and deemed current as of 05/2015	• Patients with acute streptococcal pharyngitis should receive therapy with an antimicrobial agent in a dose and for a duration that is likely to eradicate the infecting organism from the pharynx. • Penicillin or amoxicillin are the agents of choice because of their proven efficacy, safety, and narrow spectrum. • Treatment of acute streptococcal pharyngitis is penicillin-allergic patients should include a first generation cephalosporin for ten days, clindamycin or clarithromycin for ten days or azithromycin for five days. • Intramuscular administration of benzathine penicillin G is preferred for patients who are unlikely to complete a full 10- day course of oral therapy. • Most oral antibiotic therapy must be administered for the conventional 10 days to achieve maximal rates of pharyngeal eradication of group A streptococci. • When multiple episodes occur over the course of months or years, it may be difficult to differentiate viral pharyngitis in a *Streptococcus* carrier from true group A streptococcal pharyngitis. Therapy with certain antimicrobial agents, such as clindamycin and amoxicillin-clavulanate, may be beneficial, because they have been shown to yield high rates of eradication of streptococci from the pharynx under these particular circumstances.
American Academy of Otolaryngology–Head and Neck Surgery Foundation: **Clinical Practice Guideline: Adult Sinusitis (2015)**[32]	Symptomatic relief of viral rhinosinusitis • Management of viral rhinosinusitis is primarily symptomatic, with an analgesic or antipyretic provided for pain or fever, respectively. • Nasal saline may be palliative and cleansing with low risk of adverse reactions. • Oral decongestants may provide symptomatic relief and should be considered barring any medical contraindications, such as hypertension or anxiety. The use of topical decongestant is likely to be palliative, but continuous duration of use should not exceed three to five days, as recommended by the manufacturers, to avoid rebound congestion and rhinitis medicamentosa. • Clinical experience suggests oral antihistamines may provide symptomatic relief of excessive secretions and sneezing, although there are no clinical studies supporting the use of antihistamines in acute viral rhinosinusitis. • Guaifenesin (an expectorant) and dextromethorphan (a cough suppressant) are often used for symptomatic relief of viral rhinosinusitis symptoms, but evidence of clinical efficacy is lacking. Symptomatic relief of acute bacterial rhinosinusitis • Symptomatic treatments for acute bacterial rhinosinusitis include analgesics, topical intranasal steroids, and/or nasal saline irrigation. None of these products has been specifically approved by the FDA for use in acute rhinosinusitis (as of March 2014), and only some have data from controlled clinical studies supporting this use. • Over-the-counter analgesics, such as nonsteroidal anti-inflammatory drugs or acetaminophen, are usually sufficient to relieve facial pain associated with acute bacterial rhinosinusitis.

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	• Antihistamines have no role in the symptomatic relief of acute bacterial rhinosinusitis in nonatopic patients. No studies support their use in an infectious setting, and antihistamines may worsen congestion by drying the nasal mucosa. Initial management of acute bacterial rhinosinusitis • Offer watchful waiting (without antibiotics) or prescribe initial antibiotic therapy for adults with uncomplicated acute bacterial rhinosinusitis. Watchful waiting should be offered only when there is assurance of follow-up, such that antibiotic therapy is started if the patient's condition fails to improve by seven days after acute bacterial rhinosinusitis diagnosis or if it worsens at any time. Choice of antibiotic for acute bacterial rhinosinusitis • If a decision is made to treat acute bacterial rhinosinusitis with an antibiotic, the clinician should prescribe amoxicillin with or without clavulanate as first-line therapy for five to ten days for most adults. • For penicillin-allergic patients, either doxycycline or a respiratory fluoroquinolone (levofloxacin or moxifloxacin) is recommended as an alternative agent for empiric antimicrobial therapy. Treatment failure for acute bacterial rhinosinusitis • If the patient worsens or fails to improve with the initial management option by seven days after diagnosis or worsens during the initial management, the clinician should reassess the patient to confirm acute bacterial rhinosinusitis, exclude other causes of illness, and detect complications. • If acute bacterial rhinosinusitis is confirmed in the patient initially managed with observation, the clinician should begin antibiotic therapy. • If the patient was initially managed with an antibiotic, the clinician should change the antibiotic.
American Academy of Allergy, Asthma, and Immunology/ American College of Allergy, Asthma and Immunology/ Joint Council on Allergy, Asthma and Immunology: **The Diagnosis and Management of Sinusitis: A Practice Parameter Update (2014)**[33]	• Treat acute bacterial rhinosinusitis if symptoms last longer than 10 days or with recrudescence of symptoms after progressive improvement. • The most commonly reported bacterial pathogens in acute bacterial rhinosinusitis are *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Staphylococcus aureus.* • The antibiotics currently approved by the FDA for acute bacterial rhinosinusitis are azithromycin, clarithromycin, amoxicillin-clavulanate, cefprozil, cefuroxime axetil, loracarbef, levofloxacin, trimethoprim-sulfamethoxazole, and moxifloxacin. Although some studies have reported comparisons of different antibiotics for adult acute bacterial rhinosinusitis, not one was found to be superior. • Owing to concerns over bacterial resistance, the Infectious Diseases Society of America no longer recommends the use of macrolides for empiric treatment of acute bacterial rhinosinusitis. That organization recommends amoxicillin-clavulanate as first-line therapy and doxycycline, levofloxacin, and moxifloxacin in patients allergic to penicillin. • The Infectious Diseases Society of America recommends five to seven days of treatment with antibiotics for uncomplicated acute bacterial rhinosinusitis in adults and 10 to 14 days in children. • Use intranasal steroids for treatment of acute rhinosinusitis as monotherapy or with antibiotics.
American Academy of Pediatrics: **Clinical Practice Guideline for the Diagnosis and Management of**	• Antibiotic therapy should be prescribed for acute bacterial sinusitis in children with severe onset or worsening course (signs, symptoms or both). • Antibiotic therapy or additional outpatient observation for three days should be utilized for children with persistent illness (nasal discharge of any quality, cough or both for at least 10 days). • When a decision has been made to initiate antibiotic therapy for the treatment of

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Acute Bacterial Sinusitis in Children Aged 1 to 18 years (2013)[34]	acute bacterial sinusitis, amoxicillin with or without clavulanate is considered first-line. • For children ≥2 years of age with uncomplicated acute bacterial sinusitis that is mild to moderate in severity who do not attend child care and have not received antibiotics in the previous four weeks, amoxicillin 45 mg/kg/day in two divided doses is recommended. In communities with high prevalence of *Streptococcus pneumoniae* (>10%, including intermediate and high level resistance), amoxicillin may be initiated at 80 to 90 mg/kg/day in two divided doses with a maximum of 2 g per dose. • Patients with moderate to severe illness and those <2 years of age who are attending child care or have recently received antibiotics, amoxicillin-clavulanate (80 to 90 mg/kg/day of amoxicillin with 6.4 mg/kg/day of clavulanate to a maximum of 2 g per dose) may be used. • A single dose of ceftriaxone 50 mg/kg intravenous or intramuscular may be used for children who are vomiting, unable to tolerate oral medication or unlikely to adhere to initial doses of antibiotic.

Global Initiative for Chronic Obstructive Lung Disease: **Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2016)**[35]	• Prophylactic, continuous use of antibiotics has been shown to have no effect on the frequency of exacerbations in chronic obstructive pulmonary disease.
	• The use of antibiotics, other than for treating infectious exacerbations of chronic obstructive pulmonary disease and other bacterial infections, is currently not indicated.
	• Based on current available evidence, antibiotics should be given to:
	  o Patients with exacerbations of chronic obstructive pulmonary disease with the following three cardinal symptoms: dyspnea, sputum volume, and sputum purulence.
	  o Patients with exacerbations of chronic obstructive pulmonary disease with two of the cardinal symptoms, if the increased purulence of sputum is one of the two symptoms.
	  o Patients with a severe exacerbation of chronic obstructive pulmonary disease that requires mechanical ventilation (invasive or noninvasive).
	• The recommended length of antibiotic therapy is usually five to 10 days.
	• The choice of antibiotic should be based on local bacterial resistance patterns.
	  o Initial empiric treatment may include an aminopenicillin with or without clavulanic acid, macrolide, or tetracycline. In patients with frequent exacerbations, severe airflow limitation, and/or exacerbations requiring mechanical ventilation, sputum cultures or cultures from other materials from the lung should be performed, as gram-negative bacteria or resistant pathogens that may not be sensitive to the afore-mentioned antibiotics may be present.

Center for Disease Control and Prevention: **Recommended Antimicrobial Agents for the Treatment and Postexposure Prophylaxis of Pertussis (2005)**[36] **(Was reviewed and deemed current as of February 2013)**	• Macrolides (erythromycin, clarithromycin, and azithromycin) are preferred for the treatment of pertussis in patients >1 month of age. For infants <1 month of age, azithromycin is preferred; erythromycin and clarithromycin are not recommended. • For treatment of patients >2 months of age, an alternative agent to macrolides is sulfamethoxazole-trimethoprim. • The choice of antimicrobial should take into account effectiveness, safety, tolerability, and ease of adherence to the regimen. • Azithromycin and clarithromycin are as effective as erythromycin for treatment of pertussis in patients >6 months of age, are better tolerated, and are associated with fewer and milder side effects than erythromycin. • Erythromycin and clarithromycin, but not azithromycin, are inhibitors of the cytochrome P450 enzyme system (CYP3A subclass) and can interact with other drugs that are metabolized by this system. • Azithromycin and clarithromycin are more resistant to gastric acid, achieve higher tissue concentrations, and have a longer half-life than erythromycin, allowing less frequent administration (one to two doses per day) and shorter treatment regimens

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	(five to seven days).

Infectious Diseases Society of America: **Management of Community-Acquired Pneumonia in Infants and Children Older Than 3 Months of Age (2011)**[37]
 	
Reviewed and deemed current as of 04/2013
	Outpatient treatment
	• Antimicrobial therapy is not routinely required for preschool-aged children with community-acquired pneumonia, because viral pathogens are responsible for the great majority of clinical disease.
	• Amoxicillin should be used as first-line therapy for previously healthy, appropriately immunized infants and preschool children with mild to moderate community-acquired pneumonia suspected to be of bacterial origin. Amoxicillin provides appropriate coverage for *Streptococcus pneumoniae*.
	• For patients allergic to amoxicillin, the following agents are considered alternative treatment options:
	  o Second- or third-generation cephalosporin (cefpodoxime, cefuroxime, cefprozil).
	  o Levofloxacin (oral therapy).
	  o Linezolid (oral therapy).
	• Macrolide antibiotics should be prescribed for treatment of children (primarily school-aged children and adolescents) evaluated in an outpatient setting with findings compatible with community-acquired pneumonia caused by atypical pathogens.
	
	Inpatient treatment
	• Ampicillin or penicillin G should be administered to the fully immunized infant or school-aged child admitted to a hospital ward with community-acquired pneumonia when local epidemiologic data document lack of substantial high-level penicillin resistance for invasive *Streptococcus pneumoniae*.
	• Empiric therapy with a third-generation parenteral cephalosporin (ceftriaxone or cefotaxime) should be prescribed for hospitalized infants and children who are not fully immunized, in regions where local epidemiology of invasive pneumococcal strains documents high-level penicillin resistance, or for infants and children with life-threatening infection, including those with empyema.
	• Non–β-lactam agents, such as vancomycin, have not been shown to be more effective than third-generation cephalosporins in the treatment of pneumococcal pneumonia for the degree of resistance noted currently in North America.
	• Empiric combination therapy with a macrolide (oral or parenteral), in addition to a β-lactam antibiotic, should be prescribed for the hospitalized child for whom *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* are significant considerations.
	• Vancomycin or clindamycin (based on local susceptibility data) should be provided in addition to β-lactam therapy if clinical, laboratory, or imaging characteristics are consistent with infection caused by *Staphylococcus aureus*.

Infectious Diseases Society of America/American Thoracic Society: **Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults (2007)**[38]	Empirical antimicrobial therapy
	• Recommendations are generally for a class of antibiotics rather than for a specific drug, unless outcome data clearly favor one drug.
	• Because overall efficacy remains good for many classes of agents, the more potent drugs are given preference because of their benefit in decreasing the risk of selection for antibiotic resistance.
	• Outpatient treatment
	  o Previously healthy and no risk factors for drug-resistant *Streptococcus pneumoniae* infection:
	  ▪ Macrolide (azithromycin, clarithromycin, or erythromycin).
	  ▪ Doxycycline.
	  o Presence of comorbidities, such as chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressing conditions or use of immunosuppressing drugs; use of antimicrobials within the previous three months (in which case an

Clinical Guideline	Recommendation(s)
	alternative from a different class should be selected); or other risks for drug-resistant Streptococcus pneumoniae infection: ▪ Respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin). ▪ β-lactam plus a macrolide (high-dose amoxicillin or amoxicillin-clavulanate is preferred; alternatives include ceftriaxone, cefpodoxime, and cefuroxime; doxycycline is an alternative to the macrolide). o In regions with a high rate of infection with high-level macrolide-resistant *Streptococcus pneumoniae,* consider the use of alternative agents listed above for any patient, including those without comorbidities. • Inpatient, non-intensive care unit treatment o Respiratory fluoroquinolone. o β-lactam plus a macrolide (preferred β-lactam agents include cefotaxime, ceftriaxone, and ampicillin; ertapenem for selected patients; with doxycycline as an alternative to the macrolide. A respiratory fluoroquinolone should be used for penicillin-allergic patients). • Inpatient, intensive care unit treatment o β-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) plus either azithromycin or a fluoroquinolone (for penicillin-allergic patients, a respiratory fluoroquinolone and aztreonam are recommended). o For *Pseudomonas* infection, use an antipneumococcal, antipseudomonal β-lactam (piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin; OR o Antipneumococcal, antipseudomonal β-lactam (listed above) plus an aminoglycoside and azithromycin; OR o Antipneumococcal, antipseudomonal β-lactam (listed above) plus an aminoglycoside and an antipneumococcal fluoroquinolone (for penicillin-allergic patients, substitute aztreonam for the above β-lactam). o For community-acquired methicillin-resistant *Staphylococcus aureus* infection, add vancomycin or linezolid.
American Thoracic Society/ Infectious Diseases Society of America: **Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia (2005)**[39]	• Select an initial empiric therapy based on the absence or presence of risk factors for multidrug-resistant pathogens. These risk factors include prolonged duration of hospitalization (five days or more), admission from a healthcare-related facility, and recent prolonged antibiotic therapy. • Patients with healthcare-related pneumonia should be treated for potentially drug-resistant organisms, regardless of when during the hospital stay the pneumonia begins. • In selecting empiric therapy for patients who have recently received an antibiotic, an effort should be made to use an agent from a different antibiotic class, because recent therapy increases the probability of inappropriate therapy and can predispose to resistance to that same class of antibiotics. • Initial empiric antibiotic therapy for hospital-acquired pneumonia or ventilator-associated pneumonia in patients with no known risk factors for multidrug-resistant pathogens, early onset, and any disease severity: o Ceftriaxone; OR o Levofloxacin, moxifloxacin, ciprofloxacin; OR o Ampicillin-sulbactam; OR o Ertapenem. • Initial empiric antibiotic therapy for hospital-acquired pneumonia, ventilator-associated pneumonia, and healthcare-associated pneumonia in patients with late-onset disease or risk factors for multidrug-resistant pathogens and all disease severity–combination antibiotic therapy is recommended as follows: • Antipseudomonal cephalosporin (cefepime, ceftazidime) or antipseudomonal carbapenem (imipenem or meropenem) or β-lactam-β-lactamase inhibitor (piperacillin-tazobactam) plus antipseudomonal fluoroquinolone (ciprofloxacin or

Clinical Guideline	Recommendation(s)
	levofloxacin) or aminoglycoside (amikacin, gentamicin, or tobramycin) plus linezolid or vancomycin if methicillin-resistant *Staphylococcus aureus* risk factors are present or there is a high incidence locally.
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 (2016)**[40]	Primary prophylaxis of *Pneumocystis 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 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 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 jiroveci* despite sulfamethoxazole-trimethoprim prophylaxis are usually effectively treated with standard doses of sulfamethoxazole-trimethoprim. • Patients with documented or suspected *Pneumocystis 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 jiroveci* therapy. • The recommended duration of therapy for *Pneumocystis jiroveci* is 21 days. • Patients who have a history of *Pneumocystis 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 jiroveci* recurs at a CD4+ count of ≥200 cells/µL, lifelong prophylaxis should be administered.

Clinical Guideline	Recommendation(s)
	Primary prophylaxis of *Toxoplasma* encephalitis • The double-strength tablet daily dose of sulfamethoxazole-trimethoprim is recommended as the preferred regimen for *Pneumocystis jiroveci* prophylaxis and is effective against *Toxoplasma* encephalitis 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 jiroveci* pneumonia. • Atovaquone with or without pyrimethamine-leucovorin can also be considered. • 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. 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. 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.

Clinical Guideline	Recommendation(s)
	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. • Ethambutol is the recommended second drug.
American Society of Health-System Pharmacists/ Infectious Diseases Society of America/ Surgical Infection Society/ Society for Healthcare Epidemiology of America: **Clinical practice guidelines for antimicrobial prophylaxis in surgery (2013)**[41]	Common principles • The optimal time for administration of preoperative doses is within 60 minutes before surgical incision. Some agents, such as fluoroquinolones and vancomycin, require administration over one to two hours; therefore, the administration of these agents should begin within 120 minutes before surgical incision. • The selection of an appropriate antimicrobial agent for a specific patient should take into account the characteristics of the ideal agent, the comparative efficacy of the antimicrobial agent for the procedure, the safety profile, and the patient's medication allergies. • For most procedures, cefazolin is the drug of choice for prophylaxis because it is the most widely studied antimicrobial agent, with proven efficacy. It has a desirable duration of action, spectrum of activity against organisms commonly encountered in surgery, reasonable safety, and low cost. • There is little evidence to suggest that broad-spectrum antimicrobial agents (i.e., agents with broad in vitro antibacterial activity) result in lower rates of postoperative SSI compared with older antimicrobial agents with a narrower spectrum of activity. However, comparative studies are limited by small sample sizes, resulting in difficulty detecting a significant difference between antimicrobial agents. Cardiac procedures • For patients undergoing cardiac procedures, the recommended regimen is a single preincision dose of cefazolin or cefuroxime with appropriate intraoperative redosing. • For patients with serious allergy or adverse reaction to β-lactams, vancomycin or clindamycin may be an acceptable alternative. • Vancomycin should be used for prophylaxis in patients known to be colonized with MRSA. • Mupirocin should be given intranasally to all patients with documented *S. aureus* colonization. Thoracic procedures • In patients undergoing thoracic procedures, a single dose of cefazolin or ampicillin–sulbactam is recommended. • For patients with serious allergy or adverse reaction to β-lactams, vancomycin or clindamycin may be an acceptable alternative. • Vancomycin should be used for prophylaxis in patients known to be colonized with MRSA. Gastroduodenal procedures • Antimicrobial prophylaxis in gastroduodenal procedures should be considered for patients at highest risk for postoperative infections, including risk factors such as increased gastric pH (e.g., patients receiving acid-suppression therapy), gastroduodenal perforation, decreased gastric motility, gastric outlet obstruction, gastric bleeding, morbid obesity, ASA classification of ≥3, and cancer. • A single dose of cefazolin is recommended in procedures during which the lumen

Clinical Guideline	Recommendation(s)
	of the intestinal tract is entered. A single dose of cefazolin is recommended in clean procedures, such as highly selective vagotomy, and antireflux procedures only in patients at high risk of postoperative infection due to the presence of the above risk factors. • Alternative regimens for patients with β -lactam allergy include clindamycin or vancomycin plus gentamicin, aztreonam, or a fluoroquinolone. • Higher doses of antimicrobials are uniformly recommended in morbidly obese patients undergoing bariatric procedures. Higher doses of antimicrobials should be considered in significantly overweight patients undergoing gastroduodenal and endoscopic procedures. Biliary tract procedures • A single dose of cefazolin should be administered in patients undergoing open biliary tract procedures. • Alternatives include ampicillin–sulbactam and other cephalosporins (cefotetan, cefoxitin, and ceftriaxone). Alternative regimens for patients with β -lactam allergy include clindamycin or vancomycin plus gentamicin, aztreonam, or a fluoroquinolone; or metronidazole plus gentamicin or a fluoroquinolone. Appendectomy procedures • For uncomplicated appendicitis, the recommended regimen is a single dose of a cephalosporin with anaerobic activity (cefoxitin or cefotetan) or a single dose of a first-generation cephalosporin (cefazolin) plus metronidazole. • For β -lactam-allergic patients, alternative regimens include clindamycin plus gentamicin, aztreonam, or a fluoroquinolone; and metronidazole plus gentamicin or a fluoroquinolone (ciprofloxacin or levofloxacin). Small intestine procedures • For small bowel surgery without obstruction, the recommended regimen is a first generation cephalosporin (cefazolin). For small bowel surgery with intestinal obstruction, the recommended regimen is a cephalosporin with anaerobic activity (cefoxitin or cefotetan) or the combination of a first-generation cephalosporin (cefazolin) plus metronidazole. • For β -lactam-allergic patients, alternative regimens include clindamycin plus gentamicin, aztreonam, or a fluoroquinolone; and metronidazole plus gentamicin or a fluoroquinolone (ciprofloxacin or levofloxacin). Hernia repair procedures • For hernioplasty and herniorrhaphy, the recommended regimen is a single dose of a first-generation cephalosporin (cefazolin). For patients known to be colonized with MRSA, it is reasonable to add a single preoperative dose of vancomycin to the recommended agent. For β –lactam-allergic patients, alternative regimens include clindamycin and vancomycin. Colorectal procedures • A single dose of second-generation cephalosporin with both aerobic and anaerobic activities (cefoxitin or cefotetan) or cefazolin plus metronidazole is recommended for colon procedures. • In institutions where there is increasing resistance to first- and second-generation cephalosporins among gram-negative isolates from SSIs, a single dose of ceftriaxone plus metronidazole is recommended over routine use of carbapenems. An alternative regimen is ampicillin–sulbactam. • In most patients, mechanical bowel preparation combined with a combination of oral neomycin sulfate plus oral erythromycin base or oral neomycin sulfate plus oral metronidazole should be given in addition to intravenous prophylaxis. The

Clinical Guideline	Recommendation(s)

	oral antimicrobial should be given as three doses over approximately 10 hours the afternoon and evening before the operation and after the mechanical bowel preparation.
	• Alternative regimens for patients with β–lactam allergies include (1) clindamycin plus an aminoglycoside, aztreonam, or a fluoroquinolone and (2) metronidazole plus an aminoglycoside or a fluoroquinolone. Metronidazole plus aztreonam is not recommended as an alternative because this combination has no aerobic gram-positive activity.
	
	<u>Head and neck procedures</u>
	• Clean procedures:
	  o Antimicrobial prophylaxis is not required.
	• Clean-contaminated procedures:
	  o Antimicrobial prophylaxis has not been shown to benefit patients undergoing tonsillectomy or functional endoscopic sinus procedures.
	  o The preferred regimens for patients undergoing other clean-contaminated head and neck procedures are (1) cefazolin or cefuroxime plus metronidazole and (2) ampicillin–sulbactam.
	  o Clindamycin is a reasonable alternative in patients with a documented β-lactam allergy. The addition of an aminoglycoside to clindamycin may be appropriate when there is an increased likelihood of gram-negative contamination of the surgical site.
	
	<u>Neurosurgery procedures</u>
	• A single dose of cefazolin is recommended for patients undergoing clean neurosurgical procedures, CSF-shunting procedures, or intrathecal pump placement. Clindamycin or vancomycin should be reserved as an alternative agent for patients with a documented β-lactam allergy (vancomycin for MRSA-colonized patients).
	
	<u>Cesarean delivery procedures</u>
	• The recommended regimen for all women undergoing cesarean delivery is a single dose of cefazolin administered before surgical incision. For patients with β-lactam allergies, an alternative regimen is clindamycin plus gentamicin.
	
	<u>Hysterectomy procedures</u>
	• The recommended regimen for women undergoing vaginal or abdominal hysterectomy, using an open or laparoscopic approach, is a single dose of cefazolin.
	• Cefoxitin, cefotetan, or ampicillin–sulbactam may also be used. Alternative agents for patients with a b-lactam allergy include (1) either clindamycin or vancomycin plus an aminoglycoside, aztreonam, or a fluoroquinolone and (2) metronidazole plus an aminoglycoside or a fluoroquinolone.
	
	<u>Ophthalmic procedures</u>
	• Due to the lack of robust data from trials, specific recommendations cannot be made regarding choice, route, or duration of prophylaxis.
	• As a general principle, the antimicrobial prophylaxis regimens used in ophthalmic procedures should provide coverage against common ocular pathogens, including *Staphylococcus* species and gram-negative organisms, particularly *Pseudomonas* species.
	
	<u>Orthopedic procedures</u>
	• Antimicrobial prophylaxis is not recommended for patients undergoing clean orthopedic procedures, including knee, hand, and foot procedures, arthroscopy, and other procedures without instrumentation or implantation of foreign materials.

Clinical Guideline	Recommendation(s)
	• Antimicrobial prophylaxis is recommended for orthopedic spinal procedures with and without instrumentation. The recommended regimen is cefazolin. • The recommended regimen in hip fracture repair or other orthopedic procedures involving internal fixation is cefazolin. Clindamycin and vancomycin should be reserved as alternative agents. • The recommended regimen for patients undergoing total hip, elbow, knee, ankle, or shoulder replacement is cefazolin. Clindamycin and vancomycin should be reserved as alternative agents. Urologic procedures • No antimicrobial prophylaxis is recommended for clean urologic procedures in patients without risk factors for postoperative infections. • Patients with preoperative bacteriuria or UTI should be treated before the procedure, when possible, to reduce the risk of postoperative infection. • For patients undergoing lower urinary tract instrumentation with risk factors for infection, the use of a fluoroquinolone or trimethoprim– sulfamethoxazole (oral or intravenous) or cefazolin (intravenous or intramuscular) is recommended. Vascular procedures • The recommended regimen for patients undergoing vascular procedures associated with a higher risk of infection, including implantation of prosthetic material, is cefazolin. Heart, lung, heart-lung, liver, pancreas, and kidney transplantation • Antimicrobial prophylaxis is indicated for all patients undergoing heart transplantation. The recommended regimen is a single dose of cefazolin. Alternatives include vancomycin or clindamycin with or without gentamicin, aztreonam, or a single fluoroquinolone dose. • Adult patients undergoing lung transplantation should receive antimicrobial prophylaxis, because of the high risk of infection. Patients with negative pretransplantation cultures should receive antimicrobial prophylaxis as appropriate for other types of cardiothoracic procedures. The recommended regimen is a single dose of cefazolin. • The recommended agents for patients undergoing liver transplantation are (1) piperacillin–tazobactam and (2) cefotaxime plus ampicillin. The duration of prophylaxis should be restricted to 24 hours or less. • The recommended regimen for patients undergoing pancreas or SPK transplantation is cefazolin. • The recommended agent for patients undergoing kidney transplantation is cefazolin. Plastic surgery and breast procedures • Antimicrobial prophylaxis is not recommended for most clean procedures in patients without additional postoperative infection risk factors. • Although no studies have demonstrated antimicrobial efficacy in these procedures, expert opinion recommends that patients with risk factors undergoing clean plastic procedures receive antimicrobial prophylaxis. The recommendation for clean-contaminated procedures, breast cancer procedures, and clean procedures with other risk factors is a single dose of cefazolin or ampicillin–sulbactam.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the macrolides 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 Macrolides[1-12]

Indication	Azithromycin	Clarithromycin	Erythromycin	Fidaxomicin	Telithromycin
Dermatological Infections					
Erythrasma			✔		
Skin and skin-structure infections	✔ †	✔ §	✔		
Gastrointestinal Infections					
Treatment of *Clostridium difficile*-associated diarrhea				✔	
Treatment of patients with *Helicobacter pylori* infection and duodenal ulcer disease to eradicate *Helicobacter pylori* (in combination with amoxicillin and lansoprazole or omeprazole as triple therapy)		✔ §			
Treatment of patients with *Helicobacter pylori* infection and duodenal ulcer disease to eradicate *Helicobacter pylori* (in combination with omeprazole or ranitidine bismuth citrate as dual therapy)		✔ §			
Genitourinary Infections					
Chancroid	✔ †				
Pelvic inflammatory disease due to *Neisseria gonorrhoeae*			✔		
Pelvic inflammatory disease due to *Chlamydia trachomatis, Neisseria gonorrhoeae,* and *Mycoplasma hominis*	✔ *				
Syphilis			✔		
Urethral, endocervical, or rectal infections			✔		
Urethritis/cervicitis (gonococcal)	✔ †				
Urethritis/cervicitis (non-gonococcal)	✔ † ‖		✔		
Urogenital infections in pregnancy			✔		
Respiratory Infections					
Acute exacerbations of chronic bronchitis		✔ §δ			
Acute infective exacerbations of chronic obstructive pulmonary disease (mild to moderate)	✔ †				
Legionnaires' disease			✔		
Otitis media	✔ †	✔ §			
Pertussis			✔		
Pharyngitis and/or tonsillitis	✔ †	✔ §	✔		
Pneumonia (community-acquired)	✔ *†‡	✔ §δ	✔		✔
Pneumonia of infancy due to *Chlamydia trachomatis*			✔		

Indication	Azithromycin	Clarithromycin	Erythromycin	Fidaxomicin	Telithromycin
Respiratory tract infections (lower)			✔		
Respiratory tract infections (upper)			✔		
Sinusitis	✔ †‡	✔ §δ			
Miscellaneous Infections					
Conjunctivitis of the newborn due to *Chlamydia trachomatis*			✔		
Diphtheria			✔		
Intestinal amebiasis			✔ †		
Listeriosis			✔		
Mycobacterial infections due to *Mycobacterium avium* or *Mycobacterium intracellulare* (disseminated, treatment)		✔ §			
Mycobacterium avium complex disease in patients with advanced human immunodeficiency virus infection (disseminated, prevention)	✔ ‖	✔ §			
Mycobacterium avium complex disease in patients with advanced human immunodeficiency virus infection (disseminated, treatment)	✔ ‖				
Rheumatic fever (prophylaxis)			✔		

δExtended-release formulation.
§Immediate-release formulations.
*IV formulation.
‡Suspension formulation (extended-release).
†Tablet formulation (250 and 500 mg) and suspension formulation (immediate-release).
‖Tablet formulation (600 mg) and suspension formulation (1 g packet).

IV. Pharmacokinetics

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

Table 5. Pharmacokinetic Parameters of the Macrolides[1-12]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Azithromycin	38	7 to 50	Liver (35)	Renal (12) Biliary (>50)	11 to 68
Clarithromycin	50	42 to 50	Liver	Renal (20 to 40)	3 to 7
Erythromycin	>35	73 to 81	Liver	Biliary	1.5 to 2.0
Fidaxomicin	Minimal	Not reported	Intestine	Feces (>92)	11.7
Telithromycin	57	60 to 70	Liver (37)	Renal (12 to 14) Feces (75)	10 to 13

V. Drug Interactions

Major drug interactions with the macrolides are listed in Table 6.

Table 6. Major Drug Interactions with the Macrolides[2]

Generic Name(s)	Interaction	Mechanism
Macrolides (azithromycin, clarithromycin, erythromycin, telithromycin)	Antiarrhythmic agents	Co-administration may result in additive increase in the QT interval and increase risk of life-threatening cardiac arrhythmias, such as torsades de pointes.
Macrolides (azithromycin, clarithromycin, erythromycin, telithromycin)	Anticoagulants	Effects of oral anticoagulants may be potentiated. Bleeding may occur. Close monitoring of prothrombin time is recommended.
Macrolides (azithromycin, clarithromycin, erythromycin, telithromycin)	Quinolones	The risk of life-threatening cardiac arrhythmias, such as torsades de pointes may be increased.
Macrolides (clarithromycin, erythromycin)	Digoxin	Increases in serum digoxin concentrations have been observed, resulting in signs of digoxin toxicity.
Macrolides (azithromycin, clarithromycin, erythromycin, telithromycin)	Dronedarone	Co-administration may result in additive increase in the QT interval and increase risk of life-threatening cardiac arrhythmias, such as torsades de pointes. The metabolism of dronedarone may be inhibited. Co-administration is contraindicated.
Macrolides (azithromycin, clarithromycin, erythromycin, telithromycin)	Nilotinib	Increased plasma nilotinib concentrations resulting in increased risk of adverse reactions including life-threatening cardiac arrhythmias, such as torsades de pointes.
Macrolides (azithromycin, clarithromycin, erythromycin, telithromycin)	Pimozide	Cardiac arrhythmia, QT prolongation, and cardiac arrest are possible due to elevated serum pimozide concentrations. Co-administration is contraindicated.
Macrolides (azithromycin, clarithromycin, erythromycin, telithromycin)	Ergotamine and dihydroergotamine	Reports of acute ergot toxicity characterized by vasospasm and ischemia in the extremities and other tissues, including the central nervous system have been reported.
Macrolides (azithromycin, clarithromycin, erythromycin, telithromycin)	HMG-CoA reductase inhibitors	Increased concentrations of HMG-CoA reductase inhibitors have been observed. Rhabdomyolysis and liver dysfunction may occur.
Macrolides (azithromycin, clarithromycin, erythromycin, telithromycin)	Opioid analgesics	Opioid analgesic plasma concentrations may be elevated resulting in increased pharmacological effect and adverse reactions.
Macrolides	Carbamazepine	Increases in plasma carbamazepine concentrations

Generic Name(s)	Interaction	Mechanism
(clarithromycin, erythromycin, telithromycin)		have been observed.
Macrolides (azithromycin, clarithromycin, erythromycin)	Cisapride	Torsades des points, QT prolongation, and cardiac arrest are possible due to decreased cisapride metabolism.
Macrolides (clarithromycin, erythromycin, telithromycin)	Colchicine	Increases in colchicine concentration have been observed due to inhibition of CYP3A4 and P-glycoprotein.
Macrolides (azithromycin, clarithromycin, erythromycin, telithromycin)	Tacrolimus	Macrolides may increase gastrointestinal absorption and inhibit hepatic and gastrointestinal metabolism of tacrolimus via inhibition of cytochrome P450 3A4. Pharmacologic effects of macrolides and tacrolimus on myocardium may be additive
Macrolides (erythromycin)	Theophylline	Inhibition of cytochrome P450 1A2 isoenzymes by erythromycin may decrease the metabolic elimination of theophylline. Elevated theophylline plasma concentrations with toxicity characterized by nausea, vomiting, cardiovascular instability, and seizures may occur.
Macrolides (clarithromycin, erythromycin, telithromycin)	Benzodiazepines	Central nervous system effects such as somnolence and confusion have been reported with the co-administration of these medications.
Macrolides (azithromycin, clarithromycin, erythromycin, telithromycin)	Phosphodiesterase-5 inhibitors	Co-administration may result in increased exposure to phosphodiesterase-5 inhibitors. Reduction of phosphodiesterase-5 inhibitor doses may be considered.
Macrolides (azithromycin, clarithromycin, erythromycin, telithromycin)	Tyrosine kinase inhibitors	Concurrent use of macrolides and tyrosine kinase inhibitors may result in an increased risk of QT interval prolongation.
Macrolides (azithromycin, clarithromycin, erythromycin, telithromycin)	Azole antifungals	Concurrent use of macrolides and azole antifungals may result in an increased risk of QT interval prolongation.
Macrolides (azithromycin, clarithromycin, erythromycin, telithromycin)	Protease inhibitors	Plasma concentrations of protease inhibitors and macrolides are increased when the drugs are used concomitantly. Potential QT interval prolongation may occur.
Macrolides (azithromycin, clarithromycin, erythromycin, telithromycin)	Dopamine antagonists	Plasma concentrations of dopamine antagonists and macrolides are increased when the drugs are used concomitantly. Potential QT interval prolongation may occur.
Macrolides (azithromycin, clarithromycin, erythromycin, telithromycin)	Antipsychotic agents	Plasma concentrations of antipsychotic agents and macrolides are increased when the drugs are used concomitantly. Potential QT interval prolongation may occur.
Macrolides (azithromycin, clarithromycin, erythromycin, telithromycin)	Tricyclic antidepressants	Plasma concentrations of tricyclic antidepressants and macrolides are increased when the drugs are used concomitantly. Potential QT interval prolongation may occur.
Macrolides (azithromycin, clarithromycin, erythromycin, telithromycin)	Selective serotonin inhibitors (dolasetron, granisetron, ondansetron)	Concurrent use of selective serotonin inhibitors and macrolides may result in an increased risk of QT interval prolongation.
Macrolides (clarithromycin, erythromycin, telithromycin)	Rifamycins	Induction of hepatic microsomal enzymes by rifamycins may increase the metabolic elimination of macrolides. Inhibition of hepatic microsomal enzymes

Generic Name(s)	Interaction	Mechanism
		by macrolides may decrease the metabolic elimination of rifamycins.
Macrolides (clarithromycin, erythromycin, telithromycin)	Cilostazol	Increased cilostazol exposure has been reported with co-administration. Monitor blood pressure, heart rate, complete blood counts, bleeding time, routine chemistry, and blood glucose for signs of cilostazol toxicity.
Macrolides (clarithromycin, telithromycin)	Silodosin	Silodosin plasma concentrations may be elevated resulting in increased pharmacological effect and adverse reactions.

VI. Adverse Drug Events

The most common adverse drug events reported with the macrolides are listed in Table 7. The boxed warning for telithromycin is listed in Table 8.

Table 7. Adverse Drug Events (%) Reported with the Macrolides[1-12]

Adverse Events	Azithromycin	Clarithromycin	Erythromycin	Fidaxomicin	Telithromycin
Cardiovascular					
Allergic myocarditis	-	-	-	-	-
Atrial arrhythmias	-	-	-	-	✔
Bradycardia	-	-	-	-	<1
Chest pain	<1	-	✔	-	-
Cyanosis	-	-	-	-	-
Hypotension	✔	-	-	-	<1
Palpitations	<1	-	✔	-	✔
Syncope	-	-	-	-	-
Tachycardia	-	-	-	-	-
Torsades de pointes	✔	✔	✔	-	-
Ventricular tachycardia	✔	✔	✔	-	-
Central Nervous System					
Aggressive reactions	✔	-	-	-	-
Agitation	✔	-	-	-	-
Anxiety	✔	✔	-	-	<1
Asthenia	✔	-	-	-	-
Ataxia	-	-	-	-	-
Behavioral changes	-	✔	-	-	-
Confusion	-	✔	✔	-	✔
Depersonalization	-	✔	-	-	-
Depression	-	✔	-	-	-
Disorientation	-	✔	-	-	-
Dizziness	<1	✔	✔	-	2 to 3
Fever	✔	-	✔	-	-
Hallucinations	-	✔	✔	-	✔
Headache	<1	2	8	-	2 to 5
Hyperactivity	✔	-	-	-	-
Insomnia	✔	✔	-	-	<2
Intracranial hypertension	-	-	-	-	-
Loss of consciousness	-	-	-	-	✔
Manic behavior	-	✔	-	-	-

Adverse Events	Azithromycin	Clarithromycin	Erythromycin	Fidaxomicin	Telithromycin
Nervousness	✔	-	-	-	-
Nightmares	-	✔	-	-	-
Paresthesia	✔	-	-	-	<1
Peripheral neuritis	-	-	-	-	-
Psychosis	-	✔	-	-	-
Seizures	✔	✔	✔	-	-
Somnolence	<1	-	-	-	<2
Sweating	✔	-	-	-	<2
Syncope	✔	-	-	-	✔
Tinnitus	-	✔	-	-	-
Tremor	-	✔	-	-	-
Vertigo	<1	✔	✔	-	<2
Dermatological					
Desquamation	-	-	1 to 10	-	-
Dryness	-	-	1 to 10	-	-
Eczema	✔	-	-	-	<1
Erythema	-	-	1 to 10	-	-
Erythema multiforme	✔	-	✔	-	<1
Exfoliative dermatitis	-	-	-	-	-
Photosensitivity	<1	-	-	-	-
Pruritus	✔	-	1 to 10	<2	<1
Rash	<1	3	3	<2	<2
Skin eruptions	-	✔	✔	-	-
Stevens Johnson Syndrome	✔	✔	✔	-	-
Toxic epidermal necrolysis	✔	✔	✔	-	-
Urticaria	✔	✔	✔	-	<1
Gastrointestinal					
Abdominal distension	-	-	-	<2	<2
Abdominal pain	3	2 to 3	8	6	<2
Abdominal tenderness	-	-	-	<2	-
Anorexia	✔	✔	✔	-	<2
Cholestatic jaundice	<1	✔	✔	-	-
Constipation	✔	-	-	-	<2
Cramping	-	-	✔	-	-
Diarrhea	5	3 to 6	7	-	10
Dry mouth	-	-	-	-	<2
Dyspepsia	<1	2	2	<2	<2

Adverse Events	Azithromycin	Clarithromycin	Erythromycin	Fidaxomicin	Telithromycin
Dysphagia	-	-	-	<2	-
Flatulence	<1	-	2	<2	<2
Gastritis	✔	-	-	-	<2
Gastroenteritis	-	-	-	-	<2
Gastrointestinal hemorrhage	-	-	-	4	-
Gastrointestinal upset	-	-	-	-	<2
Glossitis	-	✔	-	-	<2
Hypertrophic pyloric stenosis	-	-	✔	-	-
Intestinal Obstruction	-	-	-	<2	-
Loose stools	5.0 to 11.6	-	-	-	2
Megacolon	-	-	-	<2	-
Melena	<1	-	-	-	-
Mucositis	<1	-	-	-	-
Nausea	3 to 5	3	8	11	7
Oral candidiasis	✔	✔	✔	-	<2
Pancreatitis	✔	✔	✔	-	✔
Pseudomembranous colitis	✔	-	✔	-	-
Salivary gland enlargement	-	-	-	-	-
Stomatitis	-	✔	-	-	<2
Taste perversion	✔	3 to 7	1	-	1
Tongue discoloration	✔	✔	-	-	-
Tooth discoloration	-	✔	-	-	-
Vomiting	<2	6	3	7	2
Watery stools	-	-	-	-	<2
Genitourinary					
Acute renal failure	✔	-	-	-	-
Crystalluria	-	-	-	-	-
Hematuria	-	-	-	-	-
Interstitial nephritis	✔	✔	-	-	-
Monilia	<1	-	-	-	-
Nephritis	<1	-	-	-	-
Toxic nephrosis with anuria	-	-	-	-	-
Toxic nephrosis with oliguria	-	-	-	-	-
Urinary retention	-	-	-	-	-
Vaginal candidiasis	-	-	-	-	<2
Vaginitis	<1	-	-	-	-
Hematological					

Adverse Events	Azithromycin	Clarithromycin	Erythromycin	Fidaxomicin	Telithromycin
Agranulocytosis	-	-	-	-	-
Anemia	✔	-	-	2	-
Aplastic anemia	-	-	-	-	-
Eosinophilia	-	-	1	-	<1
Hemolytic anemia	-	-	-	-	-
Leukopenia	<1	✔	-	-	-
Methemoglobinemia	-	-	-	-	-
Neutropenia	<1	✔	-	2	-
Sulfhemoglobinemia	-	-	-	-	-
Thrombocytopenia	<1	✔	-	<2	-
Thrombocytosis	-	-	-	-	<2
Hepatic					
Hepatic dysfunction	-	-	✔	-	✔
Hepatic failure	✔	✔	-	-	✔
Hepatic necrosis	✔	-	-	-	✔
Hepatitis	✔	✔	✔	-	<1
Hepatocellular necrosis	-	-	-	-	-
Hepatotoxicity	-	-	-	-	✔
Jaundice	✔	-	✔	-	-
Laboratory Test Abnormalities					
Alkaline phosphatase increased	-	<1	-	<2	-
Bicarbonate decreased	-	-	-	<2	-
Bilirubin increased	<1	-	-	-	<1
Blood urea nitrogen increased	<1	4	-	-	-
Creatine phosphokinase increased	1 to 2	-	-	-	-
Creatinine increased	<1	<1	-	-	-
Gamma-glutamyl transferase increased	1 to 2	<1	-	-	-
Hepatic enzymes increased	-	-	-	<2	-
Hyperglycemia	<1	-	-	<2	-
Hyperkalemia	1 to 2	-	-	-	-
Hypofibrinogenemia	-	-	-	-	-
Hypoglycemia	-	✔	-	-	-
Hypoprothrombinemia	-	-	-	-	-
Lactic dehydrogenase increased	<1	<1	-	-	-
Metabolic acidosis	-	-	-	<2	-
Phosphate increased	<1	-	-	-	-
Prothrombin time increased	-	1	-	-	-

Adverse Events	Azithromycin	Clarithromycin	Erythromycin	Fidaxomicin	Telithromycin
Serum glutamic oxaloacetic transaminase increased	1 to 2	<1	2	-	<2
Serum glutamic pyruvic transaminase increased	1 to 2	<1	2	-	<2
Musculoskeletal					
Arthralgia	✔	-	-	-	✔
Muscle cramps	-	-	-	-	✔
Myalgia	-	-	-	-	✔
Myasthenia gravis exacerbation	-	-	-	-	✔
Rigors	-	-	-	-	-
Weakness	-	-	2	-	-
Respiratory					
Bronchospasm	<1	-	-	-	-
Cough	✔	-	3	-	-
Dyspnea	-	-	1	-	-
Pharyngitis	✔	-	-	-	-
Pneumonitis	-	-	-	-	-
Pulmonary infiltrates	-	-	-	-	-
Rhinitis	✔	-	-	-	-
Shortness of breath	-	-	-	-	-
Other					
Allergic reactions	-	-	✔	-	-
Anaphylaxis	✔	✔	✔	-	✔
Angioedema	<1	-	-	-	✔
Arteritis	-	-	-	-	-
Blurred vision	-	-	-	-	<2
Conjunctival injection	-	-	-	-	-
Deafness	✔	-	-	-	-
Diplopia	-	-	-	-	<2
Diuresis	-	-	-	-	-
Edema	✔	-	-	-	-
Facial edema	-	-	-	-	✔
Fatigue	<1	-	-	-	<2
Flushing	-	-	-	-	<1
Goiter	-	-	-	-	-
Hearing disturbances	✔	-	-	-	-
Hearing loss	-	✔	✔	-	-
Hypersensitivity reactions	-	-	✔	-	-

Adverse Events	Azithromycin	Clarithromycin	Erythromycin	Fidaxomicin	Telithromycin
Malaise	✔	-	-	-	-
Olfactory perversion	-	✔	-	-	-
Pain	✔	-	2	-	-
Periarteritis nodosa	-	-	-	-	-
Phlebitis	-	-	✔	-	-
Scleral injection	-	-	-	-	-
Serum sickness-like reaction	-	-	-	-	-
Systemic lupus erythematosus	-	-	-	-	-
Thrombophlebitis	-	-	✔	-	-
Tinnitus	✔	-	-	-	-
Vasculitis	-	-	-	-	-

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

Table 8. Boxed Warning for Telithromycin[1]

WARNING
Telithromycin is contraindicated in patients with myasthenia gravis. There have been reports of fatal and life-threatening respiratory failure in patients with myasthenia gravis associated with the use of telithromycin.

VII. Dosing and Administration

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

Table 9. Usual Dosing Regimens for the Macrolides[1-13]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Azithromycin	Acute infective exacerbations of chronic obstructive pulmonary disease (mild to moderate): Immediate release suspension, tablet (250 mg, 500 mg): 500 mg once daily for three days or 500 mg as a single dose on day one, followed by 250 mg once daily on days two to five Chancroid: Immediate release suspension, tablet (250 mg, 500 mg): 1 g as a single dose *Mycobacterium avium* complex disease in patients with advanced human immunodeficiency virus infection (disseminated, prevention): Tablet (600 mg): 1,200 mg once weekly *Mycobacterium avium* complex disease in patients with advanced human immunodeficiency virus infection (disseminated, treatment): Tablet (600 mg): treatment: 600 mg daily Urethritis/cervicitis (gonococcal): Immediate release suspension, tablet (250 mg, 500 mg): 2 g as a single dose Urethritis/cervicitis (non-gonococcal): Immediate release suspension, tablet (250 mg, 500 mg): 1 g as a single dose Suspension (1 g): 1 g as a single dose Pelvic inflammatory disease due to	Otitis media in patients ≥6 months of age: Immediate release suspension, tablet (250 mg, 500 mg): 30 mg/kg given as a single dose or 10 mg/kg once daily for three days or 10 mg/kg as a single dose on the first day, followed by 5 mg/kg/day on days two through five Pharyngitis and/or tonsillitis in patients ≥2 years of age: Immediate release suspension, tablet (250 mg, 500 mg): 12 mg/kg once daily for five days Pneumonia (community-acquired) in patients ≥6 months of age: Extended release suspension: 60 mg/kg as a single dose Immediate release suspension, tablet (250 mg, 500 mg): 10 mg/kg on day one, followed by 5 mg/kg on days two to five Sinusitis in patients ≥6 months of age: Immediate release suspension, tablet (250 mg, 500 mg): 10 mg/kg once daily for three days	Extended release suspension: 2 g/60 mL Immediate release suspension: 100 mg/5 mL 200 mg/5 mL Injection: 500 mg Packet for suspension: 1 g Tablet: 250 mg 500 mg 600 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Chlamydia trachomatis, Neisseria gonorrhoeae, and *Mycoplasma hominis*: Injection: 500 mg as a single daily dose for one to two days Pharyngitis and/or tonsillitis: Immediate release suspension, tablet (250 mg, 500 mg): 500 mg as a single dose on day one, followed by 250 mg once daily on days two to five Pneumonia (community-acquired): Extended release suspension: 2 g as a single dose Immediate release suspension, tablet (250 mg, 500 mg): 500 mg as a single dose on day one, followed by 250 mg once daily on days two to five Injection: 500 mg as a single daily dose for at least two days Sinusitis: Extended release suspension: 2 g as a single dose Immediate release suspension, tablet (250 mg, 500 mg): 500 mg once daily for three days Skin and skin-structure infections: Immediate release suspension, tablet (250 mg, 500 mg): 500 mg as a single dose on day one, followed by 250 mg once daily on days two to five		
Clarithromycin	Acute exacerbations of chronic bronchitis: Extended release tablet:1,000 mg once daily for seven days Immediate release tablet: 250 to 500 mg every 12 hours for seven to 14 days *Mycobacterium avium* complex disease in patients with advanced human immunodeficiency virus infection (disseminated, prevention): Immediate release tablet: 500 mg every 12 hours	Mycobacterium avium complex disease in patients with advanced human immunodeficiency virus infection (disseminated, prevention) in patients ≥6 months of age: Immediate release tablet, suspension: 7.5 mg/kg orally every 12 hours, up to 500 mg every 12 hours Mycobacterial infections due to *Mycobacterium avium* or *Mycobacterium intracellulare* (disseminated, treatment):	Extended release tablet: 500 mg Immediate release tablet: 250 mg 500 mg Suspension: 125 mg/5 mL 250 mg/5 mL

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Mycobacterial infections due to *Mycobacterium avium* or *Mycobacterium intracellulare* (disseminated, treatment): Immediate release tablet: 500 mg every 12 hours Treatment of patients with *Helicobacter pylori* infection and duodenal ulcer disease to eradicate *Helicobacter pylori* (in combination with amoxicillin and lansoprazole or omeprazole as triple therapy): Immediate release tablet: 500 mg every 12 hours for 10 to 14 days given with amoxicillin and either lansoprazole or omeprazole Treatment of patients with *Helicobacter pylori* infection and duodenal ulcer disease to eradicate *Helicobacter pylori* (in combination with omeprazole or ranitidine bismuth citrate as dual therapy): Immediate release tablet: 500 mg every eight to 12 hours for 14 days given with ranitidine bismuth citrate or omeprazole Pharyngitis and/or tonsillitis: Immediate release tablet: 250 mg every 12 hours for 10 days Pneumonia (community-acquired): Extended release tablet:1,000 mg once daily for seven days Immediate release tablet: 250 mg every 12 hours for seven to 14 days Sinusitis: Extended release tablet: 1,000 mg once daily for 14 days Immediate release tablet: 500 mg every 12 hours for 14 days Skin and skin-structure infections: Immediate release tablet: 250 mg every 12 hours for seven to 14 days	Immediate release tablet, suspension: 7.5 mg/kg orally every 12 hours, up to 500 mg every 12 hours Otitis media in patients ≥6 months of age: Immediate release tablet, suspension: 15 mg/kg/day divided every 12 hours for 10 days Pharyngitis and/or tonsillitis in patients ≥6 months of age: Immediate release tablet, suspension: 15 mg/kg/day divided every 12 hours for 10 days Pneumonia (community-acquired) in patients ≥6 months of age: Immediate release tablets, suspension: 15 mg/kg/day divided every 12 hours for 10 days Sinusitis in patients ≥6 months of age: Immediate release tablet, suspension: 15 mg/kg/day divided every 12 hours for 10 days Skin and skin-structure infections in patients ≥6 months of age: Immediate release tablet, suspension: 15 mg/kg/day divided every 12 hours for 10 days	
Erythromycin base	Intestinal amebiasis: Coated-particle tablet, delayed release capsule, delayed release tablet, tablet: 500 mg every 12 hours or 250 mg every six hours for 10 to 14 days	Intestinal amebiasis: Coated-particle tablet, delayed release capsule, delayed release tablet, tablet: 30 to 50 mg/kg/day in divided doses for 10 to 14 days	Coated-particle tablet: 333 mg 500 mg Delayed release

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Legionnaires' disease: Coated-particle tablet, delayed release capsule, delayed release tablet, tablet: 1 to 4 g daily in divided doses Nongonococcal urethritis: Coated-particle tablet, delayed release capsule, delayed release tablet, tablet: 500 mg four times daily for seven days Pelvic inflammatory disease: Coated-particle tablet, delayed release capsule, delayed release tablet, tablet: 500 mg intravenous every six hours for three days followed by 500 mg orally every 12 hours for seven days Pertussis: Coated-particle tablet, delayed release capsule, delayed release tablet, tablet: 40 to 50 mg/kg/day in divided doses for five to 14 days Pharyngitis and/or tonsillitis: Coated-particle tablet, delayed release capsule, delayed release tablet, tablet: 250 mg four times daily or 500 mg every 12 hours for 10 days Syphilis: Coated-particle tablet, delayed release capsule, delayed release tablet, tablet: 30 to 40 g given in divided doses over 10 to 15 days Unspecified infections: Coated-particle tablet, delayed release capsule, delayed release tablet, tablet: 250 mg four times daily or 500 mg every 12 hours Urogenital infections in pregnancy: Coated-particle tablet, delayed release capsule, delayed release tablet, tablet: 500 mg four times daily for seven days or either 250 mg four times daily or 500 mg every 12 hours for 14 days	Unspecified infections: Coated-particle tablet, delayed release capsule, delayed release tablet, tablet: 30 to 50 mg/kg/day in two to four divided doses	capsule: 250 mg Delayed release tablet: 250 mg 333 mg 500 mg Tablet: 250 mg 500 mg
Erythromycin ethylsuccinate	Intestinal amebiasis: Suspension, tablet: 400 mg four times daily for 10 to 14 days	Intestinal amebiasis: Suspension, tablet: 30 to 50 mg/kg/day in divided doses for	Suspension: 200 mg/5 mL 400 mg/5 mL

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Legionnaires' disease: Suspension, tablet: 1.6 to 4 g daily in divided doses Pertussis: Suspension, tablet: 40 to 50 mg/kg/day in divided doses for five to 14 days Syphilis: Suspension, tablet: 48 to 64 g in divided doses over 10 to 15 days Unspecified infections: Suspension, tablet: 400 mg every six hours, or total daily dose divided every eight or every 12 hours Urethritis: Suspension, tablet: 800 mg three times daily for seven days	10 to 14 days Unspecified infections: Suspension, tablet: 30 to 50 mg/kg/day in two to four divided doses	Tablet: 400 mg
Erythromycin lactobionate	Unspecified infections: Injection: 15 to 20 mg/kg/day every six hours or 0.5 to 1 g every six hours or continuous infusion	Unspecified infections: Injection: 15 to 20 mg/kg/day divided every six hours	Injection: 500 mg
Erythromycin stearate	Unspecified infections: Tablet: 250 mg every six hours or 500 mg every 12 hours up to 4 g per day	Unspecified infections: Tablet: 30 to 50 mg/kg/day in two to four divided doses	Tablet: 250 mg
Fidaxomicin	*Clostridium difficile*-associated diarrhea: Tablet: 200 mg twice daily for 10 days	Safety and efficacy in children has not been established.	Tablet: 200 mg
Telithromycin	Pneumonia (community-acquired): Tablet: 800 mg once daily for seven to 10 days	Safety and efficacy in children has not been established.	Tablet: 300 mg 400 mg

VIII. Effectiveness

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

Table 10. Comparative Clinical Trials with the Macrolides

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Dermatological Infections				
Dey et al.[42] (2015) Azithromycin 2 g once vs azithromycin 500 mg once daily for five days	OL, PG, PRO, RCT Patients 12 years of age or older with an uncomplicated skin and skin structure infection	N=292 7 days	Primary: Clinical response (cessation of the spread of redness, edema, and induration around the lesion or reduction of the size of the lesion at 72 hours) Secondary: Clinical cure, adverse effects	Primary: The resolution of individual signs and symptoms was highly significant over seven days in both groups and remained comparable between the two dosing groups throughout. Secondary: At the end of study, cure was recorded in 145 subjects (97.97%) who received single dose azithromycin vs 144 (98.63%) subjects who received conventional five days azithromycin; the difference is statistically not significant. The differences in frequency of individual adverse events between the two groups were not statistically significant.
Wasilewski et al.[43] (2000) Dirithromycin 500 mg daily for five days vs erythromycin 250 mg every 6 hours for seven days	DB, DD, MC, PG, RCT Patients 12 years of age or older with a culturable bacterial infection of the skin and/or soft tissue	N=439 Treatment duration plus 10 to 14 days	Primary: Clinical response (cure defined as resolution of pre-treatment signs and symptoms), bacteriologic response (eradication of pathogen based on culture results) Secondary: Not reported	Primary: A favorable response was seen in 85.0% of patients in the dirithromycin group compared to 80.8% of patients in the erythromycin group. No significant differences were observed. A favorable bacteriologic response was seen in 66.4% of patients in the dirithromycin group and 63.5% in the erythromycin group. No significant differences were observed. Secondary: Not reported
Gastrointestinal Infections				
Kaushik et al.[44] (2010)	OL, RCT	N=180	Primary: Clinical success	Primary: Clinical success was 94.5% with azithromycin compared to 70.7% with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ciprofloxacin 20 mg/kg as a single dose vs azithromycin 20 mg/kg as a single dose	Children 2 to 12 years of age with watery diarrhea for ≤24 hours and severe dehydration, who tested positive for Vibrio cholerae by hanging drop examination or culture of stool	3 days	(resolution of diarrhea within 24 hours) and bacteriological success (cessation of excretion of Vibrio cholerae by day three) Secondary: Duration of diarrhea, duration of excretion of Vibrio cholerae in stool, fluid requirement, and proportion of children with clinical or bacteriological relapse	ciprofloxacin (RR, 1.34; 95% CI, 1.16 to 1.54; P<0.001). Bacteriological success was 100% with azithromycin compared to 95.5% with ciprofloxacin (RR, 1.05; 95% CI, 1.00 to 1.10; P=0.06). Secondary: Patients treated with azithromycin had a shorter duration of diarrhea compared to patients receiving ciprofloxacin (54.6 vs 71.5 hours, respectively; P<0.001). Patients receiving azithromycin had a lesser duration of excretion of Vibrio cholerae than patients receiving ciprofloxacin (34.6 vs 52.1 hours; P<0.001). The amount of IV fluid was significantly less among patients who received azithromycin compared to those who received ciprofloxacin (4,704.7 vs 3,491.1 mL; P<0.001). The proportion of children with bacteriological relapse was comparable in both groups (6.7% with azithromycin vs 2.2% with ciprofloxacin; P=0.16). None of the children in either group had a clinical relapse.
Vukelic et al.[45] (2010) Azithromycin 20 mg/kg as a single oral dose vs azithromycin 30 mg/kg as a single oral dose vs	RCT, SC Children ≤12 years of age with *Campylobacter jejuni/coli* enterocolitis	N=120 Variable duration	Primary: Clinical cure rates achieved during the 144 hours study period and safety Secondary: Not reported	Primary: The incidence of clinically cured patients during the 144-hour study period was 50% in the control, 46.6% in the azithromycin 20 mg/kg group, 66.6% in the azithromycin 30 mg/kg group, and 83.3% in the erythromycin group. Only azithromycin 30 mg/kg was significantly more effective than no treatment (P=0.011). Azithromycin 30 mg/kg was also significantly more effective than erythromycin (P=0.006). There was no difference between the erythromycin and the control group. All treatments were well tolerated. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
erythromycin 50 mg/kg/day orally divided in three daily doses for five days vs no antibiotic (control group)				
Hsu et al.[46] (2015) Reverse hybrid therapy (pantoprazole 40 mg plus amoxicillin 1 g twice daily for 12 days, and clarithromycin 500 mg plus metronidazole 500 mg twice daily for the first seven days) vs standard triple therapy (pantoprazole 40 mg plus clarithromycin 500 mg and amoxicillin 1 g twice daily for	MC, RCT, SB Patients ≥20 years of age with diagnosis of *H pylori* based on at least two positive results of rapid urease test, histology, and culture and with endoscopically proven peptic ulcer diseases or gastritis	N=440 6 weeks after treatment	Primary: Eradication rate Secondary: Frequency of adverse events, drug compliance	Primary: Intent-to-treat eradication rates were 93.6 and 86.8% for reverse hybrid and standard triple therapies, respectively. Reverse hybrid therapy achieved a higher eradication rate than standard triple therapy (95% CI, 1.3 to 12.3%; P=0.016). The modified intent-to-treat (95.4 vs 88.4%) and per-protocol analyses (95.7 vs 88.3%) yielded similar results (P=0.008 and 0.005, respectively). Secondary: The incidences of adverse events in the participants receiving reverse hybrid and standard triple therapies were 14.1% (95% CI, 9.2 to 19.0%) and 9.5% (95% CI, 5.6 to 13.4%), respectively. The two therapies exhibited similar frequencies of overall adverse events (P=0.14). Reverse hybrid and standard triple groups displayed similar compliance rates (96.8%; 95% CI, 94.5 to 99.1% and 98.6%; 95% CI, 97.1 to 100.2%, respectively).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
12 days).				
Molina-Infante et al.[47] (2013) Hybrid therapy (40 mg omeprazole and 1 g amoxicillin, twice daily for 14 days; 500 mg clarithromycin and 500 mg nitroimidazole were added, twice daily for the final seven days) vs concomitant therapy (same 4 drugs taken concurrently, twice daily for 14 days)	NI, PRO, RCT Consecutive adult patients with *H pylori* infection and dyspepsia, peptic ulcer disease, or familiar history of gastric cancer, who did not receive prior eradication therapy	N=343 8 weeks posttreatment	Primary: Eradication rates in the intent-to-treat population Secondary: Eradication rates in the per-protocol population, compliance	Primary: In the intent-to-treat analysis, eradication rates were 153 of 170 (90%; 95% CI, 86 to 93%) for hybrid and 156 of 170 (91.7%; 95% CI, 88 to 95%) for concomitant therapy (P=0.35). Secondary: Eradication rates in the per-protocol analysis were 150 of 163 (92%; 95% CI, 87 to 95%) for hybrid therapy and 150 of 156 (96.1%; 95% CI, 93 to 99%) for concomitant therapy (P=0.07). More patients were compliant (defined as compliance ≥80%) with hybrid therapy (98.8%) than concomitant therapy (95.2%; P=0.05).
Zhang et al.[48] (2015) Metronidazole 400 mg four times a day vs clarithromycin 500 mg twice a day	NI, OL, R Consecutive patients who presented with epigastric symptoms and had endoscopically proven functional dyspepsia or scarred peptic ulcers. *H pylori* infection was	N=215 6 weeks posttreatment	Primary: Eradication rates Secondary: Compliance, adverse events	Primary: In the per-protocol analysis, the lower bound of the 95% CI for difference between metronidazole and clarithromycin groups was greater than the pre-established non-inferiority margin of –10% (95% CI, −2.7 to 6.7%, P<0.0001). The same CI was derived with the intent-to-treat population. Secondary: Eight subjects in the metronidazole group and six subjects in the clarithromycin group failed to take at least 80% of the drugs due to adverse effects, including three subjects of each group that were withdrawn from the treatment because of nausea, drowsiness and skin allergy. Both regimens were well tolerated (92.6 vs 94.4%; P=0.593). Side

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Each treatment was taken in combination with lansoprazole 30 mg twice a day, bismuth potassium citrate 300 mg (220 mg elemental bismuth) twice a day, and amoxicillin 1000 mg twice a day for 14 days	diagnosed by positive rapid urease test and 13C-urea breath test or anti-*H pylori* antibody			effects were reported by 21.3% (23/108) in the metronidazole group vs 11.2% (12/107) in the clarithromycin group (P=0.045). Adverse effects included nausea, fatigue, bad taste, epigastric pain, skin rash, diarrhoea, dizziness, and fever. They all disappeared after cessation of medications. Adverse effects were more frequent in the metronidazole group than in the clarithromycin group (P=0.045). Nausea was the most frequent adverse event in the metronidazole group (P=0.031)
Ohlin et al.[49] (2002) Clarithromycin 500 mg BID, amoxicillin 1g BID, and lansoprazole 30 mg BID for 14 days (LAC) vs lansoprazole 30 mg BID and amoxicillin 1g BID for 14 days (LA) vs omeprazole 20 mg BID and amoxicillin 1g BID for 14 days (OA)	DB, MC, RCT Patients 18 to 80 years of age with *H pylori* infection and a present recurrent duodenal ulcer and/or previous recurrent duodenal ulcer	N=177 4 weeks posttreatment	Primary: Eradication of *H pylori* at least four weeks after the end of treatment period Secondary: Not reported	Primary: Triple therapy with LAC was significantly better than either dual therapy with OA or LA in ulcer healing and eradication of *H pylori* (P<0.001). There was no significant difference between dual therapy groups. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Uygun et al.[50] (2007) Tetracycline 500 mg QID, bismuth subsalicylate 300 mg QID, lansoprazole 30 mg BID, and metronidazole 500 mg TID (BLTM group) vs lansoprazole 30 mg BID, amoxicillin 1 g BID and clarithromycin 500 mg BID (LAC)	RCT, SB, SC Patients with *H pylori* infection and non-ulcer dyspepsia	N=240 14 days	Primary: *H pylori* eradication rates Secondary: Not reported	Primary: The intent to treat and per protocol populations, *H pylori* eradication rates were 70% (95% CI, 61 to 78) and 82.3% (95% CI, 74 to 89) in the BLTM group, and 57.5% (95%CI, 48 to 66) and 62.7% (95%CI, 53 to 71) in the LAC group. The BLTM treatment achieved a significantly better eradication rate than the LAC treatment in per protocol analysis (82.3 vs 62.7%; P=0.002). Although a better intent to treat rate was obtained in the BLTM group than in the LAC group, the difference was not significant (70 vs 57.5%; P=0.06). Mild to severe side-effects, which were more frequent in the BLTM group, were reported in 18.2% of the patients. Although it was not statistically significant, the number of patients ceasing the treatment for side-effects was more in BLTM group than in the LAC group. Secondary: Not reported
Kearney et al.[51] (2000) Tetracycline 500 mg QID, bismuth subsalicylate 2 tablets QID, metronidazole 250 mg QID, and cimetidine 400 mg BID or famotidine 20 mg BID for 14 days (BMT-H2) vs tetracycline 500	OL Patients with peptic ulcer disease or prescribed H2-receptor antagonists or proton pump inhibitors, and who tested positive with histology, rapid urease or urea breath testing for *H pylori* infection	N=224 6 weeks	Primary: Defining treatment success rates for *H pylori* infection at end of study Secondary: Adverse events	Primary: The intent-to-treat cure rates for BMT-H2, BMT-PPI, and MLC were 81, 87, and 90%, respectively (all; P>0.05). The per-protocol cure rates for BMT-H2, BMT-PPI, and MLC were 84, 91, and 92% (all; P>0.05). Secondary: The side-effect profile for the three treatment groups revealed no significant differences in the frequency of the most common side effects, diarrhea and constipation. Metallic taste was significantly more severe in the MLC group (P=0.04). Nausea was significantly more common in the MLC group than the BMT-H2 group (P=0.04). There were no significant differences in the frequency of dizziness/lightheadedness, cramping, or other side effects between the BMT-H2 and MLC groups, and between BMT-PPI and BMT-H2 groups. Severe headaches were significantly more frequent in the BMT-PPI group than the BMT-H2 group (P=0.02). A

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg QID, bismuth subsalicylate 2 tablets QID, metronidazole 250 mg QID, and lansoprazole 30 mg BID for 7 days (BMT-PPI) vs metronidazole 500 mg BID, lansoprazole 30 mg BID, and clarithromycin 250 mg BID for 7 days (MLC)				significantly higher number of patients discontinued therapy due to adverse events in the BMT-H2 and BMT-PPI treatment groups than the MLC group (P=0.049).
Magaret et al.[52] (2001) Tetracycline 250 mg QID, bismuth subsalicylate 2 tablets QID, lansoprazole 30 mg BID, and metronidazole 250 mg QID for 14 days vs lansoprazole 30 mg BID, amoxicillin 1,000 mg BID, and clarithromycin 500	MC, RCT Patients failing prior treatment for *H pylori*	N=48 6 weeks	Primary: Negative 14C-UBT of <50 disintegrations per minute at time of follow-up indicating cure of infection Secondary: Side effects and compliance	Primary: Per-protocol eradication rates for patients on triple therapy and quadruple therapy were 82 and 80%, respectively (P=0.85). Intention-to-treat eradication rates for triple and quadruple therapy were 72 and 65%, respectively (P=0.63). Secondary: Compliance in patients receiving triple and quadruple therapy was 89% (P=0.98). Side effects were reported in 84% of patients on triple therapy and 82% of patients on quadruple therapy (P=0.85). Side effects included nausea (33%), upset stomach (25%), diarrhea (36%), abdominal pain (16%), lightheadedness/dizziness (4%), and fatigue (8%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg BID for 14 days				
Songür et al.[53] (2009) Tetracycline 500 mg QID, bismuth subcitrate 300 mg QID, lansoprazole 30 mg BID, and metronidazole 500 mg BID for 10 days (BLTM) vs tetracycline 500 mg QID, ranitidine bismuth citrate 400 mg BID, lansoprazole 30 mg BID, and metronidazole 500 mg BID for 10 days (RBLTM) vs tetracycline 500 mg QID, lansoprazole 30 mg BID, and metronidazole 500 mg BID for 10 days (LTM) vs	RCT, SC Patients with *H pylori* infection and dyspeptic symptoms	N=464 14 days	Primary: Eradication rates, compliance Secondary: Not reported	Primary: In the per protocol analysis, eradication rates in LAC, BLTM, RBLTM, and LTM groups were 35.6, 54.9, 64.4, and 60.0%, respectively. In the intent to treat analysis, eradication r rates in LAC, BLTM, RBLTM, and LTM groups were 32.7, 47.1, 57.3, and 54.8%, respectively. The BLTM, RBLTM, and LTM treatment groups achieved a significantly better eradication rate than the LAC treatment group (P<0.001). There was no significant difference between BLTM, RBLTM, and LTM treatment groups. Compliance rates with LAC, BLTM, RBLTM, and LTM therapies were 91, 87, 90, and 94%, respectively. The treatments were generally well tolerated. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
lansoprazole 30 mg BID, amoxicillin 1,000 mg BID, and clarithromycin 500 mg BID for 14 days (LAC)				
Malfertheiner et al.[54] (2011) Tetracycline 125 mg, bismuth subcitrate potassium 140 mg, and metronidazole 125 mg (as a single three-in-one capsule) 3 capsules QID plus omeprazole 20 mg BID for 10 days (quadruple therapy) vs omeprazole 20 mg, amoxicillin 500 mg, and clarithromycin 500 mg BID for 7 days (standard therapy)	OL, RCT Patients ≥18 years of age with *H pylori* infection and upper gastrointestinal symptoms	N=399 56 days posttreatment	Primary: Eradication rates, resistance rates, and safety Secondary: Not reported	Primary: In the per protocol analysis, eradication rates were 93% with quadruple therapy compared to 70% with standard therapy (P<0.0001). Quadruple therapy was found to be non-inferior to standard therapy. In the intention-to-treat analysis, eradication rates were 80% with quadruple therapy compared to 55% with standard therapy (P<0.0001). Metronidazole sensitivity did not significantly affect the efficacy of quadruple therapy in the per protocol population (P=0.283). Clarithromycin sensitivity seemed to significantly affect the efficacy of standard therapy (P<0.0001). Simultaneous metronidazole and clarithromycin resistance reduced efficacy only in patients treated with standard therapy (P=0.001). The incidence of serious treatment emergent adverse events and discontinuations due to a treatment emergent adverse events were similar between groups (<2.0%). The main adverse events were gastrointestinal and central nervous system disorders. Secondary: Not reported
Zheng et al.[55] (2010) Tetracycline 750	OL, RCT, SC Patients 18 to 70 years of age with	N=170 7 to 10 days	Primary: Eradication rates, resistance rates, safety	Primary: In the intent to treat analysis, eradication rates were 63.5% in the PAC group and 89.4% in the PBMT groups (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg BID, colloidal bismuth subcitrate 220 mg BID, pantoprazole 40 mg BID, and metronidazole 400 mg TID for 10 days (PBMT) vs pantoprazole 40 mg BID, amoxicillin 1.0 g BID and clarithromycin 500 mg BID for 7 days (PAC)	non-ulcer dyspepsia and *H pylori* infection		Secondary: Not reported	In the per protocol analysis, the eradication rates were 65.1% in the PAC group and 91.6% in the PBMT group (P<0.05). The *H pylori* primary resistance rates to metronidazole and clarithromycin were 41.6 and 20.8%, respectively, whereas all the *H pylori* isolates were sensitive to amoxicillin and tetracycline. Adverse events were similar among the treatment groups and included bitter taste, nausea, poor appetite, and occasional symptoms, such as diarrhea, vomiting, drug eruption, insomnia, constipation, and lethargy. The adverse events rates of quadruple therapy and triple therapy were 42.3 and 60.0%, respectively. Secondary: Not reported
de Boer et al.[56] (1998) Tetracycline 500 mg QID, ranitidine bismuth citrate 400 mg BID, and metronidazole 500 mg TID for 7 days vs ranitidine bismuth citrate 400 mg BID, amoxicillin 1,000 mg BID, and clarithromycin 500 mg BID for 7 days	OL, PG, RCT Patients with upper gastrointestinal symptoms and infected with *H pylori*	N=168 8 weeks	Primary: Endoscopy performed six weeks after completion of treatment to determine *H pylori* infection, defined as a positive CLOtest, confirmed by histology or culture Secondary: Safety	Primary: Logistical regression analysis determined that there was no difference between the seven-day and 14-day treatments. Intent-to-treat analysis cure rate for the ranitidine bismuth citrate, tetracycline, and metronidazole treatment group was 86%. The cure rate for the ranitidine bismuth citrate, amoxicillin, and clarithromycin treatment group was 92%. The cure rate for the ranitidine bismuth citrate and clarithromycin treatment group was 95%. Per-protocol cure rates were 89, 93, and 96% respectively. There was no statistical difference between the three groups. Secondary: Side effects were comparable among the treatment groups. Overall, 32% of patients in the ranitidine bismuth citrate, tetracycline, metronidazole treatment group, 18% of the ranitidine bismuth citrate, amoxicillin, and clarithromycin treatment group, and 23% of the ranitidine bismuth citrate and clarithromycin treatment group reported side effects during the trial period (P=0.249).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs ranitidine bismuth citrate 400 mg BID, clarithromycin 500 mg BID for 14 days				
Altintas et al.[57] (2004) Tetracycline 1 g BID, ranitidine-bismuth citrate 400 mg BID, and metronidazole 500 mg TID for 14 days (triple therapy) vs ranitidine-bismuth citrate 1 g BID for 14 days and azithromycin 500 mg QD for 7 days (dual therapy)	RCT Patients ≥18 years of age who were resistant to triple therapy consisting of a proton pump inhibitor clarithromycin and amoxicillin for the treatment of *H pylori*	N=52 6 weeks	Primary: Eradication rates of *H pylori* as confirmed by endoscopy and biopsy Secondary: Improvement in symptoms of endoscopic gastritis	Primary: There was a significant difference between the treatment groups. Eradication rates for triple and dual therapy were 44.4 and 12.0%, respectively (P=0.01). Secondary: There were significant improvements in the severity of endoscopic gastritis in both groups (P=0.01), but no significant differences between the two groups (P=0.600).
Luther et al.[58] (2010) Tetracycline, metronidazole, bismuth-containing compound, and proton-pump inhibitor (bismuth	MA Patients with *H pylori* infection	N=1,679 (9 trials) Variable duration	Primary: Eradication rate, compliance rate, adverse events Secondary: Not reported	Primary: The eradication rate with bismuth quadruple therapy was 78.3% compared to 77% with clarithromycin triple therapy (RR, 1.002; 95% CI, 0.936 to 1.073). The compliance rate with bismuth quadruple therapy was 92.6% compared to 98.9% with clarithromycin triple therapy (RR, 0.99; 95% CI, 0.938 to 1.045).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
quadruple therapy) vs clarithromycin triple therapy (amoxicillin, clarithromycin, and proton-pump inhibitor)				The overall incidence of adverse events in patients receiving bismuth quadruple therapy was 35.5% compared to 35.4% with clarithromycin triple therapy (RR, 1.037; 95% CI, 1.037 to 1.135). Secondary: Not reported
Louie et al.[59] (2011) Fidaxomicin 200 mg BID for 10 days vs vancomycin 125 mg orally QID for 10 days	DB, MC, RCT Patients ≥16 years of age with diarrhea and a diagnosis of *Clostridium difficile* infection, as well as the presence of *Clostridium difficile* toxin A, B, or both in the stool	N=629 28 days posttreatment	Primary: Clinical cure (resolution of symptoms and no need for further therapy for *Clostridium difficile* infection as of the second day after the end of the course of therapy) Secondary: Recurrence of *Clostridium difficile* infection (diarrhea and a positive result on a stool toxin test within four weeks after treatment)	Primary: Clinical cure rates in the modified intent to treat analysis were 88.2% with fidaxomicin and 85.8% with vancomycin. Clinical cure rates in the per protocol analysis were 92.1% for fidaxomicin and 89.8% for vancomycin. The rates of clinical cure with fidaxomicin were non-inferior to those with vancomycin. Secondary: Recurrence in the modified intent to treat analysis was 15.4% with fidaxomicin compared to 25.3% with vancomycin (P=0.005). Recurrence in the per protocol analysis was 13.3% with fidaxomicin compared to 24% with vancomycin (P=0.004). Significantly fewer patients in the fidaxomicin group than in the vancomycin group had a recurrence of the infection.
Cornely, Crook et al.[60] (2012) Fidaxomicin 200	DB, MC, PRO, RCT Patients ≥16 years of age with	N=535 28 days posttreatment	Primary: Clinical cure (resolution of symptoms and no need for further	Primary: In the per protocol population, clinical cure rates in the fidaxomicin group (91.7%) were non-inferior to the rates in the vancomycin group (90.6%; one-sided 97.5% CI, -4.3). In the modified intent to treat population, clinical cure rates in the fidaxomicin group (87.7%) were non-inferior to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg every 12 hours for 10 days vs vancomycin 125 mg orally every 6 hours daily for 10 days	*Clostridium difficile* infection and either *Clostridium difficile* toxin A or B in the stool		therapy for *Clostridium difficile* infection as of the second day after the end of the course of therapy) Secondary: Recurrence of *Clostridium difficile* infection (diarrhea and a positive result on a stool toxin test within 30days of treatment completion)	the rates in the vancomycin group (86.8%; treatment difference, 0.9; 95% CI, -4.9 to 6.7; P=0.754). Secondary: In the modified intent to treat population, significantly more patients in the vancomycin group had a recurrence compared to the fidaxomicin group (26.9 vs 12.7%; treatment difference, -14.2; 95% CI, -21.4 to -6.8; P=0.0002). In this population, there was a significantly higher rate of sustained clinical response in the fidaxomicin group compared to the vancomycin group (76.6 vs 63.4%; treatment difference, 13.2; 95% CI, 5.3 to 21.0; P=0.001).
Cornely, Miller et al.[61] (2012) Fidaxomicin 200 mg BID for 10 days vs vancomycin 125 mg orally QID for 10 days	DB, MC, PRO, RCT Patients >15 years of age with *Clostridium difficile* infection and either *Clostridium difficile* toxin A or B in the stool	N=178 28 days posttreatment	Primary: Recurrence of *Clostridium difficile* infection (diarrhea and a positive result on a stool toxin test within 30 days of treatment completion) Secondary: Not reported	Primary: In patients with no prior episode of *Clostridium difficile* infection, there was a significantly greater proportion of patients in the vancomycin group (24.8%) that had a recurrence compared to the fidaxomicin group (12.9%; treatment difference, -11.8; 95% CI, 17.1 to 6.5; P<0.001). In patients with one prior episode of *Clostridium difficile* infection, there was no significant difference in recurrence between the vancomycin and fidaxomicin groups (32.3 vs 20.3%; treatment difference -12.3; 95% CI, -25.4 to 1.5; P=0.08). Secondary: Not reported
Genitourinary Infections				
Tyndall et al.[62] (1994) Azithromycin 1 g as a single dose	RCT, SB Male patients 18 to 60 years of age with genital ulcers	N=204 21 days	Primary: Response to treatment (cure defined as epithelialization of	Primary: Complete ulcer resolution was observed in 89% of men in the azithromycin group and 91% of men in the erythromycin group. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs erythromycin 500 mg QID or seven days			ulcer complete by day 21) Secondary: Not reported	Not reported
Hook et al.[63] (2002) Azithromycin 2 g as a single dose vs azithromycin 2 g as two doses given six to eight days apart vs penicillin benzathine G 2.4 million units IM as a single dose	RCT Patients 18 to 56 years of age with early syphilis	N=74 12 months	Primary: Therapeutic response Secondary: Not reported	Primary: The overall response rate for patients in the benzathine penicillin G group was 86%. The overall response rate for patients in the single-dose azithromycin group was 94%, which was not significantly different from the penicillin group (P=0.75). The overall response rate for patients in the double-dose azithromycin group was 83% and was not significantly different from the penicillin group (P=0.95). Secondary: Not reported
Hook et al.[64] (2010) Azithromycin 2 g as a single dose vs penicillin benzathine G 2.4 million units IM as a single dose	MC, OL, RCT Patients 18 to 55 years of age with early syphilis (primary, secondary, or early latent)	N=517 6 months	Primary: Serological cure of infection Secondary: Not reported	Primary: In the intent to treat analysis at the six-month follow-up visit, 77.6% of azithromycin patients and 78.5% of penicillin patients experienced serological cure (1-sided lower bound of the 95% CI of the difference, −7.2%). In the per protocol analysis at the six-month follow-up visit, 77.5%) of azithromycin patients and 78.9%) of penicillin patients experienced serological cure (1-sided 95% CI lower bound, −7.9%). The efficacy of 2 g azithromycin administered orally was non-inferior to the administration of benzathine penicillin G for the treatment of early

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				syphilis in patients without human immunodeficiency virus infection. Secondary: Not reported
Bai et al.[65] (2008) Azithromycin vs penicillin G benzathine	MA Patients ≥18 years of age with early syphilis	N=476 (4 trials) Variable duration	Primary: Cure rates and adverse events Secondary: Not reported	Primary: In the azithromycin group, serology cure occurred in 95% of patients. In the penicillin G benzathine group, serology cure occurred in 84.0% of patients (OR, 1.37; 95% CI, 1.05 to 1.77; P=0.02). The pooled OR for primary syphilis with the administration of azithromycin as compared to penicillin G benzathine was 0.69 (95% CI, 0.09 to 1.61; P=0.38). There was no significant difference in the rate of adverse events between the treatment groups. Secondary: Not reported
Mena et al.[66] (2009) Doxycycline 100 mg BID for 7 days vs azithromycin 1 g as a single dose	RCT, SC Men with nongonococcal urethritis	N=398 6 weeks	Primary: Persistence or recurrence of *Mycoplasma genitalium* infection Secondary: Not reported	Primary: From the initial study population enrolled, 36 men in the azithromycin group and 42 men in the doxycycline group tested positive at the initial study enrollment for *Mycoplasma genitalium*. Of those testing positive at initial follow-up (10 to 17 days post therapy), 13% (95% CI, 3 to 35) were from the azithromycin group compared to 55% in the doxycycline group (95% CI, 36 to 72; P=0.002). Of the 15 persistently *Mycoplasma genitalium* infected men who were clinically cured at the early initial follow-up visit, 47% experienced clinical relapse over the subsequent two to six weeks. Secondary: Not reported
Adair et al.[67] (1998) Azithromycin 1 g as a single dose	OL, RCT Pregnant females with positive deoxyribonucleic	N=106 3 weeks posttreatment	Primary: Response to therapy (eradication determined by	Primary: There was no significant difference in treatment efficacy between groups (88.1% compared to 93.0% for azithromycin and erythromycin respectively, P>0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs erythromycin 500 mg every 6 hours for seven days	acid antigen assays for *Chlamydia trachomatis*		deoxyribonucleic acid assay probe) Secondary: Not reported	Secondary: Not reported
Mikamo et al.[68] (1999) Clarithromycin 400 mg BID for 5, 7, or 14 days (CAM) vs erythromycin 600 mg TID for 5, 7, or 14 days (EM)	RCT Female patients 17 to 56 years of age with cervicitis caused by *Chlamydia trachomatis*	N=96 6 weeks	Primary: Eradication of *Chlamydia trachomatis* Secondary: Not reported	Primary: Eradication rates were significantly higher in the seven-day CAM group compared to the seven-day EM group. Eradication rates were significantly higher in the 14-day CAM group compared to the 14-day EM group. Secondary: Not reported
Respiratory Infections				
Pichichero et al.[69] (2003) Azithromycin 10 mg/kg on day one, followed by 5 mg/kg on days two to five	OL Patients 6 months to 20 years of age with a diagnosis of pertussis	N=34 21 days posttreatment	Primary: Bacteriologic eradication Secondary: Not reported	Primary: Microbiological eradication was observed in 97% of patients at days two to three of treatment and in 100% of patients at the 14 to21 day post-treatment follow-up visit. Secondary: Not reported
Albert et al.[70] (2011) Azithromycin 250 mg daily for one year vs	MC, PC, RCT Patients ≥40 years of age with COPD who were either using continuous supplemental oxygen or had received systemic	N=1,142 13 months	Primary: Time to the first acute exacerbation of COPD Secondary: Quality of life and adherence	Primary: The median time to the first exacerbation of COPD was 266 days (95% CI, 227 to 313) with azithromycin compared to 174 days (95% CI, 143 to 215) with placebo (P<0.001). The HR of having an acute exacerbation of COPD per patient-year in the azithromycin group as compared to the placebo group was 0.73 (95% CI, 0.63 to 0.84; P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo	glucocorticoids within the previous year, who had gone to an emergency room or had been hospitalized for an acute exacerbation of COPD, who had not had an acute exacerbation of COPD for at least 4 weeks before enrollment			The rates of acute exacerbations of COPD per patient-year were 1.48 with azithromycin and 1.83 with placebo (P=0.01). The frequency of acute exacerbations was lower among patients receiving azithromycin than among those receiving placebo (P=0.008). Secondary: The total SGRQ scores recorded at one year decreased a mean of 2.8 units in the azithromycin group compared to a mean of 0.6 units in the placebo group (P=0.004). No consistent changes were seen in the scores on the SF-36. The mean rate of adherence to the study medication was 67.3% in the azithromycin group and 66.9% in the placebo group (P=0.84).
Bacharier et al.[71] (2015) Azithromycin 12 mg/kg/day for five days vs placebo	DB, PC, PG, RCT Children 12 to 71 months of age with recurrent severe wheezing in the context of clinically significant lower RTIs that required systemic corticosteroids, an unscheduled physician office visit, an urgent or emergency department visit, or hospitalization	N=607 18 months	Primary: Number of RTIs not progressing to a severe lower RTI Secondary: Numbers of urgent care visits, emergency department visits, and hospitalizations; respiratory-related symptoms	Primary: The azithromycin group experienced significantly lower risk of progressing to severe lower RTI than the placebo group (HR, 0.64; 95% CI, 0.41 to 0.98; P=0.04; absolute risk for first RTI, 0.05 for azithromycin, 0.08 for placebo; risk difference, 0.03; 95% CI, 0.00 to 0.06), after adjustment for study site, age, modified asthma predictive index status,18 season during which the RTI occurred, and whether the child enrolled before or after the study was extended to 78 weeks. Secondary: Urgent care and emergency department visits occurred in 3.6% of participants receiving azithromycin and 5.4% of participants receiving placebo. There were 28 participants hospitalized for respiratory illnesses (azithromycin group, 13; placebo group, 15) over the duration of the trial. Azithromycin therapy decreased the overall severity of symptoms during severe lower RTIs compared with placebo, as reflected by lower mean total symptom scores over the duration of RTI, but not during episodes not progressing to severe lower RTI.
Jorgensen et al.[72] (2009) Azithromycin ER 2 g as a single dose	DB, MC, RCT Patients ≥13 years of age with group A β-hemolytic	N=598 Up to 45 days	Primary: Bacteriological response at the test of cure visit (days 24 to 28) in the	Primary: Bacteriological eradication was achieved in 85.4% of the patients receiving AZ-ER and in 81.4% of patients receiving AZ-IR (95% CI, -3.1 to 11.1).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(AZ-ER) vs azithromycin IR 500 mg once daily for three days (AZ-IR)	streptococcal pharyngitis or tonsillitis		bacteriological protocol population Secondary: Clinical cure rates at the test of cure visit and long term follow up visit (days 38 to 45)	Secondary: Clinical cure at the test of cure visit was 99% in the AZ-ER group and 96.7% in the AZ-IR group. The continued clinical cure rates at long term follow up were 92.1% and 95.2% for patients in the AZ-ER and AZ-IR treatment groups, respectively. One hundred percent of patients in the AZ-ER group and 98% in the AZ-IR group complied with active treatment.
Morris et al.[73] (2010) Azithromycin 30 mg/kg as a single dose vs amoxicillin 50 mg/kg/day in two divided doses for a minimum of seven days	RCT, SB Aboriginal children 6 months to 6 years of age with acute otitis media	N=320 Up to 21 days	Primary: Clinical failure (defined as persistent ear pain, bulging tympanic membrane or middle ear discharge) at the end of therapy visit (days six to 11), failure to improve (defined as no improvement in clinical signs at the end of therapy at the end of therapy visit (days six to 11) Secondary: Clinical and microbiological outcomes	Primary: At the end of therapy, 50% of patients receiving azithromycin and 54% of patients receiving amoxicillin were clinical failures (P=0.504). At the end of therapy, 45% of patients receiving azithromycin and 49% of patients receiving amoxicillin failed to improve (P=0.567). Secondary: No differences in clinical failure or failure to improve were indicated in a per protocol analysis (children seen before day 11 after commencement of treatment). Azithromycin significantly reduced the proportion of children with nasal carriage of *Streptococcus pneumoniae* compared to amoxicillin (P<0.001).
Henry et al.[74] (2003) Azithromycin 500	DB, DD, MC, RCT Patients 18 years of age or older with	N=936 28 days	Primary: Clinical success at end of study	Primary: Cure rates were 71.7% in the AZM-3 group, 73.4% in the AZM-6 group, and 71.3% in the AMC group. There was no significant difference between groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg daily for 3 days (AZM-3) vs azithromycin 500 mg daily for 6 days (AZM-6) vs amoxicillin-clavulanate 500 mg TID for 10 days (AMC)	acute bacterial sinusitis		Secondary: Not reported	Secondary: Not reported
Klapan et al.[75] (1999) Azithromycin 500 mg daily for three days vs amoxicillin-clavulanate 625 mg every 8 hours for 10 days	OL, RCT Patients 15 to 50 years of age with sinusitis	N=100 4 weeks	Primary: Clinical response and bacteriologic response Secondary: Not reported	Primary: Cure was established in 95% of patients in the azithromycin group and 74% of patients in the amoxicillin-clavulanate group at the end of therapy (day 10 to 12), and clinical improvement was seen in the remainder of patients in both groups (P=0.012 in favor of azithromycin). At the follow-up visit (four weeks), cure was established in 98% of patients in the azithromycin group and 91% in the amoxicillin-clavulanate group. No significant differences were observed between groups (P>0.05). There was no significant difference in bacteriologic response seen between groups (P=0.409). Secondary: Not reported
Marple et al.[76] (2010) Azithromycin ER 2 g as a single dose vs	MC, OL, RCT Patients ≥18 years of age with acute, uncomplicated, bacterial maxillary sinusitis based on	N=751 28 days	Primary: Symptom resolution at day five in the per protocol population Secondary:	Primary: At day five in the per protocol population, 29.7% of patients receiving azithromycin and 18.9% of patients receiving amoxicillin-clavulanate had symptom resolution (difference, 10.8%; 95% CI, 3.1 to 18.4). At day five in the intent to treat population, a significantly greater percentage of patients in the azithromycin group met the primary end point

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
amoxicillin-clavulanate 875-125 mg every 12 hours for 10 days	signs and symptoms lasting for 7 to 30 days		Time to resolution of symptoms, sinusitis-related quality of life, resource use, treatment success, and treatment satisfaction	(20.0%) than in the amoxicillin-clavulanate group (13.2%; difference, 6.8%; 95% CI, 1.5 to 12.2). Secondary: Over the course of the trial, both treatments led to similar rates of symptom resolution (HR, 1.16; 95% CI, 0.92 to 1.44). After 28 days, 67.4% of patients treated with azithromycin reported symptom resolution compared to 63.0% of patients receiving amoxicillin-clavulanate. In the per protocol population, 11.2% of patients reported receiving a prescription for a second antibiotic during the study period. The proportion of patients requiring additional antibiotics was similar in the azithromycin group (11.0%) and the amoxicillin-clavulanate group (11.3%). A similar number of patients reported unscheduled physician visits during the study in both treatment arms. Overall satisfaction with treatment was similar in the two treatment arms. Patients treated with azithromycin reported greater satisfaction with the convenience of the medication than did patients given amoxicillin-clavulanate (difference, 11.59; 95% CI, 8.78 to 14.40). Patients in the amoxicillin-clavulanate arm reported greater satisfaction with side effects than those treated with azithromycin (difference, −4.40; 95% CI, −8.13 to −0.66). More patients treated with azithromycin reported abdominal discomfort than did those receiving amoxicillin-clavulanate (70.76 vs 60.92%; P=0.02). There was no difference in the incidence of diarrhea among the treatment groups (P=0.50).
Arguedas et al.[77] (2011) Azithromycin ER 60 mg/kg as a single dose	DB, MC, RCT Patients 3 to 48 months of age with acute otitis media	N=923 28 to 64 days	Primary: Clinical response at the test of cure visit (days 12 to 14) in the bacteriologic	Primary: Clinical response at the test of cure visit was achieved in 80.5% of children in the azithromycin group compared to 84.5% in the amoxicillin-clavulanate group (difference, – 3.9%; 95% CI, –10.4 to 2.6). Azithromycin was found to be non-inferior to amoxicillin-clavulanate.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs amoxicillin-clavulanate 45-3.2 mg/kg every 12 hours for 10 days			eligible population Secondary: Bacterial response at other visits, compliance, and safety	Secondary: The eradication rate across all ages was 82.6% in the azithromycin group and 92% in the amoxicillin-clavulanate group (P=0.050). All patients receiving treatment with azithromycin received their single dose of active treatment; 59% of patients receiving amoxicillin-clavulanate received the full course of 20 doses. In the bacteriologic eligible population, 77% of patients in the amoxicillin-clavulanate arm were compliant with the full course of treatment compared to 100% of patients in the azithromycin group. Adverse events occurred in 56% of children treated with azithromycin ER and in 62.2% of children treated with amoxicillin-clavulanate. Most adverse events were of mild to moderate severity. Treatment-related vomiting was reported in 10.7% of patients receiving azithromycin and in 8.2% of patients receiving amoxicillin-clavulanate.
Panpanich et al.[78] (2008) Azithromycin vs amoxicillin or amoxicillin-clavulanate	MA Patients with acute lower respiratory tract infections	N=2,601 (15 trials) 10 to 14 days	Primary: Clinical failure Secondary: Microbial eradication, and adverse events	Primary: The pooled analysis of all trials showed that the incidence of clinical failure on day 10 to 14 in azithromycin group was 10.1% compared to 10.3% in the amoxicillin or amoxicillin-clavulanate group (RR, 1.09; 95% CI 0.64 to 1.85). Subgroup analysis stratified by age groups showed no significant difference of treatment effects between the azithromycin group and the amoxicillin or amoxicillin-clavulanate group in either adults (RR, 1.15; 95% CI, 0.60 to 2.20) or children (RR, 0.93; 95% CI, 0.45 to 1.94). Secondary: The pooled analysis showed that the incidence of microbial eradication in azithromycin group was 66.4% compared to 67.6% in amoxicillin or amoxicillin-clavulanate group. (RR, 0.95; 95% CI, 0.87 to 1.03). The overall incidence of adverse events in azithromycin group was 17.9% compared to 23.6% in amoxicillin or amoxicillin-clavulanate group (RR, 0.76; 95% CI, 0.57 to 1.00).
Swanson et al.[79] (2005)	DB, DD, MC, RCT	N=322	Primary: Clinical response	Primary: No significant differences in the clinical cure rates were found between

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Azithromycin 500 mg daily for three days vs clarithromycin 500 mg BID for 10 days	Patients with an acute exacerbation of chronic bronchitis	24 days	and bacteriologic response at the test of cure visit (21 to 24 days) Secondary: Not reported	groups at the test of cure visit (85% for azithromycin and 82% for clarithromycin). No significant differences in the bacteriologic response rates were found between groups at the test of cure visit. Secondary: Not reported
Venuta et al.[80] (1998) Azithromycin 10 mg/kg once daily for three days vs clarithromycin 7.5 mg/kg BID for 10 days	RCT, SB Patients 4 to 13 years of age diagnosed with streptococcal pharyngitis with a positive antigen test throat culture	N=174 20 days	Primary: Clinical response, bacteriologic response Secondary: Not reported	Primary: Cure rates were 95.9% in the azithromycin group and 96.8% in the clarithromycin group. There was no significant difference between groups. There was no significant difference in bacteriologic eradication rates between groups. Secondary: Not reported
Drehobl et al.[81] (2005) Azithromycin 2 g single dose vs clarithromycin ER 100 mg daily for seven days	DB, MC, RCT Patients 16 years of age and older with a diagnosis of pneumonia and suitable for outpatient treatment	N=499 35 days	Primary: Clinical response at the test of cure visit (day 14 to 21), bacteriologic response Secondary: Not reported	Primary: The clinical response at the test of cure visit was 92.6% in the azithromycin group and 94.7% in the clarithromycin group. No significant difference was found between groups. Bacteriologic eradication occurred in 91.8% of azithromycin patients and 90.5% of clarithromycin patients, although most bacteriologic responded were based on clinical response rather than follow-up cultures. No significant differences were seen between groups. Secondary: Not reported
O'Doherty et al.[82] (1998)	MC, RCT Patients 12 to 75	N=203 19 to 23 days	Primary: Clinical response and bacteriologic	Primary: A satisfactory clinical response (judged as cured or improved) was observed in 94% of azithromycin patients and 95% of clarithromycin

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Azithromycin 500 mg daily for three days vs clarithromycin 250 mg BID for 10 days	years of age with clinically diagnosed community-acquired pneumonia		response Secondary: Not reported	patients (P=0.518). In the azithromycin patients, 97% of pathogens were considered eradicated and 91% of pathogens were considered eradicated in the clarithromycin group. Secondary: Not reported
Muller[83] (1993) Azithromycin 500 mg daily for three days vs clarithromycin 250 mg BID for 10 days	MC, OL, RCT Patients 12 years of age and older with acute upper respiratory infections	N=380 14 to 28 days	Primary: Clinical response and bacteriologic response Secondary: Not reported	Primary: No significant difference was found between the two groups in clinical response for any diagnosis (P>0.05). Bacteriologic response was also similar between groups. Secondary: Not reported
Aoyama et al.[84] (1996) Azithromycin 10 mg/kg daily for five days vs clarithromycin 10 mg/kg/day in 2 divided doses for seven days vs	CS Patients with culture- positive pertussis; each patient was matched with 2 erythromycin-treated patients with culture-positive pertussis recruited from historical controls	N=17 2 weeks posttreatment	Primary: Eradication rates Secondary: Not reported	Primary: Eradication rates one week after treatment were 100% in the clarithromycin and 89% in the matched erythromycin group, and 100% in the azithromycin group and 81% in the matched erythromycin group. Eradication rates two weeks after treatment were 100% in all groups. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
erythromycin standard regimens 40 to 50 mg/kg/day for 2 weeks				
Altunaiji et al.[85] (2007) Azithromycin vs clarithromycin vs erythromycin	MA Patients with pertussis	N=2,197 (13 trials) Variable duration	Primary: Clinical response rates Secondary: Not reported	Primary: Short-term antibiotics (azithromycin for three to five days, clarithromycin for seven days, or erythromycin for seven days) were as effective as long-term antibiotics (erythromycin for 10 to 14 days) in eradicating *Bordetella pertussis* from the nasopharynx (RR, 1.02; 95% CI, 0.98 to 1.05), but were associated with fewer adverse events (RR, 0.66; 95% CI, 0.52 to 0.83). Sulfamethoxazole-trimethoprim for seven days was also effective. There were no differences in clinical outcomes or microbiological relapse between short and long-term antibiotics. Secondary: Not reported
Castaldo et al.[86] (2003) Azithromycin 500 mg on day one, then 250 mg daily for days two to five vs dirithromycin 500 mg daily for five days	RCT, SB, PG, MC Patients 35 years of age and older who are smokers or ex-smokers with an acute exacerbation of chronic bronchitis	N=86 35 days	Primary: Clinical success rates at the early (seven to 10 days) and the late (25 to 35 days) posttreatment visits Secondary: Not reported	Primary: Clinical efficacy was observed in 84.8% of patients in the dirithromycin group and 75.7% in the azithromycin group at the early post-treatment visit. No significant difference was observed. Clinical efficacy was observed in 95.5% of patients in the dirithromycin group and 86.5% in the azithromycin group at the late post-treatment visit. No significant difference was observed. Secondary: Not reported
Schonwald et al.[87] (1990) Azithromycin 250 mg BID on day one and 250 mg daily on days two	MC, OL, RCT Patients 12 years of age and older with a diagnosis of atypical pneumonia	N=101 21 days posttreatment	Primary: Clinical response to treatment Secondary: Not reported	Primary: There was no significant difference between the azithromycin group and erythromycin group in clinical response to treatment. Very good efficacy was reported in 82% of azithromycin patients and 84% of erythromycin patients.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
to five vs erythromycin 500 mg QID for 10 days				Good efficacy was reported in 18% of azithromycin patients and 16% of erythromycin patients. No clinical failures were reported in either group. Secondary: Not reported
Griffin et al.[88] (2010) Levofloxacin vs azithromycin or clarithromycin	RETRO Patients with Legionella pneumonia	N=39 Variable duration	Primary: Time to clinical stability and length of hospital stay Secondary: Not reported	Primary: The mean time to clinical stability for the macrolide group was 5.1 and 4.3 days for the levofloxacin group (P=0.43). The mean length of hospital stay for the macrolide group was 12.7 and 8.9 days for the levofloxacin group (P=0.10). Secondary: Not reported
Rechtweg et al.[89] (2004) Clarithromycin 500 mg BID for 14 days vs amoxicillin-clavulanate 500 mg TID for 14 days (A-C)	RCT, SB Patients with uncomplicated acute rhinosinusitis	N=22 4 weeks	Primary: Results of five surveys completed by the patients Secondary: Not reported	Primary: The allergy outcomes survey failed to demonstrate a significant improvement from baseline in any patient in either group (P>0.48). At day 28, the rhinoconjunctivitis quality of life questionnaire showed significant improvement in symptoms from baseline in both groups (P=0.003). The SF-36 failed to demonstrate a significant change in patients' global perception of their health at either day 14 or day 28 for all patients in both groups (P>0.25). The symptom severity survey indicated that there was a significant improvement in the clarithromycin patients at day 14 (P=0.02) and day 28 (P=0.03). The A-C patients demonstrated a significant improvement at day 28 (P=0.05), but not at day 14 (P=0.54). The visual analogue scale failed to demonstrate a significant improvement in symptoms at day 14 and day 28 in either group (P>0.30). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Not reported
Gotfried et al.[90] (2005) Clarithromycin 500 mg BID for seven days vs clarithromycin ER 1,000 mg daily for five days	DB, MC, RCT Patients 40 years of age and older with a presumptive diagnosis of an acute exacerbation of chronic bronchitis	N=485 40 days	Primary: Clinical cure, bacteriologic cure, target pathogen eradication rates at test of cure visit (days 14 to 40) Secondary: Not reported	Primary: Clinical cure rates were similar between groups (84% for both groups). Bacteriologic cure rates were 89% in the regular release group and 87% in the extended-release group. The overall pathogen eradication rates were 89% in the regular release group and 88% in the extended-release group. Secondary: Not reported
Gotfried et al.[91] (2007) Clarithromycin ER 1,000mg once daily for five days vs clarithromycin IR 500 mg BID for seven days or telithromycin 800 mg once daily for five days	DB, MC, RCT Patients ≥35 years of age with a presumptive diagnosis of acute bacterial exacerbation of chronic bronchitis	N=818 8 to 40 days	Primary: Clinical bacteriological responses Secondary: Not reported	Primary: The clinical cure rate in clinically evaluable patients at the follow-up visit was 90% each for the clarithromycin ER group and the comparator group (95% CI, -4.4 to 4.3). No significant between-group differences were observed in clinically evaluable patients based on resolution or resolution/improvement at the follow-up visit of the most common pretreatment signs/symptoms. The overall target pathogen eradication rate was 92% for the clarithromycin ER group and 93% for the comparator group at the follow-up visit (95% CI, –6.5 to 3.6). The bacteriological cure rate in clinically and bacteriologically evaluable patients was 92% for the clarithromycin ER group and 93% for the comparator group at the follow-up visit (95% CI, –7.3 to 3.9). The study drugs were well tolerated, with 1.9% of clarithromycin ER-treated patients and 1.5% of comparator-treated patients prematurely discontinuing treatment due to a drug-related adverse event(s). The overall incidence of drug-related adverse events was 18% in the clarithromycin ER group and 24% in the comparator group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				The most common drug-related adverse events (>2% of patients) or those with a statistically significant difference in incidence between groups were: abdominal pain (0.2 and 1.7% in the clarithromycin ER and comparator groups, respectively; P=0.037), diarrhea (2.4 and 4.7%, respectively; P=NS), nausea (2.7 and 4.4%, respectively; P=NS), and abnormal taste (2.4 and 4.7%, respectively; P=NS). Clarithromycin ER-treated patients reported fewer episodes of abdominal pain than did patients treated with a comparator agent (0.2 vs 1.7%, respectively; P=0.037). Secondary: Not reported
Lee et al.[92] (2008) Clarithromycin 15 mg/kg/day BID vs erythromycin 30-50 mg/kg/day QID	RCT Children <15 years of age with community-acquired pneumonia	N=97 10 days	Primary: Clinical cure rate Secondary: Adverse events	Primary: All children with mycoplasma or chlamydia infections were cured clinically at the end of the study period. Delayed defervescence was observed in 18% of clarithromycin-treated children and in 20% of erythromycin-treated children (P>0.05). Secondary: Gastrointestinal side effects, including vomiting, abdominal pain and diarrhea, were observed in 6% of children receiving clarithromycin and in 22% receiving erythromycin (P=0.039).
Esposito et al.[93] (1998) Erythromycin ethylsuccinate 15 mg/kg TID for 10 days vs cefaclor 25 mg/kg BID for 10 days	RCT Patients 2 to 12 years of age with acute pharyngotonsillitis	N=245 30 days	Primary: Clinical outcomes and bacteriologic outcomes Secondary: Not reported	Primary: On day 10, clinical cure and microbiologic eradication was observed in 91.9% of patients in the cefaclor group, 90.5% in the amoxicillin-clavulanate group, and 76.8% in the erythromycin group. At day 30, bacteriologic recurrence was observed in five patients in the cefaclor group, three in the amoxicillin-clavulanate group, and four in the erythromycin group. The clinical and bacteriologic cure rates were significantly higher in the cefaclor and amoxicillin-clavulanate groups compared to the erythromycin group (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs amoxicillin-clavulanate 15 mg/kg TID for 10 days				Secondary: Not reported
Macfarlane et al.[94] (1983) Erythromycin lactobionate 300 mg IV every 6 hours for 48 hours, followed by erythromycin stearate 500 mg orally QID for seven days vs ampicillin 500 mg IV every 6 hours for 48 hours, followed by amoxicillin 500 mg orally QID for seven days	DB, RCT Patients <80 years of age with primary pneumonia, including Legionnaires' disease	N=122 9 days	Primary: Clinical response to therapy (categorized as uncomplicated recovery, complicated recovery, or fatality) Secondary: Not reported	Primary: Clinical response to therapy in all categories was similar between the groups. Secondary: Not reported
Rodriguez et al.[95] (1985) Erythromycin-sulfisoxazole vs amoxicillin	CS, RCT Patients with acute otitis media	N=145 28 days	Primary: Cure rates Secondary: Cure rates based on organism, occurrence of middle ear effusions	Primary: Cure rates at 10 to 14 days for infections due to all organisms was 83% in the amoxicillin group and 89% in the erythromycin-sulfisoxazole group. Secondary: Cure rates in patients infected with *Haemophilus influenzae* were 84% in the amoxicillin group and 83% in the erythromycin-sulfisoxazole group. Cure rates in patients infected with *Streptococcus pneumoniae* were 82%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				in the amoxicillin group and 98% in the erythromycin-sulfisoxazole group. Cure rates in patients infected with ampicillin-resistant *Haemophilus* were 100% in the amoxicillin group (1/1) and 88% in the erythromycin-sulfisoxazole group (7/8), and one patient had persistent otitis media at day 10. By day 10 to 14, 38% of patients in the amoxicillin group had a middle ear effusion compared to 48% in the erythromycin-sulfisoxazole group. By day 28, 10% of patients in the amoxicillin group had a middle ear effusion compared to 16% in the erythromycin-sulfisoxazole group.
van Rensburg et al.[96] (2005) Telithromycin 800 mg daily for seven days	OL Patients ≥13 years of age with community-acquired pneumonia	N=831 24 days	Primary: Clinical response, bacteriologic response Secondary: Not reported	Primary: Clinical cure and bacteriologic eradication were seen in 15 of 16 patients infected with erythromycin-resistant *Streptococcus pneumonia* and/or penicillin- resistant *Streptococcus pneumonia*. The overall clinical cure rate was 89.3% and bacteriologic eradication was observed in 87.6% of patients. Secondary: Not reported
van Rensburg et al.[97] (2005) Telithromycin 800 mg daily for 5 to 10 days	MA Patients ≥18 years of age with community-acquired pneumonia	N=327 (9 trials) 24 to 28 days	Primary: Clinical response, bacteriologic response Secondary: Not reported	Primary: The clinical cure rate with telithromycin was 91.2%. Thirty-five patients had infections caused by strains resistant to erythromycin and of these, clinical cure was established in 88.6%. Clinical failure was recorded in 4 patients with penicillin- and/or erythromycin-resistant pneumococci. Thirteen patients had penicillin- and/or erythromycin- resistant pneumococcal bacteremia. Clinical cure was established in 84.6% of resistant isolates compared to 90.2% of all pneumococcal bacteremia. The overall rate of satisfactory bacteriologic outcomes was 90.4%. In patients infected with isolates demonstrating reduced susceptibility to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				penicillin and/or erythromycin, eradication was achieved in 93.4%. Secondary: Not reported
Aubier et al.[98] (2002) Telithromycin 800 mg daily for five days vs amoxicillin-clavulanate 500 mg TID for 10 days	DB, PG, RCT Patients ≥18 years of age with an acute exacerbation of chronic bronchitis	N=325 31 to 36 days	Primary: Clinical cure rate at the test of cure visit (days 17 to 21) Secondary: Clinical cure rate at the late post-therapy visit (days 31 to 36), bacteriologic outcomes at the test of cure visit (days 17 to 21) and late post-therapy visit (days 31 to 36)	Primary: There was no significant difference in clinical cure rates between groups at the test of cure visit (86.1% for telithromycin and 82.1% for the amoxicillin-clavulanate group). Secondary: There was no significant difference in clinical cure rates at the late post-therapy visit between groups (78.1% for telithromycin and 75.0% for amoxicillin-clavulanate). Bacteriologic outcome was judged as satisfactory in 69.2% of patients in the telithromycin group and 70.0% of patients in the amoxicillin-clavulanate group.
Desrosiers et al.[99] (2008) Telithromycin 800 mg once daily for five days vs amoxicillin-clavulanate 875-125 mg BID for 10 days	MC, OL Patients ≥18 years old with clinical and radiological diagnosis of acute bacterial sinusitis	N=298 Up to 49 days	Primary: Clinical success, adverse events, and quality of life Secondary: Not reported	Primary: The PP clinical success rate measured at the test-of-cure visit was 88.6% with telithromycin compared to 88.8% in the amoxicillin-clavulanate treatment group (95% CI, -8.9 to 8.5). At the follow-up visit (days 41 to 49), 84.6% of patients in the telithromycin group achieved clinical success, compared to 84.8% of those in the amoxicillin–clavulanate group. Median times to reduction of total symptom scores were shorter for telithromycin vs amoxicillin–clavulanate (seven days vs eight days [75% reduction] and four days vs five days [50% reduction] with the difference being statistically significant for the 50% reduction (P=0.044). Treatment-emergent adverse events occurred in 20.7% of telithromycin-

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				treated patients vs 31.8% of amoxicillin-clavulanate-treated patients (P=0.034). In the baseline SF-36 health questionnaire, 75.5% of patients (209/278) described themselves as feeling much or somewhat worse than a week earlier (telithromycin, 74.2% and amoxicillin–clavulanate, 76.6%). Secondary: Not reported
Siempos et al.[100] (2007) Quinolones vs amoxicillin-clavulanate vs macrolides	MA Patients >18 years old with acute bacterial exacerbation of chronic bronchitis	N=7,405 (19 RCT) 26 weeks	Primary: Treatment success, hospitalization, mortality, adverse events Secondary: Not reported	Primary: There was no difference regarding treatment success in intention-to-treat and clinically evaluable patients between macrolides and quinolones, amoxicillin-clavulanate and quinolones, or amoxicillin-clavulanate and macrolides. The treatment success in microbiologically evaluable patients was lower for macrolides compared to quinolones (OR, 0.47; 95% CI, 0.31 to 0.69). There was no difference in the need for hospitalization for patients treated with macrolides compared to patients treated with quinolones (OR, 1.37; 95% CI, 0.75 to 2.5). Data regarding need for hospitalization were only available in two trials comparing amoxicillin-clavulanate with quinolones, and in one trial comparing amoxicillin-clavulanate with macrolides. There was no difference in mortality between macrolide-treated patients with acute bacterial exacerbation of chronic bronchitis and those treated with quinolones (OR, 1.96; 95% CI 0.45to8.51). Data on mortality were provided in only two trials comparing amoxicillin-clavulanate with quinolones. Fewer quinolone-recipients experienced a recurrence of acute bacterial exacerbation of chronic bronchitis after resolution of the initial episode compared to macrolide-recipients during the 26-week period following therapy. Adverse effects in general were similar between macrolides and quinolones. Administration of amoxicillin-clavulanate was associated with

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				more adverse effects than quinolones (OR, 1.36; 95% CI 1.01to1.85). Secondary: Not reported
Miscellaneous Infections				
Dunne et al.[101] (2000) Azithromycin 250 mg daily vs azithromycin 600 mg daily vs clarithromycin 500 mg BID	DB, DD, MC, RCT Patients ≥13 years of age with a positive blood culture for *Mycobacterium avium* complex within the previous 2 months, infected with the human immunodeficiency virus and expected to survive for at least 2 months, and who had not received therapy for *Mycobacterium avium* complex since the positive blood culture	N=239 24 weeks of treatment with follow-up every 3 months	Primary: Sterilization (two consecutive negative blood cultures for *Mycobacterium avium* complex at week 24) Secondary: Time to sterilization, change from baseline in level of mycobacteremia, durability of sterilization, mortality, clinical response judged by the investigator, change in quality of life, and patient tolerance for each regimen	Primary: No significant differences were found between the azithromycin 600 mg group and the clarithromycin group in the primary endpoint. Secondary: No significant differences were found between the azithromycin 600 mg group and the clarithromycin group in any secondary endpoint. This study did not enroll the target of 200 participants; therefore, the power of the study to conclude equivalence between the two arms was only 61%.
Peirce et al.[102] (1996) Clarithromycin 500 mg BID vs	DB, MC, PC, RCT Patients >12 years of age with human immunodeficiency virus infection	N=682 10 months	Primary: Time from randomization to the detection of disseminated infection with *Mycobacterium avium* complex as	Primary: *Mycobacterium avium* complex infection developed in 19 of the 333 patients (6%) in the clarithromycin group and in 53 of the 334 patients (16%) in the placebo group (P<0.001). Secondary: During the follow-up period of 10 months, 32% of patients in the clarithromycin group died and 41% in the placebo group died (P=0.026).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
placebo			evidenced by a positive blood culture or positive culture at another usually sterile site Secondary: Effect of clarithromycin on survival	
Benson et al.[103] (2000) Clarithromycin 500 mg BID vs rifabutin 450 mg once daily vs combination therapy at the same doses	DB, MC, PC, RCT Patients 12 years of age and older with human immunodeficiency virus infection and no signs or symptoms of *Mycobacterium avium* complex disease	N=1,216 ~595 days	Primary: Development of *Mycobacterium avium* complex disease as evidenced by a positive blood culture or positive culture at another usually sterile site Secondary: Death, treatment-limiting adverse effects	Primary: Of those patients who developed *Mycobacterium avium* complex disease, 9% were in the clarithromycin group, 15% were in the rifabutin group, and 7% were in the combination group. Patients who received rifabutin were more likely to develop *Mycobacterium avium* complex compared to patients in the clarithromycin group (P=0.005) or the combination group (P=0.0003). There was no significant difference in the time to development of *Mycobacterium avium* complex disease for clarithromycin compared to combination therapy (P=0.36). Secondary: There were no differences between groups in survival rates (P>0.28). Patients in the combination therapy group were more likely to discontinue treatment compared to patients in the clarithromycin group and the rifabutin group (P<0.0001). There was no significant difference between the rifabutin and clarithromycin group (P=0.29).
Stenberg et al.[104] (1991) Erythromycin ethylsuccinate 200 mg divided into two doses for 10	RCT, SB Neonates and adults with chlamydial conjunctivitis	N=55 1 month posttreatment	Primary: Clinical response, bacteriologic response Secondary: Not reported	Primary: All patients in the neonate and adult groups were cured except for one in the neonatal group and three in the adult group. There was no significant difference in the clinical cure rate between erythromycin and roxithromycin. Ten patients in the erythromycin group were still culture-positive at the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
days (neonates) or erythromycin stearate 1,000 mg divided into two doses for 10 days (adults) vs roxithromycin 50 mg divided into 2 doses for 10 days (neonates) or 300 mg divided into 2 doses for 10 days (adults)				follow-up compared to six patients in the roxithromycin group. Secondary: Not reported

Drug regimen abbreviations: BID=twice daily, ER=extended release, IM=intramuscular, IR=immediate release, IV=intravenous, QID=four times daily, TID=three times daily
Study abbreviations: CI=confidence interval, COPD=chronic pulmonary respiratory disease, CS=comparative study, DB=double blind, DD=double dummy, *H pylori=Helicobacter pylori*, HR=hazard ratio, MA=meta-analysis, MC=multi-center, NI=non-inferiority, OL=open label, OR=odds ratio, PC=placebo controlled, PG=parallel group, PRO=prospective trial, R=randomized, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, RTI=respiratory tract illness, SB=single blind, SC=single center, SF-36=short form-36, SGRQ=St. George's Respiratory Questionnaire

Additional Evidence

Dose Simplification:
Several studies have assessed the effects of dosing regimens on compliance with antibiotics. Adair et al. compared azithromycin as a single dose to erythromycin administered every six hours in the treatment of *Chlamydia* infections in pregnant females.[67] Significantly more patients were compliant with the azithromycin regimen compared to the erythromycin regimen; however, efficacy was similar among the treatment groups. Significantly fewer gastrointestinal side effects were noted in the azithromycin group compared to the erythromycin group. Dey et al. compared azithromycin as a single dose to azithromycin once daily for five days in the treatment of uncomplicated skin and skin structure infections. No significant difference was found between groups in frequency of clinical cure, clinical response, or adverse events.[42]

Lebel et al. compared clarithromycin administered twice daily to erythromycin administered three times daily in children with pertussis.[105] Efficacy was similar among the treatment groups; however, patients in the clarithromycin group experienced significantly fewer adverse events compared to patients in the erythromycin group (45 and 62%, respectively; P=0.035). Compliance was significantly higher in the clarithromycin group compared to the erythromycin group (98.5 vs 88.6%, respectively; P<0.001).[105]

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

Impact on Physician Visits:
Milstone et al. analyzed outcomes in patients with an acute exacerbation of chronic bronchitis receiving treatment with azithromycin for three days or usual care for five to 14 days.[106] The usual care group included quinolones, amoxicillin-clavulanate, clarithromycin, or β-lactams. Patients completed two quality-of-life questionnaires. Both groups recorded similar improvements in signs and symptoms of infection, absenteeism, use of concomitant respiratory medications, health care resource utilization, compliance, and treatment satisfaction.

Burgess et al. analyzed outcomes in patients with pneumonia who were initially treated with erythromycin, clarithromycin, azithromycin, and/or a non-pseudomonal third generation cephalosporin.[107] Results indicate no significant difference in patients who did or did not receive a macrolide in terms of comorbid illness, length of hospital stay, length of intravenous antibiotic therapy or mortality.

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 Macrolides

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Azithromycin	extended-release suspension, injection, powder for suspension, suspension, tablet	Zithromax®*, Zithromax Tri-Pak®*, Zmax®	$$-$$$	$$$
Clarithromycin	extended-release tablet, suspension, tablet	Biaxin®*	$$$-$$$$	$$$
Erythromycin base	coated-particle tablet, delayed-release capsule, delayed-release tablet, tablet	PCE®	$$$	$$$$$
Erythromycin ethylsuccinate	suspension, tablet	E.E.S. 200®, E.E.S. 400®*, EryPed 200®, EryPed 400®	$$$$$	$$$$
Erythromycin lactobionate	injection	Erythrocin Lactobionate®	$$$$	N/A
Erythromycin stearate	tablet	Erythrocin Stearate®	$$$$$	N/A
Fidaxomicin	tablet	Dificid®	$$$$$	N/A
Telithromycin	Tablet	Ketek®	$$$$$	N/A

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

X. Conclusions

The macrolides are approved to treat a variety of infections, including dermatologic, gastrointestinal, genitourinary, respiratory, as well as a variety of miscellaneous infections.[1-12] Several of the macrolides are available in a generic formulation, with the exception of erythromycin lactobionate, erythromycin stearate, fidaxomicin, and telithromycin.

There are many guidelines that define the appropriate place in therapy for the macrolides. The agent that is recommended is dependent upon the infectious organism being treated and the corresponding spectrum of activity of the macrolide. The macrolides are recommended as specific therapy for the treatment of susceptible pathogens causing encephalitis, skin and soft-tissue infections, infectious diarrhea, *Helicobacter pylori* infections, *Clostridium difficile,* sexually transmitted diseases, pertussis, community-acquired pneumonia, as well as prophylaxis and treatment of disseminated *Mycobacterium avium* disease in patients with human immunodeficiency virus infection.[15-17, 18-29,36-40] They are recommended as an alternative treatment option for otitis media, pharyngitis, sinusitis, infectious exacerbations of chronic obstructive pulmonary disease, as well as for the prophylaxis of rheumatic fever.[18,30-35] Clinical trials have demonstrated comparable efficacy among the macrolides for the treatment of genital ulcers, upper/lower respiratory tract infections, and disseminated *Mycobacterium avium* disease.[62,63,67,68,79-87,92,.101] The macrolides have also been shown to be comparable in efficacy to antibacterial agents in other classes.[43,44,59-61,64-66,73-78,88,89,93-95,98-100,103,104]

Safety concerns with telithromycin have led to changes in the prescribing information, including stronger warnings regarding hepatotoxicity, visual disturbances, and loss of consciousness.[12] There have been reports of fatal and life-threatening respiratory failure in patients with myasthenia gravis; therefore, telithromycin is contraindicated in this population. This agent is only indicated for the treatment of community-acquired pneumonia and there is a lack of data demonstrating clinical advantages over other macrolides.

Therefore, all brand macrolides 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. Telithromycin possesses an extensive adverse effect profile compared to the other brands and generics products in the class (if applicable) and should be managed through the existing medical justification portion of the prior authorization process.

XI. Recommendations

No brand macrolide 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.

No brand telithromycin product is recommended for preferred status, regardless of cost.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Penicillins
AHFS Class 081216
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I. Overview

The penicillins are approved to treat a variety of infections, including central nervous system, dermatologic, gastrointestinal, genitourinary, respiratory, as well as several miscellaneous infections.[1-11] They are classified into five groups based on their spectrum of activity, including natural penicillins, penicillinase-resistant penicillins, aminopenicillins, carboxypenicillins, and ureidopenicillins.[12] Penicillins inhibit the synthesis of the bacterial peptidoglycan cell wall by binding to specific penicillin-binding proteins located inside the bacterial cell wall.

The natural penicillins (penicillin G and penicillin V) are active against many gram-positive and gram-negative cocci, gram-positive rods, and most anaerobes.[13] However, they are readily hydrolyzed by the enzyme penicillinase and are ineffective against most strains of *Staphylococcus aureus*. Penicillinase-resistant penicillins (dicloxacillin, nafcillin, and oxacillin) have a narrower spectrum of activity than the natural penicillins. They are primarily active against penicillinase-producing strains of gram-positive cocci, particularly *Staphylococcus* species. Aminopenicillins (amoxicillin and ampicillin) have an extended spectrum of activity compared to the natural penicillins and penicillinase-resistant penicillins.[13] They are active against gram-negative bacilli, but not against penicillinase-producing staphylococci. They are also inhibitors of β-lactamases of gram-negative bacilli. Piperacillin (ureidopenicillin) is active against *Pseudomonas aeroginosa*.[12] Its spectrum of activity is similar to the aminopenicillins; however, it has additional activity against gram-negative aerobic rods. It is susceptible to inactivation by beta-lactamases.

Bacteria have developed several mechanisms to counter the effects of penicillins. The most significant is the production of β-lactamases, which are enzymes that hydrolytically disrupt the β-lactam ring of the penicillin, rendering the penicillin ineffective. Another mechanism of resistance includes alteration of the penicillin-binding proteins within the bacteria so that their affinity for penicillins is decreased. Due to increased bacterial resistance, penicillins are combined with β-lactamase inhibitors, such as clavulanate, sulbactam, and tazobactam.[13] The β-lactamase inhibitors have a high, irreversible binding affinity for the β-lactamase enzyme and prevent hydrolysis of the penicillin β-lactam ring. They also bind to the penicillin-binding proteins of the bacteria, increasing the effectiveness of penicillin. However, they possess minimal antimicrobial activity by themselves; therefore, they are not used as monotherapy.[13]

The penicillins that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. The majority of the penicillins are available in a generic formulation, with the exception of penicillin G benzathine (with or without penicillin G procaine). This class was last reviewed in August 2014.

Table 1. Penicillins Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Amoxicillin	capsule, chewable tablet, extended-release tablet, suspension, tablet	Moxatag®*	amoxicillin
Ampicillin	capsule, injection, suspension	N/A	ampicillin
Dicloxacillin	capsule	N/A	dicloxacillin
Nafcillin	injection	N/A	nafcillin
Oxacillin	injection	N/A	oxacillin
Penicillin G benzathine	injection	Bicillin L-A®	none
Penicillin G potassium	injection	Pfizerpen®*	penicillin G potassium
Penicillin G procaine	injection	N/A	penicillin G procaine
Penicillin G sodium	injection	N/A	penicillin G sodium

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Penicillin V potassium	solution, tablet	N/A	penicillin V potassium
Combination Products			
Amoxicillin and clavulanate	chewable tablet, extended-release tablet, suspension, tablet	Augmentin®*, Augmentin XR®*	amoxicillin and clavulanate
Ampicillin and sulbactam	injection	Unasyn®*	ampicillin and sulbactam
Penicillin G benzathine and penicillin G procaine	injection	Bicillin C-R®	none
Piperacillin and tazobactam	injection	Zosyn®*	piperacillin and tazobactam

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

The penicillins have been shown to be active against the strains of microorganisms 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 penicillins that are noted in Tables 5 and 6. 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 Single Entity Penicillins[1-11]

Organism	Amoxicillin	Ampicillin	Dicloxacillin	Nafcillin	Oxacillin	Penicillin G	Penicillin V
Gram-Positive Aerobes							
Bacillus anthracis						✔ §	
Corynebacterium diphtheriae						✔ §	
Enterococcus faecalis	✔ *						
Enterococcus species		✔					
Erysipelothrix insidiosa						✔ §	
Listeria monocytogenes		✔				✔ §	
Staphylococcus aureus		✔					
Staphylococcus species	✔ *	✔	✔	✔	✔	✔ §	
Streptococcus pneumoniae	✔ *	✔					
Streptococcus pyogenes	✔ ‡						
Staphylococcus species						✔ †§	✔
Streptococcus species	✔ *	✔					✔
Gram-Negative Aerobes							
Alcaligenes faecalis						✔ §	
Enterobacter species						✔ §	
Escherichia coli	✔ *	✔				✔ §	
Haemophilus influenzae	✔ *	✔					
Helicobacter pylori	✔ *						
Neisseria gonorrhoeae	✔ *	✔				✔ §	
Neisseria meningitidis		✔					
Pasteurella multocida						✔ §	
Proteus mirabilis	✔ *	✔				✔ §	
Salmonella species		✔				✔ §	
Salmonella typhosa		✔					
Shigella species		✔				✔ §	
Spirillum minus						✔ §	
Streptobacillus moniliformis						✔ §	
Anaerobes							
Actinomyces species						✔ §	
Clostridium species						✔ §	
Fusobacterium species						✔ §	✔
Treponema pallidum						✔ §	

*Immediate-release formulation.
‡Extended-release formulation.
†Intramuscular formulation.
§Intravenous formulation.

Table 3. Microorganisms Susceptible to the Combination Penicillins[1-12]

Organism	Amoxicillin and Clavulanate	Ampicillin and Sulbactam	Piperacillin and Tazobactam
Gram-Positive Aerobes			
Staphylococcus aureus		✔	✔
Staphylococcus epidermidis			
Streptococcus pneumoniae	✔ ‡		
Gram-Negative Aerobes			
Acinetobacter baumannii			✔
Acinetobacter calcoaceticus		✔	
Citrobacter species			
Enterobacter cloacae			
Enterobacter species	✔ *	✔	
Escherichia coli	✔ *	✔	✔
Haemophilus influenzae	✔ *‡		✔
Haemophilus parainfluenza	✔ ‡		
Klebsiella pneumoniae	✔ ‡	✔	✔
Klebsiella species	✔ *	✔	
Moraxella catarrhalis	✔ *‡		
Proteus mirabilis		✔	
Pseudomonas aeruginosa			✔
Pseudomonas species			
Serratia marcescens			
Anaerobes			
Bacteroides fragilis		✔	✔
Bacteroides species		✔	
Prevotella melaninogenicus			

*Immediate-release formulation.
‡Extended-release formulation.

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the penicillins are summarized in Table 4.

Table 4. Treatment Guidelines Using the Penicillins

Clinical Guideline	Recommendation(s)

European Society of Cardiology: **Guidelines for the Management of Infective Endocarditis (2015)**[14]	Main principles of prevention if infective endocarditis
	• The principle of antibiotic prophylaxis when performing procedures at risk of infective endocarditis (IE) in patients with predisposing cardiac conditions is maintained.
	• Antibiotic prophylaxis must be limited to patients with the highest risk of IE undergoing the highest risk dental procedures (dental procedures requiring manipulation of the gingival or periapical region of the teeth or perforation of the oral mucosa).
	  o Patients with a prosthetic valve, including transcatheter valve, or a prosthetic material used for cardiac valve repair.
	  o Patients with previous IE.
	  o Patients with congenital heart disease.
	• Good oral hygiene and regular dental review are more important than antibiotic prophylaxis to reduce the risk of IE.
	• Aseptic measures are mandatory during venous catheter manipulation and during any invasive procedures in order to reduce the rate of health care-associated IE.
	• Recommended prophylaxis for dental procedures at high-risk:
	  o Single-dose amoxicillin or penicillin 30 to 60 minutes before procedure.
	  o If allergy to penicillin or ampicillin, single-dose clindamycin 30 to 60 minutes before procedure.
	
	Antimicrobial therapy: principles
	• The treatment of infective endocarditis relies on the combination of prolonged antimicrobial therapy and - in about half of patients - surgical eradication of the infected tissues.
	• Prolonged therapy with a combination of bactericidal drugs is the basis of IE treatment. Drug treatment of prosthetic valve endocarditis (PVE) should last longer (at least six weeks) than that of native valve endocarditis (NVE) (two to six weeks).
	• In both NVE and PVE, the duration of treatment is based on the first day of effective antibiotic therapy, not on the day of surgery. A new full course of treatment should only start if valve cultures are positive, the choice of antibiotic being based on the susceptibility of the latest recovered bacterial isolate.
	• The indications and pattern of use of aminoglycosides have changed. They are no longer recommended in staphylococcal NVE because their clinical benefits have not been demonstrated but they can increase renal toxicity; and, when they are indicated in other conditions, aminoglycosides should be given in a single daily dose in order to reduce nephrotoxicity.
	• New antibiotic regimens have emerged in the treatment of staphylococcal IE, including daptomycin and the combination of high-doses of cotrimoxazole plus clindamycin, but additional investigations are necessary in large series before they can be recommended in all patients.
	
	Antimicrobial therapy: regimens
	• Antibiotic treatment of infective endocarditis due to oral streptococci and *Streptococcus* bovis group:
	  o Penicillin-susceptible strains:
	  ▪ Penicillin G, amoxicillin, or ceftriaxone for four weeks.
	  ▪ Penicillin G, amoxicillin, or ceftriaxone plus gentamicin or netilmicin for two weeks.
	  ▪ Vancomycin for four weeks (in beta-lactam allergic patients).

Clinical Guideline	Recommendation(s)
	o Penicillin-resistant strains: ▪ Penicillin G, amoxicillin, or ceftriaxone for four weeks plus gentamicin for two weeks. ▪ Vancomycin for four weeks plus gentamicin for two weeks (in beta-lactam allergic patients). • Antibiotic treatment of infective endocarditis due to *Staphylococcus* species: o Methicillin-susceptible strains (native valves): ▪ Flucloxacillin or oxacillin for four to six weeks. ▪ Cotrimoxazole intravenous for one week and oral for five weeks plus clindamycin for one week (for *Staphylococcus aureus*). o Penicillin-allergic patients or methicillin-resistant staphylococci (native valves): ▪ Vancomycin for four to six weeks. ▪ Alternative: Daptomycin for four to six weeks. ▪ Cotrimoxazole intravenous for one week and oral for five weeks plus clindamycin for one week (for *Staphylococcus aureus*). o Methicillin-susceptible strains (prosthetic valves): ▪ Flucloxacillin or oxacillin for at least six weeks, rifampin for at least six weeks, and gentamicin for two weeks. o Penicillin-allergic patients or methicillin-resistant staphylococci (prosthetic valves): ▪ Vancomycin for at least six weeks, rifampin for at least six weeks, and gentamicin for two weeks. • Antibiotic treatment of infective endocarditis due to *Enterococcus* species: o Beta-lactam and gentamicin susceptible strains: ▪ Amoxicillin for four to six weeks plus gentamicin for two to six weeks. ▪ Ampicillin plus gentamicin for six weeks. ▪ Vancomycin plus gentamicin for six weeks. • Antibiotic treatment of blood culture-negative infective endocarditis: o *Brucella* species: ▪ Doxycycline, cotrimoxazole, and rifampin for ≥3 months. o *Coxiella burnetii* (agent of Q fever): ▪ Doxycycline plus hydroxychloroquine for >18 months. ▪ o *Bartonella* species: ▪ Doxycycline orally for four weeks plus gentamicin for two weeks. o *Legionella* species: ▪ Levofloxacin intravenous for ≥6 weeks or clarithromycin intravenous for two weeks then orally for four weeks plus rifampin. o *Mycoplasma* species: ▪ Levofloxacin for ≥6 months. o *Tropheryma whipplei* (agent of Whipple's disease): ▪ Doxycycline plus hydroxychloroquine orally for ≥18 months. • Proposed antibiotic regimens for initial empirical treatment of infective endocarditis in acute severely ill patients (before pathogen identification): o Community-acquired native valves or late prosthetic valves (≥12 months post surgery) endocarditis: ▪ Ampicillin intravenous plus flucloxacillin or oxacillin intravenous plus gentamicin intravenous for once dose. ▪ Vancomycin intravenous plus gentamicin intravenous (for penicillin allergic patients). o Early PVE (<12 months post surgery) or nosocomial and non-nosocomial healthcare associated endocarditis:

Clinical Guideline	Recommendation(s)
	▪ Vancomycin intravenous, gentamicin intravenous, and rifampin orally.
American College of Cardiology/ American Heart Association: **2008 Focused Update Incorporated Into the American College of Cardiology/American Heart Association 2006 Guidelines for the Management of Patients With Valvular Heart Disease (2008)**[15] American College of Cardiology/ American Heart Association: **Guideline for the Management of Patients With Valvular Heart Disease (2014)**[16] **(although a more current guideline more detailed information was included as part of the 2008 Focused update; as such both are summarized together)**	<u>Rheumatic fever prophylaxis</u> • Primary prevention of rheumatic heart disease: o Penicillin G benzathine intramuscular once or penicillin V orally for 10 days. o Erythromycin estolate or erythromycin ethylsuccinate orally for 10 days, or azithromycin orally for five days in patients who are allergic to penicillin. • Secondary prevention of rheumatic fever: o Penicillin G benzathine intramuscular every four weeks, or penicillin V orally twice daily, or sulfadiazine orally once daily. o Erythromycin orally twice daily for patients who are allergic to penicillin. <u>Endocarditis prophylaxis</u> • Prophylaxis against infective endocarditis is reasonable for the following patients at highest risk for adverse outcomes from infective endocarditis who undergo dental procedures that involve manipulation of either gingival tissue or the periapical region of teeth or perforation of the oral mucosa: o Patients with prosthetic cardiac valve or prosthetic material used for cardiac valve repair. o Patients with previous infective endocarditis. o Patients with congenital heart disease. o Cardiac transplant recipients with valve regurgitation due to a structurally abnormal valve. • Prophylaxis against infective endocarditis is not recommended for non-dental procedures (such as transesophageal echocardiogram, esophagogastroduodenoscopy, or colonoscopy) in the absence of active infection. • Regimens for dental procedures (single dose 30 to 60 minutes before procedure): o Oral: amoxicillin. o Unable to take oral medications: ampicillin, cefazolin or ceftriaxone. o Allergic to penicillin or ampicillin (oral): cephalexin, clindamycin, or azithromycin. o Allergic to penicillins or ampicillin and unable to take oral medication: cefazolin, ceftriaxone, or clindamycin. • Therapy of native valve endocarditis caused by highly penicillin-susceptible viridans group streptococci and *Streptococcus bovis:* o Penicillin G or ceftriaxone for four weeks. o Ceftriaxone plus gentamicin for two weeks. o Vancomycin for four weeks in patients allergic to penicillin. • Therapy of native valve endocarditis caused by strains of viridans group streptococci and *Streptococcus bovis* relatively resistant to penicillin: o Penicillin G or ceftriaxone for four weeks plus gentamicin for two weeks. o Vancomycin for four weeks in patients allergic to penicillin. • Therapy for native valve or prosthetic valve enterococcal endocarditis caused by strains susceptible to penicillin, gentamicin, and vancomycin: o Ampicillin for four to six weeks or penicillin G plus gentamicin for four to six weeks. o Vancomycin plus gentamicin for six weeks in patients allergic to penicillin. • Therapy for endocarditis caused by staphylococci in the absence of prosthetic materials: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin for six weeks plus the optional addition of gentamicin for three to five days. ▪ Cefazolin for six weeks with the optional addition of gentamicin in patients allergic to penicillin. o Oxacillin-resistant strains:

Clinical Guideline	Recommendation(s)
	▪ Vancomycin for six weeks. • Therapy for prosthetic valve endocarditis caused by staphylococci: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin, rifampin, and gentamicin for ≥6 weeks. o Oxacillin-resistant strains: ▪ Vancomycin, rifampin, and gentamicin for ≥6 weeks. • Therapy for both native and prosthetic valve endocarditis caused by *Haemophilus* species *(Haemophilus parainfluenzae, Haemophilus aphrophilus, Haemophilus paraphrophilus), Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* species microorganisms: o Ceftriaxone for four weeks. o Ampicillin-sulbactam for four weeks. o Ciprofloxacin for four weeks. • Therapy for culture-negative endocarditis including *Bartonella* endocarditis: o Native valve: ▪ Ampicillin-sulbactam plus gentamicin (or vancomycin for patients allergic to penicillin) plus ciprofloxacin for four to six weeks. o Prosthetic valve (early; ≤1 year): ▪ Vancomycin for six weeks, plus gentamicin for two weeks, plus cefepime for six weeks, plus rifampin for six weeks. o Prosthetic valve (late; >1 year): ▪ Suspected *Bartonella*, culture negative: • Ceftriaxone for six weeks plus gentamicin with/without doxycycline for six weeks. ▪ Documented *Bartonella*, culture positive: • Doxycycline for six weeks plus gentamicin for two weeks.
American Heart Association: **Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications (2015)**[17]	• Therapy for native valve endocarditis caused by viridans group streptococci and *Streptococcus gallolyticus* (Formerly Known as *Streptococcus bovis)*: o Highly penicillin-susceptible strains: ▪ Penicillin G or ceftriaxone for four weeks. ▪ Penicillin G or ceftriaxone plus gentamicin for two weeks (in patients with uncomplicated infective endocarditis, rapid response to therapy, and no underlying renal disease). ▪ Vancomycin for four weeks (recommended only for patients unable to tolerate penicillin or ceftriaxone therapy). o Relatively penicillin-resistant strains: ▪ Penicillin for four weeks plus gentamicin for the first two weeks. ▪ If the isolate is ceftriaxone susceptible, then ceftriaxone alone may be considered. ▪ Vancomycin for four weeks (recommended only for patients unable to tolerate beta-lactam therapy). • Therapy for native valve endocarditis caused by *A defectiva* and *Granulicatella* Species and viridans group streptococci: o For patients with infective endocarditis caused by *A defectiva*, *Granulicatella* species, and viridans group streptococci with a penicillin MIC ≥0.5 µg/mL, treat with a combination of ampicillin or penicillin plus gentamicin as done for enterococcal infective endocarditis with infectious diseases consultation. o If vancomycin is used in patients intolerant of ampicillin or penicillin, then the addition of gentamicin is not needed. o Ceftriaxone combined with gentamicin may be a reasonable alternative treatment option for isolates that are susceptible to ceftriaxone. • Therapy for endocarditis of prosthetic valves or other prosthetic material caused by viridans group streptococci and *Streptococcus gallolyticus* (Formerly Known as *Streptococcus bovis)*:

Clinical Guideline	Recommendation(s)
	o Penicillin for six weeks plus gentamicin for the first two weeks. o Extend gentamicin to six weeks if the MIC is >0.12 µg/mL for the infecting strain. o Vancomycin can be used in patients intolerant of penicillin, ceftriaxone, or gentamicin. • Therapy for endocarditis of prosthetic valves or other prosthetic material caused by *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and Groups B, C, F, and G β-Hemolytic Streptococci: o Penicillin, cefazolin, or ceftriaxone for four weeks is reasonable for infective endocarditis caused by *S pneumoniae*; vancomycin can be useful for patients intolerant of β-lactam therapy. o Six weeks of therapy is reasonable for prosthetic valve endocarditis caused by *S pneumoniae*. o High-dose penicillin or a third-generation cephalosporin is reasonable in patients with infective endocarditis caused by penicillin-resistant *S pneumoniae* without meningitis; if meningitis is present, then high doses of cefotaxime (or ceftriaxone) are reasonable. o The addition of vancomycin and rifampin to cefotaxime (or ceftriaxone) may be considered in patients with infective endocarditis caused by *S pneumoniae* that are resistant to cefotaxime. o Because of the complexities of infective endocarditis caused by *S pneumoniae*, consultation with an infectious diseases specialist is recommended. o For infective endocarditis caused by *S pyogenes*, four to six weeks of therapy with aqueous crystalline penicillin G or ceftriaxone is reasonable; vancomycin is reasonable only in patients intolerant of β-lactam therapy. o For infective endocarditis caused by group B, C, or G streptococci, the addition of gentamicin to penicillin G or ceftriaxone for at least the first two weeks of a four to six week treatment course may be considered. o Consultation with an infectious diseases specialist to guide treatment is recommended in patients with infective endocarditis caused by β-hemolytic streptococci. • Therapy for endocarditis caused by staphylococci in the absence of prosthetic valves or other prosthetic material: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin for six weeks. ▪ For penicillin-allergic individuals: cefazolin for six weeks. o Oxacillin-resistant strains ▪ Vancomycin for six weeks. ▪ Daptomycin for six weeks. • Therapy for prosthetic valve endocarditis caused by staphylococci: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin plus rifampin (for at least six weeks) and gentamicin (for two weeks). o Oxacillin-resistant strains: ▪ Vancomycin plus rifampin (for at least six weeks) and gentamicin (for two weeks). • Therapy for native valve or prosthetic valve enterococcal endocarditis: o Strains susceptible to penicillin and gentamicin: ▪ Ampicillin or penicillin G plus gentamicin for four to six weeks. ▪ Double β-lactam ampicillin plus ceftriaxone for six. o Strains susceptible to penicillin and resistant to aminoglycosides or streptomycin-susceptible gentamicin-resistant in patients able to tolerate β-Lactam therapy: ▪ Ampicillin plus ceftriaxone for six weeks. ▪ Ampicillin or penicillin G plus streptomycin for four to six

Clinical Guideline	Recommendation(s)
	weeks. o Vancomycin and aminoglycoside-susceptible penicillin-resistant enterococcus species in patients unable to tolerate β-lactam : ▪ Unable to tolerate β-lactams: • Vancomycin plus gentamicin for six weeks (vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone therapy). ▪ Intrinsic penicillin resistance: • Vancomycin plus gentamicin for six weeks. o Strains Resistant to Penicillin, Aminoglycosides, and Vancomycin: ▪ Linezolid or daptomycin for at least six weeks. • Therapy for both native and prosthetic valve endocarditis caused by *Haemophilus* species *(Haemophilus parainfluenzae, Haemophilus aphrophilus, Haemophilus paraphrophilus), Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* species microorganisms: o Ceftriaxone (cefotaxime or another third- or fourth-generation cephalosporin may be substituted) or ampicillin or ciprofloxacin for four weeks. Fluoroquinolone therapy recommended only for patients unable to tolerate cephalosporin and ampicillin therapy; levofloxacin or moxifloxacin may be substituted. • Therapy for culture-negative endocarditis including *Bartonella* endocarditis: o For patients with acute (days) clinical presentations of native valve infection, coverage for *S aureus*, β-hemolytic streptococci, and aerobic Gram-negative bacilli is reasonable. o For patients with a subacute (weeks) presentation of native valve endocarditis, coverage of *S aureus*, viridans group streptococci, HACEK, and enterococci is reasonable. o For patients with culture-negative prosthetic valve endocarditis, coverage for staphylococci, enterococci, and aerobic Gram-negative bacilli is reasonable if onset of symptoms is within one year of prosthetic valve placement. o If symptom onset is >1 year after valve placement, then infective endocarditis is more likely to be caused by staphylococci, viridans group streptococci, and enterococci, and antibiotic therapy for these potential pathogens is reasonable.
Infectious Diseases Society of America: **Clinical Practice Guidelines: Management of Encephalitis (2008)**[18] **(Was reviewed and deemed current as of July 2011)**	Empirical therapy • Acyclovir should be initiated in all patients with suspected encephalitis, pending results of diagnostic studies. • Other empirical antimicrobial agents should be initiated on the basis of specific epidemiologic or clinical factors, including appropriate therapy for presumed bacterial meningitis, if clinically indicated. • In patients with clinical clues suggestive of rickettsial or ehrlichial infection during the appropriate season, doxycycline should be added to empirical treatment regimens. Bacteria • *Bartonella bacilliformis:* chloramphenicol, ciprofloxacin, doxycycline, ampicillin, or sulfamethoxazole-trimethoprim is recommended. • *Bartonella henselae:* doxycycline or azithromycin, with or without rifampin, can be considered. • *Listeria monocytogenes:* ampicillin plus gentamicin is recommended; sulfamethoxazole-trimethoprim is an alternative in the penicillin-allergic patient. • *Mycoplasma pneumoniae:* antimicrobial therapy (azithromycin, doxycycline, or a fluoroquinolone) can be considered. • *Tropheryma whipplei:* ceftriaxone, followed by either sulfamethoxazole-

Clinical Guideline	Recommendation(s)
	trimethoprim or cefixime, is recommended. Helminths • *Baylisascaris procyonis:* albendazole plus diethylcarbamazine can be considered; adjunctive corticosteroids should also be considered. • *Gnathostoma* species: albendazole or ivermectin is recommended. • *Taenia solium:* need for treatment should be individualized; albendazole and corticosteroids are recommended; praziquantel can be considered as an alternative. Rickettsioses and ehrlichiosis • *Anaplasma phagocytophilum:* doxycycline is recommended. • *Ehrlichia chaffeensis:* doxycycline is recommended. • *Rickettsia rickettsii:* doxycycline is recommended; chloramphenicol can be considered an alternative in selected clinical scenarios, such as pregnancy. • *Coxiella burnetii:* doxycycline plus a fluoroquinolone plus rifampin is recommended. Spirochetes • *Borrelia burgdorferi:* ceftriaxone, cefotaxime, or penicillin G is recommended. • *Treponema pallidum:* penicillin G is recommended; ceftriaxone is an alternative. Protozoa • *Acanthamoeba:* sulfamethoxazole-trimethoprim plus rifampin plus ketoconazole or fluconazole plus sulfadiazine plus pyrimethamine can be considered. • *Balamuthia mandrillaris:* pentamidine, combined with a macrolide (azithromycin or clarithromycin), fluconazole, sulfadiazine, flucytosine, and a phenothiazine can be considered. • *Naegleria fowleri:* amphotericin B (intravenous and intrathecal) and rifampin, combined with other agents, can be considered. • *Plasmodium falciparum:* quinine, quinidine, or artemether is recommended; atovaquone-proguanil is an alternative; exchange transfusion is recommended for patients with 110% parasitemia or cerebral malaria; corticosteroids are not recommended. • *Toxoplasma gondii:* pyrimethamine plus either sulfadiazine or clindamycin is recommended; sulfamethoxazole-trimethoprim alone and pyrimethamine plus atovaquone, clarithromycin, azithromycin, or dapsone are alternatives. • *Trypanosoma brucei gambiense:* eflornithine is recommended; melarsoprol is an alternative. • *Trypanosoma brucei rhodesiense:* melarsoprol is recommended.

European Federation of Neurological Societies: **Guideline on the Management of Community-acquired Bacterial Meningitis (2008)**[19]	Empirical therapy
	• Ceftriaxone 2 g every 12 to 24 hours or cefotaxime 2 g every six to eight hours.
	• Alternative therapy: meropenem 2 g every eight hours or chloramphenicol 1 g every six hours.
	• If penicillin or cephalosporin-resistant pneumococcus is suspected, use ceftriaxone or cefotaxime plus vancomycin 60 mg/kg every 24 hours after a loading dose of 15 mg/kg.
	• Ampicillin-amoxicillin 2 g every four hours if *Listeria* is suspected.
	
	Pathogen specific therapy
	• Penicillin-sensitive pneumococcal meningitis:
	  o Benzyl penicillin 250,000 U/kg/day, ampicillin-amoxicillin 2 g every four hours, ceftriaxone 2 g every 12 hours or cefotaxime 2 g every six to eight hours.
	  o Alternative therapy: meropenem 2 g every eight hours or vancomycin 60 mg/kg every 24 hours as a continuous infusion after a 15 mg/kg loading

Clinical Guideline	Recommendation(s)
	dose plus rifampicin 600 mg every 12 hours, or moxifloxacin 400 mg daily. • Pneumococcus with reduced susceptibility to penicillin or cephalosporins: o Ceftriaxone or cefotaxime plus vancomycin±rifampicin. o Alternative therapy: moxifloxacin, meropenem or linezolid 600 mg combined with rifampicin. • Meningococcal meningitis: o Benzyl penicillin, ceftriaxone, or cefotaxime. o Alternative therapy: meropenem, chloramphenicol, or moxifloxacin. • *Haemophilus influenzae* type B: o Ceftriaxone or cefotaxime. o Alternative therapy: chloramphenicol–ampicillin-amoxicillin. • Listerial meningitis: o Ampicillin or amoxicillin 2 g every four hours±gentamicin 1 to 2 mg every eight hours for the first seven to 10 days. o Alternative therapy: Sulfamethoxazole-trimethoprim 10 to 20 mg/kg every six to 12 hours or meropenem. • *Staphylococcal* species: o Flucloxacillin 2 g every four hours or vancomycin if penicillin allergy is suspected. o Rifampicin should also be considered in addition to either agent. Linezolid should be considered for methicillin-resistant staphylococcal meningitis. • Gram-negative *Enterobacteriaceae*: o Ceftriaxone, cefotaxime or meropenem. • Pseudomonal meningitis: o Meropenem±gentamicin.
Infectious Diseases Society of America: **Practice Guidelines for the Management of Bacterial Meningitis (2004)**[20]	<u>Empiric therapy</u> • Empirical antimicrobial therapy is initiated either when the lumbar puncture is delayed or for patients with purulent meningitis and a negative cerebrospinal fluid gram stain result: o Age <1 month: ampicillin plus cefotaxime or ampicillin plus an aminoglycoside. o Age one to 23 months: vancomycin plus a third-generation cephalosporin. o Age two to 50 years: vancomycin plus a third-generation cephalosporin. o Age >50 years: vancomycin plus ampicillin plus a third-generation cephalosporin. o Basilar skull fracture: vancomycin plus a third-generation cephalosporin. o Penetrating head trauma: vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem. o Post neurosurgery: vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem. o Cerebrospinal fluid shunt: vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem. <u>Specific therapy</u> • Recommendations for specific antimicrobial therapy in bacterial meningitis are based on isolated pathogens and susceptibility. • *Streptococcus pneumoniae* o Penicillin minimum inhibitory concentrations <0.1 µg/mL: standard therapy includes penicillin G or ampicillin; alternative therapies include ceftriaxone, cefotaxime, or chloramphenicol. o Penicillin minimum inhibitory concentrations 0.1 to 1.0 µg/mL: standard therapy includes ceftriaxone or cefotaxime; alternative therapies include cefepime or meropenem. o Penicillin minimum inhibitory concentrations ≥2 µg/mL: standard therapies include vancomycin plus ceftriaxone or cefotaxime; alternative therapies include gatifloxacin or moxifloxacin.

Clinical Guideline	Recommendation(s)
	o Cefotaxime or ceftriaxone minimum inhibitory concentrations ≥1.0 µg/mL: standard therapies include vancomycin plus ceftriaxone or cefotaxime (consider addition of rifampin if minimum inhibitory concentrations of ceftriaxone is >2 µg/mL); alternative therapies include gatifloxacin or moxifloxacin. • *Neisseria meningitides* o Penicillin minimum inhibitory concentrations <0.1 µg/mL: standard therapy includes penicillin G or ampicillin; alternative therapy includes ceftriaxone, cefotaxime or chloramphenicol. o Penicillin minimum inhibitory concentrations 0.1 to 1.0 µg/mL: standard therapy includes ceftriaxone or cefotaxime; alternative therapies include chloramphenicol, a fluoroquinolone or meropenem. • *Listeria monocytogenes* o Standard therapy includes ampicillin or penicillin G; alternative therapies include sulfamethoxazole-trimethoprim or meropenem. • *Streptococcus agalactiae* o Standard therapy includes ampicillin or penicillin G; alternative therapies include ceftriaxone or cefotaxime. • *Escherichia coli* and other Enterobacteriaceae o Standard therapy includes a third-generation cephalosporin; alternative therapies include aztreonam, fluoroquinolone, meropenem, sulfamethoxazole-trimethoprim or ampicillin. • *Pseudomonas aeruginosa* o Standard therapies include cefepime or ceftazidime; alternative therapies include aztreonam, ciprofloxacin, or meropenem (addition of an aminoglycoside should be considered). • *Haemophilus influenzae* β-lactamase negative strains o Standard therapy includes ampicillin; alternative therapies include ceftriaxone, cefotaxime, cefepime, chloramphenicol or a fluoroquinolone. • *Haemophilus influenzae* β-lactamase positive strains o Standard therapy includes a third-generation cephalosporin; alternative therapies include cefepime, chloramphenicol or a fluoroquinolone. • *Staphylococcus aureus* methicillin susceptible o Standard therapy includes nafcillin or ofloxacin; alternative therapies include vancomycin or meropenem. • *Staphylococcus aureus* methicillin resistant o Standard therapy includes vancomycin (consider addition of rifampin); alternative therapies include sulfamethoxazole-trimethoprim or linezolid. • *Staphylococcus epidermidis* o Standard therapy includes vancomycin (consider addition of rifampin); alternative therapy includes linezolid. • *Enterococcus* species ampicillin susceptible o Standard therapy includes ampicillin plus gentamicin. • *Enterococcus* species ampicillin resistant o Standard therapy includes vancomycin plus gentamicin. • *Enterococcus* species ampicillin and vancomycin resistant o Standard therapy includes linezolid.
Infectious Diseases Society of America: **Practice Guidelines for the Diagnosis and Management of Skin and Soft-Tissue Infections (2014)**[21]	Impetigo and ecthyma • Gram stain and culture of the pus or exudates from skin lesions of impetigo and ecthyma are recommended to help identify whether *Staphylococcus aureus* and/or a β-hemolytic *Streptococcus* is the cause (strong, moderate), but treatment without these studies is reasonable in typical cases. • Bullous and nonbullous impetigo can be treated with oral or topical antimicrobials, but oral therapy is recommended for patients with numerous lesions or in outbreaks affecting several people to help decrease transmission

Clinical Guideline	Recommendation(s)
	of infection. Treatment for ecthyma should be an oral antimicrobial. o Treatment of bullous and nonbullous impetigo should be with either mupirocin or retapamulin twice daily for five days. o Oral therapy for ecthyma or impetigo should be a seven-day regimen with an agent active against *S. aureus* unless cultures yield streptococci alone (when oral penicillin is the recommended agent). Because *S. aureus* isolates from impetigo and ecthyma are usually methicillin susceptible, dicloxacillin or cephalexin is recommended. When MRSA is suspected or confirmed, doxycycline, clindamycin, or sulfamethoxazole-trimethoprim is recommended. Purulent skin and soft-tissue infections (cutaneous abscesses, furuncles, carbuncles, and inflamed epidermoid cysts) • Gram stain and culture of pus from carbuncles and abscesses are recommended, but treatment without these studies is reasonable in typical cases. Gram stain and culture of pus from inflamed epidermoid cysts are not recommended. • Incision and drainage is the recommended treatment for inflamed epidermoid cysts, carbuncles, abscesses, and large furuncles. • The decision to administer antibiotics directed against *S. aureus* as an adjunct to incision and drainage should be made based upon presence or absence of systemic inflammatory response syndrome (SIRS), such as temperature >38°C or <36°C, tachypnea >24 breaths per minute, tachycardia >90 beats per minute, or white blood cell count >12 000 or <400 cells/µL. An antibiotic active against MRSA is recommended for patients with carbuncles or abscesses who have failed initial antibiotic treatment or have markedly impaired host defenses or in patients with SIRS and hypotension. Recurrent skin abscesses • A recurrent abscess at a site of previous infection should prompt a search for local causes such as a pilonidal cyst, hidradenitis suppurativa, or foreign material. • Recurrent abscesses should be drained and cultured early in the course of infection. • After obtaining cultures of recurrent abscess, treat with a five to ten day course of an antibiotic active against the pathogen isolated. • Consider a five-day decolonization regimen twice daily of intranasal mupirocin, daily chlorhexidine washes, and daily decontamination of personal items such as towels, sheets, and clothes for recurrent *S. aureus* infection. • Adult patients should be evaluated for neutrophil disorders if recurrent abscesses began in early childhood. Erysipelas and cellulitis • Cultures of blood or cutaneous aspirates, biopsies, or swabs are not routinely recommended except in patients with malignancy on chemotherapy, neutropenia, severe cell-mediated immunodeficiency, immersion injuries, and animal bites. • Typical cases of cellulitis without systemic signs of infection should receive an antimicrobial agent that is active against streptococci. For cellulitis with systemic signs of infection (moderate nonpurulent), systemic antibiotics are indicated. Many clinicians could include coverage against methicillin-susceptible *S. aureus* (MSSA). For patients whose cellulitis is associated with penetrating trauma, evidence of MRSA infection elsewhere, nasal colonization with MRSA, injection drug use, or SIRS (severe nonpurulent), vancomycin or another antimicrobial effective against both MRSA and streptococci is recommended. In severely compromised patients, broad-spectrum

Clinical Guideline	Recommendation(s)
	antimicrobial coverage may be considered. Vancomycin plus either piperacillin-tazobactam or imipenem/meropenem is recommended as a reasonable empiric regimen for severe infections. • The recommended duration of antimicrobial therapy is five days, but treatment should be extended if the infection has not improved within this time period. Surgical site infections • Suture removal plus incision and drainage should be performed for surgical site infections. • Adjunctive systemic antimicrobial therapy is not routinely indicated, but in conjunction with incision and drainage may be beneficial for surgical site infections associated with a significant systemic response. • A brief course of systemic antimicrobial therapy is indicated in patients with surgical site infections following clean operations on the trunk, head and neck, or extremities that also have systemic signs of infection. • A first-generation cephalosporin or an antistaphylococcal penicillin for MSSA, or vancomycin, linezolid, daptomycin, telavancin, or ceftaroline where risk factors for MRSA are high (nasal colonization, prior MRSA infection, recent hospitalization, recent antibiotics), is recommended. • Agents active against gram-negative bacteria and anaerobes, such as a cephalosporin or fluoroquinolone in combination with metronidazole, are recommended for infections following operations on the axilla, gastrointestinal tract, perineum, or female genital tract. Necrotizing fasciitis • Empiric antibiotic treatment should be broad (e.g., vancomycin or linezolid plus piperacillin-tazobactam or a carbapenem; or plus ceftriaxone and metronidazole), as the etiology can be polymicrobial (mixed aerobic–anaerobic microbes) or monomicrobial (group A streptococci, community-acquired MRSA). • Penicillin plus clindamycin is recommended for treatment of documented group A streptococcal necrotizing fasciitis. Pyomyositis • Cultures of blood and abscess material should be obtained. • Vancomycin is recommended for initial empirical therapy. An agent active against enteric gram-negative bacilli should be added for infection in immunocompromised patients or following open trauma to the muscles. • Cefazolin or antistaphylococcal penicillin (e.g., nafcillin or oxacillin) is recommended for treatment of pyomyositis caused by MSSA. • Antibiotics should be administered intravenously initially, but once the patient is clinically improved, oral antibiotics are appropriate for patients in whom bacteremia cleared promptly and there is no evidence of endocarditis or metastatic abscess. Two to three weeks of therapy is recommended. Clostridial gas gangrene or myonecrosis • Urgent surgical exploration of the suspected gas gangrene site and surgical debridement of involved tissue should be performed. • In the absence of a definitive etiologic diagnosis, broad-spectrum treatment with vancomycin plus either piperacillin-tazobactam, ampicillin-sulbactam, or a carbapenem antimicrobial is recommended. Definitive antimicrobial therapy with penicillin and clindamycin is recommended for treatment of clostridial myonecrosis. Animal bites

Clinical Guideline	Recommendation(s)
	• Preemptive early antimicrobial therapy for three to five days is recommended for patients who: o are immunocompromised; o are asplenic; o have advanced liver disease; o have preexisting or resultant edema of the affected area; o have moderate to severe injuries, especially to the hand or face; or o have injuries that may have penetrated the periosteum or joint capsule. • 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 o β-lactam-β-lactamase combinations, piperacillin-tazobactam, second-generation cephalosporins, and carbapenems. • Tetanus toxoid should be administered to patients without toxoid vaccination within 10 years. Tetanus, diphtheria, and tetanus (Tdap) is preferred over Tetanus and diphtheria (Td) if the former has not been previously given. Cutaneous anthrax • Oral penicillin V 500 mg four times daily for seven to 10 days is the recommended treatment for naturally acquired cutaneous anthrax. • Ciprofloxacin 500 mg by mouth twice daily or levofloxacin 500 mg intravenously/orally every 24 hours for 60 days is recommended for bioterrorism cases because of presumed aerosol exposure. Bacillary angiomatosis and cat scratch disease • Azithromycin is recommended for cat scratch disease (strong, moderate) according to the following dosing protocol: o Patients >45 kg: 500 mg on day one followed by 250 mg for four additional days. o Patients <45 kg: 10 mg/kg on day one and 5 mg/kg for four more days. • Erythromycin 500 mg four times daily or doxycycline 100 mg bid for two weeks to two months is recommended for treatment of bacillary angiomatosis. Erysipeloid • Penicillin (500 mg four times daily) or amoxicillin (500 mg three times daily [tid]) for seven to 10 days is recommended for treatment of erysipeloid. Glanders • Ceftazidime, gentamicin, imipenem, doxycycline, or ciprofloxacin is recommended based on in vitro susceptibility. Bubonic plague • Bubonic plague should be diagnosed by Gram stain and culture of aspirated material from a suppurative lymph node. Streptomycin (15 mg/kg intramuscularly every 12 hours) or doxycycline (100 mg twice daily by mouth) is recommended for treatment of bubonic plague. Gentamicin could be substituted for streptomycin. Tularemia

Clinical Guideline	Recommendation(s)
	• Streptomycin (15 mg/kg every 12 hours intramuscularly) or gentamicin (1.5 mg/kg every 8 hours intravenously) is recommended for treatment of severe cases of tularemia. • Tetracycline (500 mg four times daily) or doxycycline (100 mg twice daily by mouth) is recommended for treatment of mild cases of tularemia.
Infectious Diseases Society of America: **Diagnosis and Treatment of Diabetic Foot Infections (2012)**[22]	• Empirical antibiotic regimens should be based on the clinical severity of the infection. • Current clinical data does not allow for the recommendation of any specific antibiotic regimen for diabetic foot infections. • Suggested agents are derived from available published clinical trials and expert experience. • Definitive regimens should consider results of culture and susceptibility tests, as well as the clinical response to the empirical regimen. Similar agents of the same drug class may be substituted. Some of these regimens may not have Food and Drug Administration approval for complicated skin and skin-structure infections, and only linezolid, ertapenem and piperacillin-tazobactam are currently specifically approved for diabetic foot infections. • Suggested empirical antibiotic regimens for mild infections: dicloxacillin, clindamycin, cephalexin, sulfamethoxazole-trimethoprim, amoxicillin-clavulanate, levofloxacin and doxycycline. • Suggested empirical antibiotic regimens for moderate infections: levofloxacin, cefoxitin, ceftriaxone, ampicillin-sulbactam, moxifloxacin, tigecycline, linezolid, daptomycin, ertapenem, ticarcillin-clavulanate, piperacillin-tazobactam, levofloxacin or ciprofloxacin with clindamycin, imipenem-cilastatin, vancomycin, ceftazidime, cefepime, aztreonam. • Suggested empirical antibiotic regimens for severe infections: piperacillin-tazobactam, vancomycin, ceftazidime, cefepime, aztreonam or a carbapenem.
American College of Gastroenterology: **Guideline on the Management of *Helicobacter pylori* Infection (2007)**[23]	• The recommended primary therapies for *Helicobacter pylori* infection include: a proton pump inhibitor, clarithromycin, and amoxicillin, or metronidazole (clarithromycin-based triple therapy) for 14 days or a proton pump inhibitor or histamine 2 receptor antagonist, bismuth, metronidazole, and tetracycline (bismuth quadruple therapy) for 10 to 14 days.
Canadian Helicobacter Study Group: **The Toronto Consensus for the Treatment of *Helicobacter pylori* Infection in Adults (2016)**[24]	• A quadruple combination of a proton pump inhibitor, bismuth, tetracycline, and metronidazole or a proton pump inhibitor, amoxicillin, metronidazole, and clarithromycin for 14 days can be considered first-line therapy for the eradication of *Helicobacter pylori*. • Proton pump inhibitor-based triple therapy is restricted to areas with known low clarithromycin resistance or high eradication success with these regimens. • Recommended rescue therapies include bismuth quadruple therapy and levofloxacin-containing therapy. • Rifabutin regimens should be restricted to patients who have failed to respond to at least three prior regimens.
European *Helicobacter pylori* Study Group: **Management of *Helicobacter pylori* Infection–The Maastricht IV Consensus Report (2012)**[25]	• First-line therapy should be with triple therapy using a proton pump inhibitor or ranitidine bismuth citrate, combined with clarithromycin and amoxicillin or metronidazole. • Second-line therapy should include bismuth-containing quadruple therapy or proton pump inhibitor, levofloxacin and amoxicillin.
Centers for Disease	Arthritis and arthritis-dermatitis syndrome

Clinical Guideline	Recommendation(s)
Control and Prevention: **Sexually Transmitted Diseases Treatment Guidelines (2015)**[26]	• Recommended regimen: o Ceftriaxone 1 g intramuscular or intravenous every 24 hours plus azithromycin 1 g orally in a single dose. • Alternative regimen: o Cefotaxime 1 g intravenous every eight hours or ceftizoxime 1 g intravenous every eight hours plus azithromycin 1 g orally in a single dose. Bacterial vaginosis • Recommended regimens: o Metronidazole 500 mg orally twice a day for seven days. o Metronidazole gel 0.75%, one full applicator (5 g) intravaginally, once a day for five days. o Clindamycin cream 2%, one full applicator (5 g) intravaginally at bedtime for seven days. • Alternative regimens: o Tinidazole 2 g orally once daily for two days. o Tinidazole 1 g 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. Cervicitis • Recommended regimens for presumptive treatment: o Azithromycin 1 g orally in a single dose. o Doxycycline 100 mg orally twice a day for seven days. Chancroid • Recommended regimens: o Azithromycin 1 g 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. Chlamydial infections • Recommended regimens: o Azithromycin 1 g 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. Chlamydial infections among children • 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 g orally in a single dose. • Recommended regimens for children ≥8 years of age: o Azithromycin 1 g orally in a single dose. o Doxycycline 100 mg orally twice a day for seven days. Disseminated gonococcal infection

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	• Recommended regimen:
	  o Ceftriaxone 1 g intramuscular or intravenous every 24 hours.
	• Alternative regimens:
	  o Cefotaxime 1 g intravenous every eight hours.
	  o Ceftizoxime 1 g intravenous every eight hours.
	
	Epididymitis
	• 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.
	
	Granuloma inguinale (Donovanosis)
	• Recommended regimen:
	  o Azithromycin 1 g orally once per week or 500 mg daily for at least three weeks and until all lesions have completely healed.
	• Alternative regimens:
	  o Doxycycline 100 mg orally twice a day 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 g intramuscular in a single dose plus azithromycin 1 g orally 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 25 to 50 mg/kg intravenous or intramuscular in a single dose, not to exceed 125 mg.
	• Recommended regimen for children who weigh ≤45 kg and who have bacteremia or arthritis:
	  o Ceftriaxone 50 mg/kg (maximum dose: 1 g) 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:

Clinical Guideline	Recommendation(s)
	o Ceftriaxone 1 to 2 g intravenous every 12 hours plus azithromycin 1 g orally in a single dose. 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 g 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. • Alternative regimen: o Azithromycin suspension, 20 mg/kg/day orally, one dose daily for three days. Pelvic inflammatory disease • Recommended parenteral regimen A: o Cefotetan 2 g intravenous every 12 hours. o Cefoxitin 2 g 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 g 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 g intramuscular in a single dose and probenecid, 1 g 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. Proctitis, proctocolitis, and enteritis • Recommended regimen: o Ceftriaxone 250 mg intramuscular plus doxycycline 100 mg orally twice a

Clinical Guideline	Recommendation(s)
	day for seven days. Recurrent and persistent urethritis • Recommended regimens: o Metronidazole 2 g orally in a single dose. o Tinidazole 2 g orally in a single dose plus azithromycin 1 g orally in a single dose (if not used for initial episode). Primary and secondary syphilis • 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. Early latent syphilis • 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. Late latent syphilis or latent syphilis of unknown duration • 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. Tertiary syphilis • 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. Trichomoniasis • Recommended regimen: o Metronidazole 2 g orally in a single dose. o Tinidazole 2 g orally in a single dose. • Alternative regimen: o Metronidazole 500 mg orally twice a day for seven days. Neurosyphilis • 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. Uncomplicated gonococcal infections of the cervix, urethra, and rectum • Recommended regimens: o Ceftriaxone 250 mg intramuscular in a single dose.

Clinical Guideline	Recommendation(s)
	o Cefixime 400 mg orally in a single dose. o Single-dose injectable cephalosporin regimens plus azithromycin 1g orally in a single dose or doxycycline 100 mg orally twice a day for seven days. Uncomplicated gonococcal infections of the pharynx • Recommended regimens: o Ceftriaxone 250 mg intermuscular in a single dose plus azithromycin 1g orally in a single dose or doxycycline 100 mg orally twice a day for seven 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)**[27] Reviewed and deemed current as of 07/2013	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 g 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 relatively poor efficacy and the very high prevalence of antimicrobial resistance to these agents worldwide. Acute pyelonephritis • 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 g 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 g 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 g 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

Clinical Guideline	Recommendation(s)
	parenteral antimicrobial (i.e., ceftriaxone 1 g 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.
American College of Obstetricians and Gynecologists: **Treatment of Urinary Tract Infections in Nonpregnant Women (2008)**[28]	• 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 g dose (powder) single dose.
American Academy of Pediatrics/ American Academy of Family Physicians: **Diagnosis and Management of Acute Otitis Media (2013)**[29]	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: **Practice Guidelines for the Diagnosis and Management of Group A Streptococcal Pharyngitis (2012)**[30] Reviewed and deemed current as of 05/2015	• Patients with acute streptococcal pharyngitis should receive therapy with an antimicrobial agent in a dose and for a duration that is likely to eradicate the infecting organism from the pharynx. • Penicillin or amoxicillin are the agents of choice because of their proven efficacy, safety, and narrow spectrum. • Treatment of acute streptococcal pharyngitis is penicillin-allergic patients should include a first generation cephalosporin for ten days, clindamycin or clarithromycin for ten days or azithromycin for five days. • Intramuscular administration of benzathine penicillin G is preferred for patients who are unlikely to complete a full 10- day course of oral therapy. • Most oral antibiotic therapy must be administered for the conventional 10 days to achieve maximal rates of pharyngeal eradication of group A streptococci.

Clinical Guideline	Recommendation(s)
	• When multiple episodes occur over the course of months or years, it may be difficult to differentiate viral pharyngitis in a *Streptococcus* carrier from true group A streptococcal pharyngitis. Therapy with certain antimicrobial agents, such as clindamycin and amoxicillin-clavulanate, may be beneficial, because they have been shown to yield high rates of eradication of streptococci from the pharynx under these particular circumstances.
American Academy of Otolaryngology–Head and Neck Surgery Foundation: **Clinical Practice Guideline: Adult Sinusitis (2015)**[31]	Symptomatic relief of viral rhinosinusitis • Management of viral rhinosinusitis is primarily symptomatic, with an analgesic or antipyretic provided for pain or fever, respectively. • Nasal saline may be palliative and cleansing with low risk of adverse reactions. • Oral decongestants may provide symptomatic relief and should be considered barring any medical contraindications, such as hypertension or anxiety. The use of topical decongestant is likely to be palliative, but continuous duration of use should not exceed three to five days, as recommended by the manufacturers, to avoid rebound congestion and rhinitis medicamentosa. • Clinical experience suggests oral antihistamines may provide symptomatic relief of excessive secretions and sneezing, although there are no clinical studies supporting the use of antihistamines in acute viral rhinosinusitis. • Guaifenesin (an expectorant) and dextromethorphan (a cough suppressant) are often used for symptomatic relief of viral rhinosinusitis symptoms, but evidence of clinical efficacy is lacking. Symptomatic relief of acute bacterial rhinosinusitis • Symptomatic treatments for acute bacterial rhinosinusitis include analgesics, topical intranasal steroids, and/or nasal saline irrigation. None of these products has been specifically approved by the FDA for use in acute rhinosinusitis (as of March 2014), and only some have data from controlled clinical studies supporting this use. • Over-the-counter analgesics, such as nonsteroidal anti-inflammatory drugs or acetaminophen, are usually sufficient to relieve facial pain associated with acute bacterial rhinosinusitis. • Antihistamines have no role in the symptomatic relief of acute bacterial rhinosinusitis in nonatopic patients. No studies support their use in an infectious setting, and antihistamines may worsen congestion by drying the nasal mucosa. Initial management of acute bacterial rhinosinusitis • Offer watchful waiting (without antibiotics) or prescribe initial antibiotic therapy for adults with uncomplicated acute bacterial rhinosinusitis. Watchful waiting should be offered only when there is assurance of follow-up, such that antibiotic therapy is started if the patient's condition fails to improve by seven days after acute bacterial rhinosinusitis diagnosis or if it worsens at any time. Choice of antibiotic for acute bacterial rhinosinusitis • If a decision is made to treat acute bacterial rhinosinusitis with an antibiotic, the clinician should prescribe amoxicillin with or without clavulanate as first-line therapy for five to ten days for most adults. • For penicillin-allergic patients, either doxycycline or a respiratory fluoroquinolone (levofloxacin or moxifloxacin) is recommended as an alternative agent for empiric antimicrobial therapy. Treatment failure for acute bacterial rhinosinusitis • If the patient worsens or fails to improve with the initial management option by seven days after diagnosis or worsens during the initial management, the clinician should reassess the patient to confirm acute bacterial rhinosinusitis, exclude other causes of illness, and detect complications. • If acute bacterial rhinosinusitis is confirmed in the patient initially managed with

Clinical Guideline	Recommendation(s)
	observation, the clinician should begin antibiotic therapy. • If the patient was initially managed with an antibiotic, the clinician should change the antibiotic.
American Academy of Allergy, Asthma, and Immunology/ American College of Allergy, Asthma and Immunology/ Joint Council on Allergy, Asthma and Immunology: **The Diagnosis and Management of Sinusitis: A Practice Parameter Update (2014)**[32]	• Treat acute bacterial rhinosinusitis if symptoms last longer than 10 days or with recrudescence of symptoms after progressive improvement. • The most commonly reported bacterial pathogens in acute bacterial rhinosinusitis are *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Staphylococcus aureus*. • The antibiotics currently approved by the FDA for acute bacterial rhinosinusitis are azithromycin, clarithromycin, amoxicillin-clavulanate, cefprozil, cefuroxime axetil, loracarbef, levofloxacin, trimethoprim-sulfamethoxazole, and moxifloxacin. Although some studies have reported comparisons of different antibiotics for adult acute bacterial rhinosinusitis, not one was found to be superior. • Owing to concerns over bacterial resistance, the Infectious Diseases Society of America no longer recommends the use of macrolides for empiric treatment of acute bacterial rhinosinusitis. That organization recommends amoxicillin-clavulanate as first-line therapy and doxycycline, levofloxacin, and moxifloxacin in patients allergic to penicillin. • The Infectious Diseases Society of America recommends five to seven days of treatment with antibiotics for uncomplicated acute bacterial rhinosinusitis in adults and 10 to 14 days in children. • Use intranasal steroids for treatment of acute rhinosinusitis as monotherapy or with antibiotics.
American Academy of Pediatrics: **Clinical Practice Guideline for the Diagnosis and Management of Acute Bacterial Sinusitis in Children Aged 1 to 18 years (2013)**[33]	• Antibiotic therapy should be prescribed for acute bacterial sinusitis in children with severe onset or worsening course (signs, symptoms or both). • Antibiotic therapy or additional outpatient observation for three days should be utilized for children with persistent illness (nasal discharge of any quality, cough or both for at least 10 days). • When a decision has been made to initiate antibiotic therapy for the treatment of acute bacterial sinusitis, amoxicillin with or without clavulanate is considered first-line. • For children ≥2 years of age with uncomplicated acute bacterial sinusitis that is mild to moderate in severity who do not attend child care and have not received antibiotics in the previous four weeks, amoxicillin 45 mg/kg/day in two divided doses is recommended. In communities with high prevalence of *Streptococcus pneumoniae* (>10%, including intermediate and high level resistance), amoxicillin may be initiated at 80 to 90 mg/kg/day in two divided doses with a maximum of 2 g per dose. • Patients with moderate to severe illness and those <2 years of age who are attending child care or have recently received antibiotics, amoxicillin-clavulanate (80 to 90 mg/kg/day of amoxicillin with 6.4 mg/kg/day of clavulanate to a maximum of 2 g per dose) may be used. • A single dose of ceftriaxone 50 mg/kg intravenous or intramuscular may be used for children who are vomiting, unable to tolerate oral medication or unlikely to adhere to initial doses of antibiotic.
Working Group on Civilian Biodefense: **Anthrax as a Biological Weapon, Updated Recommendations for Management (2002)**[34]	<u>Inhalation anthrax in the contained casualty setting - adults</u> • Ciprofloxacin 400 mg intravenous every 12 hours initially, then 500 mg by mouth twice daily when clinically appropriate; OR • Doxycycline 100 mg intravenous every 12 hours initially with either one or two of the following: rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, clindamycin, and/or clarithromycin. Switch to 100 mg by mouth twice daily when clinically appropriate. <u>Inhalation anthrax in the contained casualty setting - children</u> • Ciprofloxacin 10 to 15 mg/kg every 12 hours intravenous, then 10 to 15 mg/kg by

Clinical Guideline	Recommendation(s)
	mouth every 12 hours when clinically appropriate; OR • Doxycycline (if ≤45 kg, 2.2 mg/kg intravenous; if > 45 kg, 100 mg intravenous) every 12 hours initially with either one or two of the following: rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, clindamycin, and/or clarithromycin. Switch to oral therapy when clinically appropriate using same intravenous dose. Inhalation anthrax in a mass casualty setting - adults • Recommended treatment: ciprofloxacin 500 mg by mouth every 12 hours. • Alternative treatment option: doxycycline 100 mg by mouth every 12 hours or amoxicillin 500 mg by mouth every eight hours. Inhalation anthrax in a mass casualty setting - children • Recommended treatment: ciprofloxacin 10 to 15 mg/kg by mouth every 12 hours. • Alternative treatment option: amoxicillin 500 mg by mouth every eight hours (weight ≥20 kg) or amoxicillin 40 mg/kg by mouth every eight hours (weight <20 kg). Inhalation anthrax in a mass casualty setting – pregnant women • Recommended treatment: ciprofloxacin 500 mg by mouth every 12 hours. • Alternative treatment option: amoxicillin 500 mg every eight hours.

Global Initiative for Chronic Obstructive Lung Disease: **Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2016)**[35]	• Prophylactic, continuous use of antibiotics has been shown to have no effect on the frequency of exacerbations in chronic obstructive pulmonary disease.
	• The use of antibiotics, other than for treating infectious exacerbations of chronic obstructive pulmonary disease and other bacterial infections, is currently not indicated.
	• Based on current available evidence, antibiotics should be given to:
	  o Patients with exacerbations of chronic obstructive pulmonary disease with the following three cardinal symptoms: dyspnea, sputum volume, and sputum purulence.
	  o Patients with exacerbations of chronic obstructive pulmonary disease with two of the cardinal symptoms, if the increased purulence of sputum is one of the two symptoms.
	  o Patients with a severe exacerbation of chronic obstructive pulmonary disease that requires mechanical ventilation (invasive or noninvasive).
	• The recommended length of antibiotic therapy is usually five to 10 days.
	• The choice of antibiotic should be based on local bacterial resistance patterns.
	• Initial empiric treatment may include an aminopenicillin with or without clavulanic acid, macrolide, or tetracycline. In patients with frequent exacerbations, severe airflow limitation, and/or exacerbations requiring mechanical ventilation, sputum cultures or cultures from other materials from the lung should be performed, as gram-negative bacteria or resistant pathogens that may not be sensitive to the afore-mentioned antibiotics may be present.

Infectious Diseases Society of America: **Management of Community-Acquired Pneumonia in Infants and Children Older Than 3 Months of Age (2011)**[36]	Outpatient treatment • Antimicrobial therapy is not routinely required for preschool-aged children with community-acquired pneumonia, because viral pathogens are responsible for the great majority of clinical disease. • Amoxicillin should be used as first-line therapy for previously healthy, appropriately immunized infants and preschool children with mild to moderate community-acquired pneumonia suspected to be of bacterial origin. Amoxicillin provides appropriate coverage for *Streptococcus pneumoniae*. • For patients allergic to amoxicillin, the following agents are considered alternative treatment options: o Second- or third-generation cephalosporin (cefpodoxime, cefuroxime, cefprozil).

Clinical Guideline	Recommendation(s)
Reviewed and deemed current as of 04/2013	o Levofloxacin (oral therapy). o Linezolid (oral therapy). • Macrolide antibiotics should be prescribed for treatment of children (primarily school-aged children and adolescents) evaluated in an outpatient setting with findings compatible with community-acquired pneumonia caused by atypical pathogens. <u>Inpatient treatment</u> • Ampicillin or penicillin G should be administered to the fully immunized infant or school-aged child admitted to a hospital ward with community-acquired pneumonia when local epidemiologic data document lack of substantial high-level penicillin resistance for invasive *Streptococcus pneumoniae*. • Empiric therapy with a third-generation parenteral cephalosporin (ceftriaxone or cefotaxime) should be prescribed for hospitalized infants and children who are not fully immunized, in regions where local epidemiology of invasive pneumococcal strains documents high-level penicillin resistance, or for infants and children with life-threatening infection, including those with empyema. • Non–β-lactam agents, such as vancomycin, have not been shown to be more effective than third-generation cephalosporins in the treatment of pneumococcal pneumonia for the degree of resistance noted currently in North America. • Empiric combination therapy with a macrolide (oral or parenteral), in addition to a β-lactam antibiotic, should be prescribed for the hospitalized child for whom *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* are significant considerations. • Vancomycin or clindamycin (based on local susceptibility data) should be provided in addition to β-lactam therapy if clinical, laboratory, or imaging characteristics are consistent with infection caused by *Staphylococcus aureus*.
Infectious Diseases Society of America/American Thoracic Society: **Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults (2007)**[37]	<u>Empirical antimicrobial therapy</u> • Recommendations are generally for a class of antibiotics rather than for a specific drug, unless outcome data clearly favor one drug. • Because overall efficacy remains good for many classes of agents, the more potent drugs are given preference because of their benefit in decreasing the risk of selection for antibiotic resistance. • Outpatient treatment o Previously healthy and no risk factors for drug-resistant *Streptococcus pneumoniae* infection: ▪ Macrolide (azithromycin, clarithromycin, or erythromycin). ▪ Doxycycline. o Presence of comorbidities, such as chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressing conditions or use of immunosuppressing drugs; use of antimicrobials within the previous three months (in which case an alternative from a different class should be selected); or other risks for drug-resistant Streptococcus pneumoniae infection: ▪ Respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin). ▪ β-lactam plus a macrolide (high-dose amoxicillin or amoxicillin-clavulanate is preferred; alternatives include ceftriaxone, cefpodoxime, and cefuroxime; doxycycline is an alternative to the macrolide). o In regions with a high rate of infection with high-level macrolide-resistant *Streptococcus pneumoniae,* consider the use of alternative agents listed above for any patient, including those without comorbidities. • Inpatient, non-intensive care unit treatment o Respiratory fluoroquinolone. o β-lactam plus a macrolide (preferred β-lactam agents include cefotaxime,

Clinical Guideline	Recommendation(s)
	ceftriaxone, and ampicillin; ertapenem for selected patients; with doxycycline as an alternative to the macrolide. A respiratory fluoroquinolone should be used for penicillin-allergic patients). • Inpatient, intensive care unit treatment o β-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) plus either azithromycin or a fluoroquinolone (for penicillin-allergic patients, a respiratory fluoroquinolone and aztreonam are recommended). o For *Pseudomonas* infection, use an antipneumococcal, antipseudomonal β-lactam (piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin; OR o Antipneumococcal, antipseudomonal β-lactam (listed above) plus an aminoglycoside and azithromycin; OR o Antipneumococcal, antipseudomonal β-lactam (listed above) plus an aminoglycoside and an antipneumococcal fluoroquinolone (for penicillin-allergic patients, substitute aztreonam for the above β-lactam). o For community-acquired methicillin-resistant *Staphylococcus aureus* infection, add vancomycin or linezolid.
American Thoracic Society/ Infectious Diseases Society of America: **Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia (2005)**[38]	• Select an initial empiric therapy based on the absence or presence of risk factors for multidrug-resistant pathogens. These risk factors include prolonged duration of hospitalization (five days or more), admission from a healthcare-related facility, and recent prolonged antibiotic therapy. • Patients with healthcare-related pneumonia should be treated for potentially drug-resistant organisms, regardless of when during the hospital stay the pneumonia begins. • In selecting empiric therapy for patients who have recently received an antibiotic, an effort should be made to use an agent from a different antibiotic class, because recent therapy increases the probability of inappropriate therapy and can predispose to resistance to that same class of antibiotics. • Initial empiric antibiotic therapy for hospital-acquired pneumonia or ventilator-associated pneumonia in patients with no known risk factors for multidrug-resistant pathogens, early onset, and any disease severity: o Ceftriaxone; OR o Levofloxacin, moxifloxacin, ciprofloxacin; OR o Ampicillin-sulbactam; OR o Ertapenem. • Initial empiric antibiotic therapy for hospital-acquired pneumonia, ventilator-associated pneumonia, and healthcare-associated pneumonia in patients with late-onset disease or risk factors for multidrug-resistant pathogens and all disease severity–combination antibiotic therapy is recommended as follows: o Antipseudomonal cephalosporin (cefepime, ceftazidime) or antipseudomonal carbapenem (imipenem or meropenem) or β-lactam-β-lactamase inhibitor (piperacillin-tazobactam) plus antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) or aminoglycoside (amikacin, gentamicin, or tobramycin) plus linezolid or vancomycin if methicillin-resistant *Staphylococcus aureus* risk factors are present or there is a high incidence locally.
Infectious Diseases Society of America: **Diagnosis and Management of Complicated Intra-abdominal Infection in Adults and Children (2010)**[39]	<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.

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	• 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 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. <u>Health care-associated infection:</u> • 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

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	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. <u>Cholecystitis and cholangitis:</u> • 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: **Clinical Assessment, Treatment, and Prevention of Lyme Disease, Human Granulocytic Anaplasmosis, and Babesiosis (2006)**[40]	• Doxycycline, amoxicillin or cefuroxime axetil for 14 days is recommended for the treatment of adult patients with early localized or early disseminated Lyme disease associated with erythema migrans, in the absence of specific neurologic manifestations (see Lyme meningitis, below) or advanced atrioventricular heart block. • Each of these antimicrobial agents has been shown to be highly effective for the treatment of erythema migrans and associated symptoms in prospective studies. • Doxycycline has the advantage of being effective for treatment of Human Granulocytic Anaplasmosis (but not for babesiosis), which may occur simultaneously with early Lyme disease.
Infectious Diseases Society of America: **Management of Patients with Infections Caused by Methicillin-Resistant *Staphylococcus Aureus* (2011)**[41]	<u>Skin and soft-tissue infections</u> • For a cutaneous abscess, incision and drainage is the primary treatment. For simple abscesses or boils, incision and drainage alone is likely to be adequate. • Antibiotic therapy is recommended for abscesses associated with the following conditions: severe or extensive disease (e.g., involving multiple sites of infection) or rapid progression in presence of associated cellulitis, signs and symptoms of systemic illness, associated comorbidities or immunosuppression, extremes of age, abscess in an area difficult to drain (e.g., face, hand, and genitalia), associated septic phlebitis, and lack of response to incision and drainage alone. • For outpatients with purulent cellulitis, empirical therapy for community-acquired methicillin-resistant *Staphylococcus aureus* is recommended pending culture results. Empirical therapy for infection due to beta-hemolytic streptococci is likely to be unnecessary. • For outpatients with non-purulent cellulitis, empirical therapy for infection due to beta-hemolytic streptococci is recommended. Empirical coverage for community-acquired methicillin-resistant *Staphylococcus aureus* is recommended in patients who do not respond to beta-lactam therapy and may be considered in those with systemic toxicity. • For empirical coverage of community-acquired methicillin-resistant *Staphylococcus aureus* in outpatients with skin and soft-tissue infections, oral antibiotic options include the following: clindamycin, sulfamethoxazole-trimethoprim, a tetracycline (doxycycline or minocycline), and linezolid. If coverage for both beta-hemolytic streptococci and community-acquired methicillin-resistant *Staphylococcus aureus* is desired, options include the following: clindamycin alone or sulfamethoxazole-trimethoprim or a tetracycline in combination with a beta-lactam (e.g., amoxicillin) or linezolid alone. • The use of rifampin as a single agent or as adjunctive therapy for the treatment of skin and soft-tissue infections is not recommended. • For hospitalized patients with complicated skin and soft-tissue infections, in addition to surgical debridement and broad-spectrum antibiotics, empirical therapy for methicillin-resistant *Staphylococcus aureus* should be considered pending culture data. Options include the following: vancomycin intravenous, linezolid oral or intravenous, daptomycin intravenous, telavancin intravenous, and clindamycin intravenous or oral. A beta-lactam antibiotic (e.g., cefazolin) may be considered in hospitalized patients with non-purulent cellulitis with modification to methicillin-

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	resistant *Staphylococcus aureus*-active therapy if there is no clinical response. • For children with minor skin infections (such as impetigo) and secondarily infected skin lesions (such as eczema, ulcers, or lacerations), mupirocin 2% topical ointment can be used. • Tetracyclines should not be used in children <8 years of age. • In hospitalized children with skin and soft-tissue infections, vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, empirical therapy with clindamycin intravenous is an option if the clindamycin resistance rate is low (<10%) with transition to oral therapy if the strain is susceptible. Linezolid oral or intravenous is an alternative. <u>Methicillin-resistant Staphylococcus aureus and infective endocarditis (native valve)</u> • For adults with uncomplicated bacteremia, vancomycin or daptomycin intravenous for at least two weeks is recommended. For complicated bacteremia, four to six weeks of therapy is recommended, depending on the extent of infection. • For adults with infective endocarditis, intravenous vancomycin or daptomycin for six weeks is recommended. • Addition of gentamicin to vancomycin is not recommended for bacteremia or native valve infective endocarditis. <u>Methicillin-resistant *Staphylococcus aureus* bacteremia and infective endocarditis (prosthetic valve)</u> • Intravenous vancomycin plus rifampin oral or intravenous for at least six weeks plus gentamicin intravenous for two weeks. • In children, vancomycin intravenous is recommended for the treatment of bacteremia and infective endocarditis. Duration of therapy may range from two to six weeks depending on source, presence of endovascular infection, and metastatic foci of infection. • Data regarding the safety and efficacy of alternative agents in children are limited, although daptomycin intravenous may be an option. Clindamycin or linezolid should not be used if there is concern for infective endocarditis or endovascular source of infection, but may be considered in children whose bacteremia rapidly clears and is not related to an endovascular focus. • Data are insufficient to support the routine use of combination therapy with rifampin or gentamicin in children with bacteremia or infective endocarditis. <u>Management of methicillin-resistant *Staphylococcus aureus* pneumonia</u> • For hospitalized patients with severe community-acquired pneumonia, empirical therapy for methicillin-resistant *Staphylococcus aureus* is recommended pending sputum and/or blood culture results. • For health care–associated methicillin-resistant *Staphylococcus aureus* or community-acquired methicillin-resistant *Staphylococcus aureus* pneumonia, intravenous vancomycin or linezolid oral or intravenous or clindamycin oral or intravenous, if the strain is susceptible, is recommended for seven to 21 days, depending on the extent of infection. • In children, intravenous vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, clindamycin intravenous can be used as empirical therapy if the clindamycin resistance rate is low (<10%) with transition to oral therapy if the strain is susceptible. Linezolid oral or intravenous is an alternative. <u>Management of methicillin-resistant *Staphylococcus aureus* bone and joint infections</u> • Antibiotics available for parenteral administration include intravenous vancomycin and daptomycin. • Some antibiotic options with parenteral and oral routes of administration include the

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	following: sulfamethoxazole-trimethoprim in combination with rifampin, linezolid, and clindamycin. Some experts recommend the addition of rifampin. For patients with concurrent bacteremia, rifampin should be added after clearance of bacteremia.
	• A minimum eight-week course is recommended. Some experts suggest an additional one to three months (and possibly longer for chronic infection or if debridement is not performed) of oral rifampin-based combination therapy with sulfamethoxazole-trimethoprim, doxycycline-minocycline, clindamycin, or a fluoroquinolone, chosen on the basis of susceptibilities.
	• For septic arthritis, refer to antibiotic choices for osteomyelitis. A three to four-week course of therapy is suggested.
	
	<u>Management of methicillin-resistant *Staphylococcus aureus* infections of the central nervous system</u>
	• Meningitis
	  o Intravenous vancomycin for two weeks is recommended. Some experts recommend the addition of rifampin.
	  o Alternatives include the following: linezolid or sulfamethoxazole-trimethoprim.
	  o For central nervous system shunt infection, shunt removal is recommended, and it should not be replaced until cerebrospinal fluid cultures are repeatedly negative.
	• Brain abscess, subdural empyema, spinal epidural abscess
	  o Intravenous vancomycin for four to six weeks is recommended. Some experts recommend the addition of rifampin.
	  o Alternatives include the following: linezolid and sulfamethoxazole-trimethoprim.
	• Septic thrombosis of cavernous or dural venous sinus
	  o Intravenous vancomycin for four to six weeks is recommended. Some experts recommend the addition of rifampin.
	  o Alternatives include the following: linezolid and sulfamethoxazole-trimethoprim.
	  o Intravenous vancomycin is recommended in children.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the penicillins are noted in Tables 5 and 6. 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 5. FDA-Approved Indications for the Single Entity Penicillins[1-11]

Indication	Amoxi-cillin	Ampi-cillin	Dicloxa-cillin	Naf-cillin	Oxa-cillin	Penicillin G Benzathine	Penicillin G Potassium	Penicillin G Sodium	Penicillin G Procaine	Penicillin V Potassium
Central Nervous System Infections										
Chorea (prophylaxis)						✔				✔
Meningitis		✔ ‡§					✔	✔		
Neurosyphilis						✔	✔	✔	✔	
Dermatological Infections										
Bejel						✔			✔	
Erysipelas									✔	✔
Erysipeloid									✔	
Gas gangrene								✔		
Pinta						✔			✔	
Skin and skin-structure infections	✔ §								✔	✔
Yaws						✔			✔	
Gastrointestinal Infections										
Gastrointestinal infections		✔ ‡§								
Treatment of patients with *Helicobacter pylori* infection and duodenal ulcer disease (active or one year history of a duodenal ulcer) to eradicate *Helicobacter pylori* (in combination with clarithromycin plus lansoprazole as triple therapy)	✔ §									
Treatment of patients with *Helicobacter pylori* infection and duodenal ulcer disease (active or one year history of a duodenal ulcer) who are either allergic or intolerant to clarithromycin or in whom resistance to clarithromycin is known or suspected (in combination with lansoprazole delayed-release capsules as dual therapy)	✔ §									
Genitourinary Infections										
Genitourinary infections	✔ §	✔ §					✔	✔		
Gonococcal infections							✔	✔		
Gonorrhea	✔ §	✔ §								
Syphilis						✔	✔	✔	✔	
Urinary tract infections		✔ ‡								
Respiratory Infections										
Ear, nose, and throat infections	✔ §									
Diphtheria (prevention of carrier state)							✔		✔	
Diphtheria (adjunct to antitoxin and prevention of carrier state)								✔		
Otitis media										✔
Pharyngitis and/or tonsillitis	✔ †								✔	✔

Indication	Amoxi-cillin	Ampi-cillin	Dicloxa-cillin	Naf-cillin	Oxa-cillin	Penicillin G Benzathine	Penicillin G Potassium	Penicillin G Sodium	Penicillin G Procaine	Penicillin V Potassium
Pneumonia							✔	✔	✔	
Respiratory tract infections		✔ ‡§							✔	✔
Respiratory tract infections (lower)	✔ §						✔	✔		
Respiratory tract infections (upper)						✔			✔	✔
Vincent's infection							✔	✔	✔	✔
Miscellaneous Infections										
Actinomycosis							✔	✔		
Anthrax							✔	✔	✔	
Bacteremia							✔	✔		
Botulism (adjunct to antitoxin)								✔		
Clostridial infections							✔	✔		
Empyema							✔	✔		
Endocarditis		✔ ‡					✔	✔	✔	✔
Fusospirochetosis							✔	✔		✔
Haverhill fever								✔		
Listeria infections							✔	✔		
Pasteurella infections							✔	✔		
Penicillinase-producing staphylococci			✔	✔	✔					
Pericarditis							✔	✔		
Rat-bite fever							✔	✔	✔	
Rheumatic fever (prophylaxis)						✔				✔
Scarlet fever									✔	✔
Septicemia		✔ ‡					✔	✔		
Staphylococcal infections							✔			
Streptococcal infections							✔		✔	
Tetanus (adjunct)								✔		

†Extended-release oral formulations.
§Immediate-release oral formulations.
‡Injection formulation.

Table 6. FDA-Approved Indications for the Combination Penicillins[1-11]

Indication	Amoxicillin and Clavulanate	Ampicillin and Sulbactam	Penicillin G Benzathine and Penicillin G Procaine	Piperacillin and Tazobactam
Dermatological Infections				
Abscesses (cutaneous)				✔
Cellulitis				✔
Diabetic foot infections				✔
Erysipelas			✔	
Skin and skin-structure infections	✔ §	✔	✔	✔
Genitourinary Infections				
Endometritis				✔
Gynecologic infections		✔		
Pelvic inflammatory disease				✔
Urinary tract infections	✔ §			
Respiratory Infections				

Indication	Amoxicillin and Clavulanate	Ampicillin and Sulbactam	Penicillin G Benzathine and Penicillin G Procaine	Piperacillin and Tazobactam
Otitis media	✔ §		✔	
Pneumonia			✔	
Pneumonia (community-acquired)	✔ †			✔
Pneumonia (nosocomial)				✔
Respiratory tract infections (lower)	✔ §			
Respiratory tract infections (upper)			✔	
Sinusitis	✔ §†			
Miscellaneous Infections				
Appendicitis				✔
Bone and/or joint infections				
Intra-abdominal infections		✔		
Peritonitis				✔
Scarlet fever			✔	
Septicemia				

IV. Pharmacokinetics

The pharmacokinetic parameters of the penicillins are listed in Table 7.

Table 7. Pharmacokinetic Parameters of the Penicillins[1-11]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents					
Amoxicillin	89	20	Not reported	Renal (50 to 70)	1.0 to 1.3
Ampicillin	50	20	Not reported	Renal (40 to 92) Bile	1.0 to 1.9
Dicloxacillin	60 to 80	96	Not reported	Renal (35 to 90) Feces (not reported)	0.6 to 0.8
Nafcillin	N/A	90	Liver (60 to 70)	Renal (31 to 38) Bile (8) Feces (not reported)	0.5 to 1.0
Oxacillin	N/A	94	Liver (75)	Renal (39 to 66)	20 to 60 minutes
Penicillin G	Oral: <30 IM: 72	65	Liver (30)	Renal (79 to 85)	20 to 50 minutes
Penicillin V	25 to 60	60 to 80	Not reported	Renal (20 to 40) Feces (32)	30 to 40 minutes
Combination Products					
Amoxicillin and clavulanate	Well absorbed	A: 18 C: 25	C: Liver	A: Renal (50 to 70) C: Renal (25 to 40)	A: 1.0 to 1.3 C: 1.0
Ampicillin and sulbactam	A: 92 (IM) S: 100 (IM)	A: 17 to 28 S: 38	Not reported	Renal (75 to 85)	A: 1.0 to 1.8 S: 1.0 to 1.3
Penicillin G benzathine and penicillin G procaine	IM: slowly	30 to 60	Liver (30)	Renal (60 to 90)	20 to 30 minutes
Piperacillin and tazobactam	IM: 71	30	Liver	P: Renal (68) T: Renal (80)	0.7 to 1.2

IM=intramuscular, N/A=not applicable

V. Drug Interactions

Major drug interactions with the penicillins are listed in Table 8.

Table 8. Major Drug Interactions with the Penicillins[2]

Generic Name(s)	Interaction	Mechanism
Penicillins	Anticoagulants	Plasma concentrations and anticoagulant effects of anticoagulants may be decreased by these agents.
Penicillins	Tetracyclines	The antimicrobial effectiveness of penicillins may be decreased by tetracyclines.
Penicillins	Methotrexate	Penicillins may increase the serum concentrations and

Generic Name(s)	Interaction	Mechanism
		pharmacologic effects of methotrexate. Toxicity may occur.
Amoxicillin	Venlafaxine	Concurrent use my result in an increased risk of serotonin syndrome.
Nafcillin	Cyclosporine	Concurrent use may result in decreased cyclosporine concentrations.
Piperacillin	Vecuronium	Concurrent use of piperacillin and vecuronium may result in enhanced and/or prolonged neuromuscular blockade which may lead to respiratory depression and paralysis.

VI. Adverse Drug Events

The most common adverse drug events reported with the penicillins are listed in Tables 9 and 10. The boxed warning for penicillin G benzathine and penicillin G benzathine-penicillin G procaine is listed in Table 11.

Table 9. Adverse Drug Events (%) Reported with the Single Entity Penicillins[1-11]

Adverse Events	Amoxicillin	Ampicillin	Dicloxacillin	Nafcillin	Oxacillin	Penicillin G	Penicillin V
Cardiovascular							
Chest pain	-	-	-	-	-	-	-
Cardiac arrest	-	-	-	-	-	✔	-
Myocardial infarction	-	-	-	-	-	✔	-
Myocarditis	-	-	-	-	-	✔	-
Central Nervous System							
Agitation	✔	-	-	-	-		-
Anxiety	✔	-	-	-	-	-	-
Behavioral changes	✔	-	-	-	-	-	-
Chills	-	-	-	-	-	-	-
Coma	-	-	-	-	-	✔	-
Confusion	✔	-	-	-	-	-	-
Dizziness	✔	-	-	-	-	-	-
Fatigue	-	-	-	-	-	-	-
Fever	-	✔	-	-	✔	-	-
Headache	✔	-	-	-	-	-	-
Hyperactivity	✔	-	-	-	-	-	-
Hyperflexia	-	-	-	-	-	✔	-
Insomnia	✔	-	-	-	-	✔	-
Jarisch-Herxheimer reaction	-	-	-	-	-	✔	-
Myoclonus	-	-	-	-	-	-	-
Neurotoxicity	-	-	-	✔	-	-	-
Penicillin encephalopathy	-	✔	-	-	-	-	-
Seizure	✔	✔	<1	-	-	✔	<1
Dermatologic							
Acute exanthematous pustulosis	✔	-	-	-	-	-	-
Contact dermatitis	-	-	-	-	-	✔	-
Cutis laxa	-	-	-	-	-	✔	-
Diaper rash	-	-	-	-	-	-	-
Erythema	-	-	-	-	-	-	-
Erythema multiforme	✔	✔	-	-	-	-	-
Erythematous maculopapular rash	✔	-	-	-	-	-	-

Adverse Events	Amoxicillin	Ampicillin	Dicloxacillin	Nafcillin	Oxacillin	Penicillin G	Penicillin V
Erythroderma	-	✔	-	-	-	-	-
Exfoliative dermatitis	✔	✔	-	-	-	-	-
Facial swelling	-	-	-	-	-	-	-
Lipoatrophy	-	-	-	-	-	✔	-
Rash	-	✔	<1	-	✔	✔	-
Stevens-Johnson syndrome	✔	✔	-	-	-	-	-
Toxic epidermal necrolysis	✔	✔	-	-	-	-	-
Tissue necrosis	-	-	-	-	-	✔	-
Urticaria	✔	✔	-	-	-	✔	-
Gastrointestinal							
Abdominal distension	-	-	-	-	-	-	-
Abdominal pain	-	-	1 to 10	-	-	✔	-
Black hairy tongue	✔	✔	-	-	-	✔	✔
Clostridium difficile colitis	-	-	-	-	-	-	✔
Diarrhea	✔	✔	1 to 10	-	✔	-	>10
Enterocolitis	-	✔	-	-	-	-	-
Epigastric discomfort	-	-	-	-	-	-	✔
Flatulence	-	-	-	-	-	-	-
Gastritis	-	-	-	-	-	-	-
Glossitis	-	✔	-	-	-	-	-
Hemorrhagic colitis	✔	-	-	-	-	-	-
Indigestion	-	-	-	-	-	-	-
Loose stools	-	-	-	-	-	-	-
Mucocutaneous candidiasis	✔	-	-	-	-	-	-
Mucosal bleeding	-	-	-	-	-	-	-
Nausea	✔	✔	1 to 10	-	✔	✔	>10
Oral candidiasis	-	-	-	-	-	-	>10
Pseudomembranous colitis	✔	✔	<1	✔	-	✔	-
Sore mouth or tongue	-	✔	-	-	-	-	-
Stomatitis	-	✔	-	-	-	✔	-
Throat tightness	-	-	-	-	-	-	-
Tooth discoloration	✔	-	-	-	-	-	-
Vomiting	✔	✔	1 to 10	-	✔	✔	>10
Genitourinary							
Crystalluria	✔	-	-	-	-	-	-
Dysuria	-	-	-	-	-	-	-
Hematuria	-	-	-	-	✔	-	-

Adverse Events	Amoxicillin	Ampicillin	Dicloxacillin	Nafcillin	Oxacillin	Penicillin G	Penicillin V
Interstitial nephritis	-	✔	<1	✔	✔	✔	<1
Renal tubular damage	-	-	-	✔	-	✔	-
Urinary retention	-	-	-	-	-	-	-
Vaginal mycosis	-	-	-	-	-	-	-
Vaginitis	-	-	<1	-	-	-	-
Hematologic							
Agranulocytosis	✔	✔	<1	✔	✔	✔	-
Anemia	✔	✔	-	-	-	✔	-
Bone marrow depression	-	-	-	✔	-	-	-
Eosinophilia	✔	✔	<1	-	✔	✔	-
Hemolytic anemia	✔	✔	<1	-	-	✔	✔
Leukopenia	✔	✔	<1	-	✔	✔	-
Neutropenia	-	-	<1	✔	✔	✔	-
Prothrombin time increased	-	-	-	-	-	✔	-
Thrombocytopenia	✔	✔	<1	-	✔	-	-
Thrombocytopenia purpura	✔	✔	-	-	-	-	-
Thrombocytosis	-	-	-	-	-	-	-
Hepatic							
Acute cytolytic hepatitis	✔	-	-	-	-	-	-
Cholestatic jaundice	✔	-	-	-	-	✔	-
Hepatic cholestasis	✔	-	-	-	-	-	-
Hepatic dysfunction	-	-	-	-	-	-	-
Hepatitis	-	-	-	-	-	-	-
Hepatotoxicity	-	-	<1	-	✔	✔	-
Laboratory Test Abnormalities							
Alkaline phosphatase increased	-	-	-	-	-	-	-
Liver function tests increased	✔	✔	-	-	✔	-	-
Other							
Anaphylaxis	✔	✔	-	✔	-	✔	✔
Angioedema	-	-	-	-	-	-	-
Candidiasis	-	-	-	-	-	-	-
Edema	-	-	-	-	-	-	-
Epistaxis	-	-	-	-	-	-	-
Hypersensitivity reaction	-	✔	<1	✔	-	✔	✔
Hypersensitivity vasculitis	✔	-	-	-	-	-	-
Injection site reaction	-	-	-	✔	-	-	-
Laryngeal stridor	-	✔	-	-	-	-	-

Adverse Events	Amoxicillin	Ampicillin	Dicloxacillin	Nafcillin	Oxacillin	Penicillin G	Penicillin V
Malaise	-	-	-	-	-	-	-
Moniliasis	-	-	-	-	-	-	-
Pain at injection site	-	-	-	✔	-	-	-
Pruritus	-	-	-	-	-	-	-
Serum sickness-like reaction	✔	✔	<1	✔	✔	✔	-
Substernal pain	-	-	-	-	-	-	-
Thrombophlebitis	-	-	-	✔	-	✔	-
Vasculitis	-	-	-	-	-	-	-

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

Table 10. Adverse Drug Events (%) Reported with the Combination Penicillins[1-11]

Adverse Events	Amoxicillin and Clavulanate	Ampicillin and Sulbactam	Penicillin G Benzathine and Penicillin G Procaine	Piperacillin and Tazobactam
Cardiovascular				
Arrhythmia	-	-	-	≤1
Atrial fibrillation	-	-	-	≤1
Bradycardia	-	-	-	≤1
Cardiac arrest	-	-	✔	≤1
Cardiac failure	-	-	-	≤1
Chest pain	-	<1	-	≤1
Circulatory failure	-	-	-	≤1
Conduction disturbances	-	-	✔	-
Cyanosis	-	-	✔	-
Edema	-	-	-	≤1
Hypertension	-	-	-	2
Hypotension	-	-	✔	≤1
Myocardial depression	-	-	✔	-
Myocardial infarction	-	-	-	≤1
Myocarditis	-	-	-	-
Pallor	-	-	✔	-
Palpitations	-	-	✔	-
Syncope	-	-	✔	≤1
Tachycardia	-	-	✔	≤1
Vasodilation	-	-	✔	-
Vasospasm	-	-	✔	-
Vasovagal reaction	-	-	✔	-

Adverse Events	Amoxicillin and Clavulanate	Ampicillin and Sulbactam	Penicillin G Benzathine and Penicillin G Procaine	Piperacillin and Tazobactam
Ventricular fibrillation	-	-	-	≤1
Central Nervous System				
Agitation	✔	-	-	2
Anxiety	✔	-	✔	≤1
Cerebral vascular accident	-	-	✔	-
Central nervous system stimulation	-	-	✔	-
Coma	-	-	✔	-
Confusion	✔	-	✔	≤1
Depression	-	-	-	≤1
Dizziness	✔	-	✔	≤1
Drowsiness	-	-	✔	-
Euphoria	-	-	✔	-
Fatigue	-	✔	✔	-
Fever	-	-	-	2 to 5
Hallucination	-	-	-	≤1
Headache	✔	✔	✔	8
Hyperreflexia	-	-	-	-
Insomnia	✔	✔	-	7
Jarisch-Herxheimer reaction	-	-	✔	-
Myoclonus	-	-	-	-
Nervousness	-	-	✔	-
Numbness	-	-	✔	-
Seizures	-	✔	✔	≤1
Somnolence	-	-	✔	-
Tremor	-	-	✔	≤1
Vertigo	-	-	-	≤1
Dermatologic				
Acute exanthematous pustulosis	✔	-	-	-
Abscess	-	-	✔	2
Atrophy	-	-	✔	-
Bruising	-	-	✔	-
Cellulitis	-	-	✔	-
Contact dermatitis	-	-	-	-
Cutis laxa	-	-	-	-
Diaphoresis	-	✔	-	≤1
Edema	-	-	✔	-
Erythema multiforme	✔	-	-	≤1

Adverse Events	Amoxicillin and Clavulanate	Ampicillin and Sulbactam	Penicillin G Benzathine and Penicillin G Procaine	Piperacillin and Tazobactam
Flushing	-	-	-	≤1
Gangrene	-	-	✔	-
Hemorrhage	-	-	✔	-
Inflammation	-	-	✔	≤1
Lipoatrophy	-	-	-	-
Lump	-	-	✔	-
Necrosis	-	-	✔	-
Pain	-	-	✔	2
Photophobia	-	-	-	≤1
Pruritus	-	-	-	3
Purpura	-	-	-	≤1
Rash	1 to 10	1 to 10	-	4
Skin ulcer	-	-	✔	-
Stevens-Johnson syndrome	✔	-	-	≤1
Tissue necrosis	-	-	-	-
Toxic epidermal necrolysis	-	-	-	≤1
Urticaria	1 to 10	<1	-	-
Gastrointestinal				
Abdominal pain	1 to 10	-	-	1 to 2
Black hairy tongue	✔	<1	-	-
Bloody stool	-	-	✔	-
Clostridium difficile colitis	-	-	-	✔
Constipation	-	-	-	1 to 8
Diarrhea	3 to 34	1 to 10	-	7 to 11
Epigastric discomfort	✔	✔	-	-
Flatulence	✔	-	-	≤1
Gastritis	✔	✔	-	≤1
Ileus	-	-	-	≤1
Intestinal necrosis	-	-	✔	-
Nausea	1 to 10	✔	-	7
Oral candidiasis	-	-	-	-
Pseudomembranous colitis	✔	✔	✔	≤1
Stomatitis	✔	-	-	-
Stool changes	-	-	-	2
Taste perversion	-	-	-	≤1
Thirst	-	-	-	≤1
Ulcerative stomatitis	-	-	-	≤1

Adverse Events	Amoxicillin and Clavulanate	Ampicillin and Sulbactam	Penicillin G Benzathine and Penicillin G Procaine	Piperacillin and Tazobactam
Vomiting	1 to 10	<1	-	3 to 4
Genitourinary				
Dysuria	-	✔	-	≤1
Genital pruritus	-	-	-	≤1
Hematuria	✔	-	✔	≤1
Hemorrhagic cystitis	-	-	-	-
Impotence	-	-	✔	-
Incontinence	-	-	-	≤1
Interstitial nephritis	✔	✔	✔	≤1
Leukorrhea	-	-	-	≤1
Myoglobinuria	-	-	✔	-
Neurogenic bladder	-	-	✔	-
Oliguria	-	-	-	≤1
Priapism	-	-	✔	-
Proteinuria	-	-	✔	-
Renal failure	-	-	✔	≤1
Renal tubular damage	-	-	-	-
Urinary retention	-	✔	-	≤1
Vaginitis	1 to 10	-	-	≤1
Hematologic				
Agranulocytosis	✔	-	-	≤1
Anemia	✔	-	-	≤1
Bleeding	-	-	-	-
Eosinophilia	✔	-	-	-
Granulocytopenia	-	-	-	-
Hemolytic anemia	✔	-	✔	≤1
Leukopenia	✔	-	-	✔
Neutropenia	-	-	✔	✔
Pancytopenia	-	-	-	≤1
Positive Coombs' reaction	-	-	✔	-
Prothrombin time prolonged	✔	-	-	-
Thrombocytopenia	✔	✔	-	≤1
Thrombocytosis	✔	-	-	≤1
Hepatic				
Cholestatic jaundice syndrome	✔	-	-	-
Hepatitis	✔	-	-	≤1
Hepatotoxicity	✔	-	-	-

Adverse Events	Amoxicillin and Clavulanate	Ampicillin and Sulbactam	Penicillin G Benzathine and Penicillin G Procaine	Piperacillin and Tazobactam
Jaundice	-	-	-	≤1
Liver function tests increased	✔	<1	✔	1 to 10
Laboratory Test Abnormalities				
Blood urea nitrogen increased	-	-	✔	-
Electrolyte imbalance	-	-	-	-
Hypoglycemia	-	-	-	≤1
Serum creatinine increased	-	-	✔	-
Musculoskeletal				
Arthralgia	-	-	-	≤1
Arthritis exacerbation	-	-	✔	-
Back pain	-	-	-	≤1
Joint disorder	-	-	✔	-
Myalgia	-	-	-	≤1
Periostitis	-	-	✔	-
Rhabdomyolysis	-	-	✔	-
Traverse myelitis	-	-	✔	-
Weakness	-	-	✔	-
Respiratory				
Bronchospasm	-	-	-	≤1
Coughing	-	-	-	≤1
Dyspnea	-	-	-	3
Pharyngitis	-	-	-	2
Other				
Anaphylaxis	✔	✔	-	≤1
Blindness	-	-	✔	-
Blurred vision	-	-	✔	-
Candidiasis	-	<1	-	≤1
Diaphoresis	-	<1	✔	-
Epistaxis	-	-	-	≤1
Hemorrhage	-	-	-	≤1
Hiccough	-	-	-	≤1
Hypersensitivity reaction	-	1 to 10	✔	✔
Infection	-	-	-	2
Injection site reaction	-	-	-	≤1
Lymphadenopathy	-	-	✔	-
Malaise	-	-	-	≤1
Mesenteric embolism	-	-	-	≤1

Adverse Events	Amoxicillin and Clavulanate	Ampicillin and Sulbactam	Penicillin G Benzathine and Penicillin G Procaine	Piperacillin and Tazobactam
Moniliasis	-	-	-	2
Mottling	-	-	✔	-
Myoclonus	-	-	✔	-
Neurovascular damage	-	-	✔	-
Pseudoanaphylactic reaction	-	-	✔	-
Pulmonary edema	-	-	-	≤1
Pulmonary embolism	-	-	-	≤1
Rhinitis	-	-	-	≤1
Rigors	-	-	-	≤1
Sepsis	-	-	-	2
Serum sickness-like reaction	-	-	✔	-
Thrombophlebitis	-	1 to 10	✔	≤1
Tinnitus	-	-	-	≤1
Warmth	-	-	✔	-

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

Table 11. Boxed Warning for the Penicillin G Benzathine and Penicillin G Benzathine/Penicillin G Procaine[1]

WARNING
Not for intravenous use. Do not inject intravenously or admix with other intravenous solutions. There have been reports of inadvertent intravenous administration of penicillin G benzathine which has been associated with cardiorespiratory arrest and death. Prior to administration of this drug, carefully read the warnings, adverse reactions, and dosage and administration sections of the labeling.

VII. Dosing and Administration

The usual dosing regimens for the penicillins are listed in Table 12.

Table 12. Usual Dosing Regimens for the Penicillins[1-11]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Amoxicillin	Ear, nose, and throat infections (mild to moderate): Capsule, chewable tablet, suspension, tablet: 500 mg every 12 hours or 250 mg every eight hours Ear, nose, and throat infections (severe): Capsule, chewable tablet, suspension, tablet: 875 mg every 12 hours or 500 mg every eight hours Genitourinary tract infections (mild to moderate): Capsule, chewable tablet, suspension, tablet: 500 mg every 12 hours or 250 mg every eight hours Genitourinary tract infections (severe): Capsule, chewable tablet, suspension, tablet: 875 mg every 12 hours or 500 mg every eight hours Gonorrhea (acute), anogenital infections (uncomplicated), urethral infections: Capsule, chewable tablet, suspension, tablet: 3 g as a single dose *Helicobacter pylori* eradication to reduce the risk of duodenal ulcer recurrence: Dual therapy: Capsule, chewable tablet, suspension, tablet: 1 g	Ear, nose, and throat infections in patients >3 months of age (mild to moderate): Capsule, chewable tablet, suspension, tablet: 25 mg/kg/day in divided doses every 12 hours or 20 mg/kg/day in divided doses every eight hours Ear, nose, and throat infections in patients >3 months of age (severe): Capsule, chewable tablet, suspension, tablet: 45 mg/kg/day in divided doses every 12 hours or 40 mg/kg/day in divided doses every eight hours Genitourinary tract infections in patients >3 months of age (mild to moderate): Capsule, chewable tablet, suspension, tablet: 25 mg/kg/day in divided doses every 12 hours or 20 mg/kg/day in divided doses every eight hours Genitourinary tract infections in patients >3 months of age (severe): Capsule, chewable tablet, suspension, tablet: 45 mg/kg/day in divided doses every 12 hours or 40 mg/kg/day in divided doses every eight hours	Capsule: 250 mg 500 mg Chewable tablet: 125 mg 250 mg Suspension: 125 mg/5 mL 200 mg/5 mL 250 mg/5 mL 400 mg/5 mL Tablet: 500 mg 875 mg Extended-release tablet: 775 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	amoxicillin and 30 mg lansoprazole given three times daily for 14 days Triple therapy: Capsule, chewable tablet, suspension, tablet: 1 g amoxicillin, 500 mg clarithromycin, and 30 mg lansoprazole given twice daily for 14 days Respiratory tract infections (lower) (mild to moderate or severe): Capsule, chewable tablet, suspension, tablet: 875 mg every 12 hours or 500 mg every eight hours Skin and skin-structure infections (mild to moderate): Capsule, chewable tablet, suspension, tablet: 500 mg every 12 hours or 250 mg every eight hours Skin and skin-structure infections (severe): Severe: Capsule, chewable tablet, suspension, tablet: 875 mg every 12 hours or 500 mg every eight hours Tonsillitis and/or pharyngitis: Extended-release tablet: 775 mg once daily for 10 days with a meal	Gonorrhea (acute), anogenital infections (uncomplicated), urethral infections in prepubertal children (≥2 years of age): Capsule, chewable tablet, suspension, tablet: 50 mg/kg amoxicillin, combined with 25 mg/kg probenecid as a single dose Respiratory tract infections (lower) (mild to moderate or severe) in patients >3 months of age: Capsule, chewable tablet, suspension, tablet: 45 mg/kg/day in divided doses every 12 hours or 40 mg/kg/day in divided doses every eight hours Skin and skin-structure infections (mild to moderate) in patients >3 months of age: Capsule, chewable tablet, suspension, tablet: 25 mg/kg/day in divided doses every 12 hours or 20 mg/kg/day in divided doses every eight hours Skin and skin-structure infections (severe) in patients >3 months of age: Capsule, chewable tablet, suspension, tablet: 45 mg/kg/day in divided doses every 12 hours or 40 mg/kg/day in divided doses every eight hours Tonsillitis and/or pharyngitis in patients ≥12 years of age: Extended-release tablet: 775 mg once daily for 10 days with a meal Unspecified infections in patients ≤3 months of age: Capsule, chewable tablet, suspension, tablet: 30 mg/kg/day divided every 12 hours	
Ampicillin	Gastrointestinal and genitourinary tract infections:	Gastrointestinal and genitourinary tract infections:	Capsule: 250 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Injection: IM/IV 500 mg every six hours Capsule, suspension: 500 mg four times daily Gonorrhea (men and women): Capsule, suspension: 3.5 g as a single dose administered simultaneously with 1 g of probenecid Meningitis: Injection: 150 to 200 mg/kg/day, start with IV administration for at least three days and continue with the IM route every three to four hours Respiratory tract infections: Injection: IM/IV 250 to 500 mg every six hours Septicemia: Injection: 150 to 200 mg/kg/day, start with IV administration for at least three days and continue with the IM route every three to four hours Soft tissue infections: Injection (IM/IV): 250 to 500 mg every six hours Urethritis (males): Injection: IM/IV two doses of 500 mg each at an interval of eight to 12 hours	Injection: <40 kg, IM/IV 50 mg/kg/day in divided doses at six to eight hour intervals; ≥40 kg, IM/IV 500 mg every six hours Capsule, suspension: ≤20 kg, 100 mg/kg/day in divided doses administered four times daily; >20 kg: 500 mg four times daily Meningitis: Injection: 150 to 200 mg/kg/day, start with IV administration for at least three days and continue with the IM route every three to four hours Respiratory tract infections: Injection: <40 kg, IM/IV 25 to 50 mg/kg/day in divided doses at six to eight hour intervals; ≥40 kg, IM/IV 250 to 500 mg every six hours Septicemia: Injection: 150 to 200 mg/kg/day, start with IV administration for at least three days and continue with the IM route every three to four hours. Soft tissue infections: Injection: <40 kg, IM/IV 25 to 50 mg/kg/day in divided doses at six- to eight- hour intervals; ≥40 kg, IM/IV 250 to 500 mg every six hours Oral formulations: ≤20 kg, 50 mg/kg/day in divided doses administered three to four times daily; >20 kg, 250 mg four times daily	500 mg Injection: 125 mg 250 mg 500 mg 1 g 2 g 10 g Suspension: 125 mg/5 mL 250 mg/5 mL
Dicloxacillin	Unspecified infections: Capsule: 125 to 250 mg every six hours	Unspecified infections: Capsule: <40 kg, 12.5 to 25 mg/kg/day divided every six hours; ≥40 kg: 125 to 250 mg every six hours	Capsule: 250 mg 500 mg
Nafcillin	Unspecified infections (mild to moderate): Injection: 500 mg IM every four to six hours or 500 mg IV every four hours	Unspecified infections: Injection: neonates, 10 mg/kg IM twice daily; <40 kg, 25 mg/kg IM twice daily; ≥40 kg, 500 mg IM every four to six hours or 500 mg IV every four	Injection: 1 g 2 g 10 g

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Unspecified infections (severe): Injection: 1 g IM/IV every four hours	hours	
Oxacillin	Mild to moderate infections: Injection: 250 to 500 mg IM/IV every four to six hours Severe infections: Injection: 1 g IM/IV every four to six hours	Mild to moderate infections: Injection: <40 kg, 50 mg/kg/day IM/IV in divided doses every six hours; ≥40 kg, 250 to 500 mg IM/IV every four to six hours Severe infections: Injection: <40 kg, 100 mg/kg/day IM/IV in divided doses every four to six hours; ≥40 kg, 1 g IM/IV every four to six hours Unspecified infections in premature and neonates: Injection: 25 mg/kg/day IM/IV	Injection: 1 g 2 g 10 g
Penicillin G benzathine	Prophylaxis (rheumatic fever and glomerulonephritis): Injection: 1,200,000 units IM once a month or 600,000 units IM every two weeks Streptococcal (group A) upper respiratory tract infections: Injection: 1,200,00 units IM as a single dose Syphilis (primary, secondary and latent): Injection: 2,400,000 units IM as a single dose Late and neurosyphilis: Injection: 2,400,000 units IM at seven-day intervals for three doses Yaws, Bejel, Pinta: Injection: 1,200,000 units IM as a single dose	Streptococcal (group A) upper respiratory tract infections: Injection: <60 lbs, 300,000 to 600,000 units IM as a single dose; ≥60 lbs, 900,000 units IM as a single dose Syphilis (congenital) in patients <2 years of age: Injection: 50,000 units/kg IM as a single dose Syphilis (congenital) in patients two to 12 years of age: Injection: Adjust dosage based on adult dosage schedule	Injection: 600,000 units/mL 1.2 million units/2 mL 2.4 million units/4 mL
Penicillin G (potassium and sodium)	Actinomycosis (cervicofacial): Injection: 1 to 6 million units/day Actinomycosis (thoracic and abdominal disease): Injection: 10 to 20 million units/day Anthrax: Injection: A minimum of 5 to 8 million units/day until cure is	Diphtheria: Injection: 150,000 to 250,000 units/kg/day in divided doses every six hours for seven to 10 days Gonococcal infections (disseminated) (arthritis): Injection: <45 kg, 100,000 units/kg/day in four equally divided doses for seven to 10 days; ≥45 kg, 10 million	Injection (potassium): 1 million units/50 mL 2 million units/50 mL 3 million units/50 mL 5 million units 20 million units Injection (sodium):

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	effected Clostridial infections: Injection: 20 million units/day as an adjunct to antitoxin Diphtheria: Injection: 2 to 3 million units/day in divided doses for 10 to 12 days Erysipeloid endocarditis: Injection: 12 to 20 million units/day for four to six weeks Fusospirochetal infections (severe infections of oropharynx, lower respiratory tract and genital area): Injection: 5 to 10 million units/day Gonococcal infections (disseminated) (arthritis, meningitis, endocarditis): Injection: 10 million units/day Gram-negative bacillary infections (bacteremia): Injection: 20 to 80 million units/day Haverhill fever: Injection: 12 to 20 million units/day for three to four weeks Listeria infections (endocarditis): Injection: 15 to 20 million units/day for four weeks Listeria infections (meningitis): Injection: 15 to 20 million units/day for two weeks Meningococcal meningitis: Injection: 1 to 2 million units IM every two hours or 24 million units/day IV as 2 million units every two hours Pasteurella infections (bacteremia and meningitis): Injection: 4 to 6 million units/day for two weeks Rat-bite fever:	units/day in four equally divided doses Gonococcal infections (disseminated) (meningitis): Injection: <45 kg, 250,000 units/kg/day in equal doses every four hours for 10 to 14 days; ≥45 kg, 10 million units/day in four equally divided doses Gonococcal infections (disseminated) (endocarditis): Injection: <45 kg, 250,000 units/kg/day in equal doses every four hours for four weeks; ≥45 kg, 10 million units/day in four equally divided doses Haverhill fever: Injection: 150,000 to 250,000 units/kg/day in equal doses every four hours for four weeks Listeria infections in neonates: Injection: 500,000 to 1 million units/day Meningitis (pneumococcus and meningococcus): Injection: 250,000 units/kg/day divided in equal doses every four hours for seven to 14 days Rat-bite fever: Injection: 150,000 to 250,000 units/kg/day in equal doses every four hours for four weeks Serious infections (streptococci and meningococcus): Injection: 150,000 to 300,000 units/kg/day divided in equal doses every four to six hours Syphilis (congenital and neurosyphilis): Injection: 50,000 units/kg every four to six hours for 10 to 14 days	5 million units

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Injection: 12 to 20 million units/day for three to four weeks Septicemia: Injection: 1 to 2 million units IM every two hours or 24 million units/day IV as 2 million units every two hours Serious infections (streptococci, pneumococci, and staphylococci): Injection: 5 to 24 million units in divided doses every four to six hours Syphilis and neurosyphilis: Injection: 2 to 4 million units every four hours for 10 to 14 days		
Penicillin G procaine	Anthrax: Injection: 600,000 to 1 million units/day IM Anthrax, inhalational (postexposure): Injection: 1.2 million units IM every 12 hours Bacterial endocarditis: Injection: 600,000 to 1 million units/day IM Diphtheria (adjunctive therapy with antitoxin): Injection: 300,000 to 600,000 units/day IM Diphtheria (carrier state): Injection: 300,000 units/day IM for 10 days Erysipelas: Injection: 600,000 to 1 million units/day IM for at least 10 days Fusospirochetosis (Vincent's infection): Injection: 600,000 to 1 million units/day IM Pneumonia (moderately severe and uncomplicated): Injection: 600,000 to 1 million units/day IM	Anthrax, inhalational (postexposure): Injection: 25,000 units/kg every 12 hours Pneumonia: Injection: <60 lbs, 300,000 units/day IM Staphylococcal infections: Injection: <60 lbs, 300,000 units/day IM Streptococcal infections: Injection: <60 lbs, 300,000 units/day IM Syphilis (primary, secondary and latent) in patients >12 years of age: Injection: 600,000 units/day IM for eight days Syphilis (late) in patients >12 years of age: Injection: 600,000 units/day IM for 10 to 15 days; Syphilis (congenital): Injection: <70 lbs, 50,000 units/kg/day for 10 days	Injection: 600,000 units 1.2 million units/2 mL

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Rat-bite fever: Injection: 600,000 to 1 million units/day IM Scarlet fever: Injection: 600,000 to 1 million units/day IM for at least 10 days Skin and soft-tissue infections: Injection: 600,000 to 1 million units/day IM for at least 10 days Staphylococcal infections (moderately severe to severe): Injection: 600,000 to 1 million units/day IM Streptococcal infections: Injection: 600,000 to 1 million units/day IM for at least 10 days Syphilis (primary, secondary and latent): Injection: 600,000 units/day IM for eight days Syphilis (late): Injection: 600,000 units/day IM for 10 to 15 days Tonsillitis (moderately severe to severe): Injection: 600,000 to 1 million units/day IM for at least 10 days Upper respiratory tract infections: Injection: 600,000 to 1 million units/day IM for at least 10 days Yaws, Bejel, Pinta: Injection: Treatment as for syphilis in corresponding stage of disease		
Penicillin V potassium	Chorea (prophylaxis): Suspension, tablet: 125 to 250 mg twice daily on a continuing basis Erysipelas: Suspension, tablet: 125 to 250 mg every six to eight hours for 10 days Fusospirochetosis (Vincent's infection) of the oropharynx:	Chorea (prophylaxis) in patients ≥12 years of age: Suspension, tablet: 125 to 250 mg twice daily on a continuing basis Erysipelas in patients ≥12 years of age: Suspension, tablet: 125 to 250 mg every six to eight hours for 10 days	Solution: 125 mg/5 mL 250 mg/5 mL Tablet: 250 mg 500 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Suspension, tablet: 250 to 500 mg every six to eight hours Pneumococcal infections: Suspension, tablet: 250 to 500 mg every six hours Prophylaxis (procedures): Suspension, tablet: 2 g one hour before procedure and 1 g six hours later Otitis media: Suspension, tablet: 250 to 500 mg every six hours Rheumatic fever (prophylaxis): Suspension, tablet: 125 to 250 mg twice daily on a continuing basis Scarlet fever: Suspension, tablet: 125 to 250 mg every six to eight hours for 10 days Skin and soft-tissue infections: Suspension, tablet: 250 to 500 mg every six to eight hours Staphylococcal infections: Suspension, tablet: 250 to 500 mg every six to eight hours Streptococcal infections: Suspension, tablet: 125 to 250 mg every six to eight hours for 10 days	Fusospirochetosis (Vincent's infection) of the oropharynx in patients ≥12 years of age: Suspension, tablet: 250 to 500 mg every six to eight hours Fusospirochetosis (Vincent's infection) of the oropharynx in patients <12 years of age: Suspension, tablet: 25 to 50 mg/kg/day in three to four divided doses Pneumococcal infections in patients ≥12 years of age: Suspension, tablet: 250 to 500 mg every six hours Prophylaxis (procedures): Suspension, tablet: <60 lbs, 1 g one hour before procedure and 1 g six hours later Prophylaxis (procedures) in patients ≥12 years of age: Suspension, tablet: 2 g one hour before procedure and 1 g six hours later Otitis media in patients ≥12 years of age: Suspension, tablet: 250 to 500 mg every six hours Otitis media in patients <12 years of age: Suspension, tablet: 25 to 50 mg/kg/day in three to four divided doses Rheumatic fever (prophylaxis) in patients ≥12 years of age: Suspension, tablet: 125 to 250 mg twice daily on a continuing basis Scarlet fever in patients ≥12 years of age: Suspension, tablet: 125 to 250 mg every six to eight hours for 10 days Scarlet fever in patients <12 years of age: Suspension, tablet: 25 to 50 mg/kg/day in three to four	

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		divided doses Skin and soft-tissue infections in patients ≥12 years of age: Suspension, tablet: 250 to 500 mg every six to eight hours Skin and soft-tissue infections in patients <12 years of age: Suspension, tablet: 25 to 50 mg/kg/day in three to four divided doses Staphylococcal infections in patients ≥12 years of age: Suspension, tablet: 250 to 500 mg every six to eight hours Streptococcal infections in patients ≥12 years of age: Suspension, tablet: 125 to 250 mg every six to eight hours for 10 days	
Combination Products			
Amoxicillin and clavulanate	Sinusitis: Extended-release tablet: Two tablets every 12 hours for 10 days Pneumonia (community-acquired): Extended-release tablet: Two tablets every 12 hours for seven to 10 days Unspecified infections: Chewable tablet, suspension, tablet: 500 mg every 12 hours or 250 mg every eight hours	Otitis media, sinusitis, respiratory tract infections (lower), more severe infections in patients >3 months of age: Chewable tablet, suspension: 45 mg/kg/day divided every 12 hours or 40 mg/kg/day divided every eight hours Sinusitis in patients ≥40 kg: Extended-release tablet: Two tablets every 12 hours for 10 days Less severe infections in patients >3 months of age: Chewable tablet, suspension: 25 mg/kg/day divided every 12 hours or 20 mg/kg/day divided every eight hours Pneumonia (community-acquired) in patients ≥40 kg: Extended-release tablet: Two tablets every 12 hours for seven to 10 days Severe infections and infections of the respiratory tract in patients ≥40 kg: Chewable tablet, suspension, tablet: 875 mg every 12 hours	Chewable tablet: 200-28.5 mg 400-57 mg Suspension: 125-31.25 mg/5 mL 200-28.5 mg/5 mL 250-62.5 mg/5 mL 400-57 mg/5 mL 600-42.9 mg/5 mL Tablet: 250-125 mg 500-125 mg 875-125 mg Extended-release tablet: 1,000-62.5 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		or 500 mg every eight hours Unspecified infections in patients ≤3 months of age: Chewable tablet, suspension, tablet: 30 mg/kg/day divided every 12 hours Unspecified infections in patients >3 months of age: Chewable tablet, suspension, tablet: 200 to 400 mg every 12 hours or 125 to 250 mg every eight hours Unspecified infections in patients ≥40 kg: Chewable tablet, suspension, tablet: 500 mg every 12 hours or 250 mg every eight hours	
Ampicillin and sulbactam	Unspecified infections: Injection: 1.5 to 3 g IM/IV every six hours	Unspecified infections in patients ≥1 year of age: Injection: ≤40 kg, 300 mg/kg IV every six hours; >40 kg: 1.5 to 3 g IM/IV every six hours	Injection: 1.5 g 3 g 15 g
Penicillin G benzathine and penicillin G procaine	Erysipelas: Injection: 2,400,000 units IM as a single dose Pneumococcal infections (except pneumococcal meningitis): Injection: 1,200,000 units IM repeated every two to three days until the temperature is normal for 48 hours Scarlet fever: Injection: 2,400,000 units IM as a single dose Skin and skin-structure infections: Injection: 2,400,000 units IM as a single dose Respiratory tract infections (upper): Injection: 2,400,000 units IM as a single dose	Erysipelas: Injection: <30 lbs, 600,000 units IM as a single dose; 30 to 60 lbs, 900,000 to 1,200,000 units IM as a single dose; >60 lbs, 2,400,000 units IM as a single dose Pneumococcal infections (except pneumococcal meningitis): Injection: 600,000 units IM repeated every two to three days until the temperature is normal for 48 hours Scarlet fever: Injection: <30 lbs, 600,000 units IM as a single dose; 30 to 60 lbs, 900,000 to 1,200,000 units IM as a single dose; >60 lbs 2,400,000 units IM as a single dose Skin and skin-structure infections: Injection: <30 lbs, 600,000 units IM as a single dose; 30 to 60 lbs, 900,000 to 1,200,000 units IM as a single dose; >60 lbs, 2,400,000 units IM as a	Injection: 900-300 units/2 mL 600-600 units/2 mL

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		single dose Respiratory tract infections (upper): Injection: <30 pounds, 600,000 units IM as a single dose; 30 to 60 lbs, 900,000 to 1,200,000 units IM as a single dose; >60 lbs, 2,400,000 units IM as a single dose	
Piperacillin and tazobactam	Pneumonia (nosocomial): Injection: 4.5 g IV every six hours with an aminoglycoside for seven to 14 days Unspecified infections: Injection: 3.375 g IV every six hours for seven to 10 days	Appendicitis and peritonitis in patients two to nine months of age: Injection: 80 mg piperacillin-10 mg tazobactam per kg IV every 8 hours for 7 to 10 days Appendicitis and peritonitis in patients ≥9 months of age (up to 40 kg): Injection: 100 mg piperacillin/12.5 mg tazobactam per kg IV every eight hours for seven to 10 days Appendicitis and peritonitis in patients >40 kg: Injection: 3.375 g every six hours for seven to 10 days	Injection: 2.25 g 3.375 g 4.5 g 40.5 g

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the penicillins are summarized in Table 13.

Table 13. Comparative Clinical Trials with the Penicillins

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Dermatological Infections				
Dagan et al.[42] (1989) Amoxicillin 40 mg/kg/day in three divided doses for 10 days vs amoxicillin-clavulanate 40 mg/kg/day for 10 days	DB, PRO Children six months to nine years of age with culture-positive (*Staphylococcus aureus* or β-hemolytic *Streptococcus*) nonbullous impetigo	N=51 10 days	Primary: Impetigo markedly improved or cured Secondary: New lesions	Primary: Treatment with amoxicillin-clavulanate resulted in faster clinical improvement compared to amoxicillin (95 vs 68% at five days; P<0.05) and showed a trend toward more clinical improvement at 10 days (96 vs 80%; P=NS). Secondary: Amoxicillin-clavulanate resulted in fewer new lesions at 10 days (0 vs 20%; P<0.05).
Vick-Fragoso et al.[43] (2009) Moxifloxacin 400 mg IV once daily for at least 3 days followed by 400 mg orally for 7 to 21 days vs amoxicillin-clavulanate 1,000-200 mg IV TID for at least 3	MC, OL, RCT Patients ≥18 years of age with complicated skin or skin structure infections	N=804 21 days	Primary: Clinical response at test of cure for the per protocol population Secondary: Clinical response at test of cure for the intent to treat population and clinical response at test of cure by indication, bacteriological success at test of cure for the per	Primary: Clinical cure (success) rates at test of cure for the per protocol population were not significantly different between the treatment groups: 80.6% for moxifloxacin compared to 84.5% for amoxicillin-clavulanate. These efficacy findings were supported by results for the intent to treat population: 72.7% for moxifloxacin compared to 74.8% for amoxicillin/clavulanate. Moxifloxacin was not inferior to amoxicillin-clavulanate for complicated skin or skin structure infections. Clinical success rates by indication were not significantly different among the treatment groups. The highest clinical success rates were for complicated erysipelas, abscess and surgical wound infection, and the lowest clinical success rates were for necrotizing fasciitis and diabetic foot infection. Clinical response rates in patients with a diabetic foot infection were similar between the two groups in patients with the most severe infections.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
days followed by 500 mg-125 mg orally TID for 7 to 21 days The decision to switch from IV to oral therapy was based on clinical response.			protocol population	Among the per protocol population, 19.4% of moxifloxacin- treated and 15.5% of amoxicillin-clavulanate-treated patients were clinical failures at test of cure. There were no significant differences in bacteriological success rates at test of cure in the per protocol population between moxifloxacin-treated patients (76.0%) and amoxicillin-clavulanate-treated patients (81.4%; 95% CI, -12.96 to 4.41; P=0.59).
Stevens et al.[44] (2000) Oxacillin 2 g IV every six hours followed by dicloxacillin 500 mg orally every six hours vs linezolid 600 mg IV every 12 hours	DB, DD, MC, RCT Hospitalized patients ≥18 years of age with a suspected gram-positive complicated skin and soft tissue infection	N=819 10 to 21 days	Primary: Clinical outcome and microbiological outcome based on resolution or improvement of clinical signs/ symptoms of skin and soft tissue infections at the end of treatment compared to baseline Secondary: Not reported	Primary: Of clinically evaluable patients (N=600), clinical cure rate was 88.6% in the linezolid group compared to 85.8% in the oxacillin and dicloxacillin group (P=0.300). Of microbiologically evaluable patients (N=294), the cure rate was 88.1% in the linezolid group compared to 86.1% in the oxacillin and dicloxacillin group (P=0.606). No statistically significant differences were noted in the frequency of adverse events between treatment groups. Secondary: Not reported
Tong et al.[45] (2010) SMX-TMP 20 to 4 mg/kg BID for five days vs penicillin	RCT Aboriginal children 2 months to 16 years of age with impetigo	N=13 7 days	Primary: Successful treatment of impetigo lesions at day seven after the commencement of treatment Secondary: Bacterial	Primary: Treatment was successful in all seven patients assigned to SMX-TMP, and five of six patients assigned to the penicillin group seven days after randomization (P=0.46). Secondary: By day four, microbiological clearance was documented in five of seven patients treated with SMX-TMP and in two of six patients treated with penicillin (P=0.28).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
benzathine 45 mg/kg IM as a single dose			resolution of sores at day four and day seven; successful treatment at day four	By day seven, microbiological clearance was documented in all seven patients treated with SMX-TMP and in three of six patients treatment with penicillin (P=0.07). Treatment was successful after four days in six of seven treated with SMX-TMP and three of six with penicillin (P=0.27).
Harkless et al.[46] (2005) Piperacillin-tazobactam 4-0.5 g every eight hours vs ampicillin-sulbactam 2-1 g every six hours	MC, OL, RCT Adult patients with moderate-to-severe infected diabetic foot ulcers	N=314 9 to 10 days	Primary: Clinical efficacy rates (cure or improvement) Secondary: Bacteriologic success rates, adverse events	Primary: Clinical success rates were similar for both treatment groups (71.2% for piperacillin-tazobactam vs 66.7% for ampicillin-sulbactam; P=NS). Secondary: Bacteriologic success rates were similar for both treatment groups (P=NS). Incidence and severity of adverse events were similar between the two treatment groups (P=NS).
Saltoglu et al.[47] (2010) Imipenem-cilastatin 0.5 g IV every six hours for 14 to 28 days vs piperacillin-tazobactam 4.5 g IV every eight hours for 14 to 28 days	OL, RCT, SC Patients ≥18 years of age with a diagnosis of moderate to severe diabetic lower extremity foot infection	N=64 2 months post-treatment	Primary: Clinical response Secondary: Relapse rate after two months	Primary: A successful clinical response was seen in 46.7% of patients in the piperacillin-tazobactam group and in 28.1% of patients in the imipenem group (RR, 1.6; 95% CI, 0.84 to 3.25; P=0.130). Secondary: During two months follow-up, two patients in the imipenem group and none in the piperacillin-tazobactam group relapsed (RR, 2; 95% CI, 0.94 to 4.24; P=0.058). Sixty-four percent of patients had amputations. There was no significant difference in amputation rates between the piperacillin-tazobactam and imipenem groups (60 vs 68.8%; P=0.739).
Tan et al.[48] (1993)	DB, MC, RCT Hospitalized	N=251 10 to 14 days	Primary: Clinical outcome	Primary: No significant difference in the overall clinical response was observed. The percentages of cured/improved/favorable outcomes were similar

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Piperacillin-tazobactam 3 g-375 mg every six hours vs ticarcillin-clavulanate 3 g-100 mg every six hours	patients with complicated skin and skin structure infections		Secondary: Bacteriological outcome	(61/15/76% for the piperacillin-tazobactam group vs 61/16/77% for the ticarcillin-clavulanate group; P=1.00). Secondary: No statistically significant differences in microbial eradication rates were observed between treatment groups for monomicrobial infections and polymicrobial infections.
Gesser et al.[49] (2004) Ertapenem 1 g IV daily vs piperacillin-tazobactam 13.5 grams IV divided every six hours Study medications were given as outpatient parenteral antimicrobial therapy or as inpatient therapy.	DB, MC, PRO, RCT Patients 18 years of age and older with skin and skin structure infections requiring parenteral therapy	N=146 10 to 21 days post-therapy	Primary: Clinical response, adverse events Secondary: Not reported	Primary: For patients receiving outpatient parenteral antimicrobial therapy, 83.3% in the ertapenem group and 82.0% in the piperacillin-tazobactam group had a clinical response to therapy and were considered cured (P=0.78). The only significant difference in adverse event between the two treatment groups was that 10.5% of patients in the piperacillin-tazobactam group experienced moderate-severe tenderness compared to 0% in the ertapenem group; P=0.006). Secondary: Not reported
Lipsky et al.[50] (2005) Ertapenem 1 g IV daily	DB, MC, RCT Adult patients with type 2 diabetes mellitus with a foot infection not	N=445 10 days after completion of antibiotic therapy	Primary: Proportion of patients with a favorable clinical response at the discontinuation of	Primary: At the discontinuation of IV therapy visit, 94% of patients in the ertapenem group and 92% in the piperacillin-tazobactam group had a favorable clinical response. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs piperacillin-tazobactam 3.375 g every six hours Investigators switched patients to oral therapy if appropriate after five days of IV therapy.	extending above the knees		IV therapy Secondary: Proportion of patients with a favorable clinical response at follow-up assessment	At the follow-up assessment visit, 87% of patients in the ertapenem group and 83% in the piperacillin-tazobactam group had a favorable clinical response.
Genitourinary Infections				
Brathwaite et al.[51] (1979) Amoxicillin 3 g as a single dose vs ampicillin 3 g as a single dose Both groups with probenecid 1 g pretreatment.	DB, PRO, RCT Men with uncomplicated gonorrhea	N=160 14 days	Primary: Cure rate (microbial and clinical resolution) Secondary: Adverse effects	Primary: Amoxicillin and ampicillin both had 98.6% cure rates (P=NS). Secondary: No adverse effects were reported.
Felman et al.[52] (1979) Amoxicillin 3 g for one dose vs ampicillin 3.5 g for one dose	PRO, RCT Adults with uncomplicated gonorrhea	N=115 1 week	Primary: Culture negativity one week post-treatment Secondary: Adverse effects	Primary: Amoxicillin and ampicillin were similarly curative (100 vs 96.2%; P=0.18). Secondary: Four patients on amoxicillin and two patients on ampicillin had mild adverse events.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Tran et al.[53] (2001) SMX-TMP 40-80 mg/kg/day for one to three days (short-treatment course) vs SMX-TMP 40-80 mg/kg/day for 7 to 14 days (long-treatment course) or amoxicillin for one to three days (short-treatment course) vs amoxicillin for 7 to 14 days (long-treatment course)	MA Children <18 years of age with uncomplicated cystitis confirmed by urine culture	N=1,279 (22 trials) Up to 14 days	Primary: Cure rate, adverse events Secondary: Not reported	Primary: There was no difference between short- and long-courses of SMX-TMP in terms of cure rates (difference in cure rate, 6.24%; 95% CI, -3.74 to 16.2). The short-course amoxicillin therapy was less effective in curing the infection compared to the conventional length of therapy (difference in cure rate, 13%; 95% CI, 4 to 24). Consequently, eight patients would need to receive a conventional amoxicillin course of therapy to prevent one treatment failure that would have occurred with a shorter duration of treatment. Drug-related toxicity increased in proportion to the length of therapy. Secondary: Not reported
Latif et al.[54] (1984) Amoxicillin 3 g and clavulanate 250 mg for one dose vs	Unblinded Men with uncomplicated gonococcal urethritis	N=121 14 days	Primary: Microbial cure (culture negative two weeks post-treatment) Secondary: Infections due to penicillinase-	Primary: Treatment with amoxicillin resulted in a higher cure rate compared to penicillin (90.6 vs 73.7%; P=0.01). Secondary: The rate of infection due to penicillinase-producing *Neisseria* (7.8 vs 15.8%) and post-gonococcal urethritis (7.8 vs 14.0%) were not statistically different between the two groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
penicillin procaine 2.4 million units IM for one dose			producing *Neisseria*, post gonococcal urethritis	
Gallacher et al.[55] (1986) Amoxicillin-clavulanate 250-125 mg orally for five days vs amoxicillin 250 mg orally for five days	DB, RCT Elderly inpatients with urinary tract infections	N=67 5 days	Primary: Bacteriologic cure at end of treatment Secondary: Bacteriologic cure after conversion to amoxicillin-clavulanate	Primary: Treatment with amoxicillin-clavulanate was more effective than treatment with amoxicillin at achieving a negative urine culture (87.5 vs 43.0%; P<0.001). Secondary: Of the patients who failed amoxicillin, 62.5% responded to amoxicillin-clavulanate.
Karney et al.[56] (1974) Ampicillin 3.5 g orally with probenecid 1 g orally for one dose vs amoxicillin 3 g orally for one dose	DB, RCT Adults with uncomplicated gonorrhea	N=108 2 weeks	Primary: Bacteriologic culture negative at two weeks post-treatment Secondary: Not reported	Primary: Treatment with ampicillin and treatment with amoxicillin had similar bacteriologic cure rates at two weeks post-treatment (98.3 vs 95.8%) in anogenital gonorrhea. Secondary: Not reported
Hook et al.[57] (2002) Azithromycin 2 g as a single dose vs	RCT Patients 18 to 56 years of age with early syphilis	N=74 12 months	Primary: Therapeutic response Secondary: Not reported	Primary: The overall response rate for patients in the benzathine penicillin G group was 86%. The overall response rate for patients in the single-dose azithromycin group was 94%, which was not significantly different from the penicillin group (P=0.75).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
azithromycin 2 g as two doses given six to eight days apart vs penicillin benzathine G 2.4 million units IM as a single dose				The overall response rate for patients in the double-dose azithromycin group was 83% and was not significantly different from the penicillin group (P=0.95). Secondary: Not reported
Hook et al.[58] (2010) Azithromycin 2 g as a single dose vs penicillin benzathine G 2.4 million units IM as a single dose	MC, OL, RCT Patients 18 to 55 years of age with early syphilis (primary, secondary, or early latent)	N=517 6 months	Primary: Serological cure of infection Secondary: Not reported	Primary: In the intent to treat analysis at the six-month follow-up visit, 77.6% of azithromycin patients and 78.5% of penicillin patients experienced serological cure (1-sided lower bound of the 95% CI of the difference, −7.2%). In the per protocol analysis at the six-month follow-up visit, 77.5% of azithromycin patients and 78.9%) of penicillin patients experienced serological cure (1-sided 95% CI lower bound, −7.9%). The efficacy of 2 g azithromycin administered orally was non-inferior to the administration of benzathine penicillin G for the treatment of early syphilis in patients without human immunodeficiency virus infection. Secondary: Not reported
Bai et al.[59] (2008) Azithromycin vs penicillin G benzathine	MA Patients ≥18 years of age with early syphilis	N=476 (4 trials) Variable duration	Primary: Cure rates and adverse events Secondary: Not reported	Primary: In the azithromycin group, serology cure occurred in 95% of patients. In the penicillin G benzathine group, serology cure occurred in 84.0% of patients (OR, 1.37; 95% CI, 1.05 to 1.77; P=0.02). The pooled OR for primary syphilis with the administration of azithromycin as compared to penicillin G benzathine was 0.69 (95% CI, 0.09 to 1.61; P=0.38). There was no significant difference in the rate of adverse events between

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				the treatment groups. Secondary: Not reported
Ryo et al.[60] (2005) Imipenem-cilastatin 500 mg IV BID for three days plus betamethasone 12 mg SC vs penicillin or a cephalosporin or no antibiotic treatment	RETRO Pregnant women admitted to hospital with preterm premature rupture of membranes at 24 weeks and 0 days to 31 weeks and 6 days gestation	N=140 1 year	Primary: Time from preterm premature rupture of membranes to delivery, prognosis of infants (death within one year, alive with or without handicap) Secondary: Sensitivity of imipenem-cilastatin to cultured bacteria obtained at admission compared to ampicillin	Primary: The mean time from preterm premature rupture of membranes to delivery was 11 days in the imipenem-cilastatin group and 6 days in the control group (P=0.016). Also 53% of women treated with imipenem-cilastatin were able to continue pregnancy for greater than one week after preterm premature rupture of membranes as opposed to 25% in the control group (P=0.0048). There were no infant deaths in the imipenem-cilastatin group but 12.5% of the infants died in the control group (P=0.002). There was no difference in the incidence of infants with handicaps between each group (P=0.3277). Secondary: All cultured bacteria specimens in 94% of the women in the study group were sensitive to imipenem-cilastatin while all specimens found in 25% of those in the control group were sensitive to ampicillin (P<0.0001).
Landis et al.[61] (1981) Piperacillin 2 g IM for one dose vs penicillin G 4.8 million units IM for one dose, with pre-administration of probenecid 1 g orally	PRO, RCT Men with uncomplicated gonococcal urethritis	N=127 7 to 10 days post-treatment	Primary: Clinical cure, bacteriologic cure Secondary: Not reported	Primary: A total of 100% of the patients in both groups were reported as clinically and bacteriologically cured. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Namias et al.[62] (2007) Ertapenem 1 g IV once daily vs piperacillin-tazobactam 3.375 grams IV every six hours	DB, MC, RCT Patients 18 to 90 years of age with presumptive (pre-operative) or confirmed complicated intra-abdominal infections	N=500 4 to 14 days	Primary: Clinical response rates Secondary: Microbiological efficacy, clinical failure, mortality	Primary: Favorable clinical responses were demonstrated for 82.1% of the patients in the ertapenem group and 81.7% of the patients in the piperacillin-tazobactam group (95% CI, -9.6 to 10.5). At the end of therapy, 89.6 and 86.2%, and at late follow-up assessment, 78.9 and 79.3%, of the microbiologically evaluable patients had favorable clinical responses in the ertapenem and piperacillin-tazobactam treatment groups, respectively. Clinical response rates of 63.2% for ertapenem and 60.9% were similar for piperacillin-tazobactam-treated patients in the modified intent-to-treat population at early follow-up assessment (95% CI, -7.5 to 12.0). Secondary: There were no clinically important differences in the response rates of gram-positive, gram-negative, or anaerobic pathogens in the ertapenem and piperacillin-tazobactam treatment groups. Favorable overall microbiological responses were demonstrated in 82.2% in the ertapenem group and 82.5% in the piperacillin-tazobactam group (95% CI, -10.1 to 9.8) at early follow-up assessment. The pathogens isolated most frequently were *Escherichia coli, Bacteroides fragilis*, and *Bacteroides thetaiotaomicron*. At the early follow-up assessment, there were 22 clinical failures (17.9%) in the ertapenem group and 20 (18.5%) in the piperacillin-tazobactam group. The incidence of adverse events and study discontinuations because of adverse events was similar in the two groups. During the study and post-treatment follow-up period, clinical adverse events resulted in 21 deaths, nine of which occurred in the ertapenem group (3.6%) and 12 in the piperacillin-tazobactam group (4.9%; RR, 0.75; 95% CI, 0.30 to 1.77; risk difference, -1.21; 95% CI, -5.08 to 2.53).
File et al.[63]	RCT	N=47	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(1985) Ticarcillin 80 to 160 mg/kg/day plus clavulanate 0.1 mg to 0.2 g every eight hours IV vs piperacillin 125 to 200 mg/kg/day every six to eight hours	Adult patients with serious urinary tract infections	Mean 9.3 days	Clinical symptomatic response, bacterial response Secondary: Adverse events	Satisfactory symptomatic response was observed with all patients in the study. Bacteriologic eradication was achieved in 41% of patients in the ticarcillin-clavulanate group and 55% of patients in the piperacillin group. Secondary: Minimal adverse effects in two of ticarcillin-clavulanate-treated patients (rash and diarrhea).
Respiratory Infections				
Gillespie et al.[64] (2015) Amoxicillin (two 500 mg tablets three times daily for seven days) vs placebo	PC, RCT Patients ≥18 years of age with an acute uncomplicated lower RTI in whom pneumonia was not suspected by the clinician	N=2061 28 days	Primary: Clinician-rated symptom severity between days two and four, new or worsening symptoms and presence of side effects at 4-weeks, adherence Secondary: Not reported	Primary: The adjusted between-group mean difference in symptom severity score on days two to four was slightly lower in the amoxicillin group than the placebo group (adjusted mean difference of −0.07; 95% CI, −0.15 to 0.01). The odds of developing new or worsening symptoms were 21% lower for participants who were prescribed amoxicillin than for those prescribed a matched placebo (OR, 0.79; 95% CI, 0.63 to 0.99). When the effectiveness analyses were only performed on participants for whom outcome and adherence data were available, there was a 19% decrease in the odds of developing new or worsening symptoms in participants prescribed amoxicillin (OR, 0.81; 95% CI, 0.64 to 1.03). Being prescribed amoxicillin was associated with a 28% increase in the odds of reporting non-respiratory symptoms (side effects) in the four weeks postrandomisation (OR, 1.28; 95% CI, 1.03 to 1.59). Adjusting for adherence, a small increase in the between-group mean difference in symptom severity score for participants who complete their course of amoxicillin was found (−0.08; 95% CI, −0.17 to 0.01). The odds of developing new or worsening symptoms remained lower in participants who took their full course of amoxicillin (OR for 100% adherence to amoxicillin, 0.81; 95% CI, 0.66 to 0.98).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Stenstrom et al.[65] (1991) Amoxicillin 20 mg/kg/day for 10 days vs amoxicillin-clavulanate 20 mg/kg/day for seven days	DB, PRO, RCT Children six months to 10 years of age with recurrent acute otitis media or failure of penicillin	N=102 30 days post-treatment	Primary: Clinical and bacteriological response at the last visit Secondary: Adverse effects	Primary: There was no significant difference between the amoxicillin-clavulanate and amoxicillin groups in clinical improvement rate (86.7 vs 86.1%). There was no significant difference between the elimination, persistence, or re-colonization rate between the two groups, except that amoxicillin-clavulanate eliminated β-lactamase-producing *Branhamella catarrhalis* more frequently than amoxicillin (67 vs 31%; P=0.02). Secondary: The two drugs were equally well-tolerated (24 vs 20% had adverse effects; one patient vs three patients discontinued therapy).
Chan et al.[66] (1988) Amoxicillin 30 mg/kg/day given in three divided doses for 10 days vs amoxicillin-clavulanate 30 mg/kg/day given in three divided doses for 10 days	DB, MC, RCT Children seven months to 12 years of age with otitis media with effusion (secretory otitis media) without symptoms of acute otitis media	N=108 16 weeks after start of therapy for responders	Primary: Clinical response (no effusion) at day 10 and four weeks after start of therapy, recurrence of effusion up to 16 weeks post-therapy in responders at four weeks Secondary: Adverse effects	Primary: Treatment with amoxicillin-clavulanate showed a trend toward better resolution of the effusion at 10 days compared to amoxicillin (51.8 vs 32%; P=0.06), but not at four weeks (50 vs 51%). Treatment with amoxicillin-clavulanate showed a trend toward reduced recurrence of effusion during a 16-week follow-up (36.4 vs 63.2%), but the difference was not statistically significant (P=0.16). Secondary: The adverse effect rate was similar in both groups, and the adverse events were mainly gastrointestinal or dermatological.
Kuroki et al.[67] (2012) Amoxicillin 30 mg/kg/day in three divided doses for	MC, OL, RCT Children ≤15 years of age with pharyngolaryngitis or tonsilliths who	N=97 1 to 2 weeks after therapy completion	Primary: Clinical efficacy Secondary: Not reported	Primary: In the amoxicillin-clavulanate treatment group, treatment was rated as markedly effective in 92.6% of cases and effective in 5.6% of cases, yielding a clinical efficacy rate of 92.6% and a clinical response rate of 98.1%.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
10 days vs amoxicillin-clavulanate 96.4 mg/kg/day in two divided doses for three days	tested positive on the instantaneous Group A *Streptococcus* infection diagnosis kit			In the amoxicillin treatment group, treatment was rated as markedly effective in 88.1% of cases and effective in 4.8% of cases, yielding a clinical efficacy rate of 88.1% and a clinical response rate of 92.9%. There was no significant different between treatment groups in terms of clinical efficacy or response rates. Secondary: Not reported
Jibril et al.[68] (1989) Amoxicillin 250 mg-500 mg TID vs amoxicillin 250-500 mg and clavulanate 62.5-125 mg TID	OL, PRO, RCT Children with bacterial pneumonia	N=100 Median 7 days	Primary: Clinical improvement Secondary: Time to clinical improvement, adverse reactions	Primary: Treatment with amoxicillin-clavulanate was more effective at achieving clinical improvement than amoxicillin (93.8 vs 60.4%; P<0.001). Secondary: Treatment with amoxicillin-clavulanate improved the symptoms more quickly than amoxicillin (2.92 vs 3.58 days). Mild rash or diarrhea was seen in two patients on amoxicillin-clavulanate.
Jensen et al.[69] (1988) Amoxicillin 50 mg/kg/day plus probenecid 250 to 750 mg/day for 14 days vs amoxicillin 50 mg/kg/day and clavulanate (4:1 ratio) plus probenecid 250 to	SB Outpatient children and adults with COPD and ampicillin sensitive *Haemophilus influenzae*	N=71 2 week post-treatment	Primary: Clinical and microbial efficacy Secondary: Adverse events	Primary: No difference in clinical efficacy in symptomatic patients was observed (57% for amoxicillin vs 59% for amoxicillin-clavulanate). No difference in microbial eradication two weeks post-treatment between groups was observed (57% for amoxicillin vs 70% for amoxicillin-clavulanate). Treatment with amoxicillin-clavulanate was significantly better (P<0.05) than amoxicillin if more than one strain of *Haemophilus influenzae* was present. Beta-lactamase producing *Haemophilus influenzae* was detected at two weeks post-treatment in 29% of patients in the amoxicillin group and 23% of patients in the amoxicillin-clavulanate (P=NS).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
750 mg/day				Secondary: Both groups experienced similar rates of adverse events (3%).
Morris et al.[70] (2010) Azithromycin 30 mg/kg as a single dose vs amoxicillin 50 mg/kg/day in two divided doses for a minimum of seven days	RCT, SB Aboriginal children 6 months to 6 years of age with acute otitis media	N=320 Up to 21 days	Primary: Clinical failure (defined as persistent ear pain, bulging tympanic membrane or middle ear discharge) at the end of therapy visit (days six to 11), failure to improve (defined as no improvement in clinical signs at the end of therapy at the end of therapy visit (days six to 11) Secondary: Clinical and microbiological outcomes	Primary: At the end of therapy, 50% of patients receiving azithromycin and 54% of patients receiving amoxicillin were clinical failures (P=0.504). At the end of therapy, 45% of patients receiving azithromycin and 49% of patients receiving amoxicillin failed to improve (P=0.567). Secondary: No differences in clinical failure or failure to improve were indicated in a per protocol analysis (children seen before day 11 after commencement of treatment). Azithromycin significantly reduced the proportion of children with nasal carriage of *Streptococcus pneumoniae* compared to amoxicillin (P<0.001).
Feder et al.[71] (1999) Amoxicillin 750 mg orally daily for 10 days vs penicillin V 250 mg orally TID for 10 days	PRO, RCT Children with group A β-hemolytic streptococcal pharyngitis	N=152 14 to 21 day follow-up	Primary: Clinical course, bacteriologic eradication within 18 to 24 hours, bacteriologic treatment failure rate at days four to six and days 14 to 21 Secondary:	Primary: No significant differences between clinical response (about 90% for both groups) or bacteriologic response at 18 to 24 hour follow-up visit. Treatment failure occurred in 5% of the patients in the amoxicillin group and 11% of the patients in the penicillin V group. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Not reported	
Cohen et al.[72] (1996) Amoxicillin 50 mg/kg/day in two divided doses for six days vs penicillin V 45 mg/kg/day in three divided doses for 10 days	MC, OL, RCT Children with group A β-hemolytic streptococcal pharyngitis	N=318 1 month	Primary: Bacteriologic eradication at four days Secondary: Clinical efficacy, adverse events	Primary: Bacteriologic eradication at four days was similar between the amoxicillin and penicillin groups (83.7 vs 85.3%; P=0.71). Secondary: No significant differences in clinical efficacy were observed (clinical cure rate of 90.8% for amoxicillin vs 89% for penicillin). No serious adverse events were reported. Only three patients in the penicillin group discontinued treatment due to side effects.
Gopichand et al.[73] (1998) Amoxicillin 40 mg/kg/day TID for 10 days vs penicillin V 125 mg to 250 mg TID for 10 days	PRO, RCT, SB Pediatric patients with group A streptococcal pharyngitis	N=113 10 days	Primary: Culture negativity at end of treatment Secondary: Resolution of symptoms, adverse effects	Primary: Treatment with amoxicillin was more likely to eradicate group A streptococcus compared to penicillin V (79.3 vs 54.5%; P=0.005). Secondary: Treatment with amoxicillin was more likely to resolve the symptoms compared to penicillin V (87.9 vs 70.9%; P=0.025). Two patients developed hives requiring discontinuation of penicillin V.
Addo-Yobo et al.[74] (2004) Amoxicillin 45 mg/kg orally in three divided doses vs penicillin G	MC, OL, RCT Children 3 to 59 months of age who were hospitalized for severe pneumonia	N=1,702 Duration not specified	Primary: Treatment failure at 48 hours (clinical signs such as tachypnea, lower chest in-drawing) Secondary: Cumulative	Primary: The treatment failure rate for both groups was 19% at 48 hours. Secondary: The cumulative treatment failure rate was 22% for both groups at five days and was 27% in the amoxicillin group and 26% in the penicillin group at 14 days (95% CI, -5 to 5).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
200,000 units/kg/day in four divided doses			treatment failure at five and 14 days	
Atkinson et al.[75] (2007) Amoxicillin 8 mg/kg orally three times a day (children six months to 12 years) or 500 mg three times a day (children 12 to 16 years) vs penicillin benzyl 25 mg/kg IV four times a day (six months to 16 years) Children in the IV group were changed to oral amoxicillin after a median of six IV doses and received seven days of antibiotics in total.	MC, RCT Children with community-acquired pneumonia	N=246 Variable duration	Primary: Time for the temperature to be <38 degrees C for 24 continuous hours and oxygen requirement to cease Secondary: Time in hospital, complications, duration of oxygen requirement and time to resolution of illness.	Primary: The time for temperature to settle and oxygen requirement to cease for those needing oxygen was similar in the two groups (1.3 and 1.2 days in the IV and oral groups, respectively; P=0.03). Secondary: The median length of hospital stay was significantly shorter in the oral group than in the IV group (1.77 and 2.1 days, respectively; P<0.001). The duration of oxygen requirement was significantly longer in the IV group than in the oral group (median 20.5 vs 11.0 hours; P=0.04). Three children in the oral group were changed to IV antibiotics and seven children in the IV group were changed to different IV antibiotics. Median time to complete resolution of symptoms was nine days in both groups.
Lennon et al.[76] (2008) Amoxicillin 1,500 mg orally once	RCT Children with group A beta-hemolytic streptococcal	N=353 36 days	Primary: Eradication of group A beta-hemolytic streptococcal	Primary: At visit two (days three to six), the between-treatment difference in the incidence of positive cultures was 0.3% with a bacteriological failure of 5.8% for amoxicillin and 6.2% for penicillin.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
daily (or 750 mg if <30 kg) for 10 days vs penicillin V 500 mg orally BID (or 250 mg if <20 kg) for 10 days	pharyngitis		Secondary: Not reported	At visit three (days 12 to 16), bacteriological failure was similar between groups (12.7 and 11.9% for amoxicillin and penicillin, respectively). At visit four (days 26 to 36), the incidence of positive cultures had increased with a between-treatment difference of 1.9% but bacteriological failure decreased slightly (10.7% for amoxicillin and 11.3% for penicillin V). There was no evidence of inferiority of amoxicillin to penicillin V at any time period. No significant differences in resolution of symptoms were noted between treatment groups. Secondary: Not reported
Sachs et al.[77] (1995) SMX-TMP 800-160 mg BID for seven days in addition to oral corticosteroids vs amoxicillin 500 mg TID for seven days in addition to oral corticosteroids vs oral corticosteroids	DB, RCT Patients ≥18 years of age with asthma or COPD	N=195 14 days	Primary: Peak expiratory flow Secondary: Not reported	Primary: Peak expiratory flow percent predicted assessed during an exacerbation improved significantly in all three groups over the 14-day observation period (P<0.001), ranging from 0.34 to 0.78% predicted per day, finally returning to baseline value. No statistically significant difference was observed between the groups. There was no statistically significant difference between the groups in symptom scores, expressed as slopes or absolute values from days one to 14. The decrease in the symptom severity scores was significant in all three groups (P<0.001). There was no statistically significant difference between the three groups in terms of treatment failure rate. Secondary: Not reported
Garau et al.[78] (2003)	DB, DD, MC, RCT	N=230	Primary: Clinical response	Primary: Clinical success rate was higher in the amoxicillin-clavulanate extended-

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Amoxicillin-clavulanate extended-release tablets 2,000-125 mg BID for 7 to 10 days vs amoxicillin-clavulanate 875-125 mg TID for 7 to 10 days	Patients ≥ 18 years of age with radiologically confirmed community-acquired pneumonia	7 to 10 days	at follow-up (days 28 to 35) Secondary: Clinical response at end of therapy (days nine to 14), bacteriological response at end of therapy and at follow-up, radiological response at end of therapy and at follow-up, adverse events	release group compared to the amoxicillin-clavulanate group (94.7 vs 88.8%; 95% CI, 1.1 to 13.0). Secondary: Radiological efficacy at follow-up was higher in the amoxicillin-clavulanate extended-release group compared to the amoxicillin-clavulanate group (94.7 vs 87.9%). Radiological success rates at the end of therapy were similar for both treatment groups (88.1 vs 86.7%; 95% CI, -6.8 to 9.5). Bacteriological success rate at follow-up was higher in the amoxicillin-clavulanate extended-release group compared to the amoxicillin-clavulanate group (85.0 vs 77.3%; 95% CI, 15.8 to 31.2). Adverse events were similar in both treatment groups.
File et al.[79] (2004) Amoxicillin-clavulanate extended-release 2,000-125 mg BID for seven days vs amoxicillin-clavulanate 875-125 mg BID for seven days	DB, MC, PG, RCT Patients ≥ 16 years of age with a clinical and radiological diagnosis of community-acquired pneumonia	N=633 7 days	Primary: Clinical response (sufficient improvement in the signs and symptoms of pneumonia) at follow-up (days 28 to 35) Secondary: Radiological outcome, bacterial response, adverse events	Primary: Clinical success rates were similar for both treatment groups (90.3% for amoxicillin-clavulanate extended-release vs 87.6% for amoxicillin-clavulanate; 95% CI, -3.0 to 8.3). Secondary: Bacteriological response rates were similar for both treatment groups at the end of therapy (90.5% for amoxicillin-clavulanate extended-release vs 82.5% for amoxicillin-clavulanate; 95% CI, -3.8 to 20.0) and at follow-up (86.6 vs 78.4%; 95% CI, -5.8 to 22.1). Radiological response rates at follow-up were also similar for both treatment groups (93.1 vs 90.3%; 95% CI, -2.1 to 7.8). Rates of adverse events reported were similar in both treatment groups (40.4% in the amoxicillin-clavulanate extended-release group vs 42.1% in the amoxicillin-clavulanate group).
Hazir et al.[80] (2008) Amoxicillin 80 mg	OL, RCT Children 3 to 59 months of age with	N=2037 14 days	Primary: Treatment failure by day six	Primary: There were 87 (8.6%) treatment failures in the hospitalized group and 77 (7.5%) in the ambulatory group (95% CI, -1.3 to 3.5) by day six.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
to 90 mg/kg/day in two divided doses for five days (at home) vs ampicillin 100 mg/kg per day in four doses for 48 hours (inpatient), followed by three days of oral amoxicillin 80 mg to 90 mg/kg/day	severe pneumonia		Secondary: Not reported	Five (0.2%) children died within 14 days of enrollment, one in the ambulatory group and four in the hospitalized group. In each case, treatment failure was declared before death and the antibiotic had been changed. None of the deaths were considered to be associated with treatment allocation. There were no serious adverse events reported in the trial. Secondary: Not reported
Marple et al.[81] (2010) Azithromycin ER 2 g as a single dose vs amoxicillin-clavulanate 875-125 mg every 12 hours for 10 days	MC, OL, RCT Patients ≥18 years of age with acute, uncomplicated, bacterial maxillary sinusitis based on signs and symptoms lasting for 7 to 30 days	N=751 28 days	Primary: Symptom resolution at day five in the per protocol population Secondary: Time to resolution of symptoms, sinusitis-related quality of life, resource use, treatment success, and treatment satisfaction	Primary: At day five in the per protocol population, 29.7% of patients receiving azithromycin and 18.9% of patients receiving amoxicillin-clavulanate had symptom resolution (difference, 10.8%; 95% CI, 3.1 to 18.4). At day five in the intent to treat population, a significantly greater percentage of patients in the azithromycin group met the primary end point (20.0%) than in the amoxicillin-clavulanate group (13.2%; difference, 6.8%; 95% CI, 1.5 to 12.2). Secondary: Over the course of the trial, both treatments led to similar rates of symptom resolution (HR, 1.16; 95% CI, 0.92 to 1.44). After 28 days, 67.4% of patients treated with azithromycin reported symptom resolution compared to 63.0% of patients receiving amoxicillin-clavulanate. In the per protocol population, 11.2% of patients reported receiving a prescription for a second antibiotic during the study period. The proportion of patients requiring additional antibiotics was similar in the azithromycin group (11.0%) and the amoxicillin-clavulanate group (11.3%).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				A similar number of patients reported unscheduled physician visits during the study in both treatment arms. Overall satisfaction with treatment was similar in the two treatment arms. Patients treated with azithromycin reported greater satisfaction with the convenience of the medication than did patients given amoxicillin-clavulanate (difference, 11.59; 95% CI, 8.78 to 14.40). Patients in the amoxicillin-clavulanate arm reported greater satisfaction with side effects than those treated with azithromycin (difference, −4.40; 95% CI, −8.13 to −0.66). More patients treated with azithromycin reported abdominal discomfort than did those receiving amoxicillin-clavulanate (70.76 vs 60.92%; P=0.02). There was no difference in the incidence of diarrhea among the treatment groups (P=0.50).
Arguedas et al.[82] (2011) Azithromycin ER 60 mg/kg as a single dose vs amoxicillin-clavulanate 45-3.2 mg/kg every 12 hours for 10 days	DB, MC, RCT Patients 3 to 48 months of age with acute otitis media	N=923 28 to 64 days	Primary: Clinical response at the test of cure visit (days 12 to 14) in the bacteriologic eligible population Secondary: Bacterial response at other visits, compliance, and safety	Primary: Clinical response at the test of cure visit was achieved in 80.5% of children in the azithromycin group compared to 84.5% in the amoxicillin-clavulanate group (difference, – 3.9%; 95% CI, –10.4 to 2.6). Azithromycin was found to be non-inferior to amoxicillin-clavulanate. Secondary: The eradication rate across all ages was 82.6% in the azithromycin group and 92% in the amoxicillin-clavulanate group (P=0.050). All patients receiving treatment with azithromycin received their single dose of active treatment; 59% of patients receiving amoxicillin-clavulanate received the full course of 20 doses. In the bacteriologic eligible population, 77% of patients in the amoxicillin-clavulanate arm were compliant with the full course of treatment compared to 100% of patients in the azithromycin group. Adverse events occurred in 56% of children treated with azithromycin ER and in 62.2% of children treated with amoxicillin-clavulanate. Most adverse events were of mild to moderate severity. Treatment-related vomiting was reported in 10.7% of patients receiving azithromycin and in

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				8.2% of patients receiving amoxicillin-clavulanate.
Noel et al.[83] (2008) Levofloxacin 10 mg/kg BID vs amoxicillin-clavulanate (amoxicillin 45 mg/kg) BID	MC, RCT, SB Children six months to five years of age with recurrent and/or persistent acute otitis media that was unchanged or worsened after ≥three days of treatment with an antimicrobial regimen used to treat acute otitis media	N=1,650 27 days	Primary: Clinical cure rates at visit three (two to five days post-therapy) Secondary: Clinical cure rate at visit four (10 to 17 days post therapy), clinical success (cured or improved) at visits three and four, safety	Primary: Clinical cure rates were 72.4% with levofloxacin and 69.9% with amoxicillin-clavulanate (95% CI, -7.37 to 2.46). Levofloxacin was found to be non-inferior to amoxicillin-clavulanate. Cure rates were similar among different age groups: ≤24 months: 68.9 vs 66.2%, respectively (95% CI, -9.36 to 4.03); >24 months: 76.9 vs 75.1%; respectively (95% CI, -8.94 to 5.28). Secondary: Clinical cure rates at visit four were 74.9% for levofloxacin and 73.9% for amoxicillin-clavulanate (95% CI, -5.55 to 3.54). Clinical success rates at visit three were 94.0% for levofloxacin and 90.8% for amoxicillin-clavulanate (95% CI, -6.02 to -0.29). Clinical success rates at visit four were 83.6% for levofloxacin and 80.4% for amoxicillin-clavulanate (95% CI, -7.18 to 0.81). There was no difference observed between treatments regarding frequency or type of adverse events. Most adverse events were mild or moderate in severity (97% levofloxacin; 96% amoxicillin-clavulanate) with diarrhea being the most frequent.
Thomsen et al.[84] (1997) Amoxicillin-clavulanate 12.5-3.125 mg orally BID for 14 days vs amoxicillin-clavulanate 12.5-3.125 mg orally	DB, PRO, RCT Children 1 to 10 years of age with secretory otitis media of at least three months duration	N=360 2 months after initiation of therapy	Primary: Improved tympanometric findings at 14 and 28 days after start of therapy Secondary: Not reported	Primary: Amoxicillin-clavulanate treatment for 28 days was significantly more efficacious than amoxicillin-clavulanate for 14 days (P=0.07), penicillin V for 14 days (P=0.005), and penicillin V for 28 days (P<0.001) at improving tympanometric testing (44, 31, 23, and 19%, respectively). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
BID for 28 days vs penicillin V 25 mg orally BID for 14 days vs penicillin V 25 mg orally BID for 28 days				
Brook et al.[85] (1989) Amoxicillin-clavulanate 40 mg/kg/day in four divided doses for 10 days vs penicillin VK 40 mg/kg/day in four divided doses for 10 days	DB, PRO, RCT Children 4 to 16 years of age with acute recurrent group A beta-hemolytic streptococcal tonsil-litis (>2 episodes per year) despite prior treatment with antibiotics for 10 days (penicillin or erythromycin)	N=43 Up to 1 year	Primary: Group A beta-hemolytic streptococcal eradication 10 days post-therapy Secondary: Recurrence of tonsillitis in one year	Primary: Treatment with amoxicillin-clavulanate eradicated group A beta-hemolytic streptococcal more effectively than penicillin VK (100 vs 70%; P<0.001). Secondary: Treatment with amoxicillin-clavulanate prevented recurrent tonsillitis more effectively than penicillin VK (89 vs 42%; P< 0.005).
Siempos et al.[86] (2007) Quinolones vs amoxicillin-clavulanate	MA Patients >18 years old with acute bacterial exacerbation of chronic bronchitis	N=7,405 (19 RCT) 26 weeks	Primary: Treatment success, hospitalization, mortality, adverse events Secondary: Not reported	Primary: There was no difference regarding treatment success in intention-to-treat and clinically evaluable patients between macrolides and quinolones, amoxicillin-clavulanate and quinolones, or amoxicillin-clavulanate and macrolides. The treatment success in microbiologically evaluable patients was lower for macrolides compared to quinolones (OR, 0.47; 95% CI, 0.31 to 0.69).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs macrolides				There was no difference in the need for hospitalization for patients treated with macrolides compared to patients treated with quinolones (OR, 1.37; 95% CI, 0.75 to 2.5). Data regarding need for hospitalization were only available in two trials comparing amoxicillin-clavulanate with quinolones, and in one trial comparing amoxicillin-clavulanate with macrolides. There was no difference in mortality between macrolide-treated patients with acute bacterial exacerbation of chronic bronchitis and those treated with quinolones (OR, 1.96; 95% CI 0.45to8.51). Data on mortality were provided in only two trials comparing amoxicillin-clavulanate with quinolones. Fewer quinolone-recipients experienced a recurrence of acute bacterial exacerbation of chronic bronchitis after resolution of the initial episode compared to macrolide-recipients during the 26-week period following therapy. Adverse effects in general were similar between macrolides and quinolones. Administration of amoxicillin-clavulanate was associated with more adverse effects than quinolones (OR, 1.36; 95% CI 1.01to1.85). Secondary: Not reported
Feder et al.[87] (1982) SMX-TMP 37.5-7.5 mg/kg/day divided into two doses for 14 days vs ampicillin 70 mg/kg/day divided into four doses for 14 days	DB, RCT Patients two months to seven years of age with signs/symptoms of otitis media in addition to a bulging tympanic membrane with decreased mobility	N=282 14 days	Primary: Premature discontinuation of therapy due to ≥5 watery stools per day, diarrhea Secondary: Not reported	Primary: Therapy was discontinued in significantly more ampicillin-treated patients compared to amoxicillin-treated patients (P<0.01) or SMX-TMP-treated patients (P<0.03). Among patients who completed a full course of therapy, significantly more ampicillin-treated patients developed diarrhea compared to amoxicillin-treated patients (P<0.04) or SMX-TMP-treated patients (P<0.02). Initial symptom resolution occurred after approximately two days of treatment in all three groups. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs amoxicillin 30 mg/kg/day divided into three doses for 14 days				Not reported
Mackay et al.[88] (1980) Ampicillin 250 mg orally TID for seven days vs ampicillin 500 mg orally TID for seven days vs amoxicillin 250 mg orally TID for seven days vs amoxicillin 500 mg orally TID for seven days	DB, MC, RCT Patients with acute exacerbations of chronic bronchitis	N=199 7 days	Primary: Clinical response (no indication for continued antibiotics), days for sputum to become mucoid Secondary: Not reported	Primary: There was no significant difference between any of the treatment groups in clinical response (70, 74, 62, and 74%) or in days for sputum to become mucoid (5.1, 5.2, 5.0, and 5.0). Secondary: Not reported
Chodosh et al.[89] (1982) SMX-TMP 800-160 mg BID for 14 days	DB, RCT, XO Patients ≥18 years of age with chronic bronchitis who developed an acute	N=21 14 days	Primary: Chest symptoms, physical findings, vital signs, pulmonary function,	Primary: Patients in the ampicillin group experienced a longer recurrence-free time compared to patients in the SMX-TMP group (P<0.05). Sputum volumes decreased significantly in each treatment group, starting on day three of the study (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs ampicillin 500 mg, one capsule QID for 14 days	bronchial infectious exacerbation within two weeks of the study *Pseudomonas, Klebsiella*, or *Staphylococcus aureus* were isolated		laboratory values, sputum analysis, time to recurrence of exacerbation Secondary: Not reported	While none of the patients in the ampicillin group discontinued therapy due to adverse effects, three patients in the SMX-TMP group discontinued treatment. There were no significant differences noted between the two study drugs in all other outcome measures. Secondary: Not reported
Macfarlane et al.[90] (1983) Erythromycin lactobionate 300 mg IV every 6 hours for 48 hours, followed by erythromycin stearate 500 mg orally QID for seven days vs ampicillin 500 mg IV every 6 hours for 48 hours, followed by amoxicillin 500 mg orally QID for seven days	DB, RCT Patients <80 years of age with primary pneumonia, including Legionnaires' disease	N=122 9 days	Primary: Clinical response to therapy (categorized as uncomplicated recovery, complicated recovery, or fatality) Secondary: Not reported	Primary: Clinical response to therapy in all categories was similar between the groups. Secondary: Not reported
Aubier et al.[91] (2002) Telithromycin 800 mg daily for five	DB, PG, RCT Patients ≥18 years of age with an acute exacerbation of	N=325 31 to 36 days	Primary: Clinical cure rate at the test of cure visit (days 17 to 21)	Primary: There was no significant difference in clinical cure rates between groups at the test of cure visit (86.1% for telithromycin and 82.1% for the amoxicillin-clavulanate group).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
days vs amoxicillin-clavulanate 500 mg TID for 10 days	chronic bronchitis		Secondary: Clinical cure rate at the late post-therapy visit (days 31 to 36), bacteriologic outcomes at the test of cure visit (days 17 to 21) and late post-therapy visit (days 31 to 36)	Secondary: There was no significant difference in clinical cure rates at the late post-therapy visit between groups (78.1% for telithromycin and 75.0% for amoxicillin-clavulanate). Bacteriologic outcome was judged as satisfactory in 69.2% of patients in the telithromycin group and 70.0% of patients in the amoxicillin-clavulanate group.
Seki et al.[92] (2009) Ampicillin-sulbactam 3 g IV BID for 7 to 14 days vs piperacillin 2 g IV BID for 7 to 14 days	RCT Patients with mild to severe community-acquired pneumonia	N=109 7 to 14 days	Primary: Efficacy and safety Secondary: Not reported	Primary: The total efficacy rate was 77.4% in the piperacillin group and 67.3% in the ampicillin-sulbactam group. There was no significant difference among the treatment groups. There was a significant difference in efficiency between piperacillin and ampicillin-sulbactam treatments in male patients (79.4 vs 55.6%, respectively; P<0.046), patients with underlying disease (83.3 vs 57.6%, respectively; P<0.019), and in respiratory disease patients (84.6 vs 28.6%, respectively; P<0.022). There was also a significant difference in efficiency among ampicillin-sulbactam groups dependent on age. In the piperacillin group, adverse reactions were seen in 5.4% of patients and the major adverse reactions were diarrhea and hepatic dysfunction. In the ampicillin-sulbactam group, adverse reactions were seen in 9.4% of the patients, with the major adverse reactions being diarrhea and hepatic dysfunction. No significant differences were found between the groups. All reactions were mild or moderate and transient. Secondary: Not reported.
Allewelt et al.[93] (2004)	MC, OL, PRO, RCT	N=70 Mean 23.4	Primary: Clinical response	Primary: Clinical response at end of therapy in the ampicillin-sulbactam group was 73.0 vs 66.7% in the clindamycin group (P=0.06 and P=0.02,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ampicillin-sulbactam vs clindamycin with or without cephalosporin Dosing varied per patient	Patients with aspiration pneumonia and lung abscess	days	Secondary: Not reported	respectively). Clinical response at seven to 14 days after therapy was 65.7% in the ampicillin-sulbactam group vs 63.5% in the clindamycin group (P=0.10 and P=0.04). Duration of therapy was 22.7 days in the ampicillin-sulbactam group vs 24.1 days in the clindamycin group. Secondary: Not reported
Yanagihara et al.[94] (2006) Imipenem-cilastatin 0.5 g BID vs ampicillin-sulbactam 3 g BID	PRO, RCT Elderly patients >65 years of age with moderate-to-severe community-acquired pneumonia	N=67 7 to 14 days	Primary: Clinical efficacy Secondary: Bacteriological efficacy, adverse events	Primary: Overall clinical efficacy of ampicillin-sulbactam therapy was 91.4% compared to 87.5% for imipenem-cilastatin therapy (P=NS). Secondary: The eradication rate was 100% in both treatment arms (P=NS). The overall eradication rate for the pathogenic microorganism was 84% in the ampicillin-sulbactam group and 80%in the imipenem-cilastatin group (P=NS). All adverse reactions were mild or moderate and transient in both treatment groups.
Peyramond et al.[95] (1996) Penicillin V 1 million units TID for 10 days vs amoxicillin 1 g BID for six days	MC, OL, PRO, RCT Patients with group A beta-hemolytic streptococcal acute tonsillitis	N= 234 1 month posttreatment follow-up	Primary: Group A beta-hemolytic streptococcal eradication Secondary: Clinical efficacy, adverse effects	Primary: Successful group A beta-hemolytic streptococcal eradication was similar between the two treatment groups at end of treatment (92% for amoxicillin vs penicillin V 92.7%; P=0.95) and at one month post-treatment (90.8 vs 92.6%; P=0.85). Secondary: Clinical response rates were similar between the two groups at end of treatment (96% for amoxicillin vs 95.4% for penicillin; P=0.92) and at one month (91.7 vs 94.7%; P=0.59). Adverse effects occurred in 3% of patients in the amoxicillin group and 5.2% of the patients in the penicillin group, with three patients in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				penicillin group requiring discontinuation of treatment.
Curtin-Wirt et al.[96] (2003) Penicillin V 35 mg/kg/day in two divided doses vs amoxicillin 35 mg/kg/day in two divided doses	OL, OS, PRO Children with group A beta-hemolytic streptococcal tonsillo-pharyngitis	N=276 6 to 14 day posttreatment	Primary: Bacteriologic cure rate Secondary: Clinical cure rate	Primary: Bacteriologic cure rate was 76% in the amoxicillin group vs 64% in the penicillin group (P=0.04). Secondary: Clinical cure rate was 84% in the amoxicillin group vs 73% in the penicillin group (P=0.03).
Réa-Neto et al.[97] (2008) Doripenem 500 mg IV every eight hours vs piperacillin-tazobactam 4.5 grams IV every six hours	MC, OL, PRO, RCT Patients aged 18 years or older with signs and symptoms of nosocomial pneumonia, including non-ventilated patients and those with early-onset ventilator-associated pneumonia	N=448 7 to 14 days	Primary: Clinical cure rate in the clinically evaluable population and in the clinically evaluable-modified intent-to-treat population Secondary: Clinical cure rate at the end of IV therapy and at the late follow-up visit, clinical and microbiological cure rates in the microbiologically evaluable patients at the test-of-cure visit and in the microbiologically evaluable-modified	Primary: The clinical cure rates in clinically evaluable patients at the test-of-cure visit were 81.3% in the doripenem arm and 79.8% in the piperacillin-tazobactam arm (95% CI, -9.1 to 12.1). In the clinically evaluable-modified intent-to-treat population, the clinical cure rates in the doripenem and piperacillin-tazobactam arms were 69.5 and 64.1%, respectively (95% CI, -4.1 to 14.8). Secondary: Clinical response rates at the end of IV study drug therapy in clinically evaluable patients were 87% in both treatment arms (95% CI, -9.2 to 9.2%). Clinical relapse rates at the late follow-up visits were low for both the doripenem (3%) and piperacillin-tazobactam (4%) treatment arms. The clinical cure rates in microbiologically evaluable patients at the test-of-cure visit were 82.1 and 78.3% (95% CI, -9.4 to 17.1) in the doripenem and piperacillin-tazobactam arms, respectively. In the microbiologically evaluable-modified intent-to-treat population, clinical cure rates were 67.6 and 67.4%, respectively (95% CI, -11.4 to 11.9).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			intent-to-treat population, clinical and microbiological cure rates at the test-of-cure visit in microbiologically evaluable patients with early-onset ventilator-associated pneumonia, and all-cause mortality at day 28 in the clinically evaluable-modified intent-to-treat population.	Microbiological responses in the microbiologically evaluable patients at the test-of-cure visit were achieved in 84.5% of patients in the doripenem arm and 80.7% of patients in the piperacillin-tazobactam arm (95% CI, -8.9 to 16.5). The all-cause mortality at day 28 in the clinically evaluable-modified intent-to-treat population was 13.8% with doripenem and 14.6% with piperacillin-tazobactam (95% CI, -7.9 to 6.3). A Kaplan-Meier analysis found no difference in cumulative mortality rate between the two treatment arms.
Ito et al.[98] (2010) Imipenem-cilastatin 1 g IV every 12 hours for 7 to 14 days vs piperacillin-tazobactam 5 g IV every 12 hours for 7 to 14 days	OL, RCT, SC Patients aged ≥15 years of age with a risk for aspiration who had been hospitalized after developing moderate-to-severe pneumonia in the community or nursing home	N=469 30 days	Primary: Clinical response rate at the end of treatment in validated per protocol population Secondary: Clinical response during treatment (days four and seven) and at the end of study in validated per protocol population, and survival at day 30 in modified	Primary: At the end-of-treatment visit, the clinical effective rate for the validated per protocol population was 83% for piperacillin-tazobactam and 82% for imipenem-cilastatin (P=0.92). Secondary: There were no significant differences between the groups in any of the secondary outcome measures. Mortality rate within 30 days of admission in modified intention-to-treat population was 15% in the piperacillin-tazobactam group and 24% in the imipenem-cilastatin group (P=0.12). The most frequent adverse event was diarrhea in both groups, affecting 28% of patients receiving piperacillin-tazobactam and 31% of patients receiving imipenem-cilastatin.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			intention-to-treat population	
Schmitt et al.[99] (2006) Imipenem-cilastatin 4 g-500 mg every eight hours vs piperacillin-tazobactam 1 g-1 g every eight hours Additional aminoglycoside therapy was mandatory if *Pseudomonas aeruginosa* was present.	DB, MC, RCT Hospitalized patients with nosocomial pneumonia	N=221 5 to 21 days	Primary: Clinical response at the end of the treatment period Secondary: Clinical responses on the last day of treatment or on day 21 and on day 14±7 days after treatment, bacteriological responses, safety	Primary: Therapeutic response was seen in 66% [95% CI, 56.5 to 75] of patients receiving piperacillin-tazobactam and in 70% [95% CI, 60.4 to 78.2] of patients receiving imipenem-cilastatin. Failure rates were similar at 18.7 and 18.2%, respectively. On the last day of treatment or on day 21, therapeutic responses were higher and seen in 71% [95% CI, 61.3 to 79.2] and 77.3% [95% CI, 68.1 to 84.5] of patients receiving piperacillin-tazobactam and imipenem-cilastatin respectively. Failure rates were 17.8 and 16.4% respectively. Secondary: At the second follow-up (14±4 days after the end of treatment) clinical responses were 59.8% [95% CI, 49.9 to 69] and 66.4% [95% CI, 56.6 to 74.9] and failure rates were 19.6 and 15%, in patients receiving piperacillin-tazobactam and imipenem-cilastatin respectively. The majority of patients in both groups responded to treatment and the overall response rate was similar for the two agents. Failure rates were also similar for the two treatment groups at each of the observation periods. Eradication immediately after treatment with piperacillin-tazobactam or imipenem-cilastatin was 45.7 and 52.7%, respectively compared to 40.3 and 50% at the first follow-up and 34.6 and 42.2% at the second follow-up, respectively. Overall, 74.5 and 64.9% of patients receiving piperacillin-tazobactam and imipenem-cilastatin, respectively reported adverse events, the majority of which were of mild intensity. The most common related adverse events were diarrhea and fever in the piperacillin-tazobactam group and increased alkaline phosphatase, nausea and vomiting in the imipenem-cilastatin group.
Joshi et al.[100] (2006) Imipenem-cilastatin 500 mg	DB, MC, RCT Hospitalized patients with acute nosocomial	N=437 21 days	Primary: Clinical cure and microbiological response rates; pathogen	Primary: The overall clinical cure rate was 68% in piperacillin-tazobactam patients and 61% in imipenem patients in the efficacy evaluable population (P=0.256).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
IV every six hours vs piperacillin-tazobactam 4.5 grams IV every six hours Patients also received aminoglycoside therapy.	pneumonia		eradication rates; length of hospital stay; hospital readmissions; adverse events Secondary: Not reported	Microbiological response rates were comparable among efficacy evaluable patients treated with piperacillin-tazobactam and those treated with imipenem. Microbiological responses for piperacillin-tazobactam and imipenem patients were: eradication, 64 vs 59%; persistence, 29 vs 21%; relapse, 0 vs 5%; and superinfection, 7 vs 15%, respectively. Gram-positive isolates were eradicated in 83% of piperacillin-tazobactam patients and 75% of imipenem patients; Gram-negative pathogens were eradicated in 72% of piperacillin-tazobactam patients and 77% of imipenem patients. Piperacillin-tazobactam and imipenem patients had similar hospital and intensive care unit length of stay. Hospital readmission rates in both groups were small and were not significantly different. There were no significant differences in adverse events between the two treatment groups. Secondary: Not reported
Miscellaneous Infections				
Kacmar et al.[101] (2001) Amoxicillin 500 mg TID for seven days vs azithromycin 1 g single dose	RCT, SB Women with *Chlamydia trachomatis* in pregnancy before 33 weeks gestation	N=39 4 to 6 weeks post-therapy	Primary: Clinical response Secondary: Not reported	Primary: No statistically significant differences in side effects, compliance, or efficacy were observed between the two treatment groups. Secondary: Not reported.
Hsu et al.[102] (2015) Reverse hybrid therapy	MC, RCT, SB Patients ≥20 years of age diagnosis of *H pylori* was based	N=440 6 weeks after treatment	Primary: Eradication rate Secondary: Frequency of	Primary: Intent-to-treat eradication rates were 93.6 and 86.8% for reverse hybrid and standard triple therapies, respectively. Reverse hybrid therapy achieved a higher eradication rate than standard triple therapy (95% CI, 1.3 to 12.3%; P=0.016). The modified intent-to-treat (95.4 vs 88.4%) and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(pantoprazole 40 mg plus amoxicillin 1 g twice daily for 12 days, and clarithromycin 500 mg plus metronidazole 500 mg twice daily for the first seven days) vs standard triple therapy (pantoprazole 40 mg plus clarithromycin 500 mg and amoxicillin 1 g twice daily for 12 days).	on at least two positive results of rapid urease test, histology, and culture and with endoscopically proven peptic ulcer diseases or gastritis		adverse events, drug compliance	per-protocol analyses (95.7 vs 88.3%) yielded similar results (P=0.008 and 0.005, respectively). Secondary: The incidences of adverse events in the participants receiving reverse hybrid and standard triple therapies were 14.1% (95% CI, 9.2 to 19.0%) and 9.5% (95% CI, 5.6 to 13.4%), respectively. The two therapies exhibited similar frequencies of overall adverse events (P=0.14). Reverse hybrid and standard triple groups displayed similar compliance rates (96.8%; 95% CI, 94.5 to 99.1% and 98.6%; 95% CI, 97.1 to 100.2%, respectively).
Molina-Infante et al.[103] (2013) Hybrid therapy (40 mg omeprazole and 1 g amoxicillin, twice daily for 14 days; 500 mg clarithromycin and 500 mg nitroimidazole were added, twice	NI, PRO, RCT Consecutive adult patients with *H pylori* infection and dyspepsia, peptic ulcer disease, or familiar history of gastric cancer, who did not receive prior eradication therapy	N=343 8 weeks posttreatment	Primary: Eradication rates in the intent-to-treat population Secondary: Eradication rates in the per-protocol population, compliance	Primary: In the intent-to-treat analysis, eradication rates were 153 of 170 (90%; 95% CI, 86 to 93%) for hybrid and 156 of 170 (91.7%; 95% CI, 88 to 95%) for concomitant therapy (P=0.35). Secondary: Eradication rates in the per-protocol analysis were 150 of 163 (92%; 95% CI, 87 to 95%) for hybrid therapy and 150 of 156 (96.1%; 95% CI, 93 to 99%) for concomitant therapy (P=0.07). More patients were compliant (defined as compliance ≥80%) with hybrid therapy (98.8%) than concomitant therapy (95.2%; P=0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
daily for the final seven days) vs concomitant therapy (same four drugs taken concurrently, twice daily for 14 days)				
Ohlin et al.[104] (2002) Clarithromycin 500 mg BID, amoxicillin 1g BID, and lansoprazole 30 mg BID for 14 days (LAC) vs lansoprazole 30 mg BID and amoxicillin 1g BID for 14 days (LA) vs omeprazole 20 mg BID and amoxicillin 1g BID for 14 days (OA)	DB, MC, RCT Patients 18 to 80 years of age with *H pylori* infection and a present recurrent duodenal ulcer and/or previous recurrent duodenal ulcer	N=177 4 weeks posttreatment	Primary: Eradication of *H pylori* at least four weeks after the end of treatment period Secondary: Not reported	Primary: Triple therapy with LAC was significantly better than either dual therapy with OA or LA in ulcer healing and eradication of *H pylori* (P<0.001). There was no significant difference between dual therapy groups. Secondary: Not reported
Magaret et al.[105]	MC, RCT	N=48	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
(2001) Tetracycline 250 mg QID, bismuth subsalicylate 2 tablets QID, lansoprazole 30 mg BID, and metronidazole 250 mg QID for 14 days vs lansoprazole 30 mg BID, amoxicillin 1,000 mg BID, and clarithromycin 500 mg BID for 14 days	Patients years of age failing prior treatment for *H pylori*	6 weeks	Negative 14C-UBT of <50 disintegrations per minute at time of follow-up indicating cure of infection Secondary: Side effects and compliance	Per-protocol eradication rates for patients on triple therapy and quadruple therapy were 82 and 80%, respectively (P=0.85). Intention-to-treat eradication rates for triple and quadruple therapy were 72 and 65%, respectively (P=0.63). Secondary: Compliance in patients receiving triple and quadruple therapy was 89% (P=0.98). Side effects were reported in 84% of patients on triple therapy and 82% of patients on quadruple therapy (P=0.85). Side effects included nausea (33%), upset stomach (25%), diarrhea (36%), abdominal pain (16%), lightheadedness/dizziness (4%), and fatigue (8%).
Miehlk et al.[106] (2003) Tetracycline 500 mg QID, bismuth citrate 107 mg QID, omeprazole 20 mg BID, and metronidazole 500 mg QID for 14 days vs omeprazole 40 mg QID and	RCT, XO Patients 18 to 80 years of age with at least one previous failure of *H pylori* therapy documented by confirmatory examinations and antimicrobial resistance to both metronidazole and clarithromycin	N=84 26 months	Primary: Two negative biopsy-based tests, histology and rapid urease test, or a validated 13C-urea breath test to confirm successful treatment Secondary: Not reported	Primary: In the per-protocol analysis, patients on high-dose dual therapy and quadruple therapy achieved *H pylori* cure rates of 83.8 and 92.1%, respectively (P=0.71). Cure rates using intent-to-treat analysis were 75.6 and 81.4% for high-dose dual therapy and quadruple therapy, respectively, and were not significantly different (P=0.60). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
amoxicillin 750 mg QID for 14 days				
Perri et al.[107] (2001) Tetracycline 500 mg QID, bismuth citrate 240 mg BID, pantoprazole 40 mg BID, and metronidazole 250 mg TID for 10 days (quadruple therapy group) vs pantoprazole 40 mg BID, amoxicillin 1 g BID, and rifabutin 150 mg every other day for 10 days (RIF 150 mg group) vs pantoprazole 40 mg BID, amoxicillin 1 g BID, and rifabutin 300 mg every other day for 10 days (RIF 300 mg group)	OL, PRO, RCT Patients with *H pylori* infection confirmed by 13C-urea breath test after failure of one or more standard regimens	N=135 6 weeks	Primary: Eradication rates as defined by negative 13C-urea breath test four weeks after end of treatment Secondary: Side effect rates reported after end of treatment	Primary: By intent-to-treat analysis, eradication rates for the pantoprazole, amoxicillin and rifabutin 150 mg treatment group (RIF 150 mg group) were 66.6%. Eradication rates for pantoprazole, metronidazole, bismuth citrate, and tetracycline (quadruple therapy group) were also 66.6%. The eradication rate for pantoprazole, amoxicillin, and rifabutin 300 mg (RIF 300 mg group) was 86.6%, which was significantly different than the other two treatment groups (P<0.025). Secondary: There was a significant difference in the side effects observed in rifabutin-treated patients compared to patients receiving quadruple therapy. The rates of side effects were 9, 11 and 47%, (P<0.0001), for the triple therapies with the RIF 150 mg group, RIF 300 mg group, and quadruple therapy group, respectively.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Katelaris et al.[108] (2002) Tetracycline 500 mg QID, bismuth subcitrate 108 mg QID, pantoprazole 40 mg BID, metronidazole 200 mg TID and 400 mg in the evening for 7 days (PBTM7) vs tetracycline 500 mg QID, bismuth subcitrate 108 mg QID, and metronidazole 200 mg TID and 400 mg in the evening for 14 days (BTM14) vs pantoprazole 40 mg, amoxicillin 1,000 mg, and clarithromycin 500 mg BID (PAC7)	MC, OL, PG, RCT Patients ≥18 years of age with *H pylori* infection confirmed by a positive urease test and confirmatory histology and 13C-urea breath test	N=405 8 weeks	Primary: At week eight, ^{13}C-urea breath test to determine the outcome of eradication therapy Secondary: Compliance and adverse event profile	Primary: By intent-to-treat analysis, the eradication rates for the PAC7, PBTM7, and BTM14 treatment groups were 78, 82 and 69%, respectively. By per-protocol analysis, the corresponding eradication rates were 82, 88, and 74%, respectively. In both analysis, the eradication rates for PBTM7 and PAC7 were not significantly different (all P>0.05), while eradication rates for PBTM7 were significantly higher than BTM14 (P=0.01). Secondary: Adverse effects were common in all treatment groups. Adverse effects that interfered with activities of daily living were significantly higher in the BTM14 group (P<0.01). The number of patients who discontinued treatment due to adverse effects was also higher in the BTM14 group (9%) vs the PBTM7 group (3%) and the PAC7 group (2%). Noncompliance, defined as less than 90% of study drug taken, was higher in BTM14 than PBTM7 and PAC7.
Uygun et al.[109] (2007) Tetracycline 500	RCT, SB, SC Patients with *H pylori* infection and	N=240 14 days	Primary: *H pylori* eradication rates	Primary: The intent to treat and per protocol populations, *H pylori* eradication rates were 70% (95% CI, 61 to 78) and 82.3% (95% CI, 74 to 89) in the BLTM group, and 57.5% (95%CI, 48 to 66) and 62.7% (95%CI, 53 to 71) in the

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg QID, bismuth subsalicylate 300 mg QID, lansoprazole 30 mg BID, and metronidazole 500 mg TID (BLTM group) vs lansoprazole 30 mg BID, amoxicillin 1 g BID and clarithromycin 500 mg BID (LAC)	non-ulcer dyspepsia		Secondary: Not reported	LAC group. The BLTM treatment achieved a significantly better eradication rate than the LAC treatment in per protocol analysis (82.3 vs 62.7%; P=0.002). Although a better intent to treat rate was obtained in the BLTM group than in the LAC group, the difference was not significant (70 vs 57.5%; P=0.06). Mild to severe side-effects, which were more frequent in the BLTM group, were reported in 18.2% of the patients. Although it was not statistically significant, the number of patients ceasing the treatment for side-effects was more in BLTM group than in the LAC group. Secondary: Not reported
Wu et al.[110] (2011) Tetracycline 500 mg QID, bismuth subcitrate 120 mg QID, esomeprazole 40 mg BID, and metronidazole for 7 days as rescue therapy (EBTM) vs tetracycline 500 mg QID, bismuth subcitrate120 mg QID, esomeprazole 40 mg BID, and amoxicillin 500	RCT Patients ≥18 years of age with persistent *H pylori* infection who failed standard first-line therapy (proton-pump inhibitor, clarithromycin and amoxicillin)	N=120 8 weeks posttreatment	Primary: Eradication rates, adverse events, resistance rates, compliance Secondary: Not reported	Primary: In the intent to treat analysis, there was a significantly lower eradication rate for the EBTA group (62%; 95% CI, 50 to 75) than for the EBTM group (81%; 95% CI, 71 to 91; P=0.02). In the per protocol analysis, *H pylori* infection was eradicated in 64% of the EBTA group (95% CI, 52 to 76) and 83% of the EBTM group (95% CI, 74 to 92; P=0.01). A total of 19% of patients in the EBTA group and 44% of patients in the EBTM group reported at least one adverse event during eradication therapy. The EBTA group had fewer adverse events than the EBTM group (P=0.004). The frequency of nausea in the EBTA group was lower than in the EBTM group (5 vs 16%, respectively). Tetracycline- and metronidazole-resistant strains were found in 2 and 53% of the patients, respectively. No strains developed resistance to amoxicillin. In the EBTA group, the *H pylori* eradication rate for the tetracycline-susceptible strains was 67% by intent to treat analysis and 68% by per protocol analysis. All the strains in the subgroup were

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg QID for 7 days as rescue therapy (EBTA)				susceptible to amoxicillin. In the EBTM group, no tetracycline-resistant strains existed. The eradication rate of tetracycline-susceptible strains was 80 and 83% by intent to treat and per protocol analyses, respectively. With respect to metronidazole resistance, eradication rates were similar between susceptible and resistant strains by either intent to treat or per protocol analyses. Compliance rates were 97% in both treatment groups (P=1.00). Secondary: Not reported
Songür et al.[111] (2009) Tetracycline 500 mg QID, bismuth subcitrate 300 mg QID, lansoprazole 30 mg BID, and metronidazole 500 mg BID for 10 days (BLTM) vs tetracycline 500 mg QID, ranitidine bismuth citrate 400 mg BID, lansoprazole 30 mg BID, and metronidazole 500 mg BID for 10 days (RBLTM) vs	RCT, SC Patients with *H pylori* infection and dyspeptic symptoms	N=464 14 days	Primary: Eradication rates, compliance Secondary: Not reported	Primary: In the per protocol analysis, eradication rates in LAC, BLTM, RBLTM, and LTM groups were 35.6, 54.9, 64.4, and 60.0%, respectively. In the intent to treat analysis, eradication r rates in LAC, BLTM, RBLTM, and LTM groups were 32.7, 47.1, 57.3, and 54.8%, respectively. The BLTM, RBLTM, and LTM treatment groups achieved a significantly better eradication rate than the LAC treatment group (P<0.001). There was no significant difference between BLTM, RBLTM, and LTM treatment groups. Compliance rates with LAC, BLTM, RBLTM, and LTM therapies were 91, 87, 90, and 94%, respectively. The treatments were generally well tolerated. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
tetracycline 500 mg QID, lansoprazole 30 mg BID, and metronidazole 500 mg BID for 10 days (LTM) vs lansoprazole 30 mg BID, amoxicillin 1,000 mg BID, and clarithromycin 500 mg BID for 14 days (LAC)				
Malfertheiner et al.[112] (2011) Tetracycline 125 mg, bismuth subcitrate potassium 140 mg, and metronidazole 125 mg (as a single three-in-one capsule) 3 capsules QID plus omeprazole 20 mg BID for 10 days (quadruple therapy) vs	OL, RCT Patients ≥18 years of age with *H pylori* infection and upper gastrointestinal symptoms	N=399 56 days posttreatment	Primary: Eradication rates, resistance rates, and safety Secondary: Not reported	Primary: In the per protocol analysis, eradication rates were 93% with quadruple therapy compared to 70% with standard therapy (P<0.0001). Quadruple therapy was found to be non-inferior to standard therapy. In the intention-to-treat analysis, eradication rates were 80% with quadruple therapy compared to 55% with standard therapy (P<0.0001). Metronidazole sensitivity did not significantly affect the efficacy of quadruple therapy in the per protocol population (P=0.283). Clarithromycin sensitivity seemed to significantly affect the efficacy of standard therapy (P<0.0001). Simultaneous metronidazole and clarithromycin resistance reduced efficacy only in patients treated with standard therapy (P=0.001). The incidence of serious treatment emergent adverse events and discontinuations due to a treatment emergent adverse events were similar between groups (<2.0%). The main adverse events were gastrointestinal and central nervous system disorders.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
omeprazole 20 mg, amoxicillin 500 mg, and clarithromycin 500 mg BID for 7 days (standard therapy)				Secondary: Not reported
Zheng et al.[113] (2010) Tetracycline 750 mg BID, colloidal bismuth subcitrate 220 mg BID, pantoprazole 40 mg BID, and metronidazole 400 mg TID for 10 days (PBMT) vs pantoprazole 40 mg BID, amoxicillin 1.0 g BID and clarithromycin 500 mg BID for 7 days (PAC)	OL, RCT, SC Patients 18 to 70 years of age with non-ulcer dyspepsia and *H pylori* infection	N=170 7 to 10 days	Primary: Eradication rates, resistance rates, safety Secondary: Not reported	Primary: In the intent to treat analysis, eradication rates were 63.5% in the PAC group and 89.4% in the PBMT groups (P<0.05). In the per protocol analysis, the eradication rates were 65.1% in the PAC group and 91.6% in the PBMT group (P<0.05). The H pylori primary resistance rates to metronidazole and clarithromycin were 41.6 and 20.8%, respectively, whereas all the *H pylori* isolates were sensitive to amoxicillin and tetracycline. Adverse events were similar among the treatment groups and included bitter taste, nausea, poor appetite, and occasional symptoms, such as diarrhea, vomiting, drug eruption, insomnia, constipation, and lethargy. The adverse events rates of quadruple therapy and triple therapy were 42.3 and 60.0%, respectively. Secondary: Not reported
de Boer et al.[114] (1998) Tetracycline 500 mg QID, ranitidine bismuth citrate 400 mg BID, and metronidazole 500 mg TID for 7 days	OL, PG, RCT Patients with upper gastrointestinal symptoms and infected with *H pylori*	N=168 8 weeks	Primary: Endoscopy performed six weeks after completion of treatment to determine *H pylori* infection, defined as a positive	Primary: Logistical regression analysis determined that there was no difference between the seven-day and 14-day treatments. Intent-to-treat analysis cure rate for the ranitidine bismuth citrate, tetracycline, and metronidazole treatment group was 86%. The cure rate for the ranitidine bismuth citrate, amoxicillin, and clarithromycin treatment group was 92%. The cure rate for the ranitidine bismuth citrate and clarithromycin treatment group was 95%. Per-protocol cure rates were 89, 93, and 96% respectively. There was no statistical difference between the three groups.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs ranitidine bismuth citrate 400 mg BID, amoxicillin 1,000 mg BID, and clarithromycin 500 mg BID for 7 days vs ranitidine bismuth citrate 400 mg BID, clarithromycin 500 mg BID for 14 days			CLOtest, confirmed by histology or culture Secondary: Safety	Secondary: Side effects were comparable among the treatment groups. Overall, 32% of patients in the ranitidine bismuth citrate, tetracycline, metronidazole treatment group, 18% of the ranitidine bismuth citrate, amoxicillin, and clarithromycin treatment group, and 23% of the ranitidine bismuth citrate and clarithromycin treatment group reported side effects during the trial period (P=0.249).
Luther et al.[115] (2010) Tetracycline, metronidazole, bismuth-containing compound, and proton-pump inhibitor (bismuth quadruple therapy) vs clarithromycin triple therapy (amoxicillin, clarithromycin, and proton-pump	MA Patients with *H pylori* infection	N=1,679 (9 trials) Variable duration	Primary: Eradication rate, compliance rate, adverse events Secondary: Not reported	Primary: The eradication rate with bismuth quadruple therapy was 78.3% compared to 77% with clarithromycin triple therapy (RR, 1.002; 95% CI, 0.936 to 1.073). The compliance rate with bismuth quadruple therapy was 92.6% compared to 98.9% with clarithromycin triple therapy (RR, 0.99; 95% CI, 0.938 to 1.045). The overall incidence of adverse events in patients receiving bismuth quadruple therapy was 35.5% compared to 35.4% with clarithromycin triple therapy (RR, 1.037; 95% CI, 1.037 to 1.135). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
inhibitor)				
Henry et al.[116] (2003) Azithromycin 500 mg daily for 3 days (AZM-3) vs azithromycin 500 mg daily for 6 days (AZM-6) vs amoxicillin-clavulanate 500 mg TID for 10 days (AMC)	DB, DD, MC, RCT Patients 18 years of age or older with acute bacterial sinusitis	N=936 28 days	Primary: Clinical success at end of study Secondary: Not reported	Primary: Cure rates were 71.7% in the AZM-3 group, 73.4% in the AZM-6 group, and 71.3% in the AMC group. There was no significant difference between groups. Secondary: Not reported
Klapan et al.[117] (1999) Azithromycin 500 mg daily for three days vs amoxicillin-clavulanate 625 mg every 8 hours for 10 days	OL, RCT Patients 15 to 50 years of age with sinusitis	N=100 4 weeks	Primary: Clinical response and bacteriologic response Secondary: Not reported	Primary: Cure was established in 95% of patients in the azithromycin group and 74% of patients in the amoxicillin-clavulanate group at the end of therapy (day 10 to 12), and clinical improvement was seen in the remainder of patients in both groups (P=0.012 in favor of azithromycin). At the follow-up visit (four weeks), cure was established in 98% of patients in the azithromycin group and 91% in the amoxicillin-clavulanate group. No significant differences were observed between groups (P>0.05). There was no significant difference in bacteriologic response seen between groups (P=0.409). Secondary: Not reported
Gupta et al.[118] (2009)	OL, RCT, SC	N=88 (123 episodes)	Primary: Treatment success	Primary: In the per protocol analysis, treatment was successful in 90.16% of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Ceftriaxone 75 mg/kg/day IV and amikacin 15 mg/kg once daily as outpatient therapy vs ofloxacin 7.5 mg/kg orally every 12 hours and amoxicillin-clavulanate 12.5 mg/kg orally every 8 hours as outpatient therapy	Pediatric patients two to 15 years of age with low-risk febrile neutropenia	Variable duration	Secondary: Not reported	episodes in the oral group and in 93.10% of episodes in the IV group. In the intention-to-treat analysis, the success rate was 88.7% in the oral group and 88.5% in the IV group (P=0.97). There were three hospitalizations (all in the oral group) and no mortality. Secondary: Not reported
Desrosiers et al.[119] (2008) Telithromycin 800 mg once daily for five days vs amoxicillin-clavulanate 875-125 mg BID for 10 days	MC, OL Patients ≥18 years old with clinical and radiological diagnosis of acute bacterial sinusitis	N=298 Up to 49 days	Primary: Clinical success, adverse events, and quality of life Secondary: Not reported	Primary: The per protocol clinical success rate measured at the test-of-cure visit was 88.6% with telithromycin compared to 88.8% in the amoxicillin-clavulanate treatment group (95% CI, -8.9 to 8.5). At the follow-up visit (days 41 to 49), 84.6% of patients in the telithromycin group achieved clinical success, compared to 84.8% of those in the amoxicillin–clavulanate group. Median times to reduction of total symptom scores were shorter for telithromycin vs amoxicillin–clavulanate (seven days vs eight days [75% reduction] and four days vs five days [50% reduction] with the difference being statistically significant for the 50% reduction (P=0.044). Treatment-emergent adverse events occurred in 20.7% of telithromycin-treated patients vs 31.8% of amoxicillin-clavulanate-treated patients (P=0.034). In the baseline SF-36 health questionnaire, 75.5% of patients (209/278) described themselves as feeling much or somewhat worse than a week

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				earlier (telithromycin, 74.2% and amoxicillin–clavulanate, 76.6%). Secondary: Not reported
Ziogos et al.[120] (2010) Cefuroxime 1.5 g IV as a single dose vs ampicillin-sulbactam 3 g IV as a single dose	RCT Women scheduled for cesarean delivery	N=176 30 days	Primary: Development of an infection Secondary: Not reported	Primary: Postoperative infections developed in 5.9% of patients receiving cefuroxime and 8.8% of patients receiving ampicillin-sulbactam (P=0.6). In univariate analyses six or more vaginal examinations prior to the operation (P=0.004), membrane rupture for more than six hours (P=0.08) and blood loss greater than 500 mL (P=0.018) were associated with developing a postoperative surgical site infection. In logistic regression having 6 or more vaginal examinations was the most significant risk factor for a postoperative surgical site infection (OR, 6.8; 95% CI, 1.4 to 33.4; P=0.019). Regular prenatal follow-up was associated with a protective effect (OR, 0.04; 95% CI, 0.005 to 0.36; P=0.004). Patients that developed an infection had a lengthier hospital stay (median of five vs four days; P<0.001). All patients with an infection responded well to subsequent antibiotics. No adverse drug reactions were reported. Secondary: Not reported
McKinnon et al.[121] (1999) Ampicillin-sulbactam 1.5 or 3.0 g every 6 hours vs ticarcillin-	OL, MC, RETRO Patients with skin and soft tissue, intraabdominal, gynecologic, respiratory, urinary tract, or other infections requiring parenteral antibiotic	N=890 Duration not specified	Primary: Clinical response rate Secondary: Bacteriologic cure rate	Primary: Rate of satisfactory clinical response was highest with ampicillin-sulbactam 1.5 g (85.9 vs 82.5% for ampicillin-sulbactam 3.0 g vs 77.5% for ticarcillin-clavulanate; P=0.044). Secondary: Overall bacteriologic efficacy of ampicillin-sulbactam and ticarcillin-clavulanate were not statistically different, with the exception of a higher bacteriologic eradication rate for ticarcillin-clavulanate against *Pseudomonas* species (P=0.013).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
clavulanate 3.1 g every six hours	therapy			
Tanaka-Kido et al.[122] (1990) Chloramphenicol 100 mg/kg/day in 4 divided doses, which was continued for 8 days after the last fever day vs aztreonam 150 mg/kg/day IV in 3 divided doses, which was continued for 8 days after the last fever day	RCT Patients 2 to 6 years of age with typhoid fever	N=36 1 month	Primary: Clinical cure rate, fever duration, relapse rate, adverse effects Secondary: Not reported	Primary: There was no significant difference between the chloramphenicol and aztreonam groups in clinical cure rate (94 vs 100%). There was no significant difference between the chloramphenicol and aztreonam groups in fever duration (4.1 vs 5.9 days, respectively; P>0.05). There were no relapses in either of the two groups. While there was no incidence of anemia in the aztreonam group, there were five cases of anemia in the chloramphenicol group (P<0.05). There was no difference in the incidence of leukopenia and neutropenia between the two treatment groups (P>0.05). The approximate mean duration of antibiotic therapy was 15 days in the aztreonam group and 13 days in the chloramphenicol group. Secondary: Not reported
Gotuzzo et al.[123] (1994) Chloramphenicol 50 mg/kg/day oral/IV in 4 divided doses for 14 days vs aztreonam 2 g IV every 8 hours for 10 days	MC, RCT Patients >14 years of age with typhoid fever	N=44 10 weeks	Primary: Clinical cure rate, fever duration, bacteremia Secondary: Not reported	Primary: There was a significant difference between the chloramphenicol and aztreonam groups in terms of clinical cure rates (100 vs 68%, respectively; P<0.01). Defervescence occurred more quickly in patients receiving chloramphenicol compared to patients on aztreonam therapy (4.5 vs 6.6 days, respectively; P<0.03). There were no relapses in either of the two groups. While 24-hour positive blood cultures occurred in 32% of patients on chloramphenicol therapy, none of the patients in the aztreonam group had positive blood cultures (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Adverse reactions experienced by patients in each treatment group deemed unusual or mild with no statistical difference found between the two groups. Secondary: Not reported
Rodriguez et al.[124] (1986) Chloramphenicol 100 mg/kg/day IV in 4 divided doses plus ampicillin 400 mg/kg/day IV in 4-6 divided doses vs ampicillin 400 mg/kg/day IV in 4-6 divided doses plus sulbactam 50 mg/kg/day	MC, PRO, RCT Hospitalized patients 1 month to 14 years of age with meningitis	N=81 10 days	Primary: Mortality rate, resolution of symptoms, complications, adverse effects Secondary: Not reported	Primary: Of the patients with assessable CSF pathogens, the mortality rate was 3% in the ampicillin-sulbactam group and 18% in the chloramphenicol-ampicillin group. Neurologic sequelae occurred in 12% of patients on ampicillin-sulbactam and 18% of patients on chloramphenicol-ampicillin therapy. The mean time to resolution of symptoms was 4.4 days in the ampicillin-sulbactam group and 4.8 days in the chloramphenicol-ampicillin. Abnormal laboratory findings were found in 20% of the ampicillin-sulbactam group and 35% in the chloramphenicol-ampicillin group. Secondary: Not reported
Girgis et al.[125] (1988) Chloramphenicol 100 mg/kg/day plus ampicillin 160 mg/kg/day every six hours (AMCL) vs ceftriaxone 100 mg/kg once daily	RCT Patients with bacterial meningitis	N=100 6 days	Primary: Cerebrospinal fluid leukocyte count, glucose, protein content, disappearance of meningeal irritation, fever defervescence, patient alertness, mortality rate Secondary:	Primary: There was no significant difference between the two groups in the disappearance of meningeal irritation, fever defervescence, and patient alertness. There was no significant difference between the two groups in the cerebrospinal fluid leukocyte count, glucose or protein content at baseline, as well as the final evaluation. There was no significant difference between the two groups in mortality. While 20% of patients treated with AMCL died, the mortality in the ceftriaxone group was 7%.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			Not reported	Secondary: Not reported
Girgis et al.[126] (1987) Chloramphenicol 100 mg/kg/day IV plus ampicillin 160 mg/kg/day IV every six hours (group 1) vs ceftriaxone 100 mg/kg IV once daily (group 2)	RCT Patients 16 to 30 years of age with bacterial meningitis	N=30 6 days	Primary: Mortality, time taken for defervescence, time for patients to regain full consciousness Secondary: Not reported	Primary: One patient in each group died within 24 hours of initiation of therapy. Both had meningitis due to *Streptococcus pneumoniae*. The mean number of days to become afebrile were 3.4 and 3.5 for group 1 and group 2, respectively. The mean number of days to regain full consciousness was 3.9 and 2.5 for group 1 and group 2, respectively. Secondary: Not reported
Jacobs et al.[127] (1985) Chloramphenicol 25 mg/kg/dose IV plus ampicillin 50 to 100 mg/kg/dose IV every six hours vs cefotaxime 50 mg/kg/dose IV every six hours	PRO, RCT Patients one week to 16 years of age with meningitis	N=50 3 months	Primary: Clinical cure rate, survival without sequelae, duration of therapy Secondary: Not reported	Primary: There was no significant difference in the clinical cure rate between the chloramphenicol-ampicillin and cefotaxime groups (96 vs 100%, respectively; P>0.5). There was no significant difference in survival without detectable sequelae between the chloramphenicol-ampicillin and cefotaxime groups (77 vs 78%, respectively). Mean duration of therapy was similar in the chloramphenicol-ampicillin and cefotaxime groups (11.9 and 11.1 days, respectively). Secondary: Not reported
Rodriguez et al.[128] (1986) Chloramphenicol 75 to 100 mg/kg/day IV in	OL, RCT Patients one month to 15 years of age with meningitis	N=100 Up to 6 months	Primary: Clinical cure rate, clinical improvement, mortality rate, neurological	Primary: After the first 24 hours of therapy, 10% of the patients died, 2% clinically improved, and 88% were cured in the ceftazidime group. In the chloramphenicol-ampicillin group, 10% of patients died, 1% clinically improved, and 81% were cured in the ceftazidime.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
four divided doses plus ampicillin 400 mg/kg/day IV in six divided doses vs ceftazidime 150 mg/kg/day IV divided into three doses, administered every eight hours			sequelae, mean duration of therapy Secondary: Not reported	Seizures occurred in 54% of patients treated with ceftazidime and 51% of patients treated with chloramphenicol-ampicillin therapy. Mean duration of therapy was 10.2 and 10.4 days in the ceftazidime and chloramphenicol-ampicillin groups, respectively. Secondary: Not reported
Marks et al.[129] (1986) Chloramphenicol 75 to 100 mg/kg/day IV in four divided doses plus ampicillin 300 to 400 mg/kg/day IV every six hours vs cefuroxime 225 mg/kg/day IV divided into three doses, administered every eight hours	MC, RCT Patients 3 months to 16 years of age with bacterial meningitis	N=107 Up to 6 months	Primary: Clinical cure rate, cerebrospinal fluid sterilization rate Secondary: Not reported	Primary: Clinical cure rate was 95% in both treatment groups. There was no significant difference in the cerebrospinal fluid sterilization rates between the cefuroxime and chloramphenicol-ampicillin groups (90 vs 100%, respectively). Secondary: Not reported
Babinchak et al.[130] (2005) Tigecycline 100 mg as an initial	MA Adults with complicated intra-abdominal	N=1,642 (2 trials) 47 to 56 days	Primary: Clinical response (infection and associated signs and symptoms	Primary: Clinical cure rates were 86.1% for patients in the tigecycline group, vs 86.2% for patients in the imipenem-cilastatin group (P<0.0001 for non-inferiority).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
dose, followed by 50 mg IV every 12 hours vs imipenem-cilastatin 500 mg IV every 6 hours	infections		resolved) Secondary: Safety	Secondary: Nausea (24.4% tigecycline, 19.0% imipenem-cilastatin [P=0.01]), vomiting (19.2% tigecycline, 14.3% imipenem-cilastatin [P=0.008]), and diarrhea (13.8% tigecycline, 13.2% imipenem-cilastatin [P=0.719]) were the most frequently reported adverse events.
Fomin et al.[131] (2008) Tigecycline 100 mg as an initial dose, followed by 50 mg IV every 12 hours vs imipenem-cilastatin 500 mg IV every 6 hours	DB, RCT (pooled analysis) Adults with complicated intra-abdominal infections	N=1,259 5 to 14 days	Primary: Clinical response at the test-of-cure visit in the microbiologically evaluable and microbiological modified intent-to-treat populations Secondary: Safety	Primary: Clinical cure rates at the test-of-cure visit were 92.4% for tigecycline vs 88.8% for imipenem-cilastatin in the microbiologically evaluable population (95% CI, 2.2 to 9.4). Clinical cure rates for the modified intent-to-treat populations were 87.3% for tigecycline vs 83.5% for imipenem-cilastatin (95% CI, -2.5 to 10.0) at the test-of-cure visit. Secondary: The most commonly reported treatment emergent adverse events for tigecycline and imipenem-cilastatin were nausea (14.7 and 11.8%, respectively; P=0.267) and vomiting (10.7 and 7.3%, respectively; P=0.146). The imipenem-cilastatin group had significantly higher treatment emergent adverse events of fever, hyperglycemia, and dyspnea (P=0.017, P=0.031, and P=0.011, respectively) compared to tigecycline. The tigecycline treatment group had significantly higher treatment emergent adverse events of amylase and blood urea nitrogen increase (P=0.011 and P=0.003, respectively).
Mallick et al.[132] (2007) Tigecycline 100 mg as an initial dose, followed by 50 mg IV every 12	DB, RCT (pooled analysis) Adults with complicated intra-abdominal infections	N=1005 5 to 14 days	Primary: Clinical response, safety, and health care resource utilization Secondary:	Primary: Clinical cure rates were 88.1% for tigecycline and 87.0% for imipenem–cilastatin (P=0.59). Treatment-emergent adverse events, regardless of study drug causality or severity, occurred in 73.8% of tigecycline- and 71.6% of imipenem–cilastatin-treated patients (P=0.346).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
hours vs imipenem-cilastatin 500 mg IV every 6 hours			Not reported	Of the three most frequently reported adverse events, tigecycline was associated with a significantly higher rate of nausea (24.4%) relative to imipenem–cilastatin (19.0%; P<0.010) and a significantly higher rate of vomiting (19.2% relative to imipenem–cilastatin (14.3%; P<0.008). There were no significant differences between the groups in terms of occurrence of diarrhea (13.8% with tigecycline; 13.2% with imipenem–cilastatin; P=0.719). There were no significant differences between the tigecycline and the imipenem– cilastatin groups for any health resource utilization, clinical outcome, or antibiotic discontinuation rates.
Gentry et al.[133] (1997) Nafcillin vs vancomycin	RETRO Patients with staphylococcal endocarditis	N=56 Duration not specified	Primary: Clinical response Secondary: Not reported	Primary: In patients with methicillin-sensitive *Staphylococcus aureus* infection, complete response rate was 74% in the nafcillin group compared to 50% in the vancomycin group (P=0.12); however these differences were not statistically significant. Mortality rate was 22% in the nafcillin group and 28% in the vancomycin group (P=0.73). Secondary: Not reported
Fang et al.[134] (1998) Piperacillin 4 g-tazobactam 500 mg every eight hours by IV infusion vs ticarcillin 3 g-clavulanate 200 mg every eight	OL, RCT Hospitalized patients 16 years and older with lower respiratory tract infections or urinary tract infections	N=124 7 to 14 days	Primary: Overall clinical efficacy rates, bacterial eradication rates Secondary: Adverse events	Primary: No statistical differences were observed between the two groups. Overall efficacy rates for the treatment of all infections was 90.5% in the piperacillin-tazobactam group compared to 88.5% in the ticarcillin-clavulanate group (P>0.05). Bacterial clearance rates for the piperacillin-tazobactam group were 90.2 vs 92.0% for the ticarcillin-clavulanate group (P>0.05). Secondary: Adverse drug reactions were similar in both groups (7.69% for ticarcillin-clavulanate vs 8.06% for piperacillin-tazobactam; P=0.938).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
hours by IV infusion				
Kobayashi et al.[135] (2009) Aztreonam 150 mg/kg/day plus ampicillin-sulbactam 150 mg/kg/day divided into four doses vs ceftazidime 100 mg/kg/day plus piperacillin-tazobactam 125 mg/kg/day divided into four doses Treatment was continued until completion of the appropriate course of therapy for a defined clinical or microbiologic infection.	RCT Pediatric patients with hematologic disease and solid tumor with febrile neutropenia	N=54 (177 episodes) 120 hours	Primary: Treatment success Secondary: Not reported	Primary: Success rates were 57.1 and 62.5% in the piperacillin-tazobactam plus ceftazidime and ampicillin-sulbactam plus aztreonam groups, respectively ($P \geq 0.05$). There were two deaths in the piperacillin-tazobactam plus ceftazidime group. The patients died within 48 hours from onset of the febrile episode. The success rates in episodes with absolute neutrophil counts $<0.5 \times 10^9$/L at the end of treatment were 70.0 and 74.1% in the piperacillin-tazobactam plus ceftazidime and ampicillin-sulbactam plus aztreonam groups, respectively, and the success rates in bacteremia episodes were 50% in both groups. The percentages of episodes with new infections were 25.7 and 20.3%, respectively. Duration of fever and antibiotic therapy did not differ between the groups, and no major adverse effects occurred in the study. Secondary: Not reported
Uygun et al.[136] (2009) Cefepime 50 mg/kg IV every eight hours (CEF) vs	RCT, OL Patients ≤19 years of age who had been treated for hematological malignancies or solid tumors and	N=70 (131 episodes) Variable duration	Primary: Success without modification Secondary: Not reported	Primary: Success without modification was similar between the two groups (60.0 vs 61.3% for PIP/TAZO and CEF, respectively; $P>0.05$). Success without modification was 84.8 and 92.1% for PIP/TAZO and CEF treatments, respectively, in patients with fever of unknown origin episodes. Success without modification was 29.2 and 12.5% in microbiologically documented infection episodes ($P>0.05$).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
piperacillin-tazobactam 80 mg/kg-10 mg/kg IV every six hours (PIP/TAZO)	had febrile neutropenia			Modifications were done with only glycopeptides in eight episodes, only antifungals in 20 episodes, only carbapenems in 11 episodes, and only antiprotozoals in two episodes. Duration of fever and neutropenia was similar in both groups. There was no significant difference in the duration of hospitalization between the treatment groups. No treatment changes were made because of potential side or adverse effect of PIP/TAZO or CEF. The most frequent adverse events were rash (7.7% in PIP/TAZO and 6.4% in CEF) and diarrhea (6.1% in PIP/TAZO and 6.4% in CEF). Secondary: Not reported
Gómez et al.[137] (2010) Cefepime 2 g IV every 12 hours plus amikacin 15 mg/kg/day as a single dose (C-A) vs piperacillin-tazobactam 4 g/500 mg IV every eight hours plus amikacin 15 mg/kg/day as a single dose (PT-A)	OL, RCT Patients >18 years of age with an episode of febrile neutropenia	N=190 (317 episodes) Variable duration	Primary: Clinical efficacy and toxicity Secondary: Not reported	Primary: The antibiotic success rate (no change or addition of antibiotics) was recorded in 59% of episodes in the C-A group and in 64% of episodes in the PT-A group (P=NS). Resolution of the febrile episode (with or without change in therapy) was observed in 92% of episodes in the C-A group and in 92% of episodes in the PT-A group. The 28-day mortality (all-cause) was similar in both groups: 9.9% in the C-A group and 10.5% in the PT-A group (P=NS). A microbiologically documented infection was present in 35% of episodes in the C-A group and 25% of episodes in the PT-A group (P=NS). A clinically documented infection was observed in 26% of episodes in the C-A group and 28% of episodes in the PT-A group. Toxicity was observed in 4% of episodes in the C-A group and in 3% of episodes in the PT-A group.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				Secondary: Not reported
Vural et al.[138] (2010) Imipenem-cilastatin 60 mg/kg/day IV in four divided doses vs piperacillin-tazobactam 360 mg/kg/day IV in four divided doses	RCT Patients with acute leukemia, lymphoma and solid tumors who were hospitalized with febrile neutropenia	N=63 (99 episodes) Variable duration	Primary: Success and failure rate Secondary: Not reported	Primary: The overall success rate was 67% and the failure rate was 33% in both treatment groups. The success and failure rates in the piperacillin–tazobactam group were 71 and 29%, respectively. The success and failure rates in the imipenem–cilastatin group were 62 and 38%, respectively (P>0.05 vs piperacillin-tazobactam). There were no deaths in the study and no major adverse effects were seen in either group. Mild adverse effects included nausea, vomiting, transient increase in liver function tests and rash. No patient required discontinuation of the therapy due to adverse effects. Secondary: Not reported
Yellin et al.[139] (2007) Ertapenem 1 g IV once daily (13 to 17 years of age) or 15 mg/kg (2 to 12 years of age) vs ticarcillin-clavulanate 50 mg/kg four to six times daily (<60 kg) or 3.1 grams four to six times daily (≥60 kg)	MC, OL, RCT Children aged 3 months to 17 years of age with complicated intra-abdominal infections or acute pelvic infections	N=105 3 to 9 days	Primary: Incidence of any serious drug-related clinical and/or laboratory adverse experiences Secondary: Overall response rates, drug-related clinical and/or laboratory adverse experiences, incidence of moderate-to-severe administration site reactions	Primary: Forty-six percent of patients had one or more clinical adverse event as assessed by the investigator: 39% in the ertapenem group and 67% in the comparator group. Eleven patients (14%; 95% CI, 7.0 to 23.0) in the ertapenem group and eight patients (33%; 95% CI, 15.6 to 55.3) in the comparator group reported drug-related clinical and/or laboratory adverse experiences. Infusion site pain was the most common drug-related adverse event in both groups. Secondary: Overall response rates were 89% for ertapenem and 73% for the comparator. Comparable rates were seen across each of the age groups studied. In the modified intent-to-treat analysis, the age-adjusted posttreatment

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				clinical response rates were 87 and 100% in the complicated intra-abdominal infections and acute pelvic infection patients, respectively, for ertapenem and 73and 100%, respectively, for ticarcillin-clavulanate. Overall age-adjusted response rates were 91% for ertapenem and 83% for the comparator. Eleven percent (95% CI, 5.2 to 20.0) in the ertapenem group and 25% (95% CI, 9.8 to 46.7) in the comparator group experienced ≥1 local reactions of any intensity at the infusion/injection site.
Falagas et al.[140] (2008) Ertapenem vs piperacillin-tazobactam, ceftriaxone plus metronidazole, or ticarcillin-clavulanic acid	MA Patients with complicated intra-abdominal infections or acute pelvic infections	7 trials 4 to 14 days	Primary: Clinical success Secondary: Mortality, laboratory adverse events, patient withdrawals because of adverse events	Primary: No difference was found regarding clinical success in patients treated with ertapenem, compared to those treated with other antibiotics (OR, 1.11; 95% CI, 0.89 to 1.39). There was no difference in microbiological success of adult patients with complicated intra-abdominal infections treated with ertapenem compared to those treated with comparator antibiotics (OR, 1.19, 95% CI, 0.83 to 1.71). Microbiological or clinical success did not differ between compared treatments for the subsets of patients infected with either *Pseudomonas aeruginosa* (OR, 1.00; 95% CI, 0.41 to 2.45) or *Enterococcus* spp. (OR, 1.19; 95% CI, 0.60 to 2.39). Secondary: There was no difference in mortality between adult patients with complicated intra-abdominal infections treated with ertapenem or comparator antibiotics (OR, 1.14; 95% CI, 0.72 to 1.83). No difference was found regarding clinical adverse events between adult patients with complicated intra-abdominal infections treated with ertapenem compared to those treated with other antibiotics (OR, 0.86; 95% CI, 0.61 to 1.20). Significantly more laboratory adverse events were noted in patients with complicated intra-abdominal infections, treated with ertapenem compared

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				to patients treated with other antibiotics (OR, 1.73; 95% CI, 1.14 to 2.61). No difference was found regarding withdrawals from the included studies because of adverse events, between patients with complicated intra-abdominal infections treated with ertapenem compared to those treated with other antibiotics (OR, 0.94; 95% CI, 0.47 to 1.87).

Drug regimen abbreviations: BID=twice daily, ER=extended release, IM=intramuscular, IV=intravenous, QID=four times daily, SC=subcutaneous, TID=three times daily,
Study abbreviations: CI=confidence interval, DB=double-blind, DD=double-dummy, HR=hazard ratio, MA=meta-analysis, MC=multicenter, NS=not significant, OL=open-label, OR=odds ratio, OS=observational study, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=relative risk, SB=single blind, SC=single center, XO=cross over
Other abbreviations: COPD=chronic obstructive pulmonary disease, *H pylori=Helicobacter pylori*, SMX-TMP=sulfamethoxazole-trimethoprim

Additional Evidence

Dose Simplification
Previous analyses have demonstrated that oral antibiotics given once or twice daily are associated with higher adherence rates than antibiotics given three times daily.[141,142] Thanaviratananich et al. conducted a systematic review to evaluate clinical cure rates with amoxicillin (with or without clavulanate) administered once or twice daily compared to three times daily.[143] Five studies involving 1,601 patients were included. All studies were found to be at moderate to high risk for bias; therefore, the investigators did not perform a pooled data meta-analysis. The clinical cure rates at the end of therapy and at the follow-up periods of each study were shown to be comparable between the two groups.

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 14. Relative Cost of the Penicillins

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Amoxicillin	capsule, chewable tablet, extended-release tablet, suspension, tablet	Moxatag®	$$$$	$
Ampicillin	capsule, injection, suspension	N/A	N/A	$$
Dicloxacillin	capsule	N/A	N/A	$$
Nafcillin	injection	N/A	N/A	$$$$$
Oxacillin	injection	N/A	N/A	$$$$$
Penicillin G benzathine	injection	Bicillin L-A®	$$$$$	N/A
Penicillin G potassium	injection	Pfizerpen®*	$$$$	$$$$$
Penicillin G procaine	injection	N/A	N/A	$
Penicillin G sodium	injection	N/A	N/A	$$$$$

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Penicillin V potassium	solution, tablet	N/A	N/A	$
Combination Products				
Amoxicillin and clavulanate	chewable tablet, extended-release tablet, suspension, tablet	Augmentin®*, Augmentin XR®*	$$-$$$$	$$
Ampicillin and sulbactam	injection	Unasyn®*	$$$$-$$$$$	$$$$
Penicillin G benzathine and penicillin G procaine	injection	Bicillin C-R®	$$	N/A
Piperacillin and tazobactam	injection	Zosyn®*	$$$$-$$$$$	$$$$$

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

X. Conclusions

The penicillins are approved to treat a variety of infections, including central nervous system, dermatologic, gastrointestinal, genitourinary, respiratory, as well as several miscellaneous infections.[1-11] They are classified into five groups based on their spectrum of activity, including natural penicillins, penicillinase-resistant penicillins, aminopenicillins, carboxypenicillins, and ureidopenicillins. The majority of the penicillins are available in a generic formulation, with the exception of penicillin G benzathine (with or without penicillin G procaine).

There are many guidelines that define the appropriate place in therapy for the penicillins. The agent that is recommended is dependent upon the infectious organism being treated and the corresponding spectrum of activity of the penicillin. The penicillins are recommended as specific therapy for the treatment of susceptible pathogens causing endocarditis, encephalitis, meningitis, skin and soft-tissue infections, *Helicobacter pylori* infections, syphilis, pyelonephritis, otitis media, pharyngitis, sinusitis, anthrax, infectious exacerbations of chronic obstructive pulmonary disease, community-acquired pneumonia, nosocomial pneumonia, intra-abdominal infections, Lyme disease, as well as for the prophylaxis for rheumatic fever.[14-21,23-26,29-40] They are recommended as an alternative treatment option for pelvic inflammatory disease and cystitis.[26,27]

Clinical trials have demonstrated comparable efficacy among the penicillins for the treatment of skin and soft-tissue infections, genitourinary infections, upper/lower respiratory tract infections, as well as several miscellaneous infections.[46,48,51,52,56,65,66,71,72,74-76,84,92, 133,134,143] The penicillins have also been shown to be comparable in efficacy to antibacterial agents in other classes.[43-45,47,49,50,57,58,70,80,82,83,88,93,96,98,101, 118,120,121,136,137,138] Clinical data from published studies supports similar safety profiles among the penicillins.

There is insufficient evidence to support that one brand of penicillin 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 penicillins 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 penicillin 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 Quinolones
AHFS Class 081218
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I. Overview

The quinolones are approved to treat a variety of infections, including dermatologic, gastrointestinal, genitourinary, respiratory, as well as several miscellaneous infections.[1-8] They are broad-spectrum agents that directly inhibit bacterial deoxyribonucleic acid (DNA) synthesis by blocking the actions of DNA gyrase and topoisomerase IV, which leads to bacterial cell death.[9-10]

The quinolones are most active against gram-negative bacilli and gram-negative cocci.[10] Ciprofloxacin has the most potent activity against gram-negative bacteria. Levofloxacin and moxifloxacin have greater potency against gram-positive cocci, and moxifloxacin has enhanced activity against anaerobic bacteria.[9-10] Levofloxacin and moxifloxacin are considered respiratory fluoroquinolones. They possess enhanced activity against *Streptococcus pneumoniae* while maintaining efficacy against *Haemophilus influenzae, Moraxella catarrhalis,* and atypical pathogens. Resistance to the quinolones is increasing and cross-resistance among the various agents has been documented. Two mechanisms of bacterial resistance have been identified. These include mutations in chromosomal genes (DNA gyrase and/or topoisomerase IV) and altered drug permeability across the bacterial cell membranes.[9-10] In May 2016 the FDA released a Safety Alert advising restricted use of quinolones for certain uncomplicated infections, including acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections.[11] For patients with these conditions, fluoroquinolones should be reserved for those who do not have alternative treatment options. The FDA safety review found that systemic quinolone use is associated with serious side effects affecting the tendons, muscles, joints, nerves, and central nervous system.[11] In June 2016 the FDA approved an updated Boxed Warning for the quinolones, advising that the serious side effects associated with quinolones generally outweigh the benefits for patients with acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, and uncomplicated urinary tract infections who have other treatment options.[12]

The quinolones that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Ciprofloxacin, levofloxacin and ofloxacin are available in a generic formulation. This class was last reviewed in August 2014.

Table 1. Quinolones Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Ciprofloxacin	injection, extended-release tablet, suspension, tablet	Cipro®*, Cipro IV®*, Cipro XR®*	ciprofloxacin, ciprofloxacin ER
Levofloxacin	injection, solution, tablet	Levaquin®*	levofloxacin
Moxifloxacin	injection, tablet	Avelox®*	moxifloxacin
Ofloxacin	tablet	N/A	ofloxacin

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

The quinolones 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 quinolones 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 Quinolones[1-8]

Organism	Ciprofloxacin	Levofloxacin	Moxifloxacin	Ofloxacin
Gram-Positive Aerobes				
Bacillus anthracis	✔	✔		
Enterococcus faecalis	✔	✔	✔	
Staphylococcus aureus	✔	✔	✔	✔
Staphylococcus epidermidis	✔	✔		
Staphylococcus saprophyticus	✔	✔		
Streptococcus anginosus			✔	
Streptococcus constellatus			✔	
Streptococcus pneumoniae	✔	✔	✔	✔
Streptococcus pyogenes	✔	✔	✔	✔
Gram-Negative Aerobes				
Campylobacter jejuni	✔			
Citrobacter divs	✔			✔
Citrobacter freundii	✔			
Enterobacter aerogenes				✔
Enterobacter cloacae	✔	✔	✔	
Escherichia coli	✔	✔	✔	✔
Haemophilus influenzae	✔	✔	✔	✔
Haemophilus parainfluenzae	✔	✔	✔	
Klebsiella pneumoniae	✔	✔	✔	✔
Legionella pneumophila		✔		
Moraxella catarrhalis	✔	✔	✔	
Morganella morganii	✔			
Neisseria gonorrhoeae	✔			✔
Proteus mirabilis	✔	✔	✔	✔
Proteus vulgaris	✔			
Providencia rettgeri	✔			
Providencia stuartii	✔			
Pseudomonas aeruginosa	✔	✔		✔
Salmonella typhi	✔			
Serratia marcescens	✔	✔		
Shigella boydii	✔			
Shigella dysenteriae	✔			
Shigella flexneri	✔			
Shigella sonnei	✔			
Anaerobes				
Bacteroides fragilis			✔	
Bacteroides thetaiotaomicron			✔	

Organism	Ciprofloxacin	Levofloxacin	Moxifloxacin	Ofloxacin
Clostridium perfringens			✔	
Peptostreptococcus species			✔	
Miscellaneous Organisms				
Chlamydia pneumoniae		✔	✔	
Chlamydia trachomatis				✔
Mycoplasma pneumoniae		✔	✔	

II. Evidence-Based Medicine and Current Treatment Guidelines

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

Table 3. Treatment Guidelines Using the Quinolones

Clinical Guideline	Recommendation(s)

European Society of Cardiology: **Guidelines for the Management of Infective Endocarditis (2015)**[13]	Main principles of prevention if infective endocarditis
	• The principle of antibiotic prophylaxis when performing procedures at risk of infective endocarditis (IE) in patients with predisposing cardiac conditions is maintained.
	• Antibiotic prophylaxis must be limited to patients with the highest risk of IE undergoing the highest risk dental procedures (dental procedures requiring manipulation of the gingival or periapical region of the teeth or perforation of the oral mucosa).
	  o Patients with a prosthetic valve, including transcatheter valve, or a prosthetic material used for cardiac valve repair.
	  o Patients with previous IE.
	  o Patients with congenital heart disease.
	• Good oral hygiene and regular dental review are more important than antibiotic prophylaxis to reduce the risk of IE.
	• Aseptic measures are mandatory during venous catheter manipulation and during any invasive procedures in order to reduce the rate of health care-associated IE.
	• Recommended prophylaxis for dental procedures at high-risk:
	  o Single-dose amoxicillin or penicillin 30 to 60 minutes before procedure.
	  o If allergy to penicillin or ampicillin, single-dose clindamycin 30 to 60 minutes before procedure.
	
	Antimicrobial therapy: principles
	• The treatment of infective endocarditis relies on the combination of prolonged antimicrobial therapy and - in about half of patients - surgical eradication of the infected tissues.
	• Prolonged therapy with a combination of bactericidal drugs is the basis of IE treatment. Drug treatment of prosthetic valve endocarditis (PVE) should last longer (at least six weeks) than that of native valve endocarditis (NVE) (two to six weeks).
	• In both NVE and PVE, the duration of treatment is based on the first day of effective antibiotic therapy, not on the day of surgery. A new full course of treatment should only start if valve cultures are positive, the choice of antibiotic being based on the susceptibility of the latest recovered bacterial isolate.
	• The indications and pattern of use of aminoglycosides have changed. They are no longer recommended in staphylococcal NVE because their clinical benefits have not been demonstrated but they can increase renal toxicity; and, when they are indicated in other conditions, aminoglycosides should be given in a single daily dose in order to reduce nephrotoxicity.
	• New antibiotic regimens have emerged in the treatment of staphylococcal IE, including daptomycin and the combination of high-doses of cotrimoxazole plus clindamycin, but additional investigations are necessary in large series before they can be recommended in all patients.
	
	Antimicrobial therapy: regimens
	• Antibiotic treatment of infective endocarditis due to oral streptococci and *Streptococcus* bovis group:
	  o Penicillin-susceptible strains:
	  ▪ Penicillin G, amoxicillin, or ceftriaxone for four weeks.
	  ▪ Penicillin G, amoxicillin, or ceftriaxone plus gentamicin or netilmicin for two weeks.
	  ▪ Vancomycin for four weeks (in beta-lactam allergic patients).

Clinical Guideline	Recommendation(s)
	o Penicillin-resistant strains: ▪ Penicillin G, amoxicillin, or ceftriaxone for four weeks plus gentamicin for two weeks. ▪ Vancomycin for four weeks plus gentamicin for two weeks (in beta-lactam allergic patients). • Antibiotic treatment of infective endocarditis due to *Staphylococcus* species: o Methicillin-susceptible strains (native valves): ▪ Flucloxacillin or oxacillin for four to six weeks. ▪ Cotrimoxazole intravenous for one week and oral for five weeks plus clindamycin for one week (for *Staphylococcus aureus*). o Penicillin-allergic patients or methicillin-resistant staphylococci (native valves): ▪ Vancomycin for four to six weeks. ▪ Alternative: Daptomycin for four to six weeks. ▪ Cotrimoxazole intravenous for one week and oral for five weeks plus clindamycin for one week (for *Staphylococcus aureus*). o Methicillin-susceptible strains (prosthetic valves): ▪ Flucloxacillin or oxacillin for at least six weeks, rifampin for at least six weeks, and gentamicin for two weeks. o Penicillin-allergic patients or methicillin-resistant staphylococci (prosthetic valves): ▪ Vancomycin for at least six weeks, rifampin for at least six weeks, and gentamicin for two weeks. • Antibiotic treatment of infective endocarditis due to *Enterococcus* species: o Beta-lactam and gentamicin susceptible strains: ▪ Amoxicillin for four to six weeks plus gentamicin for two to six weeks. ▪ Ampicillin plus gentamicin for six weeks. ▪ Vancomycin plus gentamicin for six weeks. • Antibiotic treatment of blood culture-negative infective endocarditis: o *Brucella* species: ▪ Doxycycline, cotrimoxazole, and rifampin for ≥3 months. o *Coxiella burnetii* (agent of Q fever): ▪ Doxycycline plus hydroxychloroquine for >18 months. ▪ o *Bartonella* species: ▪ Doxycycline orally for four weeks plus gentamicin for two weeks. o *Legionella* species: ▪ Levofloxacin intravenous for ≥6 weeks or clarithromycin intravenous for two weeks then orally for four weeks plus rifampin. o *Mycoplasma* species: ▪ Levofloxacin for ≥6 months. o *Tropheryma whipplei* (agent of Whipple's disease): ▪ Doxycycline plus hydroxychloroquine orally for ≥18 months. • Proposed antibiotic regimens for initial empirical treatment of infective endocarditis in acute severely ill patients (before pathogen identification): o Community-acquired native valves or late prosthetic valves (≥12 months post surgery) endocarditis: ▪ Ampicillin intravenous plus flucloxacillin or oxacillin intravenous plus gentamicin intravenous for once dose. ▪ Vancomycin intravenous plus gentamicin intravenous (for penicillin allergic patients). o Early PVE (<12 months post surgery) or nosocomial and non-nosocomial healthcare associated endocarditis:

Clinical Guideline	Recommendation(s)
	▪ Vancomycin intravenous, gentamicin intravenous, and rifampin orally.
American College of Cardiology/ American Heart Association: **2008 Focused Update Incorporated Into the American College of Cardiology/ American Heart Association 2006 Guidelines for the Management of Patients With Valvular Heart Disease (2008)[14]** American College of Cardiology/ American Heart Association: **Guideline for the Management of Patients With Valvular Heart Disease (2014)[15] (although a more current guideline more detailed information was included as part of the 2008 Focused update; as such both are summarized together)**	<u>Rheumatic fever prophylaxis</u> • Primary prevention of rheumatic heart disease: o Penicillin G benzathine intramuscular once or penicillin V orally for 10 days. o Erythromycin estolate or erythromycin ethylsuccinate orally for 10 days, or azithromycin orally for five days in patients who are allergic to penicillin. • Secondary prevention of rheumatic fever: o Penicillin G benzathine intramuscular every four weeks, or penicillin V orally twice daily, or sulfadiazine orally once daily. o Erythromycin orally twice daily for patients who are allergic to penicillin. <u>Endocarditis prophylaxis</u> • Prophylaxis against infective endocarditis is reasonable for the following patients at highest risk for adverse outcomes from infective endocarditis who undergo dental procedures that involve manipulation of either gingival tissue or the periapical region of teeth or perforation of the oral mucosa: o Patients with prosthetic cardiac valve or prosthetic material used for cardiac valve repair. o Patients with previous infective endocarditis. o Patients with congenital heart disease. o Cardiac transplant recipients with valve regurgitation due to a structurally abnormal valve. • Prophylaxis against infective endocarditis is not recommended for non-dental procedures (such as transesophageal echocardiogram, esophagogastroduodenoscopy, or colonoscopy) in the absence of active infection. • Regimens for dental procedures (single dose 30 to 60 minutes before procedure): o Oral: amoxicillin. o Unable to take oral medications: ampicillin, cefazolin or ceftriaxone. o Allergic to penicillin or ampicillin (oral): cephalexin, clindamycin, or azithromycin. o Allergic to penicillins or ampicillin and unable to take oral medication: cefazolin, ceftriaxone, or clindamycin. • Therapy of native valve endocarditis caused by highly penicillin-susceptible viridans group streptococci and *Streptococcus bovis:* o Penicillin G or ceftriaxone for four weeks. o Ceftriaxone plus gentamicin for two weeks. o Vancomycin for four weeks in patients allergic to penicillin. • Therapy of native valve endocarditis caused by strains of viridans group streptococci and *Streptococcus bovis* relatively resistant to penicillin: o Penicillin G or ceftriaxone for four weeks plus gentamicin for two weeks. o Vancomycin for four weeks in patients allergic to penicillin. • Therapy for native valve or prosthetic valve enterococcal endocarditis caused by strains susceptible to penicillin, gentamicin, and vancomycin: o Ampicillin for four to six weeks or penicillin G plus gentamicin for four to six weeks. o Vancomycin plus gentamicin for six weeks in patients allergic to penicillin. • Therapy for endocarditis caused by staphylococci in the absence of prosthetic materials: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin for six weeks plus the optional addition of gentamicin for three to five days. ▪ Cefazolin for six weeks with the optional addition of gentamicin in patients allergic to penicillin. o Oxacillin-resistant strains:

Clinical Guideline	Recommendation(s)
	▪ Vancomycin for six weeks. • Therapy for prosthetic valve endocarditis caused by staphylococci: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin, rifampin, and gentamicin for ≥6 weeks. o Oxacillin-resistant strains: ▪ Vancomycin, rifampin, and gentamicin for ≥6 weeks. • Therapy for both native and prosthetic valve endocarditis caused by *Haemophilus* species *(Haemophilus parainfluenzae, Haemophilus aphrophilus, Haemophilus paraphrophilus), Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* species microorganisms: o Ceftriaxone for four weeks. o Ampicillin-sulbactam for four weeks. o Ciprofloxacin for four weeks. • Therapy for culture-negative endocarditis including *Bartonella* endocarditis: o Native valve: ▪ Ampicillin-sulbactam plus gentamicin (or vancomycin for patients allergic to penicillin) plus ciprofloxacin for four to six weeks. o Prosthetic valve (early; ≤1 year): ▪ Vancomycin for six weeks, plus gentamicin for two weeks, plus cefepime for six weeks, plus rifampin for six weeks. o Prosthetic valve (late; >1 year): ▪ Suspected *Bartonella*, culture negative: • Ceftriaxone for six weeks plus gentamicin with/without doxycycline for six weeks. ▪ Documented *Bartonella*, culture positive: • Doxycycline for six weeks plus gentamicin for two weeks.
American Heart Association: **Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications (2015)**[16]	• Therapy for native valve endocarditis caused by viridans group streptococci and *Streptococcus gallolyticus* (Formerly Known as *Streptococcus bovis)*: o Highly penicillin-susceptible strains: ▪ Penicillin G or ceftriaxone for four weeks. ▪ Penicillin G or ceftriaxone plus gentamicin for two weeks (in patients with uncomplicated infective endocarditis, rapid response to therapy, and no underlying renal disease). ▪ Vancomycin for four weeks (recommended only for patients unable to tolerate penicillin or ceftriaxone therapy). o Relatively penicillin-resistant strains: ▪ Penicillin for four weeks plus gentamicin for the first two weeks. ▪ If the isolate is ceftriaxone susceptible, then ceftriaxone alone may be considered. ▪ Vancomycin for four weeks (recommended only for patients unable to tolerate beta-lactam therapy). • Therapy for native valve endocarditis caused by *A defectiva* and *Granulicatella* Species and viridans group streptococci: o For patients with infective endocarditis caused by *A defectiva*, *Granulicatella* species, and viridans group streptococci with a penicillin MIC ≥0.5 µg/mL, treat with a combination of ampicillin or penicillin plus gentamicin as done for enterococcal infective endocarditis with infectious diseases consultation. o If vancomycin is used in patients intolerant of ampicillin or penicillin, then the addition of gentamicin is not needed. o Ceftriaxone combined with gentamicin may be a reasonable alternative treatment option for isolates that are susceptible to ceftriaxone. • Therapy for endocarditis of prosthetic valves or other prosthetic material caused by viridans group streptococci and *Streptococcus gallolyticus* (Formerly Known as *Streptococcus bovis)*:

Clinical Guideline	Recommendation(s)
	o Penicillin for six weeks plus gentamicin for the first two weeks. o Extend gentamicin to six weeks if the MIC is >0.12 µg/mL for the infecting strain. o Vancomycin can be used in patients intolerant of penicillin, ceftriaxone, or gentamicin. • Therapy for endocarditis of prosthetic valves or other prosthetic material caused by *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and Groups B, C, F, and G β-Hemolytic Streptococci: o Penicillin, cefazolin, or ceftriaxone for four weeks is reasonable for infective endocarditis caused by *S pneumoniae*; vancomycin can be useful for patients intolerant of β-lactam therapy. o Six weeks of therapy is reasonable for prosthetic valve endocarditis caused by *S pneumoniae*. o High-dose penicillin or a third-generation cephalosporin is reasonable in patients with infective endocarditis caused by penicillin-resistant *S pneumoniae* without meningitis; if meningitis is present, then high doses of cefotaxime (or ceftriaxone) are reasonable. o The addition of vancomycin and rifampin to cefotaxime (or ceftriaxone) may be considered in patients with infective endocarditis caused by *S pneumoniae* that are resistant to cefotaxime. o Because of the complexities of infective endocarditis caused by *S pneumoniae*, consultation with an infectious diseases specialist is recommended. o For infective endocarditis caused by *S pyogenes*, four to six weeks of therapy with aqueous crystalline penicillin G or ceftriaxone is reasonable; vancomycin is reasonable only in patients intolerant of β-lactam therapy. o For infective endocarditis caused by group B, C, or G streptococci, the addition of gentamicin to penicillin G or ceftriaxone for at least the first two weeks of a four to six week treatment course may be considered. o Consultation with an infectious diseases specialist to guide treatment is recommended in patients with infective endocarditis caused by β-hemolytic streptococci. • Therapy for endocarditis caused by staphylococci in the absence of prosthetic valves or other prosthetic material: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin for six weeks. ▪ For penicillin-allergic individuals: cefazolin for six weeks. o Oxacillin-resistant strains ▪ Vancomycin for six weeks. ▪ Daptomycin for six weeks. • Therapy for prosthetic valve endocarditis caused by staphylococci: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin plus rifampin (for at least six weeks) and gentamicin (for two weeks). o Oxacillin-resistant strains: ▪ Vancomycin plus rifampin (for at least six weeks) and gentamicin (for two weeks). • Therapy for native valve or prosthetic valve enterococcal endocarditis: o Strains susceptible to penicillin and gentamicin: ▪ Ampicillin or penicillin G plus gentamicin for four to six weeks. ▪ Double β-lactam ampicillin plus ceftriaxone for six. o Strains susceptible to penicillin and resistant to aminoglycosides or streptomycin-susceptible gentamicin-resistant in patients able to tolerate β-Lactam therapy: ▪ Ampicillin plus ceftriaxone for six weeks. ▪ Ampicillin or penicillin G plus streptomycin for four to six

Clinical Guideline	Recommendation(s)
	weeks. o Vancomycin and aminoglycoside-susceptible penicillin-resistant enterococcus species in patients unable to tolerate β-lactam : ▪ Unable to tolerate β-lactams: • Vancomycin plus gentamicin for six weeks (vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone therapy). ▪ Intrinsic penicillin resistance: • Vancomycin plus gentamicin for six weeks. o Strains Resistant to Penicillin, Aminoglycosides, and Vancomycin: ▪ Linezolid or daptomycin for at least six weeks. • Therapy for both native and prosthetic valve endocarditis caused by *Haemophilus* species *(Haemophilus parainfluenzae, Haemophilus aphrophilus, Haemophilus paraphrophilus), Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* species microorganisms: o Ceftriaxone (cefotaxime or another third- or fourth-generation cephalosporin may be substituted) or ampicillin or ciprofloxacin for four weeks. Fluoroquinolone therapy recommended only for patients unable to tolerate cephalosporin and ampicillin therapy; levofloxacin or moxifloxacin may be substituted. • Therapy for culture-negative endocarditis including *Bartonella* endocarditis: o For patients with acute (days) clinical presentations of native valve infection, coverage for *S aureus*, β-hemolytic streptococci, and aerobic Gram-negative bacilli is reasonable. o For patients with a subacute (weeks) presentation of native valve endocarditis, coverage of *S aureus*, viridans group streptococci, HACEK, and enterococci is reasonable. o For patients with culture-negative prosthetic valve endocarditis, coverage for staphylococci, enterococci, and aerobic Gram-negative bacilli is reasonable if onset of symptoms is within one year of prosthetic valve placement. o If symptom onset is >1 year after valve placement, then infective endocarditis is more likely to be caused by staphylococci, viridans group streptococci, and enterococci, and antibiotic therapy for these potential pathogens is reasonable.
Infectious Diseases Society of America: **Clinical Practice Guidelines: Management of Encephalitis (2008)**[17] **(Was reviewed and deemed current as of July 2011)**	Empirical therapy • Acyclovir should be initiated in all patients with suspected encephalitis, pending results of diagnostic studies. • Other empirical antimicrobial agents should be initiated on the basis of specific epidemiologic or clinical factors, including appropriate therapy for presumed bacterial meningitis, if clinically indicated. • In patients with clinical clues suggestive of rickettsial or ehrlichial infection during the appropriate season, doxycycline should be added to empirical treatment regimens. Bacteria • *Bartonella bacilliformis:* chloramphenicol, ciprofloxacin, doxycycline, ampicillin, or sulfamethoxazole-trimethoprim is recommended. • *Bartonella henselae:* doxycycline or azithromycin, with or without rifampin, can be considered. • *Listeria monocytogenes:* ampicillin plus gentamicin is recommended; sulfamethoxazole-trimethoprim is an alternative in the penicillin-allergic patient. • *Mycoplasma pneumoniae:* antimicrobial therapy (azithromycin, doxycycline, or a fluoroquinolone) can be considered. • *Tropheryma whipplei:* ceftriaxone, followed by either sulfamethoxazole-

Clinical Guideline	Recommendation(s)
	trimethoprim or cefixime, is recommended. Helminths • *Baylisascaris procyonis:* albendazole plus diethylcarbamazine can be considered; adjunctive corticosteroids should also be considered. • *Gnathostoma* species: albendazole or ivermectin is recommended. • *Taenia solium:* need for treatment should be individualized; albendazole and corticosteroids are recommended; praziquantel can be considered as an alternative. Rickettsioses and ehrlichiosis • *Anaplasma phagocytophilum:* doxycycline is recommended. • *Ehrlichia chaffeensis:* doxycycline is recommended. • *Rickettsia rickettsii:* doxycycline is recommended; chloramphenicol can be considered an alternative in selected clinical scenarios, such as pregnancy. • *Coxiella burnetii:* doxycycline plus a fluoroquinolone plus rifampin is recommended. Spirochetes • *Borrelia burgdorferi:* ceftriaxone, cefotaxime, or penicillin G is recommended. • *Treponema pallidum:* penicillin G is recommended; ceftriaxone is an alternative. Protozoa • *Acanthamoeba:* sulfamethoxazole-trimethoprim plus rifampin plus ketoconazole or fluconazole plus sulfadiazine plus pyrimethamine can be considered. • *Balamuthia mandrillaris:* pentamidine, combined with a macrolide (azithromycin or clarithromycin), fluconazole, sulfadiazine, flucytosine, and a phenothiazine can be considered. • *Naegleria fowleri:* amphotericin B (intravenous and intrathecal) and rifampin, combined with other agents, can be considered. • *Plasmodium falciparum:* quinine, quinidine, or artemether is recommended; atovaquone-proguanil is an alternative; exchange transfusion is recommended for patients with 110% parasitemia or cerebral malaria; corticosteroids are not recommended. • *Toxoplasma gondii:* pyrimethamine plus either sulfadiazine or clindamycin is recommended; sulfamethoxazole-trimethoprim alone and pyrimethamine plus atovaquone, clarithromycin, azithromycin, or dapsone are alternatives. • *Trypanosoma brucei gambiense:* eflornithine is recommended; melarsoprol is an alternative. • *Trypanosoma brucei rhodesiense:* melarsoprol is recommended.

European Federation of Neurological Societies: **Guideline on the Management of Community-acquired Bacterial Meningitis (2008)**[18]	Empirical therapy
	• Ceftriaxone 2 g every 12 to 24 hours or cefotaxime 2 g every six to eight hours.
	• Alternative therapy: meropenem 2 g every eight hours or chloramphenicol 1 g every six hours.
	• If penicillin or cephalosporin-resistant pneumococcus is suspected, use ceftriaxone or cefotaxime plus vancomycin 60 mg/kg every 24 hours after a loading dose of 15 mg/kg.
	• Ampicillin-amoxicillin 2 g every four hours if *Listeria* is suspected.
	
	Pathogen specific therapy
	• Penicillin-sensitive pneumococcal meningitis:
	  o Benzyl penicillin 250,000 U/kg/day, ampicillin-amoxicillin 2 g every four hours, ceftriaxone 2 g every 12 hours or cefotaxime 2 g every six to eight hours.
	  o Alternative therapy: meropenem 2 g every eight hours or vancomycin 60 mg/kg every 24 hours as a continuous infusion after a 15 mg/kg loading

Clinical Guideline	Recommendation(s)
	dose plus rifampicin 600 mg every 12 hours, or moxifloxacin 400 mg daily. • Pneumococcus with reduced susceptibility to penicillin or cephalosporins: o Ceftriaxone or cefotaxime plus vancomycin±rifampicin. o Alternative therapy: moxifloxacin, meropenem or linezolid 600 mg combined with rifampicin. • Meningococcal meningitis: o Benzyl penicillin, ceftriaxone, or cefotaxime. o Alternative therapy: meropenem, chloramphenicol, or moxifloxacin. • *Haemophilus influenzae* type B: o Ceftriaxone or cefotaxime. o Alternative therapy: chloramphenicol–ampicillin-amoxicillin. • Listerial meningitis: o Ampicillin or amoxicillin 2 g every four hours±gentamicin 1 to 2 mg every eight hours for the first seven to 10 days. o Alternative therapy: Sulfamethoxazole-trimethoprim 10 to 20 mg/kg every six to 12 hours or meropenem. • *Staphylococcal* species: o Flucloxacillin 2 g every four hours or vancomycin if penicillin allergy is suspected. o Rifampicin should also be considered in addition to either agent. Linezolid should be considered for methicillin-resistant staphylococcal meningitis. • Gram-negative *Enterobacteriaceae*: o Ceftriaxone, cefotaxime or meropenem. • Pseudomonal meningitis: o Meropenem±gentamicin.
Infectious Diseases Society of America: **Practice Guidelines for the Management of Bacterial Meningitis (2004)**[19]	<u>Empiric therapy</u> • Empirical antimicrobial therapy is initiated either when the lumbar puncture is delayed or for patients with purulent meningitis and a negative cerebrospinal fluid gram stain result: o Age <1 month: ampicillin plus cefotaxime or ampicillin plus an aminoglycoside. o Age one to 23 months: vancomycin plus a third-generation cephalosporin. o Age two to 50 years: vancomycin plus a third-generation cephalosporin. o Age >50 years: vancomycin plus ampicillin plus a third-generation cephalosporin. o Basilar skull fracture: vancomycin plus a third-generation cephalosporin. o Penetrating head trauma: vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem. o Post neurosurgery: vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem. o Cerebrospinal fluid shunt: vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem. <u>Specific therapy</u> • Recommendations for specific antimicrobial therapy in bacterial meningitis are based on isolated pathogens and susceptibility. • *Streptococcus pneumoniae* o Penicillin minimum inhibitory concentrations <0.1 µg/mL: standard therapy includes penicillin G or ampicillin; alternative therapies include ceftriaxone, cefotaxime, or chloramphenicol. o Penicillin minimum inhibitory concentrations 0.1 to 1.0 µg/mL: standard therapy includes ceftriaxone or cefotaxime; alternative therapies include cefepime or meropenem. o Penicillin minimum inhibitory concentrations ≥2 µg/mL: standard therapies include vancomycin plus ceftriaxone or cefotaxime; alternative therapies include gatifloxacin or moxifloxacin.

Clinical Guideline	Recommendation(s)
	o Cefotaxime or ceftriaxone minimum inhibitory concentrations ≥1.0 µg/mL: standard therapies include vancomycin plus ceftriaxone or cefotaxime (consider addition of rifampin if minimum inhibitory concentrations of ceftriaxone is >2 µg/mL); alternative therapies include gatifloxacin or moxifloxacin. • *Neisseria meningitides* o Penicillin minimum inhibitory concentrations <0.1 µg/mL: standard therapy includes penicillin G or ampicillin; alternative therapy includes ceftriaxone, cefotaxime or chloramphenicol. o Penicillin minimum inhibitory concentrations 0.1 to 1.0 µg/mL: standard therapy includes ceftriaxone or cefotaxime; alternative therapies include chloramphenicol, a fluoroquinolone or meropenem. • *Listeria monocytogenes* o Standard therapy includes ampicillin or penicillin G; alternative therapies include sulfamethoxazole-trimethoprim or meropenem. • *Streptococcus agalactiae* o Standard therapy includes ampicillin or penicillin G; alternative therapies include ceftriaxone or cefotaxime. • *Escherichia coli* and other Enterobacteriaceae o Standard therapy includes a third-generation cephalosporin; alternative therapies include aztreonam, fluoroquinolone, meropenem, sulfamethoxazole-trimethoprim or ampicillin. • *Pseudomonas aeruginosa* o Standard therapies include cefepime or ceftazidime; alternative therapies include aztreonam, ciprofloxacin, or meropenem (addition of an aminoglycoside should be considered). • *Haemophilus influenzae* β-lactamase negative strains o Standard therapy includes ampicillin; alternative therapies include ceftriaxone, cefotaxime, cefepime, chloramphenicol or a fluoroquinolone. • *Haemophilus influenzae* β-lactamase positive strains o Standard therapy includes a third-generation cephalosporin; alternative therapies include cefepime, chloramphenicol or a fluoroquinolone. • *Staphylococcus aureus* methicillin susceptible o Standard therapy includes nafcillin or ofloxacin; alternative therapies include vancomycin or meropenem. • *Staphylococcus aureus* methicillin resistant o Standard therapy includes vancomycin (consider addition of rifampin); alternative therapies include sulfamethoxazole-trimethoprim or linezolid. • *Staphylococcus epidermidis* o Standard therapy includes vancomycin (consider addition of rifampin); alternative therapy includes linezolid. • *Enterococcus* species ampicillin susceptible o Standard therapy includes ampicillin plus gentamicin. • *Enterococcus* species ampicillin resistant o Standard therapy includes vancomycin plus gentamicin. • *Enterococcus* species ampicillin and vancomycin resistant o Standard therapy includes linezolid.
Infectious Diseases Society of America: **Practice Guidelines for the Diagnosis and Management of Skin and Soft-Tissue Infections (2014)**[20]	Impetigo and ecthyma • Gram stain and culture of the pus or exudates from skin lesions of impetigo and ecthyma are recommended to help identify whether *Staphylococcus aureus* and/or a β-hemolytic *Streptococcus* is the cause (strong, moderate), but treatment without these studies is reasonable in typical cases. • Bullous and nonbullous impetigo can be treated with oral or topical antimicrobials, but oral therapy is recommended for patients with numerous lesions or in outbreaks affecting several people to help decrease transmission

Clinical Guideline	Recommendation(s)
	of infection. Treatment for ecthyma should be an oral antimicrobial. o Treatment of bullous and nonbullous impetigo should be with either mupirocin or retapamulin twice daily for five days. o Oral therapy for ecthyma or impetigo should be a seven-day regimen with an agent active against *S. aureus* unless cultures yield streptococci alone (when oral penicillin is the recommended agent). Because *S. aureus* isolates from impetigo and ecthyma are usually methicillin susceptible, dicloxacillin or cephalexin is recommended. When MRSA is suspected or confirmed, doxycycline, clindamycin, or sulfamethoxazole-trimethoprim is recommended. Purulent skin and soft-tissue infections (cutaneous abscesses, furuncles, carbuncles, and inflamed epidermoid cysts) • Gram stain and culture of pus from carbuncles and abscesses are recommended, but treatment without these studies is reasonable in typical cases. Gram stain and culture of pus from inflamed epidermoid cysts are not recommended. • Incision and drainage is the recommended treatment for inflamed epidermoid cysts, carbuncles, abscesses, and large furuncles. • The decision to administer antibiotics directed against *S. aureus* as an adjunct to incision and drainage should be made based upon presence or absence of systemic inflammatory response syndrome (SIRS), such as temperature >38°C or <36°C, tachypnea >24 breaths per minute, tachycardia >90 beats per minute, or white blood cell count >12 000 or <400 cells/µL. An antibiotic active against MRSA is recommended for patients with carbuncles or abscesses who have failed initial antibiotic treatment or have markedly impaired host defenses or in patients with SIRS and hypotension. Recurrent skin abscesses • A recurrent abscess at a site of previous infection should prompt a search for local causes such as a pilonidal cyst, hidradenitis suppurativa, or foreign material. • Recurrent abscesses should be drained and cultured early in the course of infection. • After obtaining cultures of recurrent abscess, treat with a five to ten day course of an antibiotic active against the pathogen isolated. • Consider a five-day decolonization regimen twice daily of intranasal mupirocin, daily chlorhexidine washes, and daily decontamination of personal items such as towels, sheets, and clothes for recurrent *S. aureus* infection. • Adult patients should be evaluated for neutrophil disorders if recurrent abscesses began in early childhood. Erysipelas and cellulitis • Cultures of blood or cutaneous aspirates, biopsies, or swabs are not routinely recommended except in patients with malignancy on chemotherapy, neutropenia, severe cell-mediated immunodeficiency, immersion injuries, and animal bites. • Typical cases of cellulitis without systemic signs of infection should receive an antimicrobial agent that is active against streptococci. For cellulitis with systemic signs of infection (moderate nonpurulent), systemic antibiotics are indicated. Many clinicians could include coverage against methicillin-susceptible *S. aureus* (MSSA). For patients whose cellulitis is associated with penetrating trauma, evidence of MRSA infection elsewhere, nasal colonization with MRSA, injection drug use, or SIRS (severe nonpurulent), vancomycin or another antimicrobial effective against both MRSA and streptococci is recommended. In severely compromised patients, broad-spectrum

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	antimicrobial coverage may be considered. Vancomycin plus either piperacillin-tazobactam or imipenem/meropenem is recommended as a reasonable empiric regimen for severe infections. • The recommended duration of antimicrobial therapy is five days, but treatment should be extended if the infection has not improved within this time period. Surgical site infections • Suture removal plus incision and drainage should be performed for surgical site infections. • Adjunctive systemic antimicrobial therapy is not routinely indicated, but in conjunction with incision and drainage may be beneficial for surgical site infections associated with a significant systemic response. • A brief course of systemic antimicrobial therapy is indicated in patients with surgical site infections following clean operations on the trunk, head and neck, or extremities that also have systemic signs of infection. • A first-generation cephalosporin or an antistaphylococcal penicillin for MSSA, or vancomycin, linezolid, daptomycin, telavancin, or ceftaroline where risk factors for MRSA are high (nasal colonization, prior MRSA infection, recent hospitalization, recent antibiotics), is recommended. • Agents active against gram-negative bacteria and anaerobes, such as a cephalosporin or fluoroquinolone in combination with metronidazole, are recommended for infections following operations on the axilla, gastrointestinal tract, perineum, or female genital tract. Necrotizing fasciitis • Empiric antibiotic treatment should be broad (e.g., vancomycin or linezolid plus piperacillin-tazobactam or a carbapenem; or plus ceftriaxone and metronidazole), as the etiology can be polymicrobial (mixed aerobic–anaerobic microbes) or monomicrobial (group A streptococci, community-acquired MRSA). • Penicillin plus clindamycin is recommended for treatment of documented group A streptococcal necrotizing fasciitis. Pyomyositis • Cultures of blood and abscess material should be obtained. • Vancomycin is recommended for initial empirical therapy. An agent active against enteric gram-negative bacilli should be added for infection in immunocompromised patients or following open trauma to the muscles. • Cefazolin or antistaphylococcal penicillin (e.g., nafcillin or oxacillin) is recommended for treatment of pyomyositis caused by MSSA. • Antibiotics should be administered intravenously initially, but once the patient is clinically improved, oral antibiotics are appropriate for patients in whom bacteremia cleared promptly and there is no evidence of endocarditis or metastatic abscess. Two to three weeks of therapy is recommended. Clostridial gas gangrene or myonecrosis • Urgent surgical exploration of the suspected gas gangrene site and surgical debridement of involved tissue should be performed. • In the absence of a definitive etiologic diagnosis, broad-spectrum treatment with vancomycin plus either piperacillin-tazobactam, ampicillin-sulbactam, or a carbapenem antimicrobial is recommended. Definitive antimicrobial therapy with penicillin and clindamycin is recommended for treatment of clostridial myonecrosis. Animal bites

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	• Preemptive early antimicrobial therapy for three to five days is recommended for patients who: o are immunocompromised; o are asplenic; o have advanced liver disease; o have preexisting or resultant edema of the affected area; o have moderate to severe injuries, especially to the hand or face; or o have injuries that may have penetrated the periosteum or joint capsule. • 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 o β-lactam-β-lactamase combinations, piperacillin-tazobactam, second-generation cephalosporins, and carbapenems. • Tetanus toxoid should be administered to patients without toxoid vaccination within 10 years. Tetanus, diphtheria, and tetanus (Tdap) is preferred over Tetanus and diphtheria (Td) if the former has not been previously given. Cutaneous anthrax • Oral penicillin V 500 mg four times daily for seven to 10 days is the recommended treatment for naturally acquired cutaneous anthrax. • Ciprofloxacin 500 mg by mouth twice daily or levofloxacin 500 mg intravenously/orally every 24 hours for 60 days is recommended for bioterrorism cases because of presumed aerosol exposure. Bacillary angiomatosis and cat scratch disease • Azithromycin is recommended for cat scratch disease (strong, moderate) according to the following dosing protocol: o Patients >45 kg: 500 mg on day one followed by 250 mg for four additional days. o Patients <45 kg: 10 mg/kg on day one and 5 mg/kg for four more days. • Erythromycin 500 mg four times daily or doxycycline 100 mg bid for two weeks to two months is recommended for treatment of bacillary angiomatosis. Erysipeloid • Penicillin (500 mg four times daily) or amoxicillin (500 mg three times daily) for seven to 10 days is recommended for treatment of erysipeloid. Glanders • Ceftazidime, gentamicin, imipenem, doxycycline, or ciprofloxacin is recommended based on in vitro susceptibility. Bubonic plague • Bubonic plague should be diagnosed by Gram stain and culture of aspirated material from a suppurative lymph node. Streptomycin (15 mg/kg intramuscularly every 12 hours) or doxycycline (100 mg twice daily by mouth) is recommended for treatment of bubonic plague. Gentamicin could be substituted for streptomycin. Tularemia

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	• Streptomycin (15 mg/kg every 12 hours intramuscularly) or gentamicin (1.5 mg/kg every 8 hours intravenously) is recommended for treatment of severe cases of tularemia. • Tetracycline (500 mg four times daily) or doxycycline (100 mg twice daily by mouth) is recommended for treatment of mild cases of tularemia.
Infectious Diseases Society of America: **Diagnosis and Treatment of Diabetic Foot Infections (2012)**[21]	• Empirical antibiotic regimens should be based on the clinical severity of the infection. • Current clinical data does not allow for the recommendation of any specific antibiotic regimen for diabetic foot infections. • Suggested agents are derived from available published clinical trials and expert experience. • Definitive regimens should consider results of culture and susceptibility tests, as well as the clinical response to the empirical regimen. Similar agents of the same drug class may be substituted. Some of these regimens may not have Food and Drug Administration approval for complicated skin and skin-structure infections, and only linezolid, ertapenem and piperacillin-tazobactam are currently specifically approved for diabetic foot infections. • Suggested empirical antibiotic regimens for mild infections: dicloxacillin, clindamycin, cephalexin, sulfamethoxazole-trimethoprim, amoxicillin-clavulanate, levofloxacin and doxycycline. • Suggested empirical antibiotic regimens for moderate infections: levofloxacin, cefoxitin, ceftriaxone, ampicillin-sulbactam, moxifloxacin, tigecycline, linezolid, daptomycin, ertapenem, ticarcillin-clavulanate, piperacillin-tazobactam, levofloxacin or ciprofloxacin with clindamycin, imipenem-cilastatin, vancomycin, ceftazidime, cefepime, aztreonam. • Suggested empirical antibiotic regimens for severe infections: piperacillin-tazobactam, vancomycin, ceftazidime, cefepime, aztreonam or a carbapenem.

World Gastroenterology Organization: **Acute Diarrhea (2012)**[22]	<u>General considerations</u>
	• 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.

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	o Alternative: fluoroquinolones (e.g., ciprofloxacin).
Infectious Diseases Society of America: **The Practice of Travel Medicine (2006)**[23]	Chemoprophylaxis • 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. Treatment • 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. • 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)**[24]	Recommendations for therapy against specific pathogens • *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. • *Escherichia coli* species:

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	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 (2015)**[25]	Arthritis and arthritis-dermatitis syndrome • Recommended regimen: o Ceftriaxone 1 g intramuscular or intravenous every 24 hours plus azithromycin 1 g orally in a single dose. • Alternative regimen: o Cefotaxime 1 g intravenous every eight hours or ceftizoxime 1 g intravenous every eight hours plus azithromycin 1 g orally in a single dose. Bacterial vaginosis • Recommended regimens: o Metronidazole 500 mg orally twice a day for seven days. o Metronidazole gel 0.75%, one full applicator (5 g) intravaginally, once a day for five days. o Clindamycin cream 2%, one full applicator (5 g) intravaginally at bedtime for seven days. • Alternative regimens: o Tinidazole 2 g orally once daily for two days. o Tinidazole 1 g 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. Cervicitis • Recommended regimens for presumptive treatment: o Azithromycin 1 g orally in a single dose. o Doxycycline 100 mg orally twice a day for seven days. Chancroid • Recommended regimens: o Azithromycin 1 g 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. Chlamydial infections • Recommended regimens:

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	o Azithromycin 1 g 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. Chlamydial infections among children • 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 g orally in a single dose. • Recommended regimens for children ≥8 years of age: o Azithromycin 1 g orally in a single dose. o Doxycycline 100 mg orally twice a day for seven days. Disseminated gonococcal infection • Recommended regimen: o Ceftriaxone 1 g intramuscular or intravenous every 24 hours. • Alternative regimens: o Cefotaxime 1 g intravenous every eight hours. o Ceftizoxime 1 g intravenous every eight hours. Epididymitis • 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. Granuloma inguinale (Donovanosis) • Recommended regimen: o Azithromycin 1 g orally once per week or 500 mg daily for at least three weeks and until all lesions have completely healed. • Alternative regimens: o Doxycycline 100 mg orally twice a day 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 g intramuscular in a single dose plus azithromycin 1 g orally in a single dose.

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	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 25 to 50 mg/kg intravenous or intramuscular in a single dose, not to exceed 125 mg. • Recommended regimen for children who weigh ≤45 kg and who have bacteremia or arthritis: o Ceftriaxone 50 mg/kg (maximum dose: 1 g) 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 g intravenous every 12 hours plus azithromycin 1 g orally in a single dose. 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 g 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. • Alternative regimen: o Azithromycin suspension, 20 mg/kg/day orally, one dose daily for three days. Pelvic inflammatory disease • Recommended parenteral regimen A: o Cefotetan 2 g intravenous every 12 hours. o Cefoxitin 2 g 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

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	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 g 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 g intramuscular in a single dose and probenecid, 1 g 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 g orally in a single dose. o Tinidazole 2 g orally in a single dose plus azithromycin 1 g orally in a single dose (if not used for initial episode). <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.

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	Trichomoniasis • Recommended regimen: o Metronidazole 2 g orally in a single dose. o Tinidazole 2 g orally in a single dose. • Alternative regimen: o Metronidazole 500 mg orally twice a day for seven days. Neurosyphilis • 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. Uncomplicated gonococcal infections of the cervix, urethra, and rectum • 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 1g orally in a single dose or doxycycline 100 mg orally twice a day for seven days. Uncomplicated gonococcal infections of the pharynx • Recommended regimens: o Ceftriaxone 250 mg intermuscular in a single dose plus azithromycin 1g orally in a single dose or doxycycline 100 mg orally twice a day for seven 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)**[26] Reviewed and deemed current as of 07/2013	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 g 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 relatively poor efficacy and the very high prevalence of antimicrobial resistance to these agents worldwide.

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	Acute pyelonephritis • 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 g 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 g 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 g 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 g 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.
American College of Obstetricians and Gynecologists: **Treatment of Urinary Tract Infections in Nonpregnant Women (2008)**[27]	• 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 g dose (powder) single dose.
Working Group on Civilian Biodefense: **Anthrax as a Biological Weapon, Updated Recommendations for Management (2002)**[28]	Inhalation anthrax in the contained casualty setting - adults • Ciprofloxacin 400 mg intravenous every 12 hours initially, then 500 mg by mouth twice daily when clinically appropriate; OR • Doxycycline 100 mg intravenous every 12 hours initially with either one or two of the following: rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, clindamycin, and/or clarithromycin. Switch to 100 mg by mouth twice daily when clinically appropriate. Inhalation anthrax in the contained casualty setting - children • Ciprofloxacin 10 to 15 mg/kg every 12 hours intravenous, then 10 to 15 mg/kg by mouth every 12 hours when clinically appropriate; OR • Doxycycline (if ≤45 kg–2.2 mg/kg intravenous; if > 45 kg–100 mg intravenous) every 12 hours initially with either one or two of the following: rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, clindamycin, and/or clarithromycin. Switch to oral therapy when clinically appropriate using same intravenous dose.

Clinical Guideline	Recommendation(s)
	Inhalation anthrax in a mass casualty setting - adults • Recommended treatment: ciprofloxacin 500 mg by mouth every 12 hours. • Alternative treatment option: doxycycline 100 mg by mouth every 12 hours or amoxicillin 500 mg by mouth every eight hours. Inhalation anthrax in a mass casualty setting - children • Recommended treatment: ciprofloxacin 10 to 15 mg/kg by mouth every 12 hours. • Alternative treatment option: amoxicillin 500 mg by mouth every eight hours (weight ≥20 kg) or amoxicillin 40 mg/kg by mouth every eight hours (weight <20 kg). Inhalation anthrax in a mass casualty setting – pregnant women • Recommended treatment: ciprofloxacin 500 mg by mouth every 12 hours. • Alternative treatment option: amoxicillin 500 mg every eight hours.
Working Group on Civilian Biodefense: **Plague as a Biological Weapon: Medical and Public Health Management Consensus Statement (2000)**[29]	• For adults with pneumonic plague in the contained casualty settings, the preferred choice is streptomycin or gentamicin and alternative choices include doxycycline, ciprofloxacin, or chloramphenicol. • For children with pneumonic plague in the contained casualty settings, the preferred choice is streptomycin or gentamicin and alternative choices include doxycycline, ciprofloxacin, or chloramphenicol. • For pregnant women with pneumonic plague in the contained casualty settings, the preferred choice is gentamicin and an alternative choice is doxycycline. • For adults with pneumonic plague in the mass casualty setting and postexposure prophylaxis, the preferred choice is doxycycline, or ciprofloxacin and the alternative choice is chloramphenicol. • For children with pneumonic plague in the mass casualty setting and postexposure prophylaxis, the preferred choice is doxycycline or ciprofloxacin and an alternative choice is chloramphenicol. • For pregnant women with pneumonic plague in the mass casualty setting and postexposure prophylaxis, the preferred choice is doxycycline or ciprofloxacin and an alternative choice is chloramphenicol.

Global Initiative for Chronic Obstructive Lung Disease: **Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2016)**[30]	• Prophylactic, continuous use of antibiotics has been shown to have no effect on the frequency of exacerbations in chronic obstructive pulmonary disease.
	• The use of antibiotics, other than for treating infectious exacerbations of chronic obstructive pulmonary disease and other bacterial infections, is currently not indicated.
	• Based on current available evidence, antibiotics should be given to:
	  o Patients with exacerbations of chronic obstructive pulmonary disease with the following three cardinal symptoms: dyspnea, sputum volume, and sputum purulence.
	  o Patients with exacerbations of chronic obstructive pulmonary disease with two of the cardinal symptoms, if the increased purulence of sputum is one of the two symptoms.
	  o Patients with a severe exacerbation of chronic obstructive pulmonary disease that requires mechanical ventilation (invasive or noninvasive).
	• The recommended length of antibiotic therapy is usually five to 10 days.
	• The choice of antibiotic should be based on local bacterial resistance patterns.
	• Initial empiric treatment may include an aminopenicillin with or without clavulanic acid, macrolide, or tetracycline. In patients with frequent exacerbations, severe airflow limitation, and/or exacerbations requiring mechanical ventilation, sputum cultures or cultures from other materials from the lung should be performed, as gram-negative bacteria or resistant pathogens that may not be sensitive to the afore-mentioned antibiotics may be present.

Infectious Diseases	Outpatient treatment

Clinical Guideline	Recommendation(s)

Society of America: **Management of Community-Acquired Pneumonia in Infants and Children Older Than 3 Months of Age (2011)**[31]
 	
Reviewed and deemed current as of 04/2013
	• Antimicrobial therapy is not routinely required for preschool-aged children with community-acquired pneumonia, because viral pathogens are responsible for the great majority of clinical disease.
	• Amoxicillin should be used as first-line therapy for previously healthy, appropriately immunized infants and preschool children with mild to moderate community-acquired pneumonia suspected to be of bacterial origin. Amoxicillin provides appropriate coverage for *Streptococcus pneumoniae*.
	• For patients allergic to amoxicillin, the following agents are considered alternative treatment options:
	  o Second- or third-generation cephalosporin (cefpodoxime, cefuroxime, cefprozil).
	  o Levofloxacin (oral therapy).
	  o Linezolid (oral therapy).
	• Macrolide antibiotics should be prescribed for treatment of children (primarily school-aged children and adolescents) evaluated in an outpatient setting with findings compatible with community-acquired pneumonia caused by atypical pathogens.
	
	<u>Inpatient treatment</u>
	• Ampicillin or penicillin G should be administered to the fully immunized infant or school-aged child admitted to a hospital ward with community-acquired pneumonia when local epidemiologic data document lack of substantial high-level penicillin resistance for invasive *Streptococcus pneumoniae*.
	• Empiric therapy with a third-generation parenteral cephalosporin (ceftriaxone or cefotaxime) should be prescribed for hospitalized infants and children who are not fully immunized, in regions where local epidemiology of invasive pneumococcal strains documents high-level penicillin resistance, or for infants and children with life-threatening infection, including those with empyema.
	• Non–β-lactam agents, such as vancomycin, have not been shown to be more effective than third-generation cephalosporins in the treatment of pneumococcal pneumonia for the degree of resistance noted currently in North America.
	• Empiric combination therapy with a macrolide (oral or parenteral), in addition to a β-lactam antibiotic, should be prescribed for the hospitalized child for whom *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* are significant considerations.
	• Vancomycin or clindamycin (based on local susceptibility data) should be provided in addition to β-lactam therapy if clinical, laboratory, or imaging characteristics are consistent with infection caused by *Staphylococcus aureus*.

Infectious Diseases Society of America/American Thoracic Society: **Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults (2007)**[32]	<u>Empirical antimicrobial therapy</u>
	• Recommendations are generally for a class of antibiotics rather than for a specific drug, unless outcome data clearly favor one drug.
	• Because overall efficacy remains good for many classes of agents, the more potent drugs are given preference because of their benefit in decreasing the risk of selection for antibiotic resistance.
	• Outpatient treatment
	  o Previously healthy and no risk factors for drug-resistant *Streptococcus pneumoniae* infection:
	  ▪ Macrolide (azithromycin, clarithromycin, or erythromycin).
	  ▪ Doxycycline.
	  o Presence of comorbidities, such as chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressing conditions or use of immunosuppressing drugs; use of antimicrobials within the previous three months (in which case an alternative from a different class should be selected); or other risks for drug-resistant Streptococcus pneumoniae infection:

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	▪ Respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin). ▪ β-lactam plus a macrolide (high-dose amoxicillin or amoxicillin-clavulanate is preferred; alternatives include ceftriaxone, cefpodoxime, and cefuroxime; doxycycline is an alternative to the macrolide). o In regions with a high rate of infection with high-level macrolide-resistant *Streptococcus pneumoniae,* consider the use of alternative agents listed above for any patient, including those without comorbidities. • Inpatient, non-intensive care unit treatment o Respiratory fluoroquinolone. o β-lactam plus a macrolide (preferred β-lactam agents include cefotaxime, ceftriaxone, and ampicillin; ertapenem for selected patients; with doxycycline as an alternative to the macrolide. A respiratory fluoroquinolone should be used for penicillin-allergic patients). • Inpatient, intensive care unit treatment o β-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) plus either azithromycin or a fluoroquinolone (for penicillin-allergic patients, a respiratory fluoroquinolone and aztreonam are recommended). o For *Pseudomonas* infection, use an antipneumococcal, antipseudomonal β-lactam (piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin; OR o Antipneumococcal, antipseudomonal β-lactam (listed above) plus an aminoglycoside and azithromycin; OR o Antipneumococcal, antipseudomonal β-lactam (listed above) plus an aminoglycoside and an antipneumococcal fluoroquinolone (for penicillin-allergic patients, substitute aztreonam for the above β-lactam). o For community-acquired methicillin-resistant *Staphylococcus aureus* infection, add vancomycin or linezolid.
American Thoracic Society/ Infectious Diseases Society of America: **Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia (2005)**[33]	• Select an initial empiric therapy based on the absence or presence of risk factors for multidrug-resistant pathogens. These risk factors include prolonged duration of hospitalization (five days or more), admission from a healthcare-related facility, and recent prolonged antibiotic therapy. • Patients with healthcare-related pneumonia should be treated for potentially drug-resistant organisms, regardless of when during the hospital stay the pneumonia begins. • In selecting empiric therapy for patients who have recently received an antibiotic, an effort should be made to use an agent from a different antibiotic class, because recent therapy increases the probability of inappropriate therapy and can predispose to resistance to that same class of antibiotics. • Initial empiric antibiotic therapy for hospital-acquired pneumonia or ventilator-associated pneumonia in patients with no known risk factors for multidrug-resistant pathogens, early onset, and any disease severity: o Ceftriaxone; OR o Levofloxacin, moxifloxacin, ciprofloxacin; OR o Ampicillin-sulbactam; OR o Ertapenem. • Initial empiric antibiotic therapy for hospital-acquired pneumonia, ventilator-associated pneumonia, and healthcare-associated pneumonia in patients with late-onset disease or risk factors for multidrug-resistant pathogens and all disease severity–combination antibiotic therapy is recommended as follows: o Antipseudomonal cephalosporin (cefepime, ceftazidime) or antipseudomonal carbapenem (imipenem or meropenem) or β-lactam-β-lactamase inhibitor (piperacillin-tazobactam) plus antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) or aminoglycoside (amikacin, gentamicin, or tobramycin) plus linezolid or vancomycin if

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	methicillin-resistant *Staphylococcus aureus* risk factors are present or there is a high incidence locally.
Infectious Diseases Society of America: **Diagnosis and Management of Complicated Intra-abdominal Infection in Adults and Children (2010)**[34]	<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 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

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	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: **Management of Patients with Infections Caused by Methicillin-Resistant *Staphylococcus Aureus* (2011)**[35]	Skin and soft-tissue infections • For a cutaneous abscess, incision and drainage is the primary treatment. For simple abscesses or boils, incision and drainage alone is likely to be adequate. • Antibiotic therapy is recommended for abscesses associated with the following conditions: severe or extensive disease (e.g., involving multiple sites of infection) or rapid progression in presence of associated cellulitis, signs and symptoms of systemic illness, associated comorbidities or immunosuppression, extremes of age, abscess in an area difficult to drain (e.g., face, hand, and genitalia), associated septic phlebitis, and lack of response to incision and drainage alone. • For outpatients with purulent cellulitis, empirical therapy for community-acquired methicillin-resistant *Staphylococcus aureus* is recommended pending culture results. Empirical therapy for infection due to beta-hemolytic streptococci is likely to be unnecessary. • For outpatients with non-purulent cellulitis, empirical therapy for infection due to beta-hemolytic streptococci is recommended. Empirical coverage for community-acquired methicillin-resistant *Staphylococcus aureus* is recommended in patients who do not respond to beta-lactam therapy and may be considered in those with systemic toxicity. • For empirical coverage of community-acquired methicillin-resistant *Staphylococcus aureus* in outpatients with skin and soft-tissue infections, oral antibiotic options include the following: clindamycin, sulfamethoxazole-trimethoprim, a tetracycline (doxycycline or minocycline), and linezolid. If coverage for both beta-hemolytic streptococci and community-acquired methicillin-resistant *Staphylococcus aureus* is desired, options include the following: clindamycin alone or sulfamethoxazole-trimethoprim or a tetracycline in combination with a beta-lactam (e.g., amoxicillin) or linezolid alone. • The use of rifampin as a single agent or as adjunctive therapy for the treatment of skin and soft-tissue infections is not recommended. • For hospitalized patients with complicated skin and soft-tissue infections, in addition to surgical debridement and broad-spectrum antibiotics, empirical therapy for methicillin-resistant *Staphylococcus aureus* should be considered pending culture data. Options include the following: vancomycin intravenous, linezolid oral or intravenous, daptomycin intravenous, telavancin intravenous, and clindamycin intravenous or oral. A beta-lactam antibiotic (e.g., cefazolin) may be considered in hospitalized patients with non-purulent cellulitis with modification to methicillin-

Clinical Guideline	Recommendation(s)
	resistant *Staphylococcus aureus*-active therapy if there is no clinical response. • For children with minor skin infections (such as impetigo) and secondarily infected skin lesions (such as eczema, ulcers, or lacerations), mupirocin 2% topical ointment can be used. • Tetracyclines should not be used in children <8 years of age. • In hospitalized children with skin and soft-tissue infections, vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, empirical therapy with clindamycin intravenous is an option if the clindamycin resistance rate is low (<10%) with transition to oral therapy if the strain is susceptible. Linezolid oral or intravenous is an alternative. <u>Methicillin-resistant Staphylococcus aureus and infective endocarditis (native valve)</u> • For adults with uncomplicated bacteremia, vancomycin or daptomycin intravenous for at least two weeks is recommended. For complicated bacteremia, four to six weeks of therapy is recommended, depending on the extent of infection. • For adults with infective endocarditis, intravenous vancomycin or daptomycin for six weeks is recommended. • Addition of gentamicin to vancomycin is not recommended for bacteremia or native valve infective endocarditis. <u>Methicillin-resistant *Staphylococcus aureus* bacteremia and infective endocarditis (prosthetic valve)</u> • Intravenous vancomycin plus rifampin oral or intravenous for at least six weeks plus gentamicin intravenous for two weeks. • In children, vancomycin intravenous is recommended for the treatment of bacteremia and infective endocarditis. Duration of therapy may range from two to six weeks depending on source, presence of endovascular infection, and metastatic foci of infection. • Data regarding the safety and efficacy of alternative agents in children are limited, although daptomycin intravenous may be an option. Clindamycin or linezolid should not be used if there is concern for infective endocarditis or endovascular source of infection, but may be considered in children whose bacteremia rapidly clears and is not related to an endovascular focus. • Data are insufficient to support the routine use of combination therapy with rifampin or gentamicin in children with bacteremia or infective endocarditis. <u>Management of methicillin-resistant *Staphylococcus aureus* pneumonia</u> • For hospitalized patients with severe community-acquired pneumonia, empirical therapy for methicillin-resistant *Staphylococcus aureus* is recommended pending sputum and/or blood culture results. • For health care–associated methicillin-resistant *Staphylococcus aureus* or community-acquired methicillin-resistant *Staphylococcus aureus* pneumonia, intravenous vancomycin or linezolid oral or intravenous or clindamycin oral or intravenous, if the strain is susceptible, is recommended for seven to 21 days, depending on the extent of infection. • In children, intravenous vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, clindamycin intravenous can be used as empirical therapy if the clindamycin resistance rate is low (<10%) with transition to oral therapy if the strain is susceptible. Linezolid oral or intravenous is an alternative. <u>Management of methicillin-resistant *Staphylococcus aureus* bone and joint infections</u> • Antibiotics available for parenteral administration include intravenous vancomycin and daptomycin. • Some antibiotic options with parenteral and oral routes of administration include the

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	following: sulfamethoxazole-trimethoprim in combination with rifampin, linezolid, and clindamycin. Some experts recommend the addition of rifampin. For patients with concurrent bacteremia, rifampin should be added after clearance of bacteremia.
	• A minimum eight-week course is recommended. Some experts suggest an additional one to three months (and possibly longer for chronic infection or if debridement is not performed) of oral rifampin-based combination therapy with sulfamethoxazole-trimethoprim, doxycycline-minocycline, clindamycin, or a fluoroquinolone, chosen on the basis of susceptibilities.
	• For septic arthritis, refer to antibiotic choices for osteomyelitis. A three to four-week course of therapy is suggested.
	
	<u>Management of methicillin-resistant *Staphylococcus aureus* infections of the central nervous system</u>
	• Meningitis
	  o Intravenous vancomycin for two weeks is recommended. Some experts recommend the addition of rifampin.
	  o Alternatives include the following: linezolid or sulfamethoxazole-trimethoprim.
	  o For central nervous system shunt infection, shunt removal is recommended, and it should not be replaced until cerebrospinal fluid cultures are repeatedly negative.
	• Brain abscess, subdural empyema, spinal epidural abscess
	  o Intravenous vancomycin for four to six weeks is recommended. Some experts recommend the addition of rifampin.
	  o Alternatives include the following: linezolid and sulfamethoxazole-trimethoprim.
	• Septic thrombosis of cavernous or dural venous sinus
	  o Intravenous vancomycin for four to six weeks is recommended. Some experts recommend the addition of rifampin.
	  o Alternatives include the following: linezolid and sulfamethoxazole-trimethoprim.
	  o Intravenous vancomycin is recommended in children.

Infectious Diseases Society of America: **Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer (2010)**[36]
 	
Reviewed and deemed current as of 04/2013
	<u>Initial antibiotic therapy</u>
	• Oral route:
	  o For low-risk adults only; use ciprofloxacin plus amoxicillin-clavulanate.
	• Monotherapy with vancomycin not indicated:
	  o Choose therapy with one of the following agents: cefepime or ceftazidime, or imipenem or meropenem.
	• Two drugs without vancomycin:
	  o Choose an aminoglycoside plus antipseudomonal penicillin, cephalosporin (cefepime or ceftazidime), or carbapenem.
	• Vancomycin plus one or two antibiotics:
	  o Choose cefepime or ceftazidime plus vancomycin, with or without an aminoglycoside; carbapenem plus vancomycin, with or without an aminoglycoside; or antipseudomonal penicillin plus an aminoglycoside and vancomycin.
	
	<u>Modification of therapy during the first week of treatment</u>
	• Patient becomes afebrile in three to five days:
	  o Adjust therapy to the most appropriate drug(s). If no etiologic agent is identified and if the patient is at low risk initially, and oral antibiotic treatment was begun with no subsequent complications, continue use of the same drugs.
	  o If the patient was at low risk initially and therapy with intravenous drugs was begun with no subsequent complications, the regimen may be changed after 48 hours to oral ciprofloxacin plus amoxicillin-clavulanate for adults

Clinical Guideline	Recommendation(s)
	or cefixime for children. o If the patient is at high risk initially with no subsequent complications, continue use of the same intravenous drugs. • Persistent fever throughout the first three to five days: o Reassess therapy on day three. If there is no clinical worsening, continue use of the same antibiotics; stop vancomycin use if cultures do not yield organisms. o If there is progressive disease, change antibiotics. o If the patient is febrile after five days, consider adding an antifungal drug. Antibiotic prophylaxis for afebrile neutropenic patients • Use of antibiotic prophylaxis is not routine because of emerging antibiotic resistance, except for the use of sulfamethoxazole-trimethoprim to prevent *Pneumocystis carinii* pneumonitis.
National Comprehensive Cancer Network: **Prevention and Treatment of Cancer-Related Infections (2016)**[37]	Low infection risk prophylaxis • Antimicrobial prophylaxis is not recommended in patients with low infection risk. Intermediate infection risk prophylaxis • Consider using fluoroquinolone prophylaxis. High infection risk prophylaxis • Consider using fluoroquinolone prophylaxis. • Additional prophylaxis may be necessary. *Pneumocystis jirovecii* prophylaxis • Sulfamethoxazole-trimethoprim is the preferred treatment. Sulfamethoxazole-trimethoprim has the additional benefit of activity against other pathogens including Nocardia, Toxoplasma, and Listeria. • Atovaquone, dapsone, and pentamidine are potential alternatives as prophylaxis for patients intolerant to sulfamethoxazole-trimethoprim. • Consider sulfamethoxazole-trimethoprim desensitization or atovaquone, dapsone, or pentamidine when *Pneumocystis* prophylaxis is required in patients who are sulfamethoxazole-trimethoprim intolerant. For patients receiving dapsone, consider assessing G6PD levels. Pneumococcal infection prophylaxis • Prophylaxis for pneumococcal infection should begin three months after patients undergo hematopoietic stem cell transplantation with penicillin, and prophylaxis should continue for at least one year after the transplant. • In regions that have pneumococcal isolates with intermediate or high-level resistance to penicillin, sulfamethoxazole-trimethoprim will likely be adequate for pneumococcal prophylaxis. Initial empiric antibiotic therapy • Patients with neutropenia should begin empiric treatment with broad spectrum antibiotics at the first sign of infection. • Intravenous antibiotic monotherapy for uncomplicated infections (choose one): o Cefepime. o Imipenem-cilastatin. o Meropenem. o Piperacillin-tazobactam. o Ceftazidime. • Oral antibiotic combination therapy for low-risk patients with uncomplicated infections: o Ciprofloxacin plus amoxicillin-clavulanate.

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	o Moxifloxacin. o Oral antibiotic regimen recommended should not be used if quinolone prophylaxis was used. • Complicated infections (choose based on local antibiotic susceptibility patterns): o Intravenous antibiotic monotherapy is preferred. o Intravenous combination therapy could be considered especially in cases of resistance. <u>Antibacterial agents: empiric gram-positive activity</u> • Vancomycin o Gram-positive organisms with the exception of VRE and a number of rare organisms. o Should not be considered as routine therapy for neutropenia and fever unless certain risk factors present. o Dosing individualized with monitoring of levels; loading dose may be considered. • Daptomycin o Has in vitro activity against VRE but is not FDA-approved for this indication. o Weekly creatine phosphokinase (CPK) to monitor for rhabdomyolysis. o Not indicated for pneumonia due to inactivation by pulmonary surfactant. • Linezolid o Gram-positive organisms including VRE. o Hematologic toxicity (typically with prolonged cases over two weeks) may occur. o Not routinely use in fever and neutropenia, although may impair neutrophil and platelet recovery for extended use. o Treatment option for VRE and MRSA. o Peripheral/optic neuropathy with long-term use. <u>Antibacterial agents: anti-pseudomonal</u> • Cefepime o Broad-spectrum activity against most gram-positive and negative organisms (not active against most anaerobes and *Enterococcus* species). o Use for suspected/proven CNS infection with susceptible organism. o Empiric therapy for neutropenic fever. • Ceftazidime o Relatively poor gram-positive activity (not active against most anaerobes and *Enterococcus* species). o Use for suspected/proven CNS infection with susceptible organism. o Empiric therapy for neutropenic fever (resistance among gram-negative rods at some centers). • Imipenem-cilastatin/ meropenem/ doripenem o Broad spectrum activity against most gram-positive, gram-negative, and anaerobic organisms. o Preferred against extended spectrum beta-lactamase and serious *Enterobacter* infections. o Carbapenem-resistant gram-negative rod infections are an increasing problem at a number of centers. o Use for suspected intra-abdominal source. o Meropenem is preferred over imipenem for suspected/proven CNS infection. o Effective in nosocomial pneumonia and intra-abdominal infections. • Piperacillin-tazobactam o Broad spectrum activity against most gram-positive, gram-negative, and anaerobic organisms.

Clinical Guideline	Recommendation(s)
	o Use for suspected intra-abdominal source. Antibacterial agents: other • Aminoglycosides o Activity primarily against gram-negative organisms. o Often used as empiric therapy in seriously ill or hemodynamically unstable patients. • Ciprofloxacin in combination with amoxicillin-clavulanate o Good activity against gram-negative and atypical organisms. Less active than "respiratory" fluoroquinolones against gram-positive organisms. o Ciprofloxacin alone has no activity against anaerobes. o Avoid for empiric therapy if patient recently treated with fluoroquinolone prophylaxis. • Levofloxacin/ moxifloxacin o Good activity against gram-negative and atypical organisms. o Levofloxacin has no activity against anaerobes. Moxifloxacin has limited activity against Pseudomonas. o Prophylaxis may increase bacterial resistance and superinfection. • Metronidazole o Good activity against anaerobic organisms. • Sulfamethoxazole-trimethoprim o Highly effective as prophylaxis against *Pneumocystis jiroveci* in high-risk patients. o Monitor for myelosuppression, hepatotoxicity, and hyperkalemia.
American Society of Health-System Pharmacists/ Infectious Diseases Society of America/ Surgical Infection Society/ Society for Healthcare Epidemiology of America: **Clinical practice guidelines for antimicrobial prophylaxis in surgery (2013)**[38]	Common principles • The optimal time for administration of preoperative doses is within 60 minutes before surgical incision. Some agents, such as fluoroquinolones and vancomycin, require administration over one to two hours; therefore, the administration of these agents should begin within 120 minutes before surgical incision. • The selection of an appropriate antimicrobial agent for a specific patient should take into account the characteristics of the ideal agent, the comparative efficacy of the antimicrobial agent for the procedure, the safety profile, and the patient's medication allergies. • For most procedures, cefazolin is the drug of choice for prophylaxis because it is the most widely studied antimicrobial agent, with proven efficacy. It has a desirable duration of action, spectrum of activity against organisms commonly encountered in surgery, reasonable safety, and low cost. • There is little evidence to suggest that broad-spectrum antimicrobial agents (i.e., agents with broad in vitro antibacterial activity) result in lower rates of postoperative SSI compared with older antimicrobial agents with a narrower spectrum of activity. However, comparative studies are limited by small sample sizes, resulting in difficulty detecting a significant difference between antimicrobial agents. Cardiac procedures • For patients undergoing cardiac procedures, the recommended regimen is a single preincision dose of cefazolin or cefuroxime with appropriate intraoperative redosing. • For patients with serious allergy or adverse reaction to β-lactams, vancomycin or clindamycin may be an acceptable alternative. • Vancomycin should be used for prophylaxis in patients known to be colonized with MRSA. • Mupirocin should be given intranasally to all patients with documented *S. aureus* colonization.

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	Thoracic procedures • In patients undergoing thoracic procedures, a single dose of cefazolin or ampicillin–sulbactam is recommended. • For patients with serious allergy or adverse reaction to β-lactams, vancomycin or clindamycin may be an acceptable alternative. • Vancomycin should be used for prophylaxis in patients known to be colonized with MRSA. Gastroduodenal procedures • Antimicrobial prophylaxis in gastroduodenal procedures should be considered for patients at highest risk for postoperative infections, including risk factors such as increased gastric pH (e.g., patients receiving acid-suppression therapy), gastroduodenal perforation, decreased gastric motility, gastric outlet obstruction, gastric bleeding, morbid obesity, ASA classification of ≥3, and cancer. • A single dose of cefazolin is recommended in procedures during which the lumen of the intestinal tract is entered. A single dose of cefazolin is recommended in clean procedures, such as highly selective vagotomy, and antireflux procedures only in patients at high risk of postoperative infection due to the presence of the above risk factors. • Alternative regimens for patients with β -lactam allergy include clindamycin or vancomycin plus gentamicin, aztreonam, or a fluoroquinolone. • Higher doses of antimicrobials are uniformly recommended in morbidly obese patients undergoing bariatric procedures. Higher doses of antimicrobials should be considered in significantly overweight patients undergoing gastroduodenal and endoscopic procedures. Biliary tract procedures • A single dose of cefazolin should be administered in patients undergoing open biliary tract procedures. • Alternatives include ampicillin–sulbactam and other cephalosporins (cefotetan, cefoxitin, and ceftriaxone). Alternative regimens for patients with β -lactam allergy include clindamycin or vancomycin plus gentamicin, aztreonam, or a fluoroquinolone; or metronidazole plus gentamicin or a fluoroquinolone. Appendectomy procedures • For uncomplicated appendicitis, the recommended regimen is a single dose of a cephalosporin with anaerobic activity (cefoxitin or cefotetan) or a single dose of a first-generation cephalosporin (cefazolin) plus metronidazole. • For β -lactam-allergic patients, alternative regimens include clindamycin plus gentamicin, aztreonam, or a fluoroquinolone; and metronidazole plus gentamicin or a fluoroquinolone (ciprofloxacin or levofloxacin). Small intestine procedures • For small bowel surgery without obstruction, the recommended regimen is a first generation cephalosporin (cefazolin). For small bowel surgery with intestinal obstruction, the recommended regimen is a cephalosporin with anaerobic activity (cefoxitin or cefotetan) or the combination of a first-generation cephalosporin (cefazolin) plus metronidazole. • For β -lactam-allergic patients, alternative regimens include clindamycin plus gentamicin, aztreonam, or a fluoroquinolone; and metronidazole plus gentamicin or a fluoroquinolone (ciprofloxacin or levofloxacin). Hernia repair procedures • For hernioplasty and herniorrhaphy, the recommended regimen is a single dose of a first-generation cephalosporin (cefazolin). For patients known to be colonized with

Clinical Guideline	Recommendation(s)

	MRSA, it is reasonable to add a single preoperative dose of vancomycin to the recommended agent. For β –lactam-allergic patients, alternative regimens include clindamycin and vancomycin.
	
	Colorectal procedures
	• A single dose of second-generation cephalosporin with both aerobic and anaerobic activities (cefoxitin or cefotetan) or cefazolin plus metronidazole is recommended for colon procedures.
	• In institutions where there is increasing resistance to first- and second-generation cephalosporins among gram-negative isolates from SSIs, a single dose of ceftriaxone plus metronidazole is recommended over routine use of carbapenems. An alternative regimen is ampicillin–sulbactam.
	• In most patients, mechanical bowel preparation combined with a combination of oral neomycin sulfate plus oral erythromycin base or oral neomycin sulfate plus oral metronidazole should be given in addition to intravenous prophylaxis. The oral antimicrobial should be given as three doses over approximately 10 hours the afternoon and evening before the operation and after the mechanical bowel preparation.
	• Alternative regimens for patients with β–lactam allergies include (1) clindamycin plus an aminoglycoside, aztreonam, or a fluoroquinolone and (2) metronidazole plus an aminoglycoside or a fluoroquinolone. Metronidazole plus aztreonam is not recommended as an alternative because this combination has no aerobic gram-positive activity.
	
	Head and neck procedures
	• Clean procedures:
	  o Antimicrobial prophylaxis is not required.
	• Clean-contaminated procedures:
	  o Antimicrobial prophylaxis has not been shown to benefit patients undergoing tonsillectomy or functional endoscopic sinus procedures.
	  o The preferred regimens for patients undergoing other clean-contaminated head and neck procedures are (1) cefazolin or cefuroxime plus metronidazole and (2) ampicillin–sulbactam.
	  o Clindamycin is a reasonable alternative in patients with a documented β-lactam allergy. The addition of an aminoglycoside to clindamycin may be appropriate when there is an increased likelihood of gram-negative contamination of the surgical site.
	
	Neurosurgery procedures
	• A single dose of cefazolin is recommended for patients undergoing clean neurosurgical procedures, CSF-shunting procedures, or intrathecal pump placement. Clindamycin or vancomycin should be reserved as an alternative agent for patients with a documented β-lactam allergy (vancomycin for MRSA-colonized patients).
	
	Cesarean delivery procedures
	• The recommended regimen for all women undergoing cesarean delivery is a single dose of cefazolin administered before surgical incision. For patients with β-lactam allergies, an alternative regimen is clindamycin plus gentamicin.
	
	Hysterectomy procedures
	• The recommended regimen for women undergoing vaginal or abdominal hysterectomy, using an open or laparoscopic approach, is a single dose of cefazolin.
	• Cefoxitin, cefotetan, or ampicillin–sulbactam may also be used. Alternative agents for patients with a b-lactam allergy include (1) either clindamycin or vancomycin plus an aminoglycoside, aztreonam, or a fluoroquinolone and (2) metronidazole

Clinical Guideline	Recommendation(s)
	plus an aminoglycoside or a fluoroquinolone. Ophthalmic procedures • Due to the lack of robust data from trials, specific recommendations cannot be made regarding choice, route, or duration of prophylaxis. • As a general principle, the antimicrobial prophylaxis regimens used in ophthalmic procedures should provide coverage against common ocular pathogens, including *Staphylococcus* species and gram-negative organisms, particularly *Pseudomonas* species. Orthopedic procedures • Antimicrobial prophylaxis is not recommended for patients undergoing clean orthopedic procedures, including knee, hand, and foot procedures, arthroscopy, and other procedures without instrumentation or implantation of foreign materials. • Antimicrobial prophylaxis is recommended for orthopedic spinal procedures with and without instrumentation. The recommended regimen is cefazolin. • The recommended regimen in hip fracture repair or other orthopedic procedures involving internal fixation is cefazolin. Clindamycin and vancomycin should be reserved as alternative agents. • The recommended regimen for patients undergoing total hip, elbow, knee, ankle, or shoulder replacement is cefazolin. Clindamycin and vancomycin should be reserved as alternative agents. Urologic procedures • No antimicrobial prophylaxis is recommended for clean urologic procedures in patients without risk factors for postoperative infections. • Patients with preoperative bacteriuria or UTI should be treated before the procedure, when possible, to reduce the risk of postoperative infection. • For patients undergoing lower urinary tract instrumentation with risk factors for infection, the use of a fluoroquinolone or trimethoprim– sulfamethoxazole (oral or intravenous) or cefazolin (intravenous or intramuscular) is recommended. Vascular procedures • The recommended regimen for patients undergoing vascular procedures associated with a higher risk of infection, including implantation of prosthetic material, is cefazolin. Heart, lung, heart-lung, liver, pancreas, and kidney transplantation • Antimicrobial prophylaxis is indicated for all patients undergoing heart transplantation. The recommended regimen is a single dose of cefazolin. Alternatives include vancomycin or clindamycin with or without gentamicin, aztreonam, or a single fluoroquinolone dose. • Adult patients undergoing lung transplantation should receive antimicrobial prophylaxis, because of the high risk of infection. Patients with negative pretransplantation cultures should receive antimicrobial prophylaxis as appropriate for other types of cardiothoracic procedures. The recommended regimen is a single dose of cefazolin. • The recommended agents for patients undergoing liver transplantation are (1) piperacillin–tazobactam and (2) cefotaxime plus ampicillin. The duration of prophylaxis should be restricted to 24 hours or less. • The recommended regimen for patients undergoing pancreas or SPK transplantation is cefazolin. • The recommended agent for patients undergoing kidney transplantation is cefazolin.

Clinical Guideline	Recommendation(s)
	Plastic surgery and breast procedures • Antimicrobial prophylaxis is not recommended for most clean procedures in patients without additional postoperative infection risk factors. Although no studies have demonstrated antimicrobial efficacy in these procedures, expert opinion recommends that patients with risk factors undergoing clean plastic procedures receive antimicrobial prophylaxis. The recommendation for clean-contaminated procedures, breast cancer procedures, and clean procedures with other risk factors is a single dose of cefazolin or ampicillin–sulbactam.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the quinolones 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 Quinolones[1-8]

Indication	Ciprofloxacin	Levofloxacin	Moxifloxacin	Ofloxacin
Dermatological Infections				
Skin and skin-structure infections	✔ §*	✔	✔	✔
Gastrointestinal Infections				
Infectious diarrhea	✔ §			
Genitourinary Infections				
Cystitis	✔ §			✔
Pelvic inflammatory disease				✔
Prostatitis	✔ §*	✔		✔
Pyelonephritis	✔ §†*	✔		
Urethritis/cervicitis (gonococcal)	✔ §			✔
Urethritis/cervicitis (non-gonococcal)				✔
Urinary tract infections	✔ §†*	✔		✔
Respiratory Infections				
Acute exacerbations of chronic bronchitis		✔	✔	✔
Inhalation anthrax (post-exposure)	✔ §*	✔		
Pneumonia (community-acquired)		✔	✔	✔
Pneumonia (nosocomial)	✔ *	✔		
Respiratory tract infections (lower)	✔ §*			
Sinusitis	✔ §*	✔	✔	
Miscellaneous Infections				
Bone and/or joint infections	✔ §*			
Empiric therapy for febrile neutropenic patients	✔ *			
Intra-abdominal infections	✔ §*		✔	
Plague	✔ §*	✔	✔	
Typhoid fever	✔ §			

§Immediate-release formulation.
†Extended-release formulation.
*IV formulation.

IV. Pharmacokinetics

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

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

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Ciprofloxacin	60 to 80	20 to 40	Liver	Renal (30 to 57) Feces (20 to 35)	IR: 3 to 6 ER: 6 to 7
Levofloxacin	99	24 to 38	Liver	Renal (61 to 87) Feces (<4)	6 to 8
Moxifloxacin	90	30 to 50	Liver (52)	Renal (20) Feces(25)	8 to 16
Ofloxacin	90 to 98	20 to 32	Liver	Renal (65 to 80) Feces (4 to 8)	5.0 to 7.5

ER=extended-release, IR=immediate-release

V. Drug Interactions

Major drug interactions with the quinolones are listed in Table 6.

Table 6. Major Drug Interactions with the Quinolones[2]

Generic Name(s)	Interaction	Mechanism
Quinolones (ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin)	Antiarrhythmic agents	Both quinolones and antiarrhythmics can cause prolongation of the QT interval. Additive prolongation may occur.
Quinolones (ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin)	Warfarin	The effect is an increased anticoagulant effect of warfarin. The mechanism is unknown.
Quinolones (ciprofloxacin, ofloxacin)	Methadone	Methadone inhibits cardiac potassium channels and prolongs QT interval. This may become significant with larger doses and in combination with other drugs that also prolong QT interval.
Quinolones (ciprofloxacin, levofloxacin)	Theophylline	Inhibition of hepatic metabolism of theophylline leads to increased theophylline levels and toxicity can occur.
Quinolones (ciprofloxacin, moxifloxacin, ofloxacin)	Butyrophenones	May cause additive QT interval prolongation.
Quinolones (ciprofloxacin, ofloxacin)	Macrolides and detolides	Pharmacologic effects of macrolides/ketolides and quinolones on the cardiac conduction system and QT interval may be additive.
Quinolones (ciprofloxacin, levofloxacin, ofloxacin)	Phenothiazines	The risk of life-threatening cardiac arrhythmias, including torsades de pointes, may be increased. The mechanism is unknown.
Quinolones (ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin)	Sulfonylureas	The hypoglycemic effect of sulfonylureas may be increased. The mechanism is unknown.
Quinolones (ciprofloxacin, ofloxacin)	Arsenic	May cause additive QT interval prolongation.
Quinolones (ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin)	Cisapride	The risk of cardiovascular side effects may be increased. The mechanism is unknown.
Quinolones (ciprofloxacin, levofloxacin,	Crizotinib	May cause additive QT interval prolongation.

Generic Name(s)	Interaction	Mechanism
moxifloxacin, ofloxacin)		
Quinolones (ciprofloxacin, ofloxacin)	Halofantrine	May cause additive QT interval prolongation.
Quinolones (ciprofloxacin, moxifloxacin, ofloxacin)	Nilotinib	May cause additive QT interval prolongation.
Quinolones (ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin)	Pimozide	May cause additive QT interval prolongation.
Quinolones (ciprofloxacin, ofloxacin)	Tacrolimus	May cause additive QT interval prolongation.
Quinolones (ciprofloxacin, ofloxacin)	Toremifene	Pharmacologic effects of toremifene and quinolones on electrical conduction of the heart may be additive.
Quinolones (ciprofloxacin, moxifloxacin, ofloxacin)	Vandetanib	May cause additive QT interval prolongation.
Quinolones (ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin)	Ziprasidone	The risk of life-threatening cardiac arrhythmias, including torsades de pointes, may be increased. The mechanism is unknown.
Quinolones (ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin)	Tizanidine	Quinolones may inhibit tizanidine metabolism (CYP1A2). Tizanidine plasma concentrations may be elevated, increasing the pharmacologic and adverse effects (e.g., dizziness, hypotension).
Quinolones (ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin)	Chloroquine	May cause additive QT interval prolongation.
Quinolones (ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin)	Aluminum salts	Gastrointestinal absorption of quinolones may be decreased, resulting in decreased pharmacologic effects of quinolones. Reduced gastrointestinal acidity may be an additional mechanism.
Quinolones (ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin)	Calcium salts	Gastrointestinal absorption of quinolones may be decreased, resulting in decreased pharmacologic effects of quinolones.
Quinolones (ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin)	Iron salts	The formation of insoluble chelates with iron decreases gastrointestinal absorption of quinolones.
Quinolones (ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin)	Magnesium salts	The gastrointestinal absorption of quinolones may be decreased due to formation of poorly soluble chelates with magnesium. Reduced gastrointestinal acidity may be an additional mechanism.
Quinolones (ciprofloxacin)	Alfuzosin	Concurrent use of alfuzosin and ciprofloxacin may result in an increased risk of QT interval prolongation.
Quinolones (ciprofloxacin, ofloxacin)	Amoxapine	Concurrent use of amoxapine and quinolones may result in an increased risk of QT interval prolongation.
Quinolones (ciprofloxacin, moxifloxacin)	Artemether-lumefantrine	Concurrent use of artemether-lumefantrine and quinolones may result in an increased risk of QT-interval prolongation.
Quinolones (ciprofloxacin, ofloxacin)	Asenapine	Concurrent use of asenapine and quinolones may result in an increased risk of QT interval prolongation.
Quinolones (ciprofloxacin, ofloxacin)	Azole antifungals	Concurrent use of quinolones and azole antifungals may result in an increased risk of QT interval prolongation.
Quinolones (ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin)	Citalopram, escitalopram	Concurrent use of quinolones and citalopram may result in increased risk of QT interval prolongation.

Generic Name(s)	Interaction	Mechanism
Quinolones (ciprofloxacin, levofloxacin, moxifloxacin, ofloxacin)	Clozapine	Inhibition of cytochrome P450 1A2 isoenzymes by ciprofloxacin may decrease the metabolic elimination of clozapine. This may increase clozapine blood levels, leading to increased risk of clozapine's adverse effects.
Quinolones (ciprofloxacin, ofloxacin)	Dasatinib	Concurrent use of quinolones and dasatinib may result in an increased risk of QT interval prolongation.
Quinolones (ciprofloxacin)	Erlotinib	Concurrent use of ciprofloxacin and erlotinib may result in increased erlotinib exposure.
Quinolones (ciprofloxacin, ofloxacin)	Iloperidone	Concurrent use of quinolones and iloperidone may result in an increased risk of QT interval prolongation.
Quinolones (ciprofloxacin, ofloxacin)	Lapatinib	May cause additive QT interval prolongation.
Quinolones (ciprofloxacin, moxifloxacin, ofloxacin)	Mifepristone	Concurrent use of quinolones and mifepristone may result in increased risk of QT-interval prolongation.
Quinolones (ciprofloxacin, levofloxacin, ofloxacin)	Ondansetron	Concurrent use of quinolones and ondansetron may result in an increased risk of QT interval prolongation.
Quinolones (ciprofloxacin)	Pirfenidone	Concurrent use of ciprofloxacin and pirfenidone may result in increased pirfenidone exposure.
Quinolones (ciprofloxacin, ofloxacin)	Quinidine	Concurrent use of quinolones and quinidine may result in an increased risk of QT interval prolongation.
Quinolones (ciprofloxacin, ofloxacin)	Quinine	Concurrent use of quinolones and quinine may result in an increased risk of QT interval prolongation.
Quinolones (ciprofloxacin, ofloxacin)	Ranolazine	Concurrent use of quinolones and ranolazine may result in an increased risk of QT interval prolongation.
Quinolones (ciprofloxacin, ofloxacin)	Mefloquine	Concurrent use of quinolones and mefloquine may result in an increased risk of QT interval prolongation.
Quinolones (ciprofloxacin, ofloxacin)	Octreotide	Concurrent use of quinolones and octreotide may result in an increased risk of QT interval prolongation.
Quinolones (ciprofloxacin, ofloxacin)	Paliperidone	Concurrent use of quinolones and paliperidone may result in an increased risk of QT interval prolongation.
Quinolones (ciprofloxacin, moxifloxacin, ofloxacin)	Pazopanib	Concurrent use of quinolones and pazopanib may result in an increased risk of QT interval prolongation.
Quinolones (ciprofloxacin)	Simvastatin	Concurrent use of ciprofloxacin and simvastatin may result in an increased risk of myopathy or rhabdomyolysis.
Quinolones (ciprofloxacin, ofloxacin)	Solifenacin	Concurrent use of quinolones and solifenacin may result in an increased risk of QT interval prolongation.
Quinolones (ciprofloxacin, ofloxacin)	Sorafenib	Concurrent use of quinolones and sorafenib may result in an increased risk of QT interval prolongation.
Quinolones (ciprofloxacin, ofloxacin)	Sunitinib	Concurrent use of quinolones and sunitinib may result in an increased risk of QT interval prolongation.
Quinolones (ciprofloxacin, ofloxacin)	Tetrabenazine	Concurrent use of quinolones and tetrabenazine may result in an increased risk of QT interval prolongation.
Quinolones (ciprofloxacin)	Trazodone	Concurrent use of ciprofloxacin and trazodone may result in an increased risk of QT interval prolongation.
Quinolones (ciprofloxacin, ofloxacin)	Tricyclic antidepressants	Concurrent use of quinolones and tricyclic antidepressants may result in an increased risk of QT interval prolongation.
Quinolones (ciprofloxacin, ofloxacin)	Vardenafil	Concurrent use of quinolones and vardenafil may result in an increased risk of vardenafil adverse effects and an increased risk of QT interval prolongation.

VI. Adverse Drug Events

The most common adverse drug events reported with the quinolones are listed in Table 7. The boxed warning for the quinolones is listed in Table 8.

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

Adverse Events	Ciprofloxacin	Levofloxacin	Moxifloxacin	Ofloxacin
Cardiovascular				
Angina pectoris	<1	-	0.1 to 1.0	-
Atrial fibrillation	-	-	0.1 to 1.0	-
Atrial flutter	<1	-	-	-
Bradycardia	-	-	0.1 to 1.0	-
Cardiac arrest	<1	0.1 to 1.0	0.1 to 1.0	<1
Cerebral thrombosis	<1	-	-	-
Congestive heart failure	-	-	0.1 to 1.0	-
Hypertension	<1	-	0.1 to 1.0	<1
Hypotension	<1	-	0.1 to 1.0	<1
Myocardial infarction	<1	-	-	-
Palpitations	<1	0.1 to 1.0	0.1 to 1.0	<1
QT prolongation	✔	✔	0.1 to 1.0	-
Syncope	<1	0.1 to 1.0	0.1 to 1.0	<1
Tachycardia	<1	✔	0.1 to 1.0	-
Ventricular arrhythmia	-	0.1 to 1.0	✔	-
Ventricular ectopy	<1	-	-	-
Ventricular tachycardia	-	0.1 to 1.0	✔	-
Central Nervous System				
Abnormal dreaming	-	0.1 to 1.0	-	<1
Abnormal gait	<1	0.1 to 1.0	✔	-
Agitation	✔	0.1 to 1.0	0.1 to 1.0	-
Anosmia	✔	✔	-	-
Anxiety	-	0.1 to 1.0	0.1 to 1.0	<1
Asthenia	-	-	0.1 to 1.0	<1
Ataxia	<1	-	-	-
Chills	<1	-	0.1 to 11	<1
Confusion	✔	0.1 to 1.0	0.1 to 1.0	<1
Delirium	✔	-	-	-
Depersonalization	<1	-	-	-
Depression	<1	0.1 to 1.0	0.1 to 1.0	<1
Dizziness	<1	0.3 to 3.0	3	1 to 5

Adverse Events	Ciprofloxacin	Levofloxacin	Moxifloxacin	Ofloxacin
Drowsiness	<1	-	-	-
Encephalopathy	-	✔	-	-
Fatigue	-	<1	0.1 to 1.0	1 to 3
Fever	<1	✔	1.1	1 to 3
Hallucinations	<1	0.1 to 1.0	0.1 to 1.0	<1
Headache	<1	0.3 to 6.0	4.2	1 to 9
Hyperkinesias	-	0.1 to 1.0	-	-
Hypertonia	-	0.1 to 1.0	-	-
Insomnia	<1	4	1.9	3 to 7
Irritability	<1	-	-	-
Lethargy	<1	<1	0.1 to 1.0	1 to 3
Lightheadedness	<1	-	✔	-
Malaise	<1	<1	0.1 to 1.0	1 to 3
Manic reaction	<1	-	-	-
Migraine	<1	-	-	-
Nightmares	<1	0.1 to 1.0	-	-
Paranoia	-	✔	-	-
Paresthesia	<1	0.1 to 1.0	0.1 to 1.0	<1
Peripheral neuropathy	✔	✔	✔	✔
Phobia	<1	-	-	-
Psychotic reactions	<1	✔	✔	-
Restlessness	<1	-	0.1 to 1.0	<1
Seizures	<1	0.1 to 1.0	✔	<1
Sleep disorder	-	0.1 to 1.0	-	-
Somnolence	<1	0.1 to 1.0	0.1 to 1.0	1 to 3
Suicide attempt or ideation	-	✔	-	-
Tinnitus	<1	✔	0.1 to 1.0	<1
Tremor	<1	0.1 to 1.0	0.1 to 1.0	<1
Weakness	<1	-	-	-
Vertigo	-	0.1 to 1.0	0.1 to 1.0	<1
Dermatological				
Cutaneous candidiasis	<1	-	-	-
Dermatitis	-	-	0.1 to 1.0	-
Erythema multiform	-	✔	-	-
Erythema nodosum	<1	-	-	-
Flushing	<1	-	-	-
Hyperpigmentation	<1	-	-	-

Adverse Events	Ciprofloxacin	Levofloxacin	Moxifloxacin	Ofloxacin
Night sweats	-	-	0.1 to 1.0	-
Petechia	<1	-	-	-
Photosensitivity	<1	✔	✔	✔
Pruritus	<1	1	0.1 to 1.0	1 to 3
Rash	1	1	0.1 to 1.0	1 to 3
Stevens-Johnson syndrome	✔	✔	✔	-
Sweating	<1	-	0.1 to 1.0	<1
Toxic epidermal necrolysis	✔	✔	✔	-
Urticaria	<1	0.1 to 1.0	0.1 to 1.0	<1
Gastrointestinal				
Abdominal pain/discomfort	<1	≤2	1.5	1 to 3
Anorexia	<1	0.1 to 1.0	0.1 to 1.0	-
Constipation	✔	3	<1	1 to 3
Diarrhea	1.6	5	6	1 to 4
Dry mouth	<1	<1	0.1 to 1.0	1 to 3
Dyspepsia	✔	2	1	<1
Dysphagia	<1	-	-	-
Esophagitis	-	0.1 to 1.0	-	-
Flatulence	<1	-	0.1 to 1.0	1 to 3
Gastritis	-	0.1 to 1.0	-	-
Gastroenteritis	-	0.1 to 1.0	0.1 to 1.0	-
Gastroesophageal reflux disease	-	-	0.1 to 1.0	-
Gastrointestinal bleeding	<1	-	0.1 to 1.0	-
Glossitis	-	0.1 to 1.0	-	-
Intestinal perforation	<1	-	-	-
Nausea	2.5	0.6 to 7.0	6.9	3 to 10
Oral candidiasis	<1	1	0.1 to 1.0	-
Painful oral mucosa	<1	-	-	-
Pancreatitis	-	0.1 to 1.0	-	-
Pseudomembranous colitis	✔	0.1 to 1.0	-	✔
Taste alterations	<1	✔	0.1 to 1.0	-
Vomiting	1	0.5 to 3.0	2.4	1 to 4
Genitourinary				
Albuminuria	✔	-	-	≥1
Breast pain	<1	-	-	-
Candiduria	✔	-	-	-
Crystalluria	✔	-	-	-

Adverse Events	Ciprofloxacin	Levofloxacin	Moxifloxacin	Ofloxacin
Cylindruria	✔	-	-	-
Dysuria	-	-	0.1 to 1.0	<1
Genital irritation (pain or rash)	-	-	-	<1
Genital moniliasis	-	0.1 to 1.0	-	-
Glucosuria	-	-	-	≥1
Hematuria	✔	-	-	≥1
Interstitial nephritis	<1	✔	✔	-
Nephritis	<1	-	-	-
Polyuria	<1	-	-	<1
Proteinuria	-	-	-	≥1
Pyuria	-	-	-	≥1
Renal Failure	<1	0.1 to 1.0	0.1 to 1.0	-
Renal function abnormal (non-specific)	-	0.1 to 1.0	✔	-
Urethral bleeding	<1	-	-	-
Urinary retention	<1	-	-	<1
Vaginitis	<1	<2	<1	1 to 5
Hematologic				
Acidosis	<1	-	-	-
Agranulocytosis	✔	-	✔	-
Anemia	<0.1	0.1 to 1.0	-	≥1
Aplastic anemia	-	✔	-	-
Eosinophilia	0.6	✔	0.1 to 1.0	≥1
Granulocytopenia	-	0.1 to 1.0	-	-
Hematocrit decreased	<0.1	-	0.1 to 1.0	-
Hemoglobin decreased	<1	-	0.1 to 1.0	-
Hemolytic anemia	-	✔	-	-
Leukocytosis	<0.1	<1	0.1 to 1.0	≥ 1
Leukopenia	0.4	✔	0.1 to 1.0	≥1
Lymphocytosis	-	-	-	≥1
Monocytes increased	<0.1	-	-	-
Neutropenia	-	-	0.1 to 1.0	≥1
Neutrophils increased	-	-	≥2	-
Pancytopenia	0.1	✔	✔	-
Platelets decreased	0.1	-	-	-
Platelets increased	0.1	-	0.1 to 1.0	-
Prothrombin time increased	<1	✔	0.1 to 1.0	-
Red blood cell decreased	-	-	≥2	-

Adverse Events	Ciprofloxacin	Levofloxacin	Moxifloxacin	Ofloxacin
Thrombocytosis	<1	-	0.1 to 1.0	≥1
Thrombocytopenia	<1	0.1 to 1.0	0.1 to 1.0	≥1
Hepatic				
Hepatic failure	✔	✔	✔	-
Hepatic function abnormal	-	0.1 to 1.0	0.1 to 1.0	-
Hepatitis	<1	✔	✔	-
Jaundice	<1	✔	✔	-
Laboratory Test Abnormalities				
Albumin decreased	-	-	≥2	-
Alkaline phosphatase increased	0.8	0.1 to 1.0	0.1 to 1.0	≥1
Alanine aminotransferase increased	1.9	-	1.1	≥1
Aspartate aminotransferase increased	1.7	-	1.1	≥1
Bilirubin abnormalities	0.3	-	0.1 to 1.0	-
Blood urea nitrogen increased	0.9	-	0.1 to 1.0	≥1
Calcium decreased	-	-	≥2	-
Cholesterol increased	✔	-	-	-
Creatinine phosphokinase increased	-	✔	-	-
Gamma-glutamyl transferase increased	-	-	1.1	-
Glucose abnormalities	<1	2	-	≥1
Hyperglycemia	-	0.1 to 1.0	0.1 to 1.0	≥1
Hyperkalemia	-	0.1 to 1.0	-	-
Hypoglycemia	<0.1	0.1 to 1.0	0.1 to 1.0	-
Hypokalemia	-	-	1	-
Lactic acid dehydrogenase increased	0.4	<1	0.1 to 1.0	-
Liver enzymes increased	-	0.1 to 1.0	0.1 to 1.0	-
Serum amylase increased	<1	-	0.1 to 1.0	-
Serum creatinine increased	1.1	-	0.1 to 1.0	≥1
Serum lipase increased	<1	-	0.1 to 1.0	-
Triglycerides increased	✔	-	0.1 to 1.0	-
Uric acid increased	<0.1	-	0.1 to 1.0	-
Musculoskeletal				
Achiness or myalgia	<1	0.1 to 1.0	0.1 to 1.0	<1
Arthralgia or back pain	<1	0.1 to 1.0	0.1 to 1.0	<1
Joint stiffness	<1	-	-	-
Muscle injury	-	✔	-	-
Muscle spasms	-	-	0.1 to 1.0	-
Neck or chest pain	<1	1	0.1 to 1.0	-

Adverse Events	Ciprofloxacin	Levofloxacin	Moxifloxacin	Ofloxacin
Rhabdomyolysis	-	✔	-	-
Skeletal pain	-	0.1 to 1.0	0.1 to 1.0	-
Tendinitis/tendon rupture	✔	0.1 to 1.0	✔	-
Respiratory				
Bronchospasm	<1	-	0.1 to 1.0	-
Cough	-	-	-	<1
Dyspnea	<1	1	0.1 to 1.0	-
Epistaxis	<1	0.1 to 1.0	-	<1
Hemoptysis	<1	-	-	-
Hiccough	<1	-	-	-
Laryngeal or pulmonary edema	<1	-	-	-
Pneumonitis	-	✔	-	-
Pulmonary embolism	<1	-	-	-
Rhinorrhea	-	-	-	<1
Wheezing	-	-	0.1 to 1	-
Other				
Allergic reaction	<1	0.1 to 1.0	-	-
Anaphylactic reactions	✔	✔	✔	-
Angioedema	<1	✔	✔	<1
Dehydration	-	-	0.1 to 1.0	-
Edema	<1	1	0.1 to 1.0	<1
Eye Pain	<1	-	-	-
Foot Pain	<1	-	-	-
Fungal Infection	-	-	0.1 to 1.0	-
Gout	<1	-	-	-
Hearing loss	<1	-	-	<1
Hypersensitivity	<1	✔	✔	✔
Injection site reaction	<1	1	0.1 to 1.0	-
Leukocytoclastic vasculitis	-	✔	-	<1
Lymphadenopathy	<1	-	-	-
Myasthenia gravis exacerbation	✔	✔	✔	-
Multi-organ failure	-	✔	-	-
Pain	<1	-	0.1 to 1.0	<1
Pain in extremities	<1	-	0.1 to 1.0	<1
Phlebitis	<1	0.1 to 1.0	0.1 to 1.0	-
Serum sickness-like reaction	-	✔	-	-
Vasodilation	-	✔	-	<1

Adverse Events	Ciprofloxacin	Levofloxacin	Moxifloxacin	Ofloxacin
Visual disturbances	<1	✔	0.1 to 1.0	1 to 3

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

Table 8. Boxed Warning for the Quinolones[1-8]

WARNING
WARNING: SERIOUS ADVERSE REACTIONS INCLUDING TENDINITIS, TENDON RUPTURE, PERIPHERAL NEUROPATHY, CENTRAL NERVOUS SYSTEM EFFECTS AND EXACERBATION OF MYASTHENIA GRAVIS • Fluoroquinolones have been associated with disabling and potentially irreversible serious adverse reactions that have occurred together, including: o Tendinitis and tendon rupture o Peripheral neuropathy o Central nervous system effects • Discontinue immediately and avoid the use of fluoroquinolones in patients who experience any of these serious adverse reactions. Fluoroquinolones may exacerbate muscle weakness in patients with myasthenia gravis. Avoid in patients with known history of myasthenia gravis. • Because fluoroquinolones have been associated with serious adverse reactions, reserve for use in patients who have no alternative treatment options for the following indications: o Acute exacerbation of chronic bronchitis o Acute uncomplicated cystitis o Acute sinusitis

VII. Dosing and Administration

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

Table 9. Usual Dosing Regimens for the Quinolones[1-8]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Ciprofloxacin	Bone and joint infections (mild to moderate): Injection: 400 mg every 12 hours for ≥four to six weeks Suspension, tablet immediate-release: 500 mg every 12 hours for ≥ four to six weeks Bone and joint infections (severe or complicated): Injection: 400 mg every eight hours for ≥ four to six weeks Suspension, tablet immediate-release: 750 mg every 12 hours for ≥ four to six weeks Empiric therapy for febrile neutropenic patients: Injection: 400 mg every eight hours for five to seven days in combination with piperacillin Urethritis/cervicitis (gonococcal): Suspension, tablet immediate-release: 250 mg in a single dose Infectious diarrhea: Suspension, tablet immediate-release:	Inhalational anthrax (post-exposure) in patients one to 17 years of age: Injection: 10 mg/kg every 12 hours for 60 days Suspension, tablet immediate-release: 15 mg/kg every 12 hours for 60 days Plague in patients from birth to 17 years of age: Injection: 10 mg/kg every eight to 12 hours for 10 to 21 days Suspension, tablet immediate-release: 15 mg/kg every eight to 12 hours for 10 to 21 days Urinary tract infections or pyelonephritis in patients one to 17 years of age: Injection: 6 to 10 mg/kg every eight hours for 10	Injection: 200 mg/20 mL 400 mg/40 mL Suspension: 250 mg/5 mL 500 mg/5 mL Tablet (extended-release): 500 mg 1,000 mg Tablet (immediate-release): 100 mg 250 mg 500 mg 750 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	500 mg every 12 hours for five to seven days Inhalational anthrax: Injection: 400 mg every 12 hours for 60 days Suspension, tablet immediate-release: 500 mg every 12 hours for 60 days Intra-abdominal infections: Injection: 400 mg every 12 hours for seven to 14 days Suspension, tablet immediate-release: 500 mg every 12 hours for seven to 14 days Plague: Injection: 400 mg every eight to 12 hours for 14 days Suspension, tablet immediate-release: 500 to 750 mg every 12 hours for 14 days Pneumonia (nosocomial): Injection: 400 mg every eight hours for 10 to 14 days Prostatitis: Injection: 400 mg every 12 hours for 28 days Suspension, tablet immediate-release: 500 mg every 12 hours for 28 days Pyelonephritis: Suspension, tablet immediate-release: 500 mg every 12 hours for seven days Tablet extended-release: 1,000 mg every 24 hours for seven days Respiratory tract infections (lower) (mild to moderate): Injection: 400 mg every 12 hours for seven to 14 days Suspension, tablet immediate-release: 500 mg every 12 hours for seven to 14 days Respiratory tract infections (lower) (sever to complicated): Injection: 400 mg every eight hours for seven to 14 days	to 21 days Suspension, tablet immediate-release: 10 to 20 mg/kg every 12 hours for 10 to 21 days	

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Suspension, tablet immediate-release: 750 mg every 12 hours for seven to 14 days Sinusitis: Injection: 400 mg every 12 hours for 10 days Suspension, tablet immediate-release: 500 mg every 12 hours for 10 days Skin and skin-structure infections (mild to moderate): Injection: 400 mg every 12 hours for seven to 14 days Suspension, tablet immediate-release: 500 mg every 12 hours for seven to 14 days Skin and skin-structure infections (severe/complicated): Injection: 400 mg every eight hours for seven to 14 days Suspension, tablet immediate-release: 750 mg every 12 hours for seven to 14 days Typhoid fever: Suspension, tablet immediate-release: 500 mg every 12 hours for 10 days Urinary tract infections (acute uncomplicated): Tablet extended-release: 500 mg every 24 hours for three days Suspension, tablet immediate-release: 250 mg every 12 hours for three days Urinary tract infections (mild/moderate): Injection: 200 mg every 12 hours for seven to 14 days Suspension, tablet immediate-release: 250 mg every 12 hours for seven to 14 days Urinary tract infections (severe/complicated): Injection: 400 mg every 12 hours for seven to 14 days Tablet extended-release: 1,000 mg every		

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	24 hours for seven to 14 days Suspension, tablet immediate-release: 500 mg every 12 hours for seven to 14 days		
Levofloxacin	Acute exacerbations of chronic bronchitis: Injection, solution, tablet: 500 mg once daily for seven days Inhalational anthrax (post-exposure): Injection, solution, tablet: 500 mg once daily for 60 days Plague: Injection, solution, tablet: 500 mg once daily for 10 to 14 days Pneumonia (community-acquired): Injection, solution, tablet: 500 mg once daily for seven to 14 days or 750 mg once daily for five days Pneumonia (nosocomial): Injection, solution, tablet: 750 mg once daily for seven to 14 days Prostatitis: Injection, solution, tablet: 500 mg once daily for 28 days Pyelonephritis: Injection, solution, tablet: 750 mg once daily for five days or 250 mg once daily for 10 days Sinusitis: Injection, solution, tablet: 750 mg once daily for five days or 500 mg once daily for 10 to 14 days Skin and skin-structure infections (complicated): Injection, solution, tablet: 750 mg once daily for seven to 14 days Skin and skin-structure infections (uncomplicated): Injection, solution, tablet: 500 mg once daily for seven to 10 days Urinary tract infections (complicated): Injection, solution, tablet: 750 mg once daily for five days or 250 mg once daily for 10 days	Inhalational anthrax (post-exposure) for patients ≥6 months of age: Injection, solution, tablet: >50 kg, 500 mg once daily for 60 days; <50 kg, 8 mg/kg every 12 hours for 60 days Plague for patients ≥6 months of age: Injection, solution, tablet: >50 kg, 500 mg once daily for 10 to 14 days; <50 kg, 8 mg/kg every 12 hours for 10 to 14 days	Injection: 25 mg/mL Solution: 250 mg/10 mL 500 mg/20 mL Tablet: 250 mg 500 mg 750 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Urinary tract infections (uncomplicated): Injection, solution, tablet: 250 mg once daily for three days		
Moxifloxacin	Acute exacerbations of chronic bronchitis: tablet: 400 mg once daily for five days Intra-abdominal infections: Injection, tablet: 400 mg once daily for five to 14 days Plague: Tablet: 400 mg once daily for 10 to 14 days Pneumonia (community-acquired): Injection, tablet: 400 mg once daily for seven to 14 days Sinusitis: Injection, tablet: 400 mg once daily for 10 days Skin and skin-structure infections (complicated): Injection, tablet: 400 mg once daily for seven to 21 days Skin and skin-structure infections (complicated): Injection, tablet: 400 mg once daily for seven days	Safety and efficacy in children have not been established.	Tablet: 400 mg
Ofloxacin	Acute exacerbations of chronic bronchitis: Tablet: 400 mg every 12 hours for 10 days Cystitis: Tablet: 200 mg every 12 hours for three to seven days Urethritis/cervicitis (gonococcal): Tablet: 400 mg in a single dose for one day Urethritis/cervicitis (non-gonococcal): Tablet: 300 mg every 12 hours for seven days Pelvic inflammatory disease: Tablet: 400 mg every 12 hours for 10 to 14 days Pneumonia (community-acquired): Tablet: 400 mg every 12 hours for 10 days	Safety and efficacy in children have not been established.	Tablet: 400 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Prostatitis: Tablet: 300 mg every 12 hours for six weeks Skin and skin-structure infections: Tablet: 400 mg every 12 hours for 10 days Urinary tract infections: Tablet: 200 mg every 12 hours for 10 days		

VIII. Effectiveness

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

Table 10. Comparative Clinical Trials with the Quinolones

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Dermatological Infections				
Nicodemo et al.[39] (1998) Ciprofloxacin 500 mg BID for 10 days vs levofloxacin 500 mg QD for seven days	DB, MC, RCT Adult patients with uncomplicated skin and skin structure infections	N=272 7 to 10 days	Primary: Clinical success rate (defined as cure or improvement in signs and symptoms) Secondary: Microbiological eradication rate	Primary: Clinical success was achieved in 96.1% of those on levofloxacin and 93.5% on ciprofloxacin (95% CI, –8.4 to 3.3). Secondary: Eradication was achieved in 93.0% of those on levofloxacin and 89.7% on ciprofloxacin (95% CI, –11.7 to 5.1). An adverse event related to the study medication was reported in 8.9% of the patients on levofloxacin and 8.2% of patients taking ciprofloxacin. Discontinuation due to an adverse event occurred in five patients taking levofloxacin and two patients taking ciprofloxacin.
Nichols et al.[40] (1997) Ciprofloxacin 500 mg BID for 10 days vs levofloxacin 500 mg QD for seven days	MC, OL, RCT Adult patients with uncomplicated skin and skin structure infections	N=469 7 to 10 days	Primary: Clinical success rate (defined as cured or improvement in signs and symptoms) Secondary: Microbiological eradication rate by patient and by pathogen	Primary: Clinical success was achieved in 98% of those on levofloxacin and 94% on ciprofloxacin (95% CI, –7.7 to 0.7). Secondary: Eradication was achieved in 98% of those on levofloxacin and 89% on ciprofloxacin (95% CI, –14.5 to –2.7). The eradication rate of the most prevalent pathogen, Staphylococcus aureus, was 100% with levofloxacin and 87% with ciprofloxacin (95% CI, –20.2 to –5.1). The eradication rate of the second most prevalent pathogen, Streptococcus pyogenes, was 100% with levofloxacin and 90% with ciprofloxacin (95% CI, –26.7 to 6.7). An adverse event related to the study medication was reported in 6% of the patients on levofloxacin and 5% of patients taking ciprofloxacin.
Gentry et al.[41]	PRO, RCT	N=51	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(1989) Ceftazidime 2 g IV every 8 eight hours vs ciprofloxacin 200 mg IV every 12 hours, then ciprofloxacin 750 mg by mouth every 12 hours	Patients with serious infections of the skin and skin structures caused by gram-negative organisms	19 to 25 days	Cure rate Secondary: Adverse events	Cure rate was reported as 75 and 58% in patients treated with ciprofloxacin and ceftazidime, respectively (P<0.05). Bacteriologic cure was reported as 78 and 72% in patients treated with ciprofloxacin and ceftazidime, respectively. Superinfection was reported as 28 and 11% in patients treated with ciprofloxacin and ceftazidime, respectively (0.01<P<0.05). Secondary: Adverse events were reported in 6 and 5% of patients treated with ciprofloxacin and ceftazidime, respectively.
Gentry et al.[42] (1989) Cefotaxime 2 g IV TID and one placebo tablet by mouth BID vs ciprofloxacin 750 mg by mouth BID and placebo IV over 30 minutes TID	DB, MC, PRO, RCT Patients with culture-confirmed skin or skin structure infections requiring hospitalization	N=461 4 to 34 days	Primary: Clinical response, bacteriologic response, overall response rate Secondary: Adverse events	Primary: For patients treated with cefotaxime, clinical response was reported as 74, 20, and 6% characterized as resolution, improvement, and failure, respectively. For patients treated with ciprofloxacin, clinical response was reported as 81, 16, and 3% characterized as resolution, improvement, and failure, respectively. For all comparisons; P=NS. Bacteriologic eradication was reported as 87 and 84% for patients treated with ciprofloxacin and cefotaxime, respectively (P=0.0123). Overall efficacy rate was reported as 76 and 75% for patients treated with ciprofloxacin and cefotaxime, respectively. Overall failure rate was higher in patients treated with cefotaxime compared to ciprofloxacin (8 vs 2%, respectively; P=0.0081). Secondary: There was no statistically significant difference in adverse events for treatment groups. However, there was a higher incidence of metabolic and nutritional systems-related events in patients treated with ciprofloxacin (0.01<P<0.05).
Vick-Fragoso et al.[43] (2009)	MC, OL, RCT Patients ≥18 years of age with	N=804 21 days	Primary: Clinical response at test of cure for the per protocol	Primary: Clinical cure (success) rates at test of cure for the per protocol population were not significantly different between the treatment groups: 80.6% for moxifloxacin compared to 84.5% for amoxicillin-clavulanate. These

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Moxifloxacin 400 mg IV QD for at least 3 days followed by 400 mg orally for 7 to 21 days vs amoxicillin-clavulanate 1,000-200 mg IV TID for at least 3 days followed by 500 mg-125 mg orally TID for 7 to 21 days The decision to switch from IV to oral therapy was based on clinical response.	complicated skin or skin structure infections		population Secondary: Clinical response at test of cure for the intent to treat population and clinical response at test of cure by indication, bacteriological success at test of cure for the per protocol population	efficacy findings were supported by results for the intent to treat population: 72.7% for moxifloxacin compared to 74.8% for amoxicillin-clavulanate. Moxifloxacin was not inferior to amoxicillin-clavulanate for complicated skin or skin structure infections. Clinical success rates by indication were not significantly different among the treatment groups. The highest clinical success rates were for complicated erysipelas, abscess and surgical wound infection, and the lowest clinical success rates were for necrotizing fasciitis and diabetic foot infection. Clinical response rates in patients with a diabetic foot infection were similar between the two groups in patients with the most severe infections. Among the per protocol population, 19.4% of moxifloxacin- treated and 15.5% of amoxicillin-clavulanate-treated patients were clinical failures at test of cure. There were no significant differences in bacteriological success rates at test of cure in the per protocol population between moxifloxacin-treated patients (76.0%) and amoxicillin-clavulanate-treated patients (81.4%; 95% CI, -12.96 to 4.41; P=0.59).
Gastrointestinal Infections				
Kaushik et al.[44] (2010) Ciprofloxacin 20 mg/kg as a single dose vs azithromycin 20 mg/kg as a single dose	OL, RCT Children 2 to 12 years of age with watery diarrhea for ≤24 hours and severe dehydration, who tested positive for Vibrio cholerae by hanging drop examination or culture of stool	N=180 3 days	Primary: Clinical success (resolution of diarrhea within 24 hours) and bacteriological success (cessation of excretion of Vibrio cholerae by day three) Secondary: Duration of	Primary: Clinical success was 94.5% with azithromycin compared to 70.7% with ciprofloxacin (RR, 1.34; 95% CI, 1.16 to 1.54; P<0.001). Bacteriological success was 100% with azithromycin compared to 95.5% with ciprofloxacin (RR, 1.05; 95% CI, 1.00 to 1.10; P=0.06). Secondary: Patients treated with azithromycin had a shorter duration of diarrhea compared to patients receiving ciprofloxacin (54.6 vs 71.5 hours, respectively; P<0.001). Patients receiving azithromycin had a lesser duration of excretion of

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			diarrhea, duration of excretion of Vibrio cholerae in stool, fluid requirement, and proportion of children with clinical or bacteriological relapse	Vibrio cholerae than patients receiving ciprofloxacin (34.6 vs 52.1 hours; P<0.001). The amount of IV fluid was significantly less among patients who received azithromycin compared to those who received ciprofloxacin (4,704.7 vs 3,491.1 mL; P<0.001). The proportion of children with bacteriological relapse was comparable in both groups (6.7% with azithromycin vs 2.2% with ciprofloxacin; P=0.16). None of the children in either group had a clinical relapse.
Genitourinary Infections				
Sandberg et al.[45] (2012) Ciprofloxacin 500 mg BID for seven days, followed by placebo for seven days vs ciprofloxacin 500 mg BID for 14 days	DB, MC, OL, PC, RCT Adult, non-pregnant female patients diagnosed with acute pyelonephritis	N=248 14 days	Primary: Clinical and bacteriological efficacy Secondary: Long-term cumulative efficacy	Primary: The cure rate for the ciprofloxacin seven-day treatment group was 97% (N=71/73) compared to 96% (N=80/83) for the 14-day treatment group. This showed statistical non-inferiority of the seven-day treatment group to the 14-day treatment group (-0.9; 90% CI, -6.5 to 4.8; P=0.004). Secondary: The cumulative efficacy rate for the ciprofloxacin seven-day treatment group was 93% (N=68/73) compared to 93% (N=78/84) for the 14-day treatment group. The seven-day treatment was shown to be non-inferior to the 14-day treatment (-0.3%; 90% CI, -7.4 to 7.2; P=0.015).
Fourcroy et al.[46] (2005) Ciprofloxacin immediate-release 250 mg BID for three days vs ciprofloxacin	DB, MC, RCT Adult female patients with uncomplicated urinary tract infections	N=1,037 3 days	Primary: Bacteriological eradication rates defined as $<10^4$ CFU/mL at four to 11 days Secondary: Bacteriological eradication rates at 28 to 42 days and	Primary: Eradication at four to 11days was observed in 93.4% of patients on the extended-release formulation compared to 89.6% in the immediate-release formulation (95% CI, –0.99 to 8.59). Secondary: Eradication at 28 to 42 days was observed in 82.4% of patients on the extended-release formulation compared to 83.2% in the immediate-release formulation (95% CI, –8.00 to 6.40). Clinical cure at four to 11 days was observed in 85.7% of patients on the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
extended-release 500 mg QD for three days			clinical cure rates at four to 11days and at 25 to 50 days after therapy	extended-release formulation compared to 86.1% in the immediate-release formulation (95% CI, –6.37 to 5.57). Clinical cure at 28 to 42 days was observed in 75.7% of patients on the extended-release formulation compared to 78.8% in the immediate-release formulation (95% CI, –10.60 to 4.40). Adverse events were reported in 12.7% of patients on the extended-release formulation and 14.7% on the immediate-release formulation (P=not specified). Seven patients on the extended-release formulation and three patients on the immediate-release formulation withdrew due to an adverse event.
Talan et al.[47] (2004) Ciprofloxacin immediate-release 500 mg BID for 7 to 10 days vs ciprofloxacin extended-release 1,000 mg QD for 7 to 10 days	DB, MC, RCT Adult patients with complicated urinary tract infections or acute uncomplicated pyelonephritis	N=1,035 7 to 14 days	Primary: Bacteriological eradication rates (defined as $<10^4$ CFU/mL) and clinical cure rates at five to 11 days and at 28 to 42 days after therapy Secondary: Adverse events	Primary: Eradication at five to 11 days was observed in 89% of patients on the extended-release formulation compared to 85% in the immediate-release formulation (95% CI, –2.4 to 10.3). Eradication at 28 to 42 days was observed in 69.3% of patients on the extended-release formulation compared to 61.2% in the immediate-release formulation (95% CI, –0.8 to 18.6). Clinical cure at five to 11 days was observed in 97% of patients on the extended-release formulation compared to 94% in the immediate-release formulation (95% CI, –1.2 to 6.9). Clinical cure at 28 to 42 days was observed in 82.9% of patients on the extended-release formulation compared to 80.7% in the immediate-release formulation (95% CI, –5.4 to 10.4). Secondary: Drug-related adverse events were reported in 13.2% of patients on the extended-release formulation and 13.5% on the immediate-release formulation. The most commonly reported adverse reactions were nausea, diarrhea, vaginal moniliasis, headache and dizziness. Sixteen patients on the extended-release formulation and 12 on the immediate-release formulation withdrew due to an adverse event.
Henry et al.[48]	DB, MC, RCT	N=891	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2002) Ciprofloxacin immediate-release 250 mg BID for three days vs ciprofloxacin extended-release 500 mg QD for three days	Adult female patients with uncomplicated urinary tract infections	3 days	Bacteriological eradication rates (defined as $<10^4$ CFU/mL) and clinical cure rates at four to 11 days and at 25 to 50 days after therapy Secondary: Adverse events	Eradication at four to 11 days was observed in 94.5% of patients on the extended-release formulation compared to 93.7% in the immediate-release formulation (95% CI, –3.5 to 5.1). Eradication at 28 to 42 days was observed in 85.8% of patients on the extended-release formulation compared to 81.3% in the immediate-release formulation (95% CI, –1.9 to 12.2). Clinical cure at four to 11 days was observed in 95.5% of patients on the extended-release formulation compared to 92.7% in the immediate-release formulation (95% CI, –1.6 to 7). Clinical cure at 28 to 42 days was observed in 89.0% of patients on the extended-release formulation compared to 86.6% in the immediate-release formulation (95% CI, –3.1 to 8.8). Secondary: Drug-related adverse events were reported in 10.4% of patients on the extended-release formulation and 9.2% on the immediate-release formulation.
Richard et al.[49] (1998) Ciprofloxacin 500 mg BID vs levofloxacin 250 mg QD vs lomefloxacin 400 mg QD	MA Adult patients with acute uncomplicated pyelonephritis	N=186 (2 trials) 7 to 14 days	Primary: Eradication rates, defined as $<10^4$ CFU/mL at five to nine days Secondary: Clinical cure rate, defined as complete resolution of symptoms	Primary: Eradication was observed in 95% of the patients on levofloxacin, 94% in patients on ciprofloxacin, and 95% in patients on lomefloxacin. Secondary: Clinical cure was observed in 92% of the patients on levofloxacin, 88% in patients on ciprofloxacin, and 80% in patients on lomefloxacin. An adverse event related to the study medication was reported in 2% of the patients on levofloxacin, 8% of patients taking ciprofloxacin, and 5% of patients taking lomefloxacin. One patient taking lomefloxacin withdrew due to an adverse event.
Bundrick et al.[50] (2003)	DB, MC, RCT	N=377	Primary: Clinical success	Primary: Clinical success was observed in 75.0% of patients taking levofloxacin

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ciprofloxacin 500 mg BID vs levofloxacin 500 mg QD	Adult male patients with a history of chronic prostatitis	28 days	and microbiological eradication rates Secondary: Adverse events	and 72.8% of those taking ciprofloxacin (95% CI, –13.27 to 8.87). Eradication was observed in 75.0% of patients taking levofloxacin and 76.8% of those taking ciprofloxacin (95% CI, –8.98 to 12.58). Secondary: Drug-related adverse effects were reported in 44.2% of patients taking levofloxacin and 37.2% taking ciprofloxacin. The most frequently reported adverse reaction was gastrointestinal in nature.
Schaeffer et al.[51] (1992) Ciprofloxacin 500 mg BID vs norfloxacin 400 mg BID	OL, PRO, RCT Adult patients with complicated urinary tract infection	N=72 10 to 21 days	Primary: Clinical cure rates, defined as complete resolution of symptoms and eradication of the infecting organism(s) after two to four days and five to nine days of therapy Secondary: Not reported	Primary: Clinical cure rates were 72% for those on norfloxacin and 79% on ciprofloxacin (P=0.56). Secondary: Not reported
Auquer et al.[52] (2002) Ciprofloxacin 500 mg once vs norfloxacin 400 mg BID for three days	DB, MC, RCT Adult female patients with uncomplicated urinary tract infection	N=226 3 days	Primary: Clinical cure and bacterial eradication (defined as $<10^5$ CFU/mL of a gram-negative bacteria or $<10^4$ CFU/mL of a gram-positive bacteria) at day seven	Primary: After seven days of treatment, clinical cure were observed in 91.2% of patients on ciprofloxacin and 93.8% in patients on norfloxacin. After seven days of treatment, eradication was observed in 91.2% of patients on ciprofloxacin and 92.0% in patients on norfloxacin. Statistical analysis yielded significant results in favor of the hypothesis of equivalence between the two treatment groups (P=0.0062). Drug-related adverse effects were reported in 17 patients taking ciprofloxacin and 13 taking norfloxacin. The most frequently reported adverse reaction was gastrointestinal in nature.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: Not reported	Secondary: Not reported
Perea et al.[53] (1989) Ciprofloxacin 500 mg BID vs ofloxacin 200 mg BID	DB, RCT Adult patients with nongonococcal urethritis	N=95 7 days	Primary: Clinical cure rates, defined as lack of symptoms and fewer than five polymorphonuclear leukocytes in a Gram-stained urethral smear Secondary: Not reported	Primary: Clinical cure rates two weeks after treatment was observed in 75% of patients on ciprofloxacin and 74% of those on ofloxacin. Secondary: Not reported
Raz et al.[54] (2000) Ciprofloxacin 250 mg BID vs ofloxacin 200 mg BID	DB, MC, RCT Adult female patients with complicated lower urinary tract infection	N=465 7 days	Primary: Bacteriological success, defined as sterile urine culture at five to nine days Secondary: Bacteriological success at 28 to 42 days and clinical resolution after five to nine days and at 28 to 42 days	Primary: Bacteriological success at five to nine days was observed in 87.2% of the patients taking ofloxacin and 90.1% of patients taking ciprofloxacin (95% CI, –4.4 to 10.0). Secondary: Bacteriological success at 28 to 42 days was observed in 76.1% of the patients taking ofloxacin and 77.1 % of patients taking ciprofloxacin (95% CI, –9.2 to 10.5). Clinical cure at five to nine days was observed in 97.2% of the patients taking ofloxacin and 97.2% of patients taking ciprofloxacin (95% CI, –3.8 to 3.9). Clinical cure at 28 to 42 days was observed in 87.3% of the patients taking ofloxacin and 87.4% of patients taking ciprofloxacin (95% CI, –8.1 to 7.4). Drug-related adverse effects were reported in 10.9% of the women taking ciprofloxacin and 13.4% taking ofloxacin. The most frequently reported adverse reaction was gastrointestinal in nature. Thirteen women on ciprofloxacin and 16 on ofloxacin withdrew from the study due to adverse

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				effects.
McCarty et al.[55] (1999) SMX-TMP 800-160 mg BID for three days vs ciprofloxacin 100 mg BID for three days vs ofloxacin 200 mg BID for three days	MC, RCT Women ≥18 years of age with primary urinary tract infection, confirmed by a positive urine culture obtained within 48 hours of study onset, presenting with signs and symptoms of dysuria, pyuria, and urinary frequency for <10 days duration	N=688 Up to 6 weeks	Primary: Pathogen eradication rate, clinical response rate (resolution of symptoms), relapse rate, premature discontinuation, adverse events Secondary: Not reported	Primary: End-of-study evaluation revealed a lack of statistically significant difference in the pre-treatment pathogen eradication rate between the study groups. Pathogen eradication occurred in 94% of ciprofloxacin, 93% of SMX-TMP, and 97% of ofloxacin-treated patients. At the four to six week follow-up evaluation, recurrence rates were 11% in the ciprofloxacin, 16% in the SMX-TMP, and 13% in the ofloxacin-treated group. Clinical success at the end of therapy was 31% in the ciprofloxacin, 41% in the SMX-TMP, and 39% in the ofloxacin-treated group. The frequency of adverse effects was 93% in the ciprofloxacin, 95% in the SMX-TMP, and 96% in the ofloxacin-treated group (P=0.03). Premature discontinuation of the study drug due to side effects was more common in the SMX-TMP group, compared to the ciprofloxacin and ofloxacin groups (P=0.02). Secondary: Not reported
Peterson et al.[56] (2008) Levofloxacin 750 mg IV/by mouth QD for five days vs ciprofloxacin 400 mg IV or 500 mg orally BID for 10 days	DB, MC, RCT Patients with complicated urinary tract infection	N=1,109 45 days	Primary: Microbiological eradication and clinical cure Secondary: Not reported	Primary: At end of therapy, eradication rates in the intent to treat population were 79.8% for levofloxacin and 77.5% for ciprofloxacin-treated patients (95% CI, -8.8 to 4.1). In the microbiological eradication population, eradication rates were 88.3% for levofloxacin and 86.7% for ciprofloxacin-treated patients (95% CI, -7.4 to 4.2). Clinical success at the end-of-therapy was 91.3 and 87.1% for levofloxacin-treated and ciprofloxacin-treated patients, respectively (95% CI, -9.6 to 1.2). At the post-therapy assessment, clinical response was 86.4% for

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				levofloxacin-treated and 88.4% for ciprofloxacin-treated patients (95% CI, -3.9 to 7.8). Clinical success rates for complicated urinary tract infections (78.9 vs 79.9%) were similar for levofloxacin and ciprofloxacin, respectively.
Klausner et al.[57] (2007) Levofloxacin 750 mg IV/by mouth QD for 5 days vs ciprofloxacin 400 mg IV and/or 500 mg orally BID for 10 days	DB, RCT Adult male and female patients with clinical signs and symptoms of complicated urinary tract infections	N=311 45 days	Primary: Microbiologic eradication post-therapy (study days 15 to 22) Secondary: Clinical response, safety, tolerability	Primary: In the intent to treat population, 83% of levofloxacin-treated and 79.6% of ciprofloxacin-treated patients achieved microbiological eradication (95% CI, -14.4 to 7.6). In the microbiologic eradication population 92.5% of levofloxacin-treated vs 93.4% of ciprofloxacin-treated patients achieved microbiologic eradication (95% CI, -7.1 to 8.9). Secondary: Clinical success was achieved in 86.2 vs 80.6% (intent to treat) and in 92.5 vs 89.5% (microbiologic eradication) of levofloxacin-treated and ciprofloxacin-treated patients, respectively. Escherichia coli was the most commonly uropathogen that was isolate. Few (2.1%) of the pathogens were fluoroquinolone-resistant. Adverse events were similar to those seen previously with both agents.
Wagenlehner et al.[58] (2015) ASPECT-cUTI Ceftolozane sulfate/ tazobactam sodium 1.5 gm IV every eight hours for seven days (doses were adjusted on the basis of creatinine clearance) vs	DB, DD, MN, NI, RCT Adults ≥ 18 years of age with pyuria (WBC count > 0.01x109/L in unspun urine or 0.01x109/L or more WBCs per high-power field in spun urine) with a diagnosis of pyelonephritis or	N=1,083 (MITT: N=1,068 mMITT: N=800) 7 days	Primary: Composite cure (i.e., achieving clinical cure and microbiological eradication of all baseline uropathogens) at the test-of-cure visit Secondary: Clinical cure (defined as	Primary: Ceftolozane/tazobactam was noninferior to levofloxacin for composite cure in the mMITT and per-protocol populations and achieved a significantly greater percentage of patients compared to levofloxacin for composite cure in both populations. For composite cure in the mMITT group, a total of 76.9% of patients in the ceftolozane sulfate/tazobactam group vs 68.4% in the levofloxacin group achieved the outcome, corresponding to an 8.5% between-group difference (95% CI, 2.3 to 14.6; P value not reported). Among the per-protocol population, the composite cure was achieved by 83.3% in the ceftolozane sulfate/tazobactam group and 75.4% in the levofloxacin group, corresponding to an 8.0% between-group difference

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
levofloxacin 750 mg IV QD for seven days	complicated lower UTI infections, admitted to the hospital for IV antibiotic therapy, and a pretreatment baseline urine culture specimen obtained within 36 hours before the first dose of study drug Two identical studies conducted and results pooled together.		complete resolution, substantial improvement [i.e., reduction in severity of all baseline signs and symptoms and no worsening], or return to preinfection signs and symptoms of complicated lower UTI infections or pyelonephritis without the need for additional antibiotic therapy) and microbiological eradication (defined as a test-of-cure urine culture with $<10^4$ CFU/mL of the baseline uropathogen) at the TOC visit five to nine days after the last dose of study drug was administered, safety outcomes	(95% CI, 2.0 to 14.0; P value not reported). Secondary: Ceftolozane/tazobactam achieved higher overall microbiological eradication compared to levofloxacin for in the mMITT and per-protocol populations. Ceftolozane sulfate/tazobactam was also achieved greater microbiological eradication than levofloxacin for in patients in the per-protocol population who had *Enterobacteriaceae* species infections at baseline and showed higher per-pathogen microbiological eradication in patients infected with *P aeruginosa.* Clinical cure in the mMITT population was achieved by 92.0% of those treated with ceftolozane sulfate/tazobactam and 88.6% treated with levofloxacin, corresponding to a between-group difference of 3.4% (95% CI, -0.7 to 7.6; P value not reported). Among the per-protocol population, clinical cure was achieved by 95.9% of those treated with ceftolozane sulfate/tazobactam and 93.2% treated with levofloxacin, representing a between-group difference of 2.7% (95% CI, -0.8 to 6.2; P value not reported). Microbiologic eradication in the mMITT population was achieved by 80.4% of those treated with ceftolozane sulfate/tazobactam and 72.1% treated with levofloxacin, representing a between-group difference of 8.3% (95% CI, 2.4 to 14.1; P value not reported). Among the per-protocol population, microbiological eradication was achieved by 86.2 vs 77.6% of those treated with ceftolozane sulfate/tazobactam and levofloxacin, respectively, corresponding to a between-group difference of 8.6% (95% CI, 2.9 to 14.3; P value not reported). The incidence of adverse events, including serious adverse events, was similar in the two treatment groups with 34.7% reported in the ceftolozane sulfate/tazobactam and 34.4% reported in the levofloxacin group. Most events were mild to moderate in severity, with the most commonly reported events being headache and gastrointestinal symptoms.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Redman et al.[59] (2010) Study 1 Doripenem 500 mg IV every eight hours vs levofloxacin 250 mg IV QD Study 2 Doripenem 500 mg IV every eight hours After a minimum of three days of IV therapy, investigators could switch patients from IV therapy to oral levofloxacin 250 mg daily.	DB, RCT Patients ≥18 years of age with complicated urinary tract infections and pyelonephritis	N=1,179 42 days after the last dose	Primary: Microbiological response at the test-of-cure visit (five to 11 days after the last dose); clinical cure rates Secondary: Not reported	Primary: Microbiological eradication rates in the microbiologically evaluable patient population at the test-of-cure visit were 82.1% with doripenem and 83.4% with levofloxacin in study 1, and 83.6% with doripenem in study 2. The combined analysis demonstrated that doripenem was non-inferior to levofloxacin. Microbiological eradication rates in the microbiologically evaluable-modified intent-to-treat population at the test-of-cure visit were 79.2% with doripenem and 78.2% with levofloxacin in study 1, and 82.5% with doripenem in study 2.The combined analysis in the evaluable-modified intent-to-treat population demonstrated that doripenem was non-inferior to levofloxacin. The pooled microbiological eradication rates in the microbiologically evaluable populations at the test-of-cure and end-of-treatment visits from both studies were 99.8% with doripenem and 88.4% with levofloxacin (95% CI, 7.2 to 15.6). These results suggest that the eradication preceded a switch from IV to oral levofloxacin therapy. Clinical cure rates for the combined clinically evaluable population at the test-of-cure visit were 95.1% with doripenem and 90.2% with levofloxacin in study 1, and 93.0% with doripenem in study 2. The pooled clinical cure rates in the clinically evaluable populations at the test-of-cure and end-of-treatment visits showed that clinical improvement preceded a switch to oral levofloxacin; 98.9% with doripenem and 93.2% with levofloxacin in study 1, and 99.6% with doripenem in study 2. Secondary: Not reported
Naber et al.[60] (2009) Doripenem 500 mg IV every eight hours	DB, MC, RCT Patients ≥18 years of age with complicated urinary tract	N=753 Up to 14 days	Primary: Microbiological cure rate in the microbiologically evaluable and microbiologically	Primary: The microbiologically evaluable population achieved microbiological cure rates of 82.1 and 83.4% with doripenem and levofloxacin, respectively. Patients in the microbiologically evaluable-modified intent-to-treat population achieved microbiological cure rates of 79.2 and 78.2%, respectively. Doripenem was not therapeutically inferior to levofloxacin

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs levofloxacin 250 mg IV QD Patients in both treatment arms were eligible to switch to oral levofloxacin after three days of IV therapy to complete a 10-day treatment course if they demonstrated significant clinical and microbiological improvements.	infections or pyelonephritis who required initial treatment with a parenterally administered antibacterial agent		evaluable-modified intent-to-treat population Secondary: Clinical cure rate at the test-of-cure visit for the clinically evaluable population and the microbiological cure rate for the microbiologically evaluable patients infected with Escherichia coli	for the treatment of complicated urinary tract infections or pyelonephritis. In the microbiologically evaluable population, the microbiological cure rates at the end-of-treatment were 100% for the doripenem-treated patients and 88% for the levofloxacin-treated patients (P<0.001). The non-inferior response demonstrated for the doripenem-treated patients at the test-of-cure visit could be attributed to the IV portion of the therapeutic regimen, independently of a switch to oral levofloxacin. Secondary: In the clinically evaluable population, the clinical cure rates at end-of-treatment were 98.3 and 93.2% in the doripenem and levofloxacin arms, respectively. At the test-of-cure visit, the clinical cure rates were 95.1 and 90.2%, respectively (95% CI, 0.2 to 9.6). Clinical cure rates at the late follow-up visit of 90.8% for the doripenem-treated patients and 95.2% for the levofloxacin-treated patients who were clinically evaluable were sustained. For the patients who received the IV study drug only, the clinical cure rates at the test-of-cure visit were 78.1% with doripenem and 52.3% with levofloxacin. The microbiological cure rates for Escherichia coli infections of microbiologically evaluable patients at the test-of-cure visit were 84.4% for the doripenem arm and 87.2% for the levofloxacin arm (P=0.83).
Heystek et al.[61] (2009) Moxifloxacin 400 mg QD for 14 days vs doxycycline 100 mg BID for 14 days, metronidazole 400	DB, MC, RCT Women with uncomplicated pelvic inflammatory disease	N=434 14 days	Primary: Clinical success two to 14 days posttreatment (clinical cure and improvement combined) Secondary: Clinical cure rate at two to 14 days	Primary: Clinical success rates two to 14 days following treatment were 96.6% with moxifloxacin and 98% with the comparator regimen in the per protocol population (95% CI -4.5 to 1.6) Clinical success rates were 77.0% with moxifloxacin and 76.7% with the comparator regimen in the intent to treat population (95% CI, -5.8 to 6.9). Moxifloxacin was found to be non-inferior to the comparator arm. Secondary: At two to 14 days posttreatment, clinical cure rates were 81.5% with moxifloxacin and 83.2% with the comparator regimen in the per protocol

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg TID for 14 days, ciprofloxacin 500 mg as a single dose			posttreatment, clinical success rate at 21 to 35 days posttreatment (clinical failures at day two to 14 posttreatment carried forward for follow-up), bacteriological response	population (95% CI -9.2 to 5.1). Clinical cure rates were 64.7% with moxifloxacin and 65.0% with the comparator regimen in the intent to treat population (95% CI, -7.5 to 7.0). Clinical success rates 21 to 35 days following treatment were 93.8% with moxifloxacin and 91.3% with the comparator regimen in the per protocol population (95% CI -3.8 to 7.4). Clinical success rates were 60.1% with moxifloxacin and 56.8% with the comparator regimen in the intent to treat (95% CI, -5.8 to 9.1).
Judlin et al.[62] (2010) Moxifloxacin 400 mg QD for 14 days vs levofloxacin 500 mg QD and metronidazole 500 mg BID for 14 days All patients positive for *Neisseria gonorrhoeae* also received ceftriaxone 250 mg IM as a single dose.	DB, MC, RCT Women with uncomplicated pelvic inflammatory disease	N=460 6 weeks	Primary: Clinical cure at test of cure visit (seven to 14 days after last dose of study drug) in the per protocol population Secondary: Clinical response during therapy and at the four week follow-up, microbiological response at test of cure, safety	Primary: The clinical cure rate at the test of cure visit was 78.4% with moxifloxacin and 81.6% with levofloxacin-metronidazole (P=0.460). Moxifloxacin was found to be non-inferior to levofloxacin-metronidazole. Secondary: In the intent to treat analysis 56.6% of patients receiving moxifloxacin and 56.9% of patients receiving levofloxacin-metronidazole experienced adverse events. A total of 4% of patients receiving moxifloxacin and 5.2% of patients receiving levofloxacin-metronidazole experienced at least one drug-related adverse event that resulted in premature termination of the study drug.
Ross et al.[63] (2006) Moxifloxacin 400 mg QD for 14 days vs	DB, MC, RCT Women with uncomplicated pelvic inflammatory disease	N=741 14 days	Primary: Clinical resolution rates at five to 24 days post-therapy Secondary: Clinical resolution	Primary: Clinical resolution was observed in 90.2% of patients on moxifloxacin and 90.7% of patients on ofloxacin and metronidazole (95% CI, –5.7 to 4.0). Secondary: Clinical resolution at 28 to 42 days was observed in 85.8% of patients on moxifloxacin and 87.9% of patients on ofloxacin and metronidazole (95%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
ofloxacin 400 mg BID in combination with metronidazole 500 mg BID			at 28 to 42 days post-therapy and bacteriological response at five to 24 days	CI, –8.0 to 3.1). Bacteriological response at 5 to 24 days was observed in 87.5% of patients on moxifloxacin and 82.1% of patients on ofloxacin and metronidazole (95% CI, –8.3 to 8.8). Significantly more patients taking ofloxacin and metronidazole reported a drug-related adverse event (30.9%) than those taking moxifloxacin (22.5%; P=0.01). Most commonly reported adverse events were gastrointestinal in nature. Withdrawals due to a drug-related adverse event occurred in 6.3% of patients receiving moxifloxacin compared to 5.0% in the ofloxacin/metronidazole group (P=0.41).
Boothby et al.[64] (2010) Moxifloxacin 400 mg QD for 14 days vs ofloxacin 400 mg BID and metronidazole 400 mg BID	RETRO Women with uncomplicated pelvic inflammatory disease	N=741 14 days	Primary: Clinical response (significant improvement or response, marginal improvement, or no change/worse) Secondary: Tolerability	Primary: There was no significant difference in clinical response rates with moxifloxacin compared to ofloxacin-metronidazole (significant improvement/resolved: 70 and 77%, respectively; marginal improvement: 11 and 3%, respectively; no change/worse: 18 and 20%; P=0.14). Secondary: For those patients who attended clinic for follow-up, adverse events occurred in 16% of patients receiving moxifloxacin and in 19% of patients receiving ofloxacin-metronidazole. Most were gastrointestinal in nature.
Rafalsky et al.[65] (2006) Quinolones (ciprofloxacin, ciprofloxacin extended-release, fleroxacin, gemifloxacin, levofloxacin, norfloxacin, ofloxacin, pefloxacin, or	MA Women with uncomplicated acute cystitis	N=7,535 (11 Trials) Variable duration	Primary: Clinical response, bacteriological eradication, and clinical success (cure or improvement) and bacteriological eradication Secondary: Not reported	Primary: For all primary endpoint measures in all 11 trials, there were no significant differences in clinical or microbiological efficacy between the quinolones. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
rufloxacin)				
Respiratory Infections				
Nouira et al.[66] (2010) SMX-TMP 800-160 mg BID for 10 days vs ciprofloxacin 750 mg BID for 10 days	DB, RCT Patients ≥40 years of age with an acute exacerbation of COPD requiring mechanical ventilation	N=170 10 days	Primary: Hospital death and need for an additional course of antibiotics Secondary: Duration of mechanical ventilation, length of hospital stay, and exacerbation-free interval	Primary: Combined hospital death and additional antibiotic prescription rates were similar in the two groups (16.4 vs 15.3% in the SMX-TMP vs ciprofloxacin group; 95% CI, -9.8% to 12.0; P=0.832). During the study, 15 patients died in the hospital, eight (8.2%) in the SMX-TMP group and eight (9.4%) in the ciprofloxacin group (P>0.05). Secondary: The mean exacerbation-free interval was similar in both treatment groups (83 vs 79 days in the SMX-TMP vs ciprofloxacin group; P=0.41). Of 38 patients initially receiving noninvasive ventilation in the SMX-TMP group, 17 (45%) were secondarily intubated vs 13 (34%) in the ciprofloxacin group (P=0.347). The duration of mechanical ventilation and length of hospital stay were similar in the two study groups. Adverse events were minor and comparably distributed in both treatment groups.
Sethi et al.[67] (2004) Gemifloxacin 320 mg QD for five days vs levofloxacin 500 mg QD for seven days	DB, MC, RCT Patients >40 years of age with acute exacerbation of chronic bronchitis	N=360 5 days	Primary: Clinical success rate (defined as resolution or significant improvement of symptoms) at days 14 to 21 Secondary: Clinical success rate at days nine to 11 and at 28 to 35 days, bacteriologic	Primary: Clinical success at 14 to 21 days was observed in 88.2% of patients treated with gemifloxacin and 85.1% in those treated with levofloxacin (95% CI, –4.67 to 10.72). Secondary: Clinical success at nine to 11 days was observed in 97.5% of patients treated with gemifloxacin and 93.5% in those treated with levofloxacin (95% CI, –0.61 to 8.51). Clinical success at 28 to 35 days was observed in 83.7% of patients treated with gemifloxacin and 78.4% in those treated with levofloxacin (95% CI, –3.83 to 14.34). Eradication at nine to 11 days was observed in 87.5% of patients treated with gemifloxacin and 90.4% in those treated with levofloxacin.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			eradication rate at nine to 11, 14 to 21 and at 28 to 35 days	Eradication at 14 to 21 days was observed in 78.4% of patients treated with gemifloxacin and 85.7% in those treated with levofloxacin. Eradication at 28 to 35 days was observed in 77.8% of patients treated with gemifloxacin and 70.5% in those treated with levofloxacin. Adverse events were reported in 39.6% of patients taking gemifloxacin and 33.7% of patients taking levofloxacin. Withdrawals due to adverse events occurred in four patients on gemifloxacin and 10 patients taking levofloxacin.
Blasi et al.[68] (2013) Prulifloxacin 600 mg QD for seven days vs levofloxacin 500 mg QD for seven days	DB, MC, RCT Patients at least 40 years of age with severe COPD, smokers or ex-smokers with > 10 pack years, diagnosed with an acute exacerbation of chronic bronchitis	N=346 7 days	Primary: Clinical assessment at the test of cure visit. Secondary: Clinical efficacy at visit four (six-week follow-up), clinical efficacy at visit five (six-month follow-up) and microbiological efficacy	Primary: At the test of cure visit, 92.5% (N=161/174) of patients treated with prulifloxacin in the intent to treat population were cured. 96.5% (N=166/172) of patients treated with levofloxacin in the intent to treat population were cured. The difference in the percentage of cured patients was -3.98 (95% CI, -8.76 to 0.79), which demonstrates non-inferiority of prulifloxacin to levofloxacin. Secondary: At visit four, patients cured by prulifloxacin had a treatment success rate of 96.8% (N=150/155), as defined by patients with mild relapse plus persistent resolution. Patients cured by levofloxacin had a treatment success rate of 98.1% (N=153/156) at visit four. At visit five, patients cured by prulifloxacin had a treatment success rate of 95.7% (N=135/141). Patients cured by levofloxacin had a treatment success rate of 98.6% (N=140/142) at visit five. Success rate for microbiological efficacy was defined as eradication plus presumed eradication. The success rate for patients treated with prulifloxacin was 83.3% (N=70/84) in the intent to treat population compared to 89.5% (N=68/76) in patients treated with levofloxacin.
Noel et al.[69] (2008) Levofloxacin 10 mg/kg BID	MC, RCT, SB Children six months to five years of age with recurrent and/or	N=1,650 27 days	Primary: Clinical cure rates at visit three (two to five days post-therapy)	Primary: Clinical cure rates were 72.4% with levofloxacin and 69.9% with amoxicillin-clavulanate (95% CI, -7.37 to 2.46). Levofloxacin was found to be non-inferior to amoxicillin-clavulanate. Cure rates were similar among different age groups: ≤24 months: 68.9 vs

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs amoxicillin-clavulanate (amoxicillin 45 mg/kg) BID	persistent acute otitis media that was unchanged or worsened after ≥three days of treatment with an antimicrobial regimen used to treat acute otitis media		Secondary: Clinical cure rate at visit four (10 to 17 days post therapy), clinical success (cured or improved) at visits three and four, safety	66.2%, respectively (95% CI, -9.36 to 4.03); >24 months: 76.9 vs 75.1%; respectively (95% CI, -8.94 to 5.28). Secondary: Clinical cure rates at visit four were 74.9% for levofloxacin and 73.9% for amoxicillin-clavulanate (95% CI, -5.55 to 3.54). Clinical success rates at visit three were 94.0% for levofloxacin and 90.8% for amoxicillin-clavulanate (95% CI, -6.02 to -0.29). Clinical success rates at visit four were 83.6% for levofloxacin and 80.4% for amoxicillin-clavulanate (95% CI, -7.18 to 0.81). There was no difference observed between treatments regarding frequency or type of adverse events. Most adverse events were mild or moderate in severity (97% levofloxacin; 96% amoxicillin-clavulanate) with diarrhea being the most frequent.
Griffin et al.[70] (2010) Levofloxacin vs azithromycin or clarithromycin	RETRO Patients with Legionella pneumonia	N=39 Variable duration	Primary: Time to clinical stability and length of hospital stay Secondary: Not reported	Primary: The mean time to clinical stability for the macrolide group was 5.1 and 4.3 days for the levofloxacin group (P=0.43). The mean length of hospital stay for the macrolide group was 12.7 and 8.9 days for the levofloxacin group (P=0.10). Secondary: Not reported
Mokabberi et al.[71] (2010) Levofloxacin 500 mg IV QD vs doxycycline 100 mg IV BID	DB, PRO, RCT Patients ≥18 years of age with pneumonia requiring hospitalization	N=65 two months	Primary: Response to treatment, failure to treatment and complications, length of stay Secondary: Not reported	Primary: Efficacy of treatment was not significantly different between the treatment groups (P=0.844). There were two failures in the levofloxacin group and one failure in the doxycycline group (P=0.893). Two patients in the levofloxacin group had side effects (mild diarrhea), while no side effects were noted for doxycycline (P=0.375). The mean time to change from IV to oral for levofloxacin group was 2.73

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Patients were allowed to switch from IV to oral therapy at the discretion of the physician.				and 2.88 days for doxycycline group (P=0.647). Length of stay was 5.7 days for levofloxacin and 4.0 days for doxycycline (P<0.001). Secondary: Not reported
Anzueto et al.[72] (2006) Levofloxacin 500 mg IV then by mouth for 7 to 14 days vs moxifloxacin 400 mg IV then by mouth for 7 to 14 days All patients received IV study medications and were converted to oral therapy after ≥ two days if they exhibited response to therapy and were able to tolerate oral food and medications.	DB, PRO, RCT Patients ≥65 years of age with community-acquired pneumonia	N=394 7 to 14 days	Primary: Clinical cure rate (defined as disappearance of symptoms or improvement that additional/ alternative therapy was not necessary) at five to 21 days after therapy Secondary: Clinical recovery (defined as disappearance to acute symptoms or reduction in severity or number of symptoms) during therapy (three to five days after start or therapy), bacteriologic eradication, and health resource utilization	Primary: Clinical cure was observed in 92.9% of the patients taking moxifloxacin and 87.9% of those on levofloxacin (95% CI, –1.9 to 11.9, P=0.2). Secondary: Significantly more patients taking moxifloxacin (97.9%) exhibited clinical recovery at three to five days than those on levofloxacin (90.0%, 95% CI: 1.7 to 14.1; P=0.01). Bacteriologic eradication was observed in 81.0% of patients taking moxifloxacin and 75.0% in patients taking levofloxacin (P=0.9). The total duration of hospital stay was 7.5±4.2 days on moxifloxacin compared to 7.5±4.6 days with levofloxacin (P=0.95). For patients in the intensive care unit, total duration of stay was similar between treatment groups. The rate of drug-related and serious adverse events was comparable between the two treatments. Ten patients on moxifloxacin and 7 taking levofloxacin withdrew due to a drug-related adverse event. There was no difference in mortality in the two treatment groups (P=0.5).
Tanaseanu et al.[73] (2008)	DB, MC, RCT,	N=891	Primary: Clinical response	Primary: At the test of cure assessment in the clinically evaluable and clinical

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Levofloxacin 500 mg IV QD or BID vs tigecycline 100 mg IV as an initial dose, followed by 50 mg IV BID Patients were allowed to switch to oral levofloxacin after 3 days if specific criteria were met.	Patients >18 years of age hospitalized with community-acquired pneumonia	7 to 14 days	in clinically evaluable and clinical modified intent to treat populations at test of cure Secondary: Health care resource utilization, safety	modified intent to treat populations, there were no significant differences in the clinical cure rates for tigecycline as compared to levofloxacin. Tigecycline cured 89.7% of patients and levofloxacin cured 86.3% of patients (95% CI, -2.2 to 9.1; P<0.001 for non-inferiority). In the study in which patients were allowed to switch to oral levofloxacin therapy after ≥3 days of IV administration of either study medication, there were no significant differences in the percentage of patients who switched to oral therapy (tigecycline, 89.9%; levofloxacin, 87.8%) or in the median duration of oral therapy in either group (3.9 days for tigecycline vs 3.32 for levofloxacin). In the clinical modified intent to treat population, tigecycline 81% of patients and levofloxacin cured 79.7% of patients (95% CI -4.5 to 7.1, P<0.001 for non-inferiority). Secondary: In the pooled studies, there was no significant difference between the two treatment groups in hospital length of stay during the primary hospitalization (tigecycline: mean [SD], 9.8 [6.0] days; levofloxacin, 9.8 [6.0] days; P=0.883). There was no difference in mean duration of study antibiotic therapy (tigecycline, 9.8 [3.1] days; levofloxacin, 10.0 [3.2] days; P=0.453). There were no significant differences between the treatment groups in the rate of rehospitalization, admission for intensive care unit care, admission to emergency room care, use of home health care, or nursing home admissions after discharge from the primary hospitalization. More tigecycline-treated patients than levofloxacin-treated patients reported that adverse events were considered drug related, and nausea and vomiting occurred at a significantly higher rate for tigecycline versus levofloxacin (P<0.001). Discontinuations for adverse events were low (tigecycline, 6.1% and levofloxacin, 8.1%).
Tanaseanu et al.[74]	DB, MC, RCT	N=428	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2009) Levofloxacin 500 mg IV QD or BID vs tigecycline 100 mg IV as an initial dose, followed by 50 mg IV every 12 hours	Patients ≥18 years of age with a community-acquired pneumonia	7 to 14 days	Clinical response in the clinically evaluable population and clinical modified intent to treat populations at the test of cure visit (10 to 21days posttreatment) Secondary: Microbiologic eradication rates	In the clinically evaluable population, clinical cure rates at the test of cure visit were 88.9% for tigecycline and 85.3% for levofloxacin (P=0.4025). In the clinical modified intent to treat population, clinical cure rates were 83.7% for tigecycline and 81.5% for levofloxacin (P<0.6269). Tigecycline was found to be non-inferior to levofloxacin (P<0.001). Secondary: In the microbiologically evaluable population, eradication rates at the test of cure visit were similar among the treatment groups for common pathogens. The most common isolate was *Streptococcus pneumoniae*, with similar eradication for tigecycline (92%) and levofloxacin (89%). Both therapies eradicated 100% of penicillin-intermediate and penicillin-resistant strains. *Mycoplasma pneumoniae* was the most commonly identified atypical organism, and was eradicated in 96% of tigecycline patients and 92% of levofloxacin patients. No obvious differences in eradication rates of other organisms were found, though the number of other isolates was small.
Siempos et al.[75] (2007) Quinolones vs amoxicillin-clavulanate vs macrolides	MA Patients >18 years old with acute bacterial exacerbation of chronic bronchitis	N=7,405 (19 RCT) 26 weeks	Primary: Treatment success, hospitalization, mortality, adverse events Secondary: Not reported	Primary: There was no difference regarding treatment success in intention-to-treat and clinically evaluable patients between macrolides and quinolones, amoxicillin-clavulanate and quinolones, or amoxicillin-clavulanate and macrolides. The treatment success in microbiologically evaluable patients was lower for macrolides compared to quinolones (OR, 0.47; 95% CI, 0.31 to 0.69). There was no difference in the need for hospitalization for patients treated with macrolides compared to patients treated with quinolones (OR, 1.37; 95% CI, 0.75 to 2.5). Data regarding need for hospitalization were only available in two trials comparing amoxicillin-clavulanate with quinolones, and in one trial comparing amoxicillin-clavulanate with macrolides. There was no difference in mortality between macrolide-treated patients with acute bacterial exacerbation of chronic bronchitis and those treated with quinolones (OR, 1.96; 95% CI 0.45to8.51). Data on mortality were provided in only two trials comparing amoxicillin-clavulanate with quinolones.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Fewer quinolone-recipients experienced a recurrence of acute bacterial exacerbation of chronic bronchitis after resolution of the initial episode compared to macrolide-recipients during the 26-week period following therapy. Adverse effects in general were similar between macrolides and quinolones. Administration of amoxicillin-clavulanate was associated with more adverse effects than quinolones (OR, 1.36; 95% CI 1.01to1.85). Secondary: Not reported
Miscellaneous Infections				
Metallidis et al.[76] (2008) Ceftriaxone 4 g IV every 24 hours plus ciprofloxacin 400 mg IV BID vs ceftazidime 2 g IV every eight hours plus amikacin 500 mg IV every eight hours or 20 mg/kg divided in three doses	RCT Patients with febrile neutropenia	N=95 ≥3 days	Primary: Microbiologically and clinically documented infections and adverse events Secondary: Not reported	Primary: The overall incidence of microbiologically and clinically documented infections was 81.3% (80.85% in the ceftriaxone-ciprofloxacin group and 82.14% in the ceftazidime-amikacin group). There was no significant difference between the groups. The overall incidence of documented infections was 45.9% (51.1% in the ceftriaxone-ciprofloxacin group and 37% in the ceftazidime-amikacin group; P=0.011). The ceftriaxone-ciprofloxacin group had an overall incidence of resolution and improvement of 95.7% in comparison to 75% in the ceftazidime-amikacin group. Thirty-nine organisms were isolated, 66.67% gram-negative and 33.33% gram-positive. There was a low incidence of adverse events in both groups. Secondary: Not reported
Keramat et al.[77] (2009) Ciprofloxacin 15 mg/kg BID plus	PRO, RCT Patients ≥18 years of age with acute brucellosis	N=178 8 to 12 weeks	Primary: Response and relapse rates Secondary:	Primary: Response to therapy was observed in 93.7% of patients at the end of treatment for all three groups (DR, 96.7%; CR, 95.2%; CD, 87.3%). There were no significant differences among the treatment groups (P=0.09).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
rifampin 15 mg/kg QD (CR group) vs ciprofloxacin 15 mg/kg BID plus doxycycline 200 mg QD (CD group) vs doxycycline 200 mg PO QD plus rifampin 15 mg/kg QD (DR group)			Not reported	Therapeutic failure was seen in 12 cases, though no significant differences were noted among the three groups (P=0.88). After six months, 12 patients relapsed (DR, 7.7%; CR, 8.3%; CD, 17.5%; P=0.35).
GIMEMA Infection Program[78] (1991) Ciprofloxacin 500 mg BID vs norfloxacin 400 mg BID	MC, RCT, SB Patients ≥14 years of age with neutropenia with hematologic malignancies or had bone marrow transplantation or chemotherapy-induced neutropenia expected to last >10 days	N=801 Mean 29 days	Primary: Number of patients with febrile episodes, the number of days with a fever, the number of days parenteral antibiotics were used, interval to first febrile episode or infection, compliance, classification of febrile episodes or infection, discontinuation due to adverse reactions and mortality	Primary: Significantly less patients on ciprofloxacin (34%) developed fevers than norfloxacin 25% (P=0.01). The number of days with a fever did not differ significantly between treatment groups. Mean duration of parenteral antibiotic use was significantly shorter with ciprofloxacin (10.1 days) vs norfloxacin (12.0 days; P=0.02). The interval to first febrile episode was longer with ciprofloxacin (8.3 days) compared to norfloxacin (7.2 days; P=0.055). Patients with ciprofloxacin had a lower rate of microbiologically documented infections (17% vs 24%; P=0.058). Differences among other febrile classifications (clinically documented infection, fever of unknown origin, or bacteremia) were not significant. Compliance was >90% and comparable between treatment groups. Discontinuation due to adverse events occurred in 2% of patients on

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Secondary: Not reported	norfloxacin and 4% of patients on ciprofloxacin. The mortality rate during neutropenic episodes was 13% with norfloxacin and 14% with ciprofloxacin.
Arjyal et al.[79] (2011) Gatifloxacin 10 mg/kg QD for 7 days vs chloramphenicol 75 mg/kg/day in four divided doses for 14 days	OL, RCT Patients with uncomplicated enteric fever	N=853 6 months	Primary: Treatment failure Secondary: Fever clearance time, late relapse, and fecal carriage	Primary: There were 14 treatment failures in the chloramphenicol group and 12 treatment failures in the gatifloxacin group (HR, 0.86; 95% CI, 0.40 to 1.86; P=0.70). Secondary: The median time to fever clearance was 3.95 days in the chloramphenicol group and 3.90 in the gatifloxacin group (P=0.64). There was no significant difference between the treatment groups in relapses until day 31 (P=0.35) or day 62 (P=0.77). Only three of 148 patients receiving chloramphenicol and none of 154 patients receiving gatifloxacin were stool-culture-positive at the end of one month (P=0.12). At the end of three months, only one patient in the chloramphenicol group had a positive stool culture, and at six months no patients had a positive stool culture. In the chloramphenicol group, 25% of culture-positive patients experienced at least one adverse event. In the gatifloxacin group, 16.9% of culture-positive patients experienced at least one adverse event.
Solomkin et al.[80] (2009) Ceftriaxone 2 g IV QD plus metronidazole 500 mg IV BID for three to 14 days vs moxifloxacin 400	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	Primary: At the test-of-cure visit, cure rates were 90.2% for moxifloxacin and 96.5% for ceftriaxone plus metronidazole (95% CI, −11.7 to −1.7). In the intention-to-treat population, the clinical cure rates were 87.2% for moxifloxacin and 91.2% for ceftriaxone plus metronidazole (95% CI, −10.7 to 1.9). Moxifloxacin was found to be non-inferior to ceftriaxone plus metronidazole in the per protocol and intention-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 plus metronidazole group (28.1%). In the intention-to-treat

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg IV QD for three to 14 days			during treatment and at the end-of-therapy; bacteriological 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	population, clinical improvement occurred in 30.6% of patients receiving moxifloxacin and 27.1% of patients receiving ceftriaxone plus metronidazole. In the per protocol population, clinical resolution at end-of-therapy occurred in 92.5% of patients receiving moxifloxacin and in 97.1% of patients receiving ceftriaxone plus metronidazole (95% CI, −9.8 to −0.2). In the intention-to-treat population, clinical resolution at end-of-therapy occurred in 91.1% of patients receiving moxifloxacin and in 94.5% of patients receiving ceftriaxone plus metronidazole. The overall incidence of treatment-emergent adverse events was similar between the two treatment groups (31.7% with moxifloxacin vs 24.3% with ceftriaxone plus metronidazole; P=0.129).
Gupta et al.[81] (2009) Ceftriaxone 75 mg/kg/day IV and amikacin 15 mg/kg QD as outpatient therapy vs ofloxacin 7.5 mg/kg orally every 12 hours and amoxicillin-clavulanate 12.5 mg/kg orally every 8 hours as outpatient therapy	OL, RCT, SC Pediatric patients two to 15 years of age with low-risk febrile neutropenia	N=88 (123 episodes) Variable duration	Primary: Treatment success Secondary: Not reported	Primary: In the per protocol analysis, treatment was successful in 90.16% of episodes in the oral group and in 93.10% of episodes in the IV group. In the intention-to-treat analysis, the success rate was 88.7% in the oral group and 88.5% in the IV group (P=0.97). There were three hospitalizations (all in the oral group) and no mortality. Secondary: Not reported

Drug regimen abbreviations: BID=twice daily, IM=intramuscular, IV=intravenous, QD=once daily, TID=three times daily
Study abbreviations: CI=confidence interval, COPD=chronic obstructive pulmonary disease, DB=double-blind, DD=double-dummy, HR=hazard ratio, MA=meta-analysis, MC=multicenter, MITT=modified intention to treat, OL=open-label, OR=odds ratio, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, RR=rate ratio, SB=single-blind, SC=single center, SD=standard deviation, SMX-TMP=sulfamethoxazole-trimethoprim, UTI=urinary tract infection, WBC=white blood cell

Additional Evidence

Dose Simplification
Three clinical trials directly compared ciprofloxacin extended-release tablets (dosed once daily) with the immediate-release formulation (dosed twice daily). Fourcroy et al. and Henry et al. evaluated women with uncomplicated urinary tract infections receiving treatment for three days.[46,48] Talan et al. evaluated men and women with complicated urinary tract infections or uncomplicated pyelonephritis receiving treatment for seven to 14 days.[47] In all three trials, patients receiving the extended-release formulation demonstrated similar clinical cure rates, bacteriological eradication rates, and adverse event rates compared to patients receiving the immediate-release formulation.[46-48]

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 Quinolones

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Ciprofloxacin	injection, extended-release tablet, suspension, tablet	Cipro®*, Cipro IV®*, Cipro XR®	$$$$	$
Levofloxacin	injection, solution, tablet	Levaquin®*	$$$$-$$$$$	$
Moxifloxacin	injection, tablet	Avelox®*,	$$$$	$$$
Ofloxacin	tablet	N/A	N/A	$$$-$$$$

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

X. Conclusions

The quinolones are approved to treat a variety of infections, including dermatologic, gastrointestinal, genitourinary, respiratory, as well as several miscellaneous infections.[1-8] Ciprofloxacin, levofloxacin, and ofloxacin are available in a generic formulation.

There are many guidelines that define the appropriate place in therapy for the quinolones. The specific agent that is recommended is dependent upon the infectious organism being treated and the corresponding spectrum of activity of the quinolone. The quinolones are recommended as specific therapy for the treatment of susceptible pathogens causing endocarditis, encephalitis, diabetic foot infections, infectious diarrhea, chancroid, pyelonephritis, anthrax, community-acquired pneumonia, nosocomial pneumonia, intra-abdominal infections, and febrile neutropenia.[13-17,21- 26,28,29,31-34,36]They are recommended as an alternative treatment option for meningitis, skin and soft-tissue infections, sexually transmitted diseases, and cystitis.[18-20,25,26]

Clinical trials have demonstrated comparable efficacy among the quinolones for the treatment of skin and soft-tissue infections, genitourinary infections, and respiratory tract infections.[39,40,49-57,62-65,67,72] Data from published studies supports similar safety profiles among the quinolones. There's an increased risk of tendinitis and tendon rupture with the use of quinolones. This risk is further increased in older patients, patients taking corticosteroid drugs, and patients with kidney, heart, or lung transplants.[1] Because of this risk, the use of quinolones has been limited in the pediatric population. The quinolones may also exacerbate muscle weakness in patients with myasthenia gravis. In May 2016 the FDA released a Safety Alert advising restricted use of quinolones for certain uncomplicated infections, including acute sinusitis, acute bronchitis, and uncomplicated urinary tract infections.[11] For patients with these conditions, fluoroquinolones should be reserved for those who do not have alternative treatment options. The FDA safety review found that systemic quinolone use is associated with serious side effects affecting the tendons, muscles, joints, nerves, and central nervous system.[11] In June 2016 the FDA approved an updated Boxed Warning for the quinolones, advising that the serious side effects associated with quinolones generally outweigh the benefits for patients with acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, and uncomplicated urinary tract infections who have other treatment options.[12]

There is insufficient evidence to support that one brand quinolone 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 quinolones 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 quinolone 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 Sulfonamides
AHFS Class 081220
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I. Overview

Sulfadiazine and sulfamethoxazole-trimethoprim are approved to treat a variety of infections, including central nervous system, dermatologic, gastrointestinal, genitourinary, respiratory, as well as several miscellaneous infections.[1-6] These agents are bacteriostatic and interfere with bacterial growth by inhibiting the synthesis of dihydrofolic acid. Trimethoprim blocks the production of tetrahydrofolic acid from dihydrofolic acid by binding to and reversibly inhibiting the required enzyme, dihydrofolate reductase. Due to synergism, the combination of sulfamethoxazole-trimethoprim is often bactericidal and active against a variety of organisms. Resistance to sulfonamides is widespread and cross-resistance among the various sulfonamides is common.

Sulfasalazine is approved for the treatment of ulcerative colitis and rheumatoid arthritis.[1-2,5-6] It is a prodrug that is metabolized into sulfapyridine and 5-aminosalicyclic acid (5-ASA). It is absorbed from the small intestine and must be formulated as an enteric-coated product to reach the systemic circulation.

The sulfonamides that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. All of the products are available in a generic formulation. This class was last reviewed in August 2014.

Table 1. Sulfonamides Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Sulfadiazine	tablet	N/A	sulfadiazine
Sulfasalazine	delayed-release tablet, tablet	Azulfidine®*	sulfasalazine
Combination Products			
Sulfamethoxazole and trimethoprim	injection, suspension, tablet	Bactrim®*, Bactrim DS®*, Sulfatrim®*	sulfamethoxazole and trimethoprim

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

The sulfonamides 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 sulfonamides 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 Sulfonamides[1-6]

Organism	Sulfadiazine	Sulfamethoxazole and Trimethoprim
Gram-Positive Aerobes		
Nocardia species	✔	
Staphylococcus aureus	✔	
Streptococcus pneumoniae		✔
Gram-Negative Aerobes		
Chlamydia trachomatis	✔	
Enterobacter species	✔	✔
Escherichia coli	✔	✔
Haemophilus influenzae	✔	✔
Klebsiella species	✔	✔

Organism	Sulfadiazine	Sulfamethoxazole and Trimethoprim
Morganella morganii		✔
Proteus mirabilis	✔	✔
Proteus vulgaris	✔	✔
Shigella flexneri		✔
Shigella sonnei		✔
Protozoan Parasites		
Plasmodium falciparum	✔	
Toxoplasma gondii	✔	
Miscellaneous Organisms		
Pneumocystis carinii		✔

II. Evidence-Based Medicine and Current Treatment Guidelines

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

Table 3. Treatment Guidelines Using the Sulfonamides

Clinical Guideline	Recommendation(s)
American College of Cardiology/American Heart Association: **2008 Focused Update Incorporated Into the American College of Cardiology/ American Heart Association 2006 Guidelines for the Management of Patients With Valvular Heart Disease (2008)**[7] American College of Cardiology/American Heart Association: **Guideline for the Management of Patients With Valvular Heart Disease (2014)**[8] **(although a more current guideline more detailed information was included as part of the 2008 Focused update; as such both are summarized together)**	<u>Rheumatic fever prophylaxis</u> • Primary prevention of rheumatic heart disease: o Penicillin G benzathine intramuscular once or penicillin V orally for 10 days. o Erythromycin estolate or erythromycin ethylsuccinate orally for 10 days, or azithromycin orally for five days in patients who are allergic to penicillin. • Secondary prevention of rheumatic fever: o Penicillin G benzathine intramuscular every four weeks, or penicillin V orally twice daily, or sulfadiazine orally once daily. o Erythromycin orally twice daily for patients who are allergic to penicillin. <u>Endocarditis prophylaxis</u> • Prophylaxis against infective endocarditis is reasonable for the following patients at highest risk for adverse outcomes from infective endocarditis who undergo dental procedures that involve manipulation of either gingival tissue or the periapical region of teeth or perforation of the oral mucosa: o Patients with prosthetic cardiac valve or prosthetic material used for cardiac valve repair. o Patients with previous infective endocarditis. o Patients with congenital heart disease. o Cardiac transplant recipients with valve regurgitation due to a structurally abnormal valve. • Prophylaxis against infective endocarditis is not recommended for non-dental procedures (such as transesophageal echocardiogram, esophagogastroduodenoscopy, or colonoscopy) in the absence of active infection. • Regimens for dental procedures (single dose 30 to 60 minutes before procedure): o Oral: amoxicillin. o Unable to take oral medications: ampicillin, cefazolin or ceftriaxone. o Allergic to penicillin or ampicillin (oral): cephalexin, clindamycin, or azithromycin. o Allergic to penicillins or ampicillin and unable to take oral medication: cefazolin, ceftriaxone, or clindamycin. • Therapy of native valve endocarditis caused by highly penicillin-susceptible viridans group streptococci and *Streptococcus bovis:* o Penicillin G or ceftriaxone for four weeks.

Clinical Guideline	Recommendation(s)
	o Ceftriaxone plus gentamicin for two weeks. o Vancomycin for four weeks in patients allergic to penicillin. • Therapy of native valve endocarditis caused by strains of viridans group streptococci and *Streptococcus bovis* relatively resistant to penicillin: o Penicillin G or ceftriaxone for four weeks plus gentamicin for two weeks. o Vancomycin for four weeks in patients allergic to penicillin. • Therapy for native valve or prosthetic valve enterococcal endocarditis caused by strains susceptible to penicillin, gentamicin, and vancomycin: o Ampicillin for four to six weeks or penicillin G plus gentamicin for four to six weeks. o Vancomycin plus gentamicin for six weeks in patients allergic to penicillin. • Therapy for endocarditis caused by staphylococci in the absence of prosthetic materials: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin for six weeks plus the optional addition of gentamicin for three to five days. ▪ Cefazolin for six weeks with the optional addition of gentamicin in patients allergic to penicillin. o Oxacillin-resistant strains: ▪ Vancomycin for six weeks. • Therapy for prosthetic valve endocarditis caused by staphylococci: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin, rifampin, and gentamicin for ≥6 weeks. o Oxacillin-resistant strains: ▪ Vancomycin, rifampin, and gentamicin for ≥6 weeks. • Therapy for both native and prosthetic valve endocarditis caused by *Haemophilus* species *(Haemophilus parainfluenzae, Haemophilus aphrophilus, Haemophilus paraphrophilus), Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* species microorganisms: o Ceftriaxone for four weeks. o Ampicillin-sulbactam for four weeks. o Ciprofloxacin for four weeks. • Therapy for culture-negative endocarditis including *Bartonella* endocarditis: o Native valve: ▪ Ampicillin-sulbactam plus gentamicin (or vancomycin for patients allergic to penicillin) plus ciprofloxacin for four to six weeks. o Prosthetic valve (early; ≤1 year): ▪ Vancomycin for six weeks, plus gentamicin for two weeks, plus cefepime for six weeks, plus rifampin for six weeks. o Prosthetic valve (late; >1 year): ▪ Suspected *Bartonella*, culture negative: • Ceftriaxone for six weeks plus gentamicin with/without doxycycline for six weeks. ▪ Documented *Bartonella*, culture positive: o Doxycycline for six weeks plus gentamicin for two weeks.
Infectious Diseases Society of America: **Clinical Practice Guidelines: Management of Encephalitis (2008)**[9] **(Was reviewed and**	<u>Empirical therapy</u> • Acyclovir should be initiated in all patients with suspected encephalitis, pending results of diagnostic studies. • Other empirical antimicrobial agents should be initiated on the basis of specific epidemiologic or clinical factors, including appropriate therapy for presumed bacterial meningitis, if clinically indicated. • In patients with clinical clues suggestive of rickettsial or ehrlichial infection during the appropriate season, doxycycline should be added to empirical treatment regimens.

Clinical Guideline	Recommendation(s)
deemed current as of July 2011)	<u>Bacteria</u> • *Bartonella bacilliformis:* chloramphenicol, ciprofloxacin, doxycycline, ampicillin, or sulfamethoxazole-trimethoprim is recommended. • *Bartonella henselae:* doxycycline or azithromycin, with or without rifampin, can be considered. • *Listeria monocytogenes:* ampicillin plus gentamicin is recommended; sulfamethoxazole-trimethoprim is an alternative in the penicillin-allergic patient. • *Mycoplasma pneumoniae:* antimicrobial therapy (azithromycin, doxycycline, or a fluoroquinolone) can be considered. • *Tropheryma whipplei:* ceftriaxone, followed by either sulfamethoxazole-trimethoprim or cefixime, is recommended. <u>Helminths</u> • *Baylisascaris procyonis:* albendazole plus diethylcarbamazine can be considered; adjunctive corticosteroids should also be considered. • *Gnathostoma* species: albendazole or ivermectin is recommended. • *Taenia solium:* need for treatment should be individualized; albendazole and corticosteroids are recommended; praziquantel can be considered as an alternative. <u>Rickettsioses and ehrlichiosis</u> • *Anaplasma phagocytophilum:* doxycycline is recommended. • *Ehrlichia chaffeensis:* doxycycline is recommended. • *Rickettsia rickettsii:* doxycycline is recommended; chloramphenicol can be considered an alternative in selected clinical scenarios, such as pregnancy. • *Coxiella burnetii:* doxycycline plus a fluoroquinolone plus rifampin is recommended. <u>Spirochetes</u> • *Borrelia burgdorferi:* ceftriaxone, cefotaxime, or penicillin G is recommended. • *Treponema pallidum:* penicillin G is recommended; ceftriaxone is an alternative. <u>Protozoa</u> • *Acanthamoeba:* sulfamethoxazole-trimethoprim plus rifampin plus ketoconazole or fluconazole plus sulfadiazine plus pyrimethamine can be considered. • *Balamuthia mandrillaris:* pentamidine, combined with a macrolide (azithromycin or clarithromycin), fluconazole, sulfadiazine, flucytosine, and a phenothiazine can be considered. • *Naegleria fowleri:* amphotericin B (intravenous and intrathecal) and rifampin, combined with other agents, can be considered. • *Plasmodium falciparum:* quinine, quinidine, or artemether is recommended; atovaquone-proguanil is an alternative; exchange transfusion is recommended for patients with 110% parasitemia or cerebral malaria; corticosteroids are not recommended. • *Toxoplasma gondii:* pyrimethamine plus either sulfadiazine or clindamycin is recommended; sulfamethoxazole-trimethoprim alone and pyrimethamine plus atovaquone, clarithromycin, azithromycin, or dapsone are alternatives. • *Trypanosoma brucei gambiense:* eflornithine is recommended; melarsoprol is an alternative. • *Trypanosoma brucei rhodesiense:* melarsoprol is recommended.
European Federation of Neurological Societies: **Guideline on the**	<u>Empirical therapy</u> • Ceftriaxone 2 g every 12 to 24 hours or cefotaxime 2 g every six to eight hours. • Alternative therapy: meropenem 2 g every eight hours or chloramphenicol 1 g every six hours.

Clinical Guideline	Recommendation(s)
Management of Community-acquired Bacterial Meningitis (2008)[10]	• If penicillin or cephalosporin-resistant pneumococcus is suspected, use ceftriaxone or cefotaxime plus vancomycin 60 mg/kg every 24 hours after a loading dose of 15 mg/kg. • Ampicillin-amoxicillin 2 g every four hours if *Listeria* is suspected. <u>Pathogen specific therapy</u> • Penicillin-sensitive pneumococcal meningitis: o Benzyl penicillin 250,000 U/kg/day, ampicillin-amoxicillin 2 g every four hours, ceftriaxone 2 g every 12 hours or cefotaxime 2 g every six to eight hours. o Alternative therapy: meropenem 2 g every eight hours or vancomycin 60 mg/kg every 24 hours as a continuous infusion after a 15 mg/kg loading dose plus rifampicin 600 mg every 12 hours, or moxifloxacin 400 mg daily. • Pneumococcus with reduced susceptibility to penicillin or cephalosporins: o Ceftriaxone or cefotaxime plus vancomycin±rifampicin. o Alternative therapy: moxifloxacin, meropenem or linezolid 600 mg combined with rifampicin. • Meningococcal meningitis: o Benzyl penicillin, ceftriaxone, or cefotaxime. o Alternative therapy: meropenem, chloramphenicol, or moxifloxacin. • *Haemophilus influenzae* type B: o Ceftriaxone or cefotaxime. o Alternative therapy: chloramphenicol–ampicillin-amoxicillin. • Listerial meningitis: o Ampicillin or amoxicillin 2 g every four hours±gentamicin 1 to 2 mg every eight hours for the first seven to 10 days. o Alternative therapy: sulfamethoxazole-trimethoprim 10 to 20 mg/kg every six to 12 hours or meropenem. • *Staphylococcal* species: o Flucloxacillin 2 g every four hours or vancomycin if penicillin allergy is suspected. o Rifampicin should also be considered in addition to either agent. Linezolid should be considered for methicillin-resistant staphylococcal meningitis. • Gram-negative *Enterobacteriaceae*: o Ceftriaxone, cefotaxime or meropenem. • Pseudomonal meningitis: o Meropenem±gentamicin.
Infectious Diseases Society of America: **Practice Guidelines for the Management of Bacterial Meningitis (2004)[11]**	<u>Empiric therapy</u> • Empirical antimicrobial therapy is initiated either when the lumbar puncture is delayed or for patients with purulent meningitis and a negative cerebrospinal fluid gram stain result: o Age <1 month: ampicillin plus cefotaxime or ampicillin plus an aminoglycoside. o Age one to 23 months: vancomycin plus a third-generation cephalosporin. o Age two to 50 years: vancomycin plus a third-generation cephalosporin. o Age >50 years: vancomycin plus ampicillin plus a third-generation cephalosporin. o Basilar skull fracture: vancomycin plus a third-generation cephalosporin. o Penetrating head trauma: vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem. o Post neurosurgery: vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem.

Clinical Guideline	Recommendation(s)
	o Cerebrospinal fluid shunt: vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem. Specific therapy • Recommendations for specific antimicrobial therapy in bacterial meningitis are based on isolated pathogens and susceptibility. • *Streptococcus pneumoniae* o Penicillin minimum inhibitory concentrations <0.1 µg/mL: standard therapy includes penicillin G or ampicillin; alternative therapies include ceftriaxone, cefotaxime, or chloramphenicol. o Penicillin minimum inhibitory concentrations 0.1 to 1.0 µg/mL: standard therapy includes ceftriaxone or cefotaxime; alternative therapies include cefepime or meropenem. o Penicillin minimum inhibitory concentrations ≥2 µg/mL: standard therapies include vancomycin plus ceftriaxone or cefotaxime; alternative therapies include gatifloxacin or moxifloxacin. o Cefotaxime or ceftriaxone minimum inhibitory concentrations ≥1.0 µg/mL: standard therapies include vancomycin plus ceftriaxone or cefotaxime (consider addition of rifampin if minimum inhibitory concentrations of ceftriaxone is >2 µg/mL); alternative therapies include gatifloxacin or moxifloxacin. • *Neisseria meningitides* o Penicillin minimum inhibitory concentrations <0.1 µg/mL: standard therapy includes penicillin G or ampicillin; alternative therapy includes ceftriaxone, cefotaxime or chloramphenicol. o Penicillin minimum inhibitory concentrations 0.1 to 1.0 µg/mL: standard therapy includes ceftriaxone or cefotaxime; alternative therapies include chloramphenicol, a fluoroquinolone or meropenem. • *Listeria monocytogenes* o Standard therapy includes ampicillin or penicillin G; alternative therapies include sulfamethoxazole-trimethoprim or meropenem. • *Streptococcus agalactiae* o Standard therapy includes ampicillin or penicillin G; alternative therapies include ceftriaxone or cefotaxime. • *Escherichia coli* and other Enterobacteriaceae o Standard therapy includes a third-generation cephalosporin; alternative therapies include aztreonam, fluoroquinolone, meropenem, sulfamethoxazole-trimethoprim or ampicillin. • *Pseudomonas aeruginosa* o Standard therapies include cefepime or ceftazidime; alternative therapies include aztreonam, ciprofloxacin, or meropenem (addition of an aminoglycoside should be considered). • *Haemophilus influenzae* β-lactamase negative strains o Standard therapy includes ampicillin; alternative therapies include ceftriaxone, cefotaxime, cefepime, chloramphenicol or a fluoroquinolone. • *Haemophilus influenzae* β-lactamase positive strains o Standard therapy includes a third-generation cephalosporin; alternative therapies include cefepime, chloramphenicol or a fluoroquinolone. • *Staphylococcus aureus* methicillin susceptible o Standard therapy includes nafcillin or ofloxacin; alternative therapies include vancomycin or meropenem. • *Staphylococcus aureus* methicillin resistant o Standard therapy includes vancomycin (consider addition of rifampin); alternative therapies include sulfamethoxazole-trimethoprim or linezolid.

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	• *Staphylococcus epidermidis*
	  o Standard therapy includes vancomycin (consider addition of rifampin); alternative therapy includes linezolid.
	• *Enterococcus* species ampicillin susceptible
	  o Standard therapy includes ampicillin plus gentamicin.
	• *Enterococcus* species ampicillin resistant
	  o Standard therapy includes vancomycin plus gentamicin.
	• *Enterococcus* species ampicillin and vancomycin resistant
	  o Standard therapy includes linezolid.

Infectious Diseases Society of America: **Practice Guidelines for the Diagnosis and Management of Skin and Soft-Tissue Infections (2014)**[12]	Impetigo and ecthyma
	• Gram stain and culture of the pus or exudates from skin lesions of impetigo and ecthyma are recommended to help identify whether *Staphylococcus aureus* and/or a β-hemolytic *Streptococcus* is the cause (strong, moderate), but treatment without these studies is reasonable in typical cases.
	• Bullous and nonbullous impetigo can be treated with oral or topical antimicrobials, but oral therapy is recommended for patients with numerous lesions or in outbreaks affecting several people to help decrease transmission of infection. Treatment for ecthyma should be an oral antimicrobial.
	  o Treatment of bullous and nonbullous impetigo should be with either mupirocin or retapamulin twice daily for five days.
	  o Oral therapy for ecthyma or impetigo should be a seven-day regimen with an agent active against *S. aureus* unless cultures yield streptococci alone (when oral penicillin is the recommended agent). Because *S. aureus* isolates from impetigo and ecthyma are usually methicillin susceptible, dicloxacillin or cephalexin is recommended. When MRSA is suspected or confirmed, doxycycline, clindamycin, or sulfamethoxazole-trimethoprim is recommended.
	
	Purulent skin and soft-tissue infections (cutaneous abscesses, furuncles, carbuncles, and inflamed epidermoid cysts)
	• Gram stain and culture of pus from carbuncles and abscesses are recommended, but treatment without these studies is reasonable in typical cases. Gram stain and culture of pus from inflamed epidermoid cysts are not recommended.
	• Incision and drainage is the recommended treatment for inflamed epidermoid cysts, carbuncles, abscesses, and large furuncles.
	• The decision to administer antibiotics directed against *S. aureus* as an adjunct to incision and drainage should be made based upon presence or absence of systemic inflammatory response syndrome (SIRS), such as temperature >38°C or <36°C, tachypnea >24 breaths per minute, tachycardia >90 beats per minute, or white blood cell count >12 000 or <400 cells/µL. An antibiotic active against MRSA is recommended for patients with carbuncles or abscesses who have failed initial antibiotic treatment or have markedly impaired host defenses or in patients with SIRS and hypotension.
	
	Recurrent skin abscesses
	• A recurrent abscess at a site of previous infection should prompt a search for local causes such as a pilonidal cyst, hidradenitis suppurativa, or foreign material.
	• Recurrent abscesses should be drained and cultured early in the course of infection.
	• After obtaining cultures of recurrent abscess, treat with a five to ten day course of an antibiotic active against the pathogen isolated.
	• Consider a five-day decolonization regimen twice daily of intranasal mupirocin, daily chlorhexidine washes, and daily decontamination of

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	personal items such as towels, sheets, and clothes for recurrent *S. aureus* infection. • Adult patients should be evaluated for neutrophil disorders if recurrent abscesses began in early childhood. Erysipelas and cellulitis • Cultures of blood or cutaneous aspirates, biopsies, or swabs are not routinely recommended except in patients with malignancy on chemotherapy, neutropenia, severe cell-mediated immunodeficiency, immersion injuries, and animal bites. • Typical cases of cellulitis without systemic signs of infection should receive an antimicrobial agent that is active against streptococci. For cellulitis with systemic signs of infection (moderate nonpurulent), systemic antibiotics are indicated. Many clinicians could include coverage against methicillin-susceptible *S. aureus* (MSSA). For patients whose cellulitis is associated with penetrating trauma, evidence of MRSA infection elsewhere, nasal colonization with MRSA, injection drug use, or SIRS (severe nonpurulent), vancomycin or another antimicrobial effective against both MRSA and streptococci is recommended. In severely compromised patients, broad-spectrum antimicrobial coverage may be considered. Vancomycin plus either piperacillin-tazobactam or imipenem/meropenem is recommended as a reasonable empiric regimen for severe infections. • The recommended duration of antimicrobial therapy is five days, but treatment should be extended if the infection has not improved within this time period. Surgical site infections • Suture removal plus incision and drainage should be performed for surgical site infections. • Adjunctive systemic antimicrobial therapy is not routinely indicated, but in conjunction with incision and drainage may be beneficial for surgical site infections associated with a significant systemic response. • A brief course of systemic antimicrobial therapy is indicated in patients with surgical site infections following clean operations on the trunk, head and neck, or extremities that also have systemic signs of infection. • A first-generation cephalosporin or an antistaphylococcal penicillin for MSSA, or vancomycin, linezolid, daptomycin, telavancin, or ceftaroline where risk factors for MRSA are high (nasal colonization, prior MRSA infection, recent hospitalization, recent antibiotics), is recommended. • Agents active against gram-negative bacteria and anaerobes, such as a cephalosporin or fluoroquinolone in combination with metronidazole, are recommended for infections following operations on the axilla, gastrointestinal tract, perineum, or female genital tract. Necrotizing fasciitis • Empiric antibiotic treatment should be broad (e.g., vancomycin or linezolid plus piperacillin-tazobactam or a carbapenem; or plus ceftriaxone and metronidazole), as the etiology can be polymicrobial (mixed aerobic–anaerobic microbes) or monomicrobial (group A streptococci, community-acquired MRSA). • Penicillin plus clindamycin is recommended for treatment of documented group A streptococcal necrotizing fasciitis. Pyomyositis • Cultures of blood and abscess material should be obtained.

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	• Vancomycin is recommended for initial empirical therapy. An agent active against enteric gram-negative bacilli should be added for infection in immunocompromised patients or following open trauma to the muscles.
	• Cefazolin or antistaphylococcal penicillin (e.g., nafcillin or oxacillin) is recommended for treatment of pyomyositis caused by MSSA.
	• Antibiotics should be administered intravenously initially, but once the patient is clinically improved, oral antibiotics are appropriate for patients in whom bacteremia cleared promptly and there is no evidence of endocarditis or metastatic abscess. Two to three weeks of therapy is recommended.
	
	Clostridial gas gangrene or myonecrosis
	• Urgent surgical exploration of the suspected gas gangrene site and surgical debridement of involved tissue should be performed.
	• In the absence of a definitive etiologic diagnosis, broad-spectrum treatment with vancomycin plus either piperacillin-tazobactam, ampicillin-sulbactam, or a carbapenem antimicrobial is recommended. Definitive antimicrobial therapy with penicillin and clindamycin is recommended for treatment of clostridial myonecrosis.
	
	Animal bites
	• Preemptive early antimicrobial therapy for three to five days is recommended for patients who:
	  o are immunocompromised;
	  o are asplenic;
	  o have advanced liver disease;
	  o have preexisting or resultant edema of the affected area;
	  o have moderate to severe injuries, especially to the hand or face; or
	  o have injuries that may have penetrated the periosteum or joint capsule.
	• 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
	  o β-lactam-β-lactamase combinations, piperacillin-tazobactam, second-generation cephalosporins, and carbapenems.
	• Tetanus toxoid should be administered to patients without toxoid vaccination within 10 years. Tetanus, diphtheria, and tetanus (Tdap) is preferred over Tetanus and diphtheria (Td) if the former has not been previously given.
	
	Cutaneous anthrax
	• Oral penicillin V 500 mg four times daily for seven to 10 days is the recommended treatment for naturally acquired cutaneous anthrax.
	• Ciprofloxacin 500 mg by mouth twice daily or levofloxacin 500 mg intravenously/orally every 24 hours for 60 days is recommended for bioterrorism cases because of presumed aerosol exposure.
	
	Bacillary angiomatosis and cat scratch disease
	• Azithromycin is recommended for cat scratch disease (strong, moderate) according to the following dosing protocol:
	  o Patients >45 kg: 500 mg on day one followed by 250 mg for four additional days.

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	o Patients <45 kg: 10 mg/kg on day one and 5 mg/kg for four more days. • Erythromycin 500 mg four times daily or doxycycline 100 mg bid for two weeks to two months is recommended for treatment of bacillary angiomatosis. Erysipeloid • Penicillin (500 mg four times daily) or amoxicillin (500 mg three times daily [tid]) for seven to 10 days is recommended for treatment of erysipeloid. Glanders • Ceftazidime, gentamicin, imipenem, doxycycline, or ciprofloxacin is recommended based on in vitro susceptibility. Bubonic plague • Bubonic plague should be diagnosed by Gram stain and culture of aspirated material from a suppurative lymph node. Streptomycin (15 mg/kg intramuscularly [IM] every 12 hours) or doxycycline (100 mg twice daily by mouth) is recommended for treatment of bubonic plague. Gentamicin could be substituted for streptomycin. Tularemia • Streptomycin (15 mg/kg every 12 hours intramuscularly) or gentamicin (1.5 mg/kg every 8 hours intravenously) is recommended for treatment of severe cases of tularemia. • Tetracycline (500 mg four times daily) or doxycycline (100 mg twice daily by mouth) is recommended for treatment of mild cases of tularemia.
Infectious Diseases Society of America: **Diagnosis and Treatment of Diabetic Foot Infections (2012)**[13]	• Empirical antibiotic regimens should be based on the clinical severity of the infection. • Current clinical data does not allow for the recommendation of any specific antibiotic regimen for diabetic foot infections. • Suggested agents are derived from available published clinical trials and expert experience. • Definitive regimens should consider results of culture and susceptibility tests, as well as the clinical response to the empirical regimen. Similar agents of the same drug class may be substituted. Some of these regimens may not have Food and Drug Administration approval for complicated skin and skin-structure infections, and only linezolid, ertapenem and piperacillin-tazobactam are currently specifically approved for diabetic foot infections. • Suggested empirical antibiotic regimens for mild infections: dicloxacillin, clindamycin, cephalexin, sulfamethoxazole-trimethoprim, amoxicillin-clavulanate, levofloxacin and doxycycline. • Suggested empirical antibiotic regimens for moderate infections: levofloxacin, cefoxitin, ceftriaxone, ampicillin-sulbactam, moxifloxacin, tigecycline, linezolid, daptomycin, ertapenem, ticarcillin-clavulanate, piperacillin-tazobactam, levofloxacin or ciprofloxacin with clindamycin, imipenem-cilastatin, vancomycin, ceftazidime, cefepime, aztreonam. • Suggested empirical antibiotic regimens for severe infections: piperacillin-tazobactam, vancomycin, ceftazidime, cefepime, aztreonam or a carbapenem.
World Gastroenterology Organization: **Acute Diarrhea (2012)**[14]	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. • Consider antimicrobial treatment for: o *Shigella*, *Salmonella*, *Campylobacter* (dysenteric form), or parasitic

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	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)**[15]	<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. • Antibiotics are effective in the treatment of traveler's diarrhea and can reduce the average duration of disease from several days to ~1 day.

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	• 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)**[16]	Recommendations for therapy against specific pathogens
	• *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.
	• *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: **Ulcerative Colitis Practice Guidelines in Adults (2010)**[17]	Recommendations for management of mild-moderate distal colitis • Patients with mild to moderate distal colitis may be treated with oral aminosalicylates, topical mesalamine, or topical steroids. • Topical mesalamine agents are more effective than topical steroids or oral aminosalicylates. • The combination of oral and topical aminosalicylates is more effective than either alone. • In patients refractory to oral aminosalicylates or topical corticosteroids, mesalamine enemas or suppositories may still be effective. • The unusual patient who is refractory to all of the above agents in maximal doses, or who is systemically ill, may require treatment with oral prednisone in doses up to 40 to 60 mg per day, or infliximab with an induction regimen of 5 mg/kg at

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	weeks 0, two, and six, although the latter two agents have not been studied specifically in patients with distal disease. <u>Recommendations for maintenance of remission in distal disease</u> • Mesalamine suppositories are effective in the maintenance of remission in patients with proctitis, whereas mesalamine enemas are effective in patients with distal colitis when dosed even as infrequently as every third night. • Sulfasalazine, mesalamine compounds, and balsalazide are also effective in maintaining remission; the combination of oral and topical mesalamine is more effective than either one alone. • Topical corticosteroids have not proven effective for maintaining remission in distal colitis. • When all of these measures fail to maintain remission in distal disease, thiopurines (6-mercaptopurine) or azathioprine) and infliximab, but not corticosteroids, may prove effective. <u>Recommendations for management of mild-moderate extensive colitis: active disease</u> • Patients with mild to moderate extensive colitis should begin therapy with oral sulfasalazine in daily doses titrated up to 4 to 6 g per day, or an alternate aminosalicylate in doses up to 4.8 g per day of the active 5-aminosalicylate acid moiety. • Oral steroids are generally reserved for patients who are refractory to oral aminosalicylates in combination with topical therapy, or for patients whose symptoms are so troubling as to demand rapid improvement. • 6-mercaptopurine and azathioprine are effective for patients who do not respond to oral steroids, and continue to have moderate disease, and are not so acutely ill as to require intravenous therapy. • Infliximab is an effective treatment for patients who are steroid refractory or steroid dependent despite adequate doses of a thiopurine, or who are intolerant of these medications. The infliximab induction dose is 5 mg/kg intravenously at weeks 0, two, and six weeks. • Infliximab is contraindicated in patients with active infection, untreated latent tuberculosis, preexisting demyelinating disorder or optic neuritis, moderate to severe congestive heart failure, or current or recent malignancies. <u>Recommendations for mild-moderate extensive colitis: maintenance of remission</u> • Once the acute attack is controlled, a maintenance regimen is usually required, especially in patients with extensive or relapsing disease. • Sulfasalazine, olsalazine, mesalamine, and balsalazide are all effective in reducing relapses. • Patients should not be treated chronically with steroids. Azathioprine or 6-mercaptopurine may be useful as steroid-sparing agents for steroid-dependent patients and for maintenance of remission not adequately sustained by aminosalicylates, and occasionally for patients who are steroid dependent but not acutely ill. • Infliximab is effective in maintaining improvement and remission in the patients responding to the infliximab induction regimen. <u>Recommendations for management of severe colitis</u> • The patient with severe colitis refractory to maximal oral treatment with prednisone, oral aminosalicylate drugs, and topical medications may be treated with infliximab 5 mg/kg if urgent hospitalization is not necessary. • The patient who presents with toxicity should be admitted to hospital for a course of intravenous steroids. • Failure to show significant improvement within three to five days is an indication

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	for either colectomy or treatment with intravenous cyclosporine in the patient with severe colitis. • Long-term remission in these patients is significantly enhanced with the addition of maintenance 6-mercaptopurine. • Infliximab may also be effective in avoiding colectomy in patients failing intravenous steroids but its long-term efficacy is unknown in this setting.
Centers for Disease Control and Prevention: **Sexually Transmitted Diseases Treatment Guidelines (2015)**[18]	Arthritis and arthritis-dermatitis syndrome • Recommended regimen: o Ceftriaxone 1 g intramuscular or intravenous every 24 hours plus azithromycin 1 g orally in a single dose. • Alternative regimen: o Cefotaxime 1 g intravenous every eight hours or ceftizoxime 1 g intravenous every eight hours plus azithromycin 1 g orally in a single dose. Bacterial vaginosis • Recommended regimens: o Metronidazole 500 mg orally twice a day for seven days. o Metronidazole gel 0.75%, one full applicator (5 g) intravaginally, once a day for five days. o Clindamycin cream 2%, one full applicator (5 g) intravaginally at bedtime for seven days. • Alternative regimens: o Tinidazole 2 g orally once daily for two days. o Tinidazole 1 g 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. Cervicitis • Recommended regimens for presumptive treatment: o Azithromycin 1 g orally in a single dose. o Doxycycline 100 mg orally twice a day for seven days. Chancroid • Recommended regimens: o Azithromycin 1 g 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. Chlamydial infections • Recommended regimens: o Azithromycin 1 g 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. Chlamydial infections among children • Recommended regimen for children <45 kg: o Erythromycin base or ethylsuccinate 50 mg/kg/day orally divided into

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	four doses daily for 14 days. • Recommended regimen for children ≥45 kg and <8 years of age: o Azithromycin 1 g orally in a single dose. • Recommended regimens for children ≥8 years of age: o Azithromycin 1 g orally in a single dose. o Doxycycline 100 mg orally twice a day for seven days. Disseminated gonococcal infection • Recommended regimen: o Ceftriaxone 1 g intramuscular or intravenous every 24 hours. • Alternative regimens: o Cefotaxime 1 g intravenous every eight hours. o Ceftizoxime 1 g intravenous every eight hours. Epididymitis • 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. Granuloma inguinale (Donovanosis) • Recommended regimen: o Azithromycin 1 g orally once per week or 500 mg daily for at least three weeks and until all lesions have completely healed. • Alternative regimens: o Doxycycline 100 mg orally twice a day 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 g intramuscular in a single dose plus azithromycin 1 g orally 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 25 to 50 mg/kg intravenous or intramuscular in a single dose, not to exceed 125 mg. • Recommended regimen for children who weigh ≤45 kg and who have bacteremia or arthritis:

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	o Ceftriaxone 50 mg/kg (maximum dose: 1 g) 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 g intravenous every 12 hours plus azithromycin 1 g orally in a single dose. 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 g 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. • Alternative regimen: o Azithromycin suspension, 20 mg/kg/day orally, one dose daily for three days. Pelvic inflammatory disease • Recommended parenteral regimen A: o Cefotetan 2 g intravenous every 12 hours. o Cefoxitin 2 g 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 g 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 g intramuscular in a single dose and probenecid, 1 g orally

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	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. Proctitis, proctocolitis, and enteritis • Recommended regimen: o Ceftriaxone 250 mg intramuscular plus doxycycline 100 mg orally twice a day for seven days. Recurrent and persistent urethritis • Recommended regimens: o Metronidazole 2 g orally in a single dose. o Tinidazole 2 g orally in a single dose plus azithromycin 1 g orally in a single dose (if not used for initial episode). Primary and secondary syphilis • 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. Early latent syphilis • 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. Late latent syphilis or latent syphilis of unknown duration • 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. Tertiary syphilis • 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. Trichomoniasis • Recommended regimen: o Metronidazole 2 g orally in a single dose. o Tinidazole 2 g orally in a single dose. • Alternative regimen: o Metronidazole 500 mg orally twice a day for seven days. Neurosyphilis • Recommended regimen:

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	○ 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: ○ Procaine penicillin 2.4 million units intramuscular once daily plus probenecid 500 mg orally four times a day, both for 10 to 14 days. Uncomplicated gonococcal infections of the cervix, urethra, and rectum • Recommended regimens: ○ Ceftriaxone 250 mg intramuscular in a single dose. ○ Cefixime 400 mg orally in a single dose. ○ Single-dose injectable cephalosporin regimens plus azithromycin 1g orally in a single dose or doxycycline 100 mg orally twice a day for seven days. Uncomplicated gonococcal infections of the pharynx • Recommended regimens: ○ Ceftriaxone 250 mg intermuscular in a single dose plus azithromycin 1g orally in a single dose or doxycycline 100 mg orally twice a day for seven 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)**[19] Reviewed and deemed current as of 07/2013	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 g 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 relatively poor efficacy and the very high prevalence of antimicrobial resistance to these agents worldwide. Acute pyelonephritis • 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 g 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

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	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 g 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 g 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 g 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)**[20]	• 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 g dose (powder) single dose.
American Academy of Pediatrics/American Academy of Family Physicians: **Diagnosis and Management of Acute Otitis Media (2013)**[21]	<u>Observation option</u> • 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. <u>Antibacterial options - temperature <39°C without severe otalgia</u> • 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. <u>Antibacterial options - temperature ≥39°C and/or severe otalgia</u> • 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.

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American Academy of Otolaryngology–Head and Neck Surgery Foundation: **Clinical Practice Guideline: Adult Sinusitis (2015)**[22]	Symptomatic relief of viral rhinosinusitis • Management of viral rhinosinusitis is primarily symptomatic, with an analgesic or antipyretic provided for pain or fever, respectively. • Nasal saline may be palliative and cleansing with low risk of adverse reactions. • Oral decongestants may provide symptomatic relief and should be considered barring any medical contraindications, such as hypertension or anxiety. The use of topical decongestant is likely to be palliative, but continuous duration of use should not exceed three to five days, as recommended by the manufacturers, to avoid rebound congestion and rhinitis medicamentosa. • Clinical experience suggests oral antihistamines may provide symptomatic relief of excessive secretions and sneezing, although there are no clinical studies supporting the use of antihistamines in acute viral rhinosinusitis. • Guaifenesin (an expectorant) and dextromethorphan (a cough suppressant) are often used for symptomatic relief of viral rhinosinusitis symptoms, but evidence of clinical efficacy is lacking. Symptomatic relief of acute bacterial rhinosinusitis • Symptomatic treatments for acute bacterial rhinosinusitis include analgesics, topical intranasal steroids, and/or nasal saline irrigation. None of these products has been specifically approved by the FDA for use in acute rhinosinusitis (as of March 2014), and only some have data from controlled clinical studies supporting this use. • Over-the-counter analgesics, such as nonsteroidal anti-inflammatory drugs or acetaminophen, are usually sufficient to relieve facial pain associated with acute bacterial rhinosinusitis. • Antihistamines have no role in the symptomatic relief of acute bacterial rhinosinusitis in nonatopic patients. No studies support their use in an infectious setting, and antihistamines may worsen congestion by drying the nasal mucosa. Initial management of acute bacterial rhinosinusitis • Offer watchful waiting (without antibiotics) or prescribe initial antibiotic therapy for adults with uncomplicated acute bacterial rhinosinusitis. Watchful waiting should be offered only when there is assurance of follow-up, such that antibiotic therapy is started if the patient's condition fails to improve by seven days after acute bacterial rhinosinusitis diagnosis or if it worsens at any time. Choice of antibiotic for acute bacterial rhinosinusitis • If a decision is made to treat acute bacterial rhinosinusitis with an antibiotic, the clinician should prescribe amoxicillin with or without clavulanate as first-line therapy for five to ten days for most adults. • For penicillin-allergic patients, either doxycycline or a respiratory fluoroquinolone (levofloxacin or moxifloxacin) is recommended as an alternative agent for empiric antimicrobial therapy. Treatment failure for acute bacterial rhinosinusitis • If the patient worsens or fails to improve with the initial management option by seven days after diagnosis or worsens during the initial management, the clinician should reassess the patient to confirm acute bacterial rhinosinusitis, exclude other causes of illness, and detect complications. • If acute bacterial rhinosinusitis is confirmed in the patient initially managed with observation, the clinician should begin antibiotic therapy. • If the patient was initially managed with an antibiotic, the clinician should change the antibiotic.
American Academy of Allergy, Asthma, and	• Treat acute bacterial rhinosinusitis if symptoms last longer than 10 days or with recrudescence of symptoms after progressive improvement.

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Immunology/ American College of Allergy, Asthma and Immunology/ Joint Council on Allergy, Asthma and Immunology: **The Diagnosis and Management of Sinusitis: A Practice Parameter Update (2014)**[23]	• The most commonly reported bacterial pathogens in acute bacterial rhinosinusitis are *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Staphylococcus aureus.* • The antibiotics currently approved by the FDA for acute bacterial rhinosinusitis are azithromycin, clarithromycin, amoxicillin-clavulanate, cefprozil, cefuroxime axetil, loracarbef, levofloxacin, trimethoprim-sulfamethoxazole, and moxifloxacin. Although some studies have reported comparisons of different antibiotics for adult acute bacterial rhinosinusitis, not one was found to be superior. • Owing to concerns over bacterial resistance, the Infectious Diseases Society of America no longer recommends the use of macrolides for empiric treatment of acute bacterial rhinosinusitis. That organization recommends amoxicillin-clavulanate as first-line therapy and doxycycline, levofloxacin, and moxifloxacin in patients allergic to penicillin. • The Infectious Diseases Society of America recommends five to seven days of treatment with antibiotics for uncomplicated acute bacterial rhinosinusitis in adults and 10 to 14 days in children. • Use intranasal steroids for treatment of acute rhinosinusitis as monotherapy or with antibiotics.
American Academy of Pediatrics: **Clinical Practice Guideline for the Diagnosis and Management of Acute Bacterial Sinusitis in Children Aged 1 to 18 years (2013)**[24]	• Antibiotic therapy should be prescribed for acute bacterial sinusitis in children with severe onset or worsening course (signs, symptoms or both). • Antibiotic therapy or additional outpatient observation for three days should be utilized for children with persistent illness (nasal discharge of any quality, cough or both for at least 10 days). • When a decision has been made to initiate antibiotic therapy for the treatment of acute bacterial sinusitis, amoxicillin with or without clavulanate is considered first-line. • For children ≥2 years of age with uncomplicated acute bacterial sinusitis that is mild to moderate in severity who do not attend child care and have not received antibiotics in the previous four weeks, amoxicillin 45 mg/kg/day in two divided doses is recommended. In communities with high prevalence of *Streptococcus pneumoniae* (>10%, including intermediate and high level resistance), amoxicillin may be initiated at 80 to 90 mg/kg/day in two divided doses with a maximum of 2 g per dose. • Patients with moderate to severe illness and those <2 years of age who are attending child care or have recently received antibiotics, amoxicillin-clavulanate (80 to 90 mg/kg/day of amoxicillin with 6.4 mg/kg/day of clavulanate to a maximum of 2 g per dose) may be used. • A single dose of ceftriaxone 50 mg/kg intravenous or intramuscular may be used for children who are vomiting, unable to tolerate oral medication or unlikely to adhere to initial doses of antibiotic.

Global Initiative for Chronic Obstructive Lung Disease: **Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2016)**[25]	• Prophylactic, continuous use of antibiotics has been shown to have no effect on the frequency of exacerbations in chronic obstructive pulmonary disease.
	• The use of antibiotics, other than for treating infectious exacerbations of chronic obstructive pulmonary disease and other bacterial infections, is currently not indicated.
	• Based on current available evidence, antibiotics should be given to:
	  o Patients with exacerbations of chronic obstructive pulmonary disease with the following three cardinal symptoms: dyspnea, sputum volume, and sputum purulence.
	  o Patients with exacerbations of chronic obstructive pulmonary disease with two of the cardinal symptoms, if the increased purulence of sputum is one of the two symptoms.
	  o Patients with a severe exacerbation of chronic obstructive pulmonary disease that requires mechanical ventilation (invasive or noninvasive).

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	• The recommended length of antibiotic therapy is usually five to 10 days. • The choice of antibiotic should be based on local bacterial resistance patterns. • Initial empiric treatment may include an aminopenicillin with or without clavulanic acid, macrolide, or tetracycline. In patients with frequent exacerbations, severe airflow limitation, and/or exacerbations requiring mechanical ventilation, sputum cultures or cultures from other materials from the lung should be performed, as gram-negative bacteria or resistant pathogens that may not be sensitive to the afore-mentioned antibiotics may be present.
Center for Disease Control and Prevention: **Recommended Antimicrobial Agents for the Treatment and Postexposure Prophylaxis of Pertussis (2005)**[26] **(Was reviewed and deemed current as of February 2013)**	• Macrolides (erythromycin, clarithromycin, and azithromycin) are preferred for the treatment of pertussis in patients >1 month of age. For infants <1 month of age, azithromycin is preferred; erythromycin and clarithromycin are not recommended. • For treatment of patients >2 months of age, an alternative agent to macrolides is sulfamethoxazole-trimethoprim. • The choice of antimicrobial should take into account effectiveness, safety, tolerability, and ease of adherence to the regimen. • Azithromycin and clarithromycin are as effective as erythromycin for treatment of pertussis in patients >6 months of age, are better tolerated, and are associated with fewer and milder side effects than erythromycin. • Erythromycin and clarithromycin, but not azithromycin, are inhibitors of the cytochrome P450 enzyme system (CYP3A subclass) and can interact with other drugs that are metabolized by this system. • Azithromycin and clarithromycin are more resistant to gastric acid, achieve higher tissue concentrations, and have a longer half-life than erythromycin, allowing less frequent administration (one to two doses per day) and shorter treatment regimens (five to seven days).
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 (2016)**[27]	Primary prophylaxis of *Pneumocystis 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 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 jiroveci* pneumonia • Sulfamethoxazole-trimethoprim is the treatment of choice. The dose must be adjusted for abnormal renal function. Multiple randomized clinical trials indicate

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	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 jiroveci* despite sulfamethoxazole-trimethoprim prophylaxis are usually effectively treated with standard doses of sulfamethoxazole-trimethoprim. • Patients with documented or suspected *Pneumocystis 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 jiroveci* therapy. • The recommended duration of therapy for *Pneumocystis jiroveci* is 21 days. • Patients who have a history of *Pneumocystis 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 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 is recommended as the preferred regimen for *Pneumocystis jiroveci* prophylaxis and is effective against *Toxoplasma* encephalitis 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 jiroveci* pneumonia. • Atovaquone with or without pyrimethamine-leucovorin can also be considered. • 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.

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	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. Ethambutol is the recommended second drug.
Infectious Diseases Society of America: **Management of Patients with Infections Caused by Methicillin-Resistant *Staphylococcus Aureus* (2011)**[28]	Skin and soft-tissue infections • For a cutaneous abscess, incision and drainage is the primary treatment. For simple abscesses or boils, incision and drainage alone is likely to be adequate. • Antibiotic therapy is recommended for abscesses associated with the following conditions: severe or extensive disease (e.g., involving multiple sites of infection) or rapid progression in presence of associated cellulitis, signs and symptoms of systemic illness, associated comorbidities or immunosuppression, extremes of age, abscess in an area difficult to drain (e.g., face, hand, and genitalia), associated septic phlebitis, and lack of response to incision and drainage alone. • For outpatients with purulent cellulitis, empirical therapy for community-acquired methicillin-resistant *Staphylococcus aureus* is recommended pending culture results. Empirical therapy for infection due to beta-hemolytic streptococci is likely to be unnecessary. • For outpatients with non-purulent cellulitis, empirical therapy for infection due to beta-hemolytic streptococci is recommended. Empirical coverage for community-acquired methicillin-resistant *Staphylococcus aureus* is recommended in patients who do not respond to beta-lactam therapy and may be considered in those with systemic toxicity. • For empirical coverage of community-acquired methicillin-resistant *Staphylococcus aureus* in outpatients with skin and soft-tissue infections, oral antibiotic options include the following: clindamycin, sulfamethoxazole-

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	trimethoprim, a tetracycline (doxycycline or minocycline), and linezolid. If coverage for both beta-hemolytic streptococci and community-acquired methicillin-resistant *Staphylococcus aureus* is desired, options include the following: clindamycin alone or sulfamethoxazole-trimethoprim or a tetracycline in combination with a beta-lactam (e.g., amoxicillin) or linezolid alone. • The use of rifampin as a single agent or as adjunctive therapy for the treatment of skin and soft-tissue infections is not recommended. • For hospitalized patients with complicated skin and soft-tissue infections, in addition to surgical debridement and broad-spectrum antibiotics, empirical therapy for methicillin-resistant *Staphylococcus aureus* should be considered pending culture data. Options include the following: vancomycin intravenous, linezolid oral or intravenous, daptomycin intravenous, telavancin intravenous, and clindamycin intravenous or oral. A beta-lactam antibiotic (e.g., cefazolin) may be considered in hospitalized patients with non-purulent cellulitis with modification to methicillin-resistant *Staphylococcus aureus*-active therapy if there is no clinical response. • For children with minor skin infections (such as impetigo) and secondarily infected skin lesions (such as eczema, ulcers, or lacerations), mupirocin 2% topical ointment can be used. • Tetracyclines should not be used in children <8 years of age. • In hospitalized children with skin and soft-tissue infections, vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, empirical therapy with clindamycin intravenous is an option if the clindamycin resistance rate is low (<10%) with transition to oral therapy if the strain is susceptible. Linezolid oral or intravenous is an alternative. <u>Methicillin-resistant Staphylococcus aureus and infective endocarditis (native valve)</u> • For adults with uncomplicated bacteremia, vancomycin or daptomycin intravenous for at least two weeks is recommended. For complicated bacteremia, four to six weeks of therapy is recommended, depending on the extent of infection. • For adults with infective endocarditis, intravenous vancomycin or daptomycin for six weeks is recommended. • Addition of gentamicin to vancomycin is not recommended for bacteremia or native valve infective endocarditis. <u>Methicillin-resistant *Staphylococcus aureus* bacteremia and infective endocarditis (prosthetic valve)</u> • Intravenous vancomycin plus rifampin oral or intravenous for at least six weeks plus gentamicin intravenous for two weeks. • In children, vancomycin intravenous is recommended for the treatment of bacteremia and infective endocarditis. Duration of therapy may range from two to six weeks depending on source, presence of endovascular infection, and metastatic foci of infection. • Data regarding the safety and efficacy of alternative agents in children are limited, although daptomycin intravenous may be an option. Clindamycin or linezolid should not be used if there is concern for infective endocarditis or endovascular source of infection, but may be considered in children whose bacteremia rapidly clears and is not related to an endovascular focus. • Data are insufficient to support the routine use of combination therapy with rifampin or gentamicin in children with bacteremia or infective endocarditis. <u>Management of methicillin-resistant *Staphylococcus aureus* pneumonia</u> • For hospitalized patients with severe community-acquired pneumonia, empirical therapy for methicillin-resistant *Staphylococcus aureus* is recommended pending

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	sputum and/or blood culture results.
	• For health care–associated methicillin-resistant *Staphylococcus aureus* or community-acquired methicillin-resistant *Staphylococcus aureus* pneumonia, intravenous vancomycin or linezolid oral or intravenous or clindamycin oral or intravenous, if the strain is susceptible, is recommended for seven to 21 days, depending on the extent of infection.
	• In children, intravenous vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, clindamycin intravenous can be used as empirical therapy if the clindamycin resistance rate is low (<10%) with transition to oral therapy if the strain is susceptible. Linezolid oral or intravenous is an alternative.
	
	<u>Management of methicillin-resistant *Staphylococcus aureus* bone and joint infections</u>
	• Antibiotics available for parenteral administration include intravenous vancomycin and daptomycin.
	• Some antibiotic options with parenteral and oral routes of administration include the following: sulfamethoxazole-trimethoprim in combination with rifampin, linezolid, and clindamycin. Some experts recommend the addition of rifampin. For patients with concurrent bacteremia, rifampin should be added after clearance of bacteremia.
	• A minimum eight-week course is recommended. Some experts suggest an additional one to three months (and possibly longer for chronic infection or if debridement is not performed) of oral rifampin-based combination therapy with sulfamethoxazole-trimethoprim, doxycycline-minocycline, clindamycin, or a fluoroquinolone, chosen on the basis of susceptibilities.
	• For septic arthritis, refer to antibiotic choices for osteomyelitis. A three to four-week course of therapy is suggested.
	
	<u>Management of methicillin-resistant *Staphylococcus aureus* infections of the central nervous system</u>
	• Meningitis
	  o Intravenous vancomycin for two weeks is recommended. Some experts recommend the addition of rifampin.
	  o Alternatives include the following: linezolid or sulfamethoxazole-trimethoprim.
	  o For central nervous system shunt infection, shunt removal is recommended, and it should not be replaced until cerebrospinal fluid cultures are repeatedly negative.
	• Brain abscess, subdural empyema, spinal epidural abscess
	  o Intravenous vancomycin for four to six weeks is recommended. Some experts recommend the addition of rifampin.
	  o Alternatives include the following: linezolid and sulfamethoxazole-trimethoprim.
	• Septic thrombosis of cavernous or dural venous sinus
	  o Intravenous vancomycin for four to six weeks is recommended. Some experts recommend the addition of rifampin.
	  o Alternatives include the following: linezolid and sulfamethoxazole-trimethoprim.
	  o Intravenous vancomycin is recommended in children.

Infectious Diseases Society of America: **Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients**	<u>Initial antibiotic therapy</u>
	• Oral route:
	  o For low-risk adults only; use ciprofloxacin plus amoxicillin-clavulanate.
	• Monotherapy with vancomycin not indicated:
	  o Choose therapy with one of the following agents: cefepime or ceftazidime, or imipenem or meropenem.

Clinical Guideline	Recommendation(s)

with Cancer (2010)[29]
 	
Reviewed and deemed current as of 04/2013
	• Two drugs without vancomycin:
	  o Choose an aminoglycoside plus antipseudomonal penicillin, cephalosporin (cefepime or ceftazidime), or carbapenem.
	• Vancomycin plus one or two antibiotics:
	  o Choose cefepime or ceftazidime plus vancomycin, with or without an aminoglycoside; carbapenem plus vancomycin, with or without an aminoglycoside; or antipseudomonal penicillin plus an aminoglycoside and vancomycin.
	
	Modification of therapy during the first week of treatment
	• Patient becomes afebrile in three to five days:
	  o Adjust therapy to the most appropriate drug(s). If no etiologic agent is identified and if the patient is at low risk initially, and oral antibiotic treatment was begun with no subsequent complications, continue use of the same drugs.
	  o If the patient was at low risk initially and therapy with intravenous drugs was begun with no subsequent complications, the regimen may be changed after 48 hours to oral ciprofloxacin plus amoxicillin-clavulanate for adults or cefixime for children.
	  o If the patient is at high risk initially with no subsequent complications, continue use of the same intravenous drugs.
	• Persistent fever throughout the first three to five days:
	  o Reassess therapy on day three. If there is no clinical worsening, continue use of the same antibiotics; stop vancomycin use if cultures do not yield organisms.
	  o If there is progressive disease, change antibiotics.
	  o If the patient is febrile after five days, consider adding an antifungal drug.
	
	Antibiotic prophylaxis for afebrile neutropenic patients
	• Use of antibiotic prophylaxis is not routine because of emerging antibiotic resistance, except for the use of sulfamethoxazole-trimethoprim to prevent *Pneumocystis carinii* pneumonitis.

National Comprehensive Cancer Network: **Prevention and Treatment of Cancer-Related Infections (2016)**[30]	Low infection risk prophylaxis • Antimicrobial prophylaxis is not recommended in patients with low infection risk. Intermediate infection risk prophylaxis • Consider using fluoroquinolone prophylaxis. High infection risk prophylaxis • Consider using fluoroquinolone prophylaxis. • Additional prophylaxis may be necessary. *Pneumocystis jirovecii* prophylaxis • Sulfamethoxazole-trimethoprim is the preferred treatment. Sulfamethoxazole-trimethoprim has the additional benefit of activity against other pathogens including Nocardia, Toxoplasma, and Listeria. • Atovaquone, dapsone, and pentamidine are potential alternatives as prophylaxis for patients intolerant to sulfamethoxazole-trimethoprim. • Consider sulfamethoxazole-trimethoprim desensitization or atovaquone, dapsone, or pentamidine when *Pneumocystis* prophylaxis is required in patients who are sulfamethoxazole-trimethoprim intolerant. For patients receiving dapsone, consider assessing G6PD levels.

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	Pneumococcal infection prophylaxis
	• Prophylaxis for pneumococcal infection should begin three months after patients undergo hematopoietic stem cell transplantation with penicillin, and prophylaxis should continue for at least one year after the transplant.
	• In regions that have pneumococcal isolates with intermediate or high-level resistance to penicillin, sulfamethoxazole-trimethoprim will likely be adequate for pneumococcal prophylaxis.
	
	Initial empiric antibiotic therapy
	• Patients with neutropenia should begin empiric treatment with broad spectrum antibiotics at the first sign of infection.
	• Intravenous antibiotic monotherapy for uncomplicated infections (choose one):
	  o Cefepime.
	  o Imipenem-cilastatin.
	  o Meropenem.
	  o Piperacillin-tazobactam.
	  o Ceftazidime.
	• Oral antibiotic combination therapy for low-risk patients with uncomplicated infections:
	  o Ciprofloxacin plus amoxicillin-clavulanate.
	  o Moxifloxacin.
	  o Oral antibiotic regimen recommended should not be used if quinolone prophylaxis was used.
	• Complicated infections (choose based on local antibiotic susceptibility patterns):
	  o Intravenous antibiotic monotherapy is preferred.
	  o Intravenous combination therapy could be considered especially in cases of resistance.
	
	Antibacterial agents: empiric gram-positive activity
	• Vancomycin
	  o Gram-positive organisms with the exception of VRE and a number of rare organisms.
	  o Should not be considered as routine therapy for neutropenia and fever unless certain risk factors present.
	  o Dosing individualized with monitoring of levels; loading dose may be considered.
	• Daptomycin
	  o Has in vitro activity against VRE but is not FDA-approved for this indication.
	  o Weekly creatine phosphokinase (CPK) to monitor for rhabdomyolysis.
	  o Not indicated for pneumonia due to inactivation by pulmonary surfactant.
	• Linezolid
	  o Gram-positive organisms including VRE.
	  o Hematologic toxicity (typically with prolonged cases over two weeks) may occur.
	  o Not routinely use in fever and neutropenia, although may impair neutrophil and platelet recovery for extended use.
	  o Treatment option for VRE and MRSA.
	  o Peripheral/optic neuropathy with long-term use.
	
	Antibacterial agents: anti-pseudomonal
	• Cefepime
	  o Broad-spectrum activity against most gram-positive and negative organisms (not active against most anaerobes and *Enterococcus* species).

Clinical Guideline	Recommendation(s)
	o Use for suspected/proven CNS infection with susceptible organism. o Empiric therapy for neutropenic fever. • Ceftazidime o Relatively poor gram-positive activity (not active against most anaerobes and *Enterococcus* species). o Use for suspected/proven CNS infection with susceptible organism. o Empiric therapy for neutropenic fever (resistance among gram-negative rods at some centers). • Imipenem-cilastatin/ meropenem/ doripenem o Broad spectrum activity against most gram-positive, gram-negative, and anaerobic organisms. o Preferred against extended spectrum beta-lactamase and serious *Enterobacter* infections. o Carbapenem-resistant gram-negative rod infections are an increasing problem at a number of centers. o Use for suspected intra-abdominal source. o Meropenem is preferred over imipenem for suspected/proven CNS infection. o Effective in nosocomial pneumonia and intra-abdominal infections. • Piperacillin-tazobactam o Broad spectrum activity against most gram-positive, gram-negative, and anaerobic organisms. o Use for suspected intra-abdominal source. <u>Antibacterial agents: other</u> • Aminoglycosides o Activity primarily against gram-negative organisms. o Often used as empiric therapy in seriously ill or hemodynamically unstable patients. • Ciprofloxacin in combination with amoxicillin-clavulanate o Good activity against gram-negative and atypical organisms. Less active than "respiratory" fluoroquinolones against gram-positive organisms. o Ciprofloxacin alone has no activity against anaerobes. o Avoid for empiric therapy if patient recently treated with fluoroquinolone prophylaxis. • Levofloxacin/ moxifloxacin o Good activity against gram-negative and atypical organisms. o Levofloxacin has no activity against anaerobes. Moxifloxacin has limited activity against Pseudomonas. o Prophylaxis may increase bacterial resistance and superinfection. • Metronidazole o Good activity against anaerobic organisms. • Sulfamethoxazole-trimethoprim o Highly effective as prophylaxis against *Pneumocystis jiroveci* in high-risk patients. o Monitor for myelosuppression, hepatotoxicity, and hyperkalemia.
American College of Rheumatology: **2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis (2015)[31]**	<u>Recommendations for Early RA Patients</u> • Using a treat-to-target strategy rather than a non-targeted approach, regardless of disease activity level is strongly recommended. The ideal target should be low disease activity or remission, as determined by the clinician and the patient. In some cases, another target may be chosen because risk tolerance by patients or comorbidities may mitigate the usual choices. • For DMARD-naïve patients with early, symptomatic RA, DMARD monotherapy over double or triple DMARD therapy in patients with low disease activity is strongly recommended and DMARD monotherapy over double or triple DMARD therapy in patients with moderate or high disease

Clinical Guideline	Recommendation(s)
	activity is conditionally recommended. Methotrexate should be the preferred initial therapy for most patients with early RA with active disease. • For patients with moderate or high disease activity despite DMARD therapy (with or without glucocorticoids), treatment with a combination of DMARDs or a TNF-α inhibitor or a non-TNF biologic, with or without methotrexate (MTX) in no particular order of preference, rather than continuing DMARD monotherapy alone is strongly recommend. Biologic therapy should be used in combination with MTX over biologic monotherapy, when possible, due to superior efficacy. • For patients with moderate or high disease activity despite any of the above DMARD or biologic therapies, adding low-dose glucocorticoids (defined as ≤10 mg/day of prednisone or equivalent) is conditionally recommended. Low-dose glucocorticoids may also be used in patients who need a bridge until realizing the benefits of DMARD therapy. The risk/benefit ratio of glucocorticoid therapy is favorable as long as the dose is low and the duration of therapy is short. • For patients experiencing a flare of RA, adding short-term glucocorticoids (less than three months of treatment) at the lowest possible dose for the shortest possible duration, to provide a favorable benefit-risk ratio for the patient is conditionally recommended. Recommendations for Established RA Patients • Using a treat-to-target strategy rather than a non-targeted approach, regardless of disease activity level is strongly recommended. • For DMARD-naïve patients with low disease activity, using DMARD monotherapy over a TNF-α inhibitor is strongly recommended. For DMARD-naïve patients with moderate or high disease activity, DMARD monotherapy over double or triple DMARD therapy and DMARD monotherapy over tofacitinib is conditionally recommend. In general, MTX should be the preferred initial therapy for most patients with established RA with active disease. • For patients with moderate or high disease activity despite DMARD monotherapy including methotrexate, using combination DMARDs or adding a TNF-α inhibitor or a non-TNF biologic or tofacitinib (all choices with or without methotrexate) in no particular order of preference, rather than continuing DMARD monotherapy alone is strongly recommended. Biologic therapy should be used in combination with MTX over biologic monotherapy, when possible, due to its superior efficacy. *For all scenarios for established RA below, treatment may be with or without MTX:* • For moderate or high disease activity despite TNF-α inhibitor therapy in patients currently not on a DMARD, it is strongly recommended that one or two DMARDs be added to TNF-α inhibitor therapy rather than continuing TNF-α inhibitor therapy alone. • If disease activity is moderate or high despite single TNF-α inhibitor biologic therapy, it is conditionally recommended to use a non-TNF biologic. • If disease activity is moderate or high despite non-TNF biologic therapy, using another non-TNF biologic is conditionally recommended. However, if a patient has failed multiple non-TNF biologics and they are TNF-α inhibitor -naïve with moderate or high disease activity, treatment with a TNF-α inhibitor is conditionally recommended. • For patients with moderate or high disease activity despite prior treatment with at least one TNF-α inhibitor and at least one non-TNF-biologic (sequentially, not combined), first treating with another non-TNF biologic is conditionally recommended. However, when a non-TNF biologic is not an option (e.g., patient declines non-TNF biologic therapy due to inefficacy or side effects), treatment with tofacitinib is conditionally recommended.

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	• If disease activity is moderate or high despite the use of multiple (two or more) TNF-α inhibitor therapies (in sequence, not concurrently), non-TNF biologic therapy is conditionally recommended and then conditionally treating with tofacitinib when a non-TNF biologic is not an option. • If disease activity is moderate or high despite any of the above DMARD or biologic therapies, adding low-dose glucocorticoids is conditionally recommended. • If patients with established RA experience an RA flare while on DMARD, TNF-α inhibitor, or non-TNF biologic therapy, it is conditionally recommended to add short-term glucocorticoids (less than three months of treatment) at the lowest possible dose and for shortest possible duration to provide the best benefit-risk ratio for the patient. • In patients with established RA and low disease activity but not remission, continuing DMARD therapy, TNF-α inhibitor, non-TNF biologic or tofacitinib rather than discontinuing respective medication is strongly recommended. • In patients with established RA currently in remission, tapering DMARD therapy, TNF-α inhibitor, non-TNF biologic, or tofacitinib is conditionally recommended. • It is strongly recommended not to discontinue all therapies in patients with established RA in disease remission. Recommendations for RA patients with high-risk comorbidities • In patients with established RA with moderate or high disease activity and New York Heart Association (NYHA) class III or IV congestive heart failure (CHF), using combination DMARD therapy, a non-TNF biologic, or tofacitinib rather than a TNF-α inhibitor is conditionally recommended. If patients in this population are treated with a TNF-α inhibitor and their CHF worsens while on the TNF-α inhibitor, it is conditionally recommended to switch to combination DMARD therapy, a non-TNF biologic, or tofacitinib rather than a different TNF-α inhibitor. • In patients with established RA with moderate or high disease activity and evidence of active hepatitis B infection (hepatitis surface antigen positive > 6 months), who are receiving or have received effective antiviral treatment, treating them the same as patients without this condition is strongly recommended. For patients with chronic hepatitis B who are untreated, referral for antiviral therapy is appropriate prior to immunosuppressive therapy. • In patients with established RA with moderate or high disease activity and evidence of chronic hepatitis C virus (HCV) infection, who are receiving or have received effective antiviral treatment, treating them the same as the patients without this condition is conditionally recommended. If the same patient is not requiring or receiving antiviral treatment for their hepatitis C, using DMARD therapy rather than TNF-α inhibitor is conditionally recommended. • In patients with established RA and moderate or high disease activity and a history of previously treated or untreated skin cancer (melanoma or non-melanoma), the use of DMARD therapy over biologics or tofacitinib is conditionally recommended. • In patients with established RA with moderate or high disease activity and a history of a previously treated lymphoproliferative disorder, using rituximab rather than a TNF-α inhibitor is strongly recommended and using combination DMARD therapy, abatacept, or tocilizumab rather than TNF-α inhibitor is conditionally recommended. • In patients with established RA with moderate or high disease activity and previously treated solid organ cancer, it is conditionally recommended that they be treated for RA just as one would treat an RA patient without a history of

Clinical Guideline	Recommendation(s)
	solid organ cancer. • In patients with established RA with moderate or high disease activity and previous serious infection(s), using combination DMARD therapy or abatacept rather than TNF-α inhibitor is conditionally recommended. Recommendations for the Use of Vaccines in RA patients on DMARD and/or biologic therapy • In early or established RA patients aged 50 and over, giving the herpes zoster vaccine before the patient receives biologic therapy or tofacitinib for their RA is conditionally recommended. • In early or established RA patients who are currently receiving biologics, it is conditionally recommended that live attenuated vaccines such as the herpes zoster (shingles) vaccine not be given. • In patients with early or established RA who are currently receiving biologics, using appropriately indicated killed/inactivated vaccines is strongly recommended.
European League Against Rheumatism: **Management Of Rheumatoid Arthritis With Synthetic And Biological Disease-Modifying Antirheumatic Drugs: 2013 Update (2013)**[32] .	• Treatment of rheumatoid arthritis must be based on a shared decision between the patient and the rheumatologist. • Rheumatoid arthritis incurs high individual, societal and medical costs, all of which should be considered in its management. • Therapy with DMARDs should be started as soon as the diagnosis of rheumatoid arthritis is made. • Treatment should be aimed at reaching a target of remission or low disease activity in every patient. • Methotrexate should be part of the first treatment strategy in patients with active rheumatoid arthritis. • If methotrexate is contraindicated or is not tolerated, treatment with sulfasalazine or leflunomide should be considered. • In DMARD-naïve patients, treatment with conventional synthetic DMARD monotherapy or combination therapy of conventional synthetic DMARDs is recommended. • Low-dose glucocorticoids should be considered as part of the initial treatment strategy (in combination with one or more conventional synthetic DMARDs) for up to six months, but should be tapered as rapidly as clinically feasible. • If the treatment target is not achieved with the first DMARD strategy, in the absence of poor prognostic factors, change to another conventional synthetic DMARD strategy should be considered; when poor prognostic factors are present, addition of a biologic DMARD should be considered. • In patients with inadequate response to methotrexate and/or other conventional synthetic DMARDs, biologic DMARDs (TNF-α inhibitors, abatacept or tocilizumab) should be commenced with methotrexate; treatment with rituximab may be considered in the patients with recent history of lymphoma, latent tuberculosis with contraindications to the use of chemoprophylaxis, living in a tuberculosis-endemic region, or a previous history of demyelinating disease. • If a first biologic DMARD has failed, patients should be treated with another biologic DMARD; if a first TNF-α inhibitor therapy has failed, patients may receive another TNF-α inhibitor or a biological agent with a different mechanism of action. • Given the paucity of clinical experience and long-term safety data, tofacitinib should primarily be used when biological treatment has failed; additional clinical experience and safety data from registries, with a particular focus on serious infections, herpes zoster and malignancies, will be needed before the place of tofacitinib in the treatment sequence can be clarified. • If a patient is in persistent remission after having tapered glucocorticoids, tapering of biologic DMARDs can be considered, especially if this treatment is

Clinical Guideline	Recommendation(s)
	combined with a conventional synthetic DMARD. • In cases of sustained long-term remission, cautious reduction of the conventional synthetic DMARD dose could be considered, as a shared decision between patient and physician.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the sulfonamides 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 Sulfonamides[1-6]

Indication	Single Entity Agents		Combination Products
	Sulfadiazine	Sulfasalazine	Sulfamethoxazole and Trimethoprim
Central Nervous System Infections			
Haemophilus influenzae meningitis (adjunctive therapy with parental streptomycin)	✔		
Meningococcal meningitis	✔		
Toxoplasmic encephalitis (adjunctive therapy with pyrimethamine)	✔		
Gastrointestinal Indications			
Prolongation of the remission period between acute attacks of ulcerative colitis		✔ †‡	
Shigellosis			✔
Traveler's diarrhea			✔
Treatment of mild to moderate ulcerative colitis and adjunctive therapy for severe ulcerative colitis		✔ †‡	
Genitourinary Infections			
Chancroid	✔		
Urinary tract infections	✔		✔
Respiratory Infections			
Acute exacerbations of chronic bronchitis			✔
Otitis media			✔
Otitis media (adjunctive therapy with penicillin)	✔		
Pneumocystis carinii pneumonia			✔
Miscellaneous Infections			
Adjunctive treatment of malaria due to chloroquine-resistant strains of *Plasmodium falciparum*	✔		
Inclusive conjunctivitis	✔		
Nocardiosis	✔		
Rheumatic fever (prophylaxis)	✔		
Toxoplasmosis			
Trachoma	✔		
Treatment of patients with rheumatoid arthritis who have responded inadequately to salicylates or other nonsteroidal anti-inflammatory drugs		✔ †	
Treatment of pediatric patients with polyarticular-course juvenile rheumatoid arthritis who have responded inadequately to salicylates or other nonsteroidal anti-inflammatory drugs		✔ †	

†Delayed-release tablets.
‡Immediate-release tablets.

IV. Pharmacokinetics

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

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

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Single Entity Agents					
Sulfadiazine	Well absorbed	38 to 48	Liver	Renal (45 to 84)	7.0 to 16.8
Sulfasalazine	<15	99	Intestinal tract	Renal (37)	4.2 to 11
Combination Products					
Sulfamethoxazole and trimethoprim	90 to 100	Sulfa-methoxazole: 70 Trimethoprim: 44 to 62	Liver	Sulfa-methoxazole: Renal (84.5) Trimethoprim: Renal (66.8)	Sulfa-methoxazole: 8 to 11 Trimethoprim: 6 to 17

V. Drug Interactions

Major drug interactions with the sulfonamides are listed in Table 6.

Table 6. Major Drug Interactions with the Sulfonamides[2]

Generic Name(s)	Interaction	Mechanism
Sulfasalazine	Mercaptopurine	Concurrent use of mercaptopurine and sulfasalazine may result in an increased risk of bone marrow suppression.
Sulfonamides	Methenamine	Methenamine is contraindicated for use with sulfonamides due to the potential for formation of insoluble precipitates in the urine. Methenamine is broken down in acidic urine to formaldehyde. Insoluble precipitates may form when certain sulfonamides are exposed to formaldehyde.
Sulfasalazine	Riluzole	Concurrent use of sulfasalazine and riluzole may result in an increased risk of hepatotoxicity.
Sulfamethoxazole and trimethoprim	Anticoagulants	Sulfamethoxazole-trimethoprim may increase the hypoprothrombinemic effects of anticoagulants, possibly with bleeding. Inhibition of the hepatic metabolism of the S(-) warfarin enantiomorph appears to be the primary mechanism.
Sulfamethoxazole and trimethoprim	Methotrexate	The pharmacologic effects of methotrexate may be increased. Sulfonamides may displace methotrexate from plasma protein binding sites, competitively inhibit renal tubular secretion of methotrexate, and exert additive antifolate activity.
Sulfamethoxazole and trimethoprim	Tricyclic antidepressants	Concurrent use of sulfamethoxazole-trimethoprim and tricyclic antidepressants may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
Sulfamethoxazole and trimethoprim	Antiarrhythmic agents	Concurrent use of sulfamethoxazole-trimethoprim and antiarrhythmic agents may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
Sulfamethoxazole and trimethoprim	Leucovorin	Concurrent use of leucovorin calcium and sulfamethoxazole-trimethoprim may result in an increased rate of treatment failure.
Sulfamethoxazole and trimethoprim	Pyrimethamine	Concurrent use of sulfamethoxazole-trimethoprim and pyrimethamine may result in an increased risk of megaloblastic anemia and pancytopenia.
Sulfamethoxazole and trimethoprim	Gemifloxacin	Concurrent use of gemifloxacin and sulfamethoxazole-trimethoprim may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).

VI. Adverse Drug Events

The most common adverse drug events reported with the sulfonamides are noted in Table 7. The use of sulfonamides has been associated with rare cases of fatal adverse events, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia and other blood dyscrasias. Sulfonamide therapy should be discontinued at the first sign of these serious adverse events.

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

Adverse Events	Single Entity Agents		Combination Products
	Sulfadiazine	Sulfasalazine	Sulfamethoxazole and Trimethoprim
Cardiovascular			
Pericarditis	-	✔ †‡	-
Pleuritis	-	✔ †‡	-
Polyarteritis nodosa	-	✔ †‡	-
Central Nervous System			
Apathy	-	-	✔
Aseptic meningitis	-	-	✔
Ataxia	✔	✔ †‡	✔
Cauda equina syndrome	-	✔ †‡	-
Chills	✔	-	✔
Depression	✔	✔ †‡	✔
Dizziness	✔	4‡	-
Drowsiness	-	✔ †‡	-
Fatigue	-	-	✔
Fever	✔	≤5‡	✔
Guillain-Barre syndrome	-	✔ †‡	-
Hallucinations	✔	✔ †‡	✔
Headache	✔	≤9‡	✔
Hearing loss	-	✔ †‡	-
Insomnia	✔	✔ †‡	✔
Kernicterus	-	-	✔
Meningitis	-	✔ †‡	-
Nervousness	-	-	✔
Peripheral neuritis	✔	-	✔
Peripheral neuropathy	-	✔ †‡	-
Seizures	✔	✔ †‡	✔
Tinnitus	✔	✔ †‡	✔
Transverse myelitis	-	✔ †‡	-
Vertigo	✔	✔ †‡	✔
Dermatological			
Alopecia	-	✔ †‡	-
Erythema multiforme	✔	-	✔
Exfoliative dermatitis	✔	✔ †‡	✔
Henoch-Schonlein purpura	-	-	✔
Lyell's syndrome	✔	✔ †‡	-
Mucha-Habermann syndrome	-	✔ †‡	-
Photosensitivity	✔	✔ †‡	✔
Pruritus	✔	≤4‡	✔
Rash	✔	≤13‡	✔
Skin discoloration	-	✔ †‡	-
Skin eruption	✔	-	✔
Stevens-Johnson syndrome	✔	✔ †‡	✔
Toxic epidermal necrolysis	✔	-	✔

Adverse Events	Single Entity Agents		Combination Products
	Sulfadiazine	Sulfasalazine	Sulfamethoxazole and Trimethoprim
Urticaria	✔	✔ ‡	✔
Endocrine and Metabolic			
Goiter production	✔	-	-
Thyroid function disturbance	✔	-	-
Gastrointestinal			
Abdominal pain	✔	≤8†‡	✔
Anorexia	✔	✔ ‡	✔
Clostridium difficile diarrhea	-	-	✔
Diarrhea	✔	✔ †‡	✔
Dyspepsia	-	13‡	-
Enterocolitis	-	✔ †‡	-
Gastric distress	-	✔ ‡	-
Glossitis	-	-	✔
Loss of appetite	-	✔	✔
Nausea	✔	≤19‡	✔
Pancreatitis	✔	✔ †‡	✔
Pseudomembranous colitis	-	-	✔
Stomatitis	✔	✔ †, 4‡	✔
Vomiting	✔	≤8‡	✔
Genitourinary			
Acute nephropathy	✔	-	-
Anuria	✔	✔ †‡	✔
Crystalluria	✔	✔ †‡	✔
Diuresis	✔	-	✔
Hematuria	✔	✔ †‡	-
Hemolytic-uremic syndrome	-	✔ †‡	-
Interstitial nephritis	✔	✔ †‡	✔
Nephrotic syndrome	-	✔ †‡	-
Nephrotoxicity	-	-	✔
Oliguria	✔	✔ †‡	✔
Periarteritis nodosa	✔	-	✔
Proteinuria	-	✔ †‡	-
Renal failure	-	-	✔
Stone formation	✔	-	-
Toxic nephrosis	✔	✔ †‡	✔
Urinary tract infections	-	✔ †‡	-
Urine discoloration	-	✔ †‡	-
Hematologic			
Agranulocytosis	✔	✔ †‡	✔
Aplastic anemia	✔	✔ †‡	✔
Cyanosis	-	✔ ‡	-
Eosinophilia	-	-	✔
Granulocytopenia	✔	-	-
Heinz body anemia	-	✔ ‡	-
Hemolysis	-	-	✔
Hemolytic anemia	✔	✔ ‡	✔
Hypoprothrombinemia	✔	✔ †‡	✔
Leukopenia	✔	✔ †, 3‡	✔
Megaloblastic anemia	-	✔ †‡	✔
Methemoglobinemia	✔	✔ †‡	✔

Adverse Events	Single Entity Agents		Combination Products
	Sulfadiazine	Sulfasalazine	Sulfamethoxazole and Trimethoprim
Myelodysplastic syndrome	-	✔ †‡	-
Neutropenia	-	✔ †‡	✔
Purpura	✔	✔ †‡	-
Thrombocytopenia	✔	✔ †, 1‡	✔
Vasculitis	-	✔ †‡	-
Hepatic			
Cirrhosis	-	✔ †‡	-
Hepatic failure	-	✔ †‡	-
Hepatic necrosis	-	✔ †‡	✔
Hepatitis	✔	✔ †‡	-
Hepatotoxicity	-	✔ †‡	✔
Jaundice	✔	✔ †‡	-
Transaminases increased	-	✔ †, 4‡	✔
Laboratory Test Abnormalities			
Blood urea nitrogen increased	-	-	✔
Hyperbilirubinemia	-	-	✔
Hyperkalemia	-	-	✔
Hypoglycemia	✔	-	✔
Hyponatremia	-	-	✔
Serum creatinine increased	-	-	✔
Musculoskeletal			
Arthralgia	✔	✔ †‡	✔
Myalgia	-	-	✔
Rhabdomyolysis	-	✔ †‡	✔
Weakness	-	-	✔
Respiratory			
Cough	-	-	✔
Dyspnea	-	-	✔
Fibrosing alveolitis	-	✔ †‡	-
Interstitial lung disease	-	✔ †‡	-
Pneumonitis	-	✔ †‡	-
Pulmonary infiltrates	-	-	✔
Other			
Allergic reaction	-	-	✔
Allergic myocarditis	✔	✔ †‡	✔
Anaphylactoid reactions	✔	-	-
Anaphylaxis	✔	✔ †‡	✔
Angioedema	-	-	✔
Conjunctival injection	✔	✔ †‡	-
Drug fever	✔	-	-
Lupus-like symptoms	-	✔ †‡	✔
Periorbital edema	✔	✔ †‡	-
Scleral injection	✔	✔ †‡	-
Serum sickness-like reactions	✔	✔ †‡	✔

✔ Percent not specified.
- Event not reported or incidence <1%.
†Immediate-release formulation.
‡Delayed-release formulation.

VII. Dosing and Administration

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

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

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Sulfadiazine	Unspecified infections: Tablet: Initial, 2 to 4 g; maintenance, 2 to 4 g, divided into three to six doses, every 24 hours	Rheumatic fever prophylaxis for patients ≥2 months of age: Tablet: <30 kg, 500 mg every 24 hours; ≥30 kg, 1 g every 24 hours Unspecified infections ≥2 months of age: Tablet: Initial, one-half the 24-hour dose; maintenance, 150 mg/kg or 4 g/m^2, divided into four to six doses, every 24 hours	Tablet: 500 mg
Sulfasalazine	Treatment of patients with rheumatoid arthritis who have responded inadequately to salicylates or other nonsteroidal anti-inflammatory drugs: Delayed-release tablet: 0.5 to 1 g/day in one or two doses Prolongation of the remission period between acute attacks of ulcerative colitis, treatment of mild to moderate ulcerative colitis and adjunctive therapy for severe ulcerative colitis: Delayed-release tablet, tablet: Initial, 3 to 4 g daily in evenly divided doses; maintenance, 2 g daily	Treatment of pediatric patients with polyarticular-course juvenile rheumatoid arthritis who have responded inadequately to salicylates or other nonsteroidal anti-inflammatory drugs in patients ≥6 years of age: Delayed-release tablet: 30 to 50 mg/kg/day in two divided doses Prolongation of the remission period between acute attacks of ulcerative colitis, treatment of mild to moderate ulcerative colitis and adjunctive therapy for severe ulcerative colitis in patients ≥6 years of age: Delayed-release tablet, tablet: Initial, 40 to 60 mg/kg/day in three to six divided doses; maintenance, 30 mg/kg/day divided into four doses	Tablet: 500 mg Delayed-release tablet: 500 mg
Combination Products			
Sulfamethoxazole and trimethoprim	Acute exacerbations of chronic bronchitis: Suspension, tablet: 800-160 mg every 12 hours for 14 days *Pneumocystis Carinii* pneumonia prophylaxis: Suspension, tablet: 800-160 mg daily *Pneumocystis Carinii* pneumonia treatment: Injection, tablet, suspension: 75 to 100 mg/kg sulfamethoxazole and 15 to 20 mg/kg trimethoprim per day	Acute otitis media in patients ≥2 months of age: Suspension, tablet: 40 mg/kg sulfamethoxazole and 8 mg/kg trimethoprim per day given in two divided doses every 12 hours for 10 days *Pneumocystis Carinii pneumonia* prophylaxis in patients ≥2 months of age: Suspension, tablet: 750 mg/m^2/day sulfamethoxazole and 150 mg/m^2/day trimethoprim given in equally divided doses twice daily on three consecutive	Injection: 80-16 mg/mL Suspension: 200-40 mg/5 mL 800-160 mg/20 mL Tablet: 400-80 mg 800-160 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	given in equally divided doses every six hours for 14 to 21 days Shigellosis: Injection, suspension, tablet: 800-160 mg every 12 hours for five days Traveler's diarrhea: Suspension, tablet: 800-160 mg every 12 hours for five days Urinary tract infections: Suspension, tablet: 800-160 mg every 12 hours for 10 to 14 days	days per week *Pneumocystis Carinii* pneumonia treatment in patients ≥2 months of age: Injection, tablet, suspension: 75 to 100 mg/kg sulfamethoxazole and 15 to 20 mg/kg trimethoprim per day given in equally divided doses every six hours for 14 to 21 days Shigellosis in patients ≥2 months of age: Injection, tablet, suspension: 40 mg/kg sulfamethoxazole and 8 mg/kg trimethoprim per day given in two divided doses every 12 hours for five days Urinary tract infections in patients ≥2 months of age: Injection, tablet, suspension: 40 mg/kg sulfamethoxazole and 8 mg/kg trimethoprim per day given in two divided doses every 12 hours for 10 days	

VIII. Effectiveness

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

Table 9. Comparative Clinical Trials with the Sulfonamides

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Central Nervous System Infections				
Torre et al.[33] (1998) Sulfadiazine 60 mg/kg/day, pyrimethamine 50 mg QD, folinic acid 10 mg QD for four weeks, followed by three months maintenance therapy at half of the original dosage vs SMX-TMP 50 to 10 mg/kg/day for four weeks, followed by three months maintenance therapy at half of the original dosage	MC, PRO, RCT Patients >18 years of age with AIDS and toxoplasmic encephalitis	N=77 4 months	Primary: Clinical efficacy, radiologic efficacy, death, adverse events Secondary: Not reported	Primary: There was no statistically significant difference in complete clinical response rate between the sulfadiazine-pyrimethamine and the SMX-TMP groups at the end of acute therapy (65.7 vs 62.1%, respectively). A complete resolution of radiologic lesions was noted in 39.3% of patients in the sulfadiazine and pyrimethamine group compared to 62.1% patients in the SMX-TMP group (P=0.0478). There was no significant difference in survival between the two groups. Adverse effects occurred more frequently in the sulfadiazine and pyrimethamine treatment group compared to the SMX-TMP group (37.8 vs 12.5%, respectively; P=0.0162). Skin rashes were observed only in the sulfadiazine-pyrimethamine group. Secondary: Not reported
Chirgwin et al.[34] (2002) Sulfadiazine 1,500 mg QID and atovaquone suspension 1,500 mg QD for six	OL, RCT Patients with either presumptive or definitive toxoplasmic encephalitis, either acute or relapsed,	N=49 48 weeks	Primary: Clinical and radiographic response to treatment for acute disease and as maintenance therapy, adverse	Primary: Out of patients assigned to atovaquone and pyrimethamine, 75% experienced an overall response to treatment for acute disease compared to 82% in the atovaquone and sulfadiazine group. All patients demonstrated complete resolution of lesions on radiologic examinations performed at weeks 12 and 16 during the maintenance therapy phase.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
weeks of acute treatment and 42 week maintenance period vs atovaquone suspension 1,500 mg QD and pyrimethamine 200 mg on day one, followed by 75 mg QD for six weeks of acute treatment and 42 week maintenance period	HIV-positive or diagnosed with AIDS		effects Secondary: Not reported	Adverse events requiring treatment discontinuation occurred in 32% of patients receiving pyrimethamine and 17% of those on sulfadiazine regimen. Secondary: Not reported
Dermatological Infections				
Talan et al.[35] (2016) SMX-TMP 1600-320 mg BID for seven days vs placebo	DB, MC, RCT Patients >12 years of age had a cutaneous lesion that was suspected to be an abscess	N=1247 Test-of-cure: 14 to 21 days Extended follow-up: 49 to 63 days	Primary: Clinical cure at test-of-cure visit Secondary: Composite cure (resolution of all symptoms and signs of infection, or improvement such that no additional antibiotic therapy or surgical drainage procedure was necessary), surgical drainage procedures, changes in abscess,	Primary: The abscess cure rate was 80.5% in the SMX-TMP group and 73.6% in the placebo group in the modified ITT population (difference, 6.9 percentage points; 95% CI, 2.1 to 11.7; P=0.005). Secondary: SMX-TMP achieved more favorable responses compared to placebo in most secondary outcomes, resulting in lower rates of subsequent surgical drainage procedures (3.4 vs 8.6%; difference, −5.2 percentage points; 95% CI, −8.2 to −2.2), skin infections at a new site (3.1 vs 10.3%; difference, −7.2 percentage points; 95% CI, −10.4 to −4.1), and infections among household members (1.7 vs 4.1%; difference, −2.4 percentage points; 95% CI, −4.6 to −0.2) through the test-of-cure visit. SMX-TMP was associated with slightly more gastrointestinal side effects (mostly mild) than placebo. At seven to 14 days after the treatment period, invasive infections had developed in two of 524 participants (0.4%) in the SMX-TMP group and in two of 533 participants (0.4%) in the placebo group; at 42 to 56 days after the treatment period, an invasive infection

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			invasive infections, hospitalizations, days missed	had developed in one participant (0.2%) in the SMX-TMP group.
Tong et al.[36] (2010) SMX-TMP 20-4 mg/kg BID for five days vs penicillin benzathine 45 mg/kg IM as a single dose	RCT Aboriginal children 2 months to 16 years of age with impetigo	N=13 7 days	Primary: Successful treatment of impetigo lesions at day seven after the commencement of treatment Secondary: Bacterial resolution of sores at day four and day seven; successful treatment at day four	Primary: Treatment was successful in all seven patients assigned to SMX-TMP, and five of six patients assigned to the penicillin group seven days after randomization (P=0.46). Secondary: By day four, microbiological clearance was documented in five of seven patients treated with SMX-TMP and in two of six patients treated with penicillin (P=0.28). By day seven, microbiological clearance was documented in all seven patients treated with SMX-TMP and in three of six patients treatment with penicillin (P=0.07). Treatment was successful after four days in six of seven treated with SMX-TMP and three of six with penicillin (P=0.27).
Khawcharoenporn et al.[37] (2010) SMX-TMP one double strength tablet BID vs cephalexin 500 mg QID vs clindamycin 300 mg QID	RETRO Patients ≥18 years of age with cellulitis	N=405 Variable duration	Primary: Treatment success rate, compliance, safety Secondary: Not reported	Primary: The overall treatment success rate with SMX-TMP was significantly higher than the success rate with cephalexin (91 vs 74%; P<0.001). Clindamycin success rate was higher than that of cephalexin but did not reach statistical significance (85 vs 74%; P=0.22). The success rates of SMX-TMP and clindamycin were comparable. The treatment success rate with SMX-TMP was significantly more successful than cephalexin in patients who were male (P=0.001), were Pacific Islanders (P=0.001), had diabetes mellitus (P=0.001), were obese (P=0.002), had positive cultures for MRSA (P=0.01), and were cigarette smokers (P=0.04). The treatment success rate with clindamycin was higher than with cephalexin in patients who had MRSA infections (P<0.01), had moderately severe cellulitis (P<0.03), and were obese (P<0.04). MRSA was recovered in 62% of positive culture specimens.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Compliance and adverse drug reaction rates were not significantly different among patients who received these three antibiotics. Factors associated with treatment failure included therapy with an antibiotic that was not active against community-associated MRSA (P<0.001) and severity of cellulitis (P<0.001). Secondary: Not reported
Gastrointestinal Infections				
Ericsson et al.[38] (1990) SMX-TMP 1,600-320 mg given as one dose vs SMX-TMP 800-160 mg given orally BID for three days vs loperamide 4 mg given as a loading dose, followed by 2 mg after each loose stool movement (maximum dose 16 mg) vs SMX-TMP 800-160	DB, PC, RCT Patients with >3 unformed stools within 24 hours of study entry in addition to another symptom of enteric disease, such as abdominal cramps, nausea, or vomiting	N=227 3 days	Primary: Duration of diarrhea, failure rate Secondary: Not reported	Primary: Patients treated with the combination therapy had the shortest duration of diarrhea (one hour) compared to the placebo group (59 hours) and the three-day SMX-TMP therapy (34 hours; P<0.005 compared to placebo). The proportion of treatment failures was significantly lower in all treatment groups compared to the placebo group (P<0.005). Patients presenting with mild diarrhea at baseline randomized to the loperamide group exhibited shorter duration of diarrhea (18 hours) compared to the placebo group (96 hours; P=0.02). Patients treated solely with loperamide exhibited longer diarrhea duration compared to patients on combination therapy (P=0.02). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg given orally BID for three days, in addition to loperamide, 4 mg given as a loading dose, followed by 2 mg after each loose stool movement (maximum dose 16 mg) vs placebo				
Genitourinary Infections				
Tran et al.[39] (2001) SMX-TMP 40-8 mg/kg/day for one to three days (short-treatment course) vs SMX-TMP 40-8 mg/kg/day for 7 to 14 days (long-treatment course) or amoxicillin for one to three days (short-treatment course) vs	MA Children <18 years of age with uncomplicated cystitis confirmed by urine culture	N=1,279 (22 trials) Up to 14 days	Primary: Cure rate, adverse events Secondary: Not reported	Primary: There was no difference between short- and long-courses of SMX-TMP in terms of cure rates (difference in cure rate, 6.24%; 95% CI, -3.74 to 16.2). The short-course amoxicillin therapy was less effective in curing the infection compared to the conventional length of therapy (difference in cure rate, 13%; 95% CI, 4 to 24). Consequently, eight patients would need to receive a conventional amoxicillin course of therapy to prevent one treatment failure that would have occurred with a shorter duration of treatment. Drug-related toxicity increased in proportion to the length of therapy. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
amoxicillin for 7 to 14 days (long-treatment course)				
Mårild et al.[40] (2009) SMX-TMP 15-3 mg/kg oral suspension BID for 10 days vs ceftibuten 9 mg/kg oral suspension QD for 10 days	MC, OL, RCT Patients 1 month to 12 years of age with a first-time febrile UTI	N=547 14 to 20 days	Primary: Bacteriological and clinical outcomes Secondary: Not reported	Primary: In the intention-to-treat population, the bacteriological elimination rates in the ceftibuten and SMX-TMP groups were 91 and 95%, respectively (P=NS). In the per protocol population, the bacteriological elimination rates in the ceftibuten and SMX-TMP groups were 91 and 97%, respectively (P<0.01). In the intention-to-treat population, the clinical cure rates among patients treated with ceftibuten and SMX-TMP were 93 and 83%, respectively (P=0.008). In the per protocol population, the clinical cure rates were 93 and 90%, respectively (P=NS). Adverse events were reported by 3% of the patients in the ceftibuten group and by 5% in the SMX-TMP group (P=NS). Gastrointestinal symptoms were reported most frequently. There were no serious adverse events reported. Secondary: Not reported
McCarty et al.[41] (1999) SMX-TMP 800-160 mg BID for three days vs ciprofloxacin 100	MC, RCT Women ≥18 years of age with primary UTI, confirmed by a positive urine culture obtained within 48 hours of study onset,	N=688 Up to 6 weeks	Primary: Pathogen eradication rate, clinical response rate (resolution of symptoms), relapse rate, premature discontinuation, adverse events	Primary: End-of-study evaluation revealed a lack of statistically significant difference in the pre-treatment pathogen eradication rate between the study groups. Pathogen eradication occurred in 94% of ciprofloxacin, 93% of SMX-TMP, and 97% of ofloxacin-treated patients. At the four to six week follow-up evaluation, recurrence rates were 11% in the ciprofloxacin, 16% in the SMX-TMP, and 13% in the ofloxacin-treated group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg BID for three days vs ofloxacin 200 mg BID for three days	presenting with signs and symptoms of dysuria, pyuria, and urinary frequency for <10 days duration		Secondary: Not reported	Clinical success at the end of therapy was 31% in the ciprofloxacin, 41% in the SMX-TMP, and 39% in the ofloxacin-treated group. The frequency of adverse effects was 93% in the ciprofloxacin, 95% in the SMX-TMP, and 96% in the ofloxacin-treated group (P=0.03). Premature discontinuation of the study drug due to side effects was more common in the SMX-TMP group, compared to the ciprofloxacin and ofloxacin groups (P=0.02). Secondary: Not reported
Gupta et al.[42] (2007) SMX-TMP 800-160 mg tablets BID for three days vs nitrofurantoin 100 mg BID for five days	OL, RCT Women18 to 45 years of age who had symptoms of acute cystitis (dysuria, frequency, and/or urgency)	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 a 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).
Buckwold et al.[43] (1982) SMX-TMP 800-160 mg two tablets as a single dose	MC, RCT Women with symptoms suggestive of acute cystitis (dysuria, frequency of	N=117 Up to 4 weeks	Primary: Pathogen eradication rate, clinical response rate (resolution of symptoms), relapse rate, premature	Primary: Overall cure rates varied from 85 to 95%, but there was no statistically significant difference between the study groups (P>0.05). SMX-TMP regimens were associated with a significantly greater minimum inhibitory concentration at 24 hours postdose compared to the sulfisoxazole group (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs SMX-TMP 1,600-320 mg four tablets as a single dose vs sulfisoxazole 1 g two tablets as a single dose vs sulfisoxazole 2 g two tablets as a single dose	urination, suprapubic discomfort)		discontinuation, adverse events Secondary: Not reported	None of the regimens predisposed patients to re-infection (P>0.05). Secondary: Not reported
Varde et al.[44] (1981) SMX-TMP 400-80 mg two tablets BID for 14 days vs trimethoprim-sulfadiazine 75-225 mg two tablets BID for 14 days	RCT Patients 11 to 66 years of age with an uncomplicated UTI confirmed by urine culture	N=37 14 days	Primary: Microbiological and clinical response, adverse events Secondary: Not reported	Primary: The number of patients exhibiting good response (defined as symptomatic improvement with sterile urine culture after three days of treatment) was greater in the trimethoprim-sulfadiazine group compared to the SMX-TMP group (74 vs 61%, respectively). While 37% of patients in the trimethoprim-sulfadiazine group exhibited clinical response (defined as being asymptomatic on the first day of treatment with significant bacteriuria), 44% of patients in the SMX-TMP group exhibited a clinical response. Only one patient in the trimethoprim-sulfadiazine group developed a macular rash, which was the only adverse event observed during the study period. Secondary: Not reported
Respiratory Infections				
Chintu et al.[45] (2004)	DB, RCT	N = 534	Primary: Mortality,	Primary: The study was conducted in an area of high SMX-TMP resistance (60 to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
SMX-TMP 240 mg suspension daily (children <5 years of age); 480 mg suspension daily (children ≥5 years of age) vs placebo	Children 1 to 14 years of age with a positive HIV antibody test and, for those younger than 18 months of age, clinical features suggestive of an HIV infection	19 months	hospitalization, adverse events, PCP Secondary: Not reported	80%). A 33% reduction in mortality was seen in the SMX-TMP group compared to placebo (RR, 0.67; 95% CI, 0.53 to 0.85). SMX-TMP was associated with a statistically significant reduction in hospitalization rate compared to placebo (RR, 0.77; 95% CI, 0.62 to 0.96). There was no significant difference in adverse effects between the two groups (P=0.06). This benefit applied across all ages (test for heterogeneity P=0.82) and baseline CD4 counts (test for heterogeneity P=0.36). *Pneumocystis carinii* was identified in only one (placebo) of 73 nasopharyngeal aspirates from children with pneumonia. Secondary: Not reported
Toma et al.[46] (1998) SMX-TMP 1,600-320 mg (≥60 kg) or 1,200-240 mg (<60 mg) QID for 21 days vs clindamycin 450 mg QID and primaquine 15 mg QD for 21 days	DB, MC, RCT Patients ≥16 years of age with HIV-related PCP	N=116 21 days	Primary: Treatment success (>2-point improvement in the PCP score, calculated on the basis of body temperature, respiratory rate, cough, chest tightness, dyspnea, supplemental oxygen requirements, and chest radiograph), steroid use, duration of therapy, adverse	Primary: There was no statistically significant difference in the duration of therapy between the treatment groups (P=0.68). The treatment success rates for SMX-TMP and clindamycin-primaquine were 76% and 74%, respectively. There were no statistically significant differences between the treatment regimens with respect to dyspnea scores, PCP scores and lactate dehydrogenase values at any time. There was no statistically significant difference between treatment groups with respect to the use of steroids (12 patients per group; P=0.74). There was no significant difference in the rate of PCP recurrence between the two treatment arms (P=0.99). There was no significant difference in the rate of adverse effects experienced by the two treatment groups (P=0.57). Rash was the most frequent side effect in both groups. The incidence of rash was similar in

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			events Secondary: Not reported	both groups (P=0.78). Secondary: Not reported
Klein et al.[47] (1992) SMX-TMP 100-20 mg/kg/day IV divided into four doses vs pentamidine 4 mg/kg/day IV administered over one hour	DB, PRO, RCT Patients with PCP, confirmed by either a bronchoalveolar lavage or lung biopsy	N=163 21 days	Primary: Treatment failure (defined as persistent fever, worsening hypoxemia, and/or progressive roentgenographic deterioration), change in therapy due to toxicity, five-day mortality rate, survival rate, adverse effects Secondary: Not reported	Primary: Slightly more patients in the SMX-TMP group (42%) experienced treatment failure compared to the pentamidine group (40%; P=0.733). Slightly more patients in the SMX-TMP group (34%) had to discontinue therapy due to toxicity compared to the pentamidine group (25%; P=0.235). The mortality rate during the first five days of therapy was 4% in each of the two treatment groups (P=0.984). The overall survival rates were similar in the SMX-TMP (67%) and pentamidine groups (74%; P=0.402). The survival rates for patients requiring a change in therapy because of failure to respond was 46% for the SMX-TMP group compared to 56% for the pentamidine group. When a change in therapy was made because of toxicity, survival rates were 97% for those receiving SMX-TMP vs 94% for those receiving pentamidine. Secondary: Not reported
Bucher et al.[48] (1997) SMX-TMP 800-160 mg daily to three times weekly vs	MA Patients with HIV receiving antiretroviral treatment	N=4,832 (22 trials) Mean 13.2 months	Primary: PCP events, all-cause mortality, toxoplasmosis events, drug-related toxicity Secondary: Not reported	Primary: The risk ratio of dapsone-pyrimethamine compared to pentamidine in terms of PCP infection was 0.90 (95% CI, 0.71 to 1.15), 0.72 for toxoplasma encephalitis (95% CI, 0.54 to 0.97), and 1.07 (95% CI, 0.90 to 1.27) for mortality. Patients with higher CD4 counts at baseline (>100 cells/mm3) were found to be at a higher risk for experiencing drug-related toxicity compared to those with lower CD4 cell counts (P=0.01).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
pentamidine 300 to 400 mg monthly to 300 mg bimonthly vs dapsone 50 mg QD to 100 mg twice weekly or dapsone-pyrimethamine 350-50 mg weekly				High-dose dapsone-pyrimethamine regimens (≥200/50 mg) were more effective compared to the low-dose regimens. Compared to aerosolized pentamidine, SMX-TMP was more effective at reducing the rate of PCP infections (RR, 0.59; 95% CI, 0.45 to 0.76). However the difference in the risk of toxoplasma encephalitis (RR, 0.78; 95% CI, 0.55 to 1.11) and mortality (RR, 0.88; 95% CI, 0.74 to 1.06) was not statistically significant. SMX-TMP was more effective at preventing PCP infections in patients with higher CD4 counts at baseline (>100 cells/mm^3) compared to those with lower CD4 cell counts (P=0.02). Compared to dapsone-pyrimethamine, SMX-TMP was more effective at reducing the rate of PCP infections (RR, 0.49; 95% CI, 0.26 to 0.92). However the difference in the risk of toxoplasma encephalitis (RR, 1.17; 95% CI, 0.26 to 2.18), mortality (RR, 0.98; 95% CI, 0.80 to 1.08), and drug-limiting toxicity (RR, 1.08; 95% CI, 0.88 to 1.25) was not statistically significant. The reduction of mortality risk due to SMX-TMP treatment was greater among patients with lower CD4 counts at baseline (<100 cells/mm3) compared to those with higher CD4 cell counts (P=0.03). Drug limiting toxicity was experienced by 31.5%, 29.7%, and 6.8% of patients treated with SMX-TMP, dapsone-pyrimethamine, and aerosolized pentamidine, respectively. Compared to aerosolized pentamidine, SMX-TMP administered to 100 patients will prevent three to seven cases of PCP at a risk of 21 additional patients experiencing toxicity. Secondary: Not reported.
Ioannidis et al.[49] (1996)	MA	N=6,583 (35 trials)	Primary: PCP events, PCP-	Primary: SMX-TMP was effective in preventing PCP infection; the failure rate was

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
SMX-TMP vs pentamidine vs dapsone-based regimen vs placebo	Patients ≥18 years of age with HIV	Up to 2 years	related mortality, all-cause mortality, toxoplasmosis events Secondary: Not reported	close to zero (0.5%). Patients randomized to SMX-TMP exhibited less prophylactic failures (42% reduction; 95% CI, 24 to 55) compared to patients receiving aerosolized pentamidine. The overall rate of treatment-limiting adverse events (per 100 patient-years) was 19 (95% CI, 18 to 21) for SMX-TMP and 15 (95% CI, 14 to 17) for dapsone-based regimens. The risk of adverse effects requiring SMX-TMP discontinuation decreased by 43% in patients taking SMX-TMP three times weekly as opposed to QD (95% CI, 30 to 54). Secondary: Not reported
Sachs et al.[50] (1995) SMX-TMP 800-160 mg BID for seven days in addition to oral corticosteroids vs amoxicillin 500 mg TID for seven days in addition to oral corticosteroids vs oral corticosteroids	DB, RCT Patients ≥18 years of age with asthma or COPD	N=195 14 days	Primary: PEF Secondary: Not reported	Primary: PEF percent predicted assessed during an exacerbation improved significantly in all three groups over the 14-day observation period (P<0.001), ranging from 0.34 to 0.78% predicted per day, finally returning to baseline value. No statistically significant difference was observed between the groups. There was no statistically significant difference between the groups in symptom scores, expressed as slopes or absolute values from days one to 14. The decrease in the symptom severity scores was significant in all three groups (P<0.001). There was no statistically significant difference between the three groups in terms of treatment failure rate. Secondary: Not reported
Nouira et al.[51] (2010) SMX-TMP 800-160	DB, RCT Patients ≥40 years of age with an	N=170 10 days	Primary: Hospital death and need for an additional course	Primary: Combined hospital death and additional antibiotic prescription rates were similar in the two groups (16.4 vs 15.3% in the SMX-TMP vs ciprofloxacin group; 95% CI, -9.8% to 12.0; P=0.832).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg BID for 10 days vs ciprofloxacin 750 mg BID for 10 days	acute exacerbation of COPD requiring mechanical ventilation		of antibiotics Secondary: Duration of mechanical ventilation, length of hospital stay, and exacerbation-free interval	During the study, 15 patients died in the hospital, eight (8.2%) in the SMX-TMP group and eight (9.4%) in the ciprofloxacin group (P>0.05). Secondary: The mean exacerbation-free interval was similar in both treatment groups (83 vs 79 days in the SMX-TMP vs ciprofloxacin group; P=0.41). Of 38 patients initially receiving noninvasive ventilation in the SMX-TMP group, 17 (45%) were secondarily intubated vs 13 (34%) in the ciprofloxacin group (P=0.347). The duration of mechanical ventilation and length of hospital stay were similar in the two study groups. Adverse events were minor and comparably distributed in both treatment groups.
Chodosh et al.[52] (1982) SMX-TMP 800-160 mg BID for 14 days vs ampicillin 500 mg, one capsule QID for 14 days	DB, RCT, XO Patients ≥18 years of age with chronic bronchitis who developed an acute bronchial infectious exacerbation within two weeks of the study *Pseudomonas, Klebsiella*, or *Staphylococcus aureus* were isolated	N=21 14 days	Primary: Chest symptoms, physical findings, vital signs, pulmonary function, laboratory values, sputum analysis, time to recurrence of exacerbation Secondary: Not reported	Primary: Patients in the ampicillin group experienced a longer recurrence-free time compared to patients in the SMX-TMP group (P<0.05). Sputum volumes decreased significantly in each treatment group, starting on day three of the study (P<0.05). While none of the patients in the ampicillin group discontinued therapy due to adverse effects, three patients in the SMX-TMP group discontinued treatment. There were no significant differences noted between the two study drugs in all other outcome measures. Secondary: Not reported
Feder et al.[53] (1982) SMX-TMP 37.5-7.5	DB, RCT Patients two months to seven	N=282 14 days	Primary: Premature discontinuation of therapy due to ≥5	Primary: Therapy was discontinued in significantly more ampicillin-treated patients compared to amoxicillin-treated patients (P<0.01) or SMX-TMP-treated patients (P<0.03).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg/kg/day divided into two doses for 14 days vs ampicillin 70 mg/kg/day divided into four doses for 14 days vs amoxicillin 30 mg/kg/day divided into three doses for 14 days	years of age with signs/symptoms of otitis media in addition to a bulging tympanic membrane with decreased mobility		watery stools per day, diarrhea Secondary: Not reported	Among patients who completed a full course of therapy, significantly more ampicillin-treated patients developed diarrhea compared to amoxicillin-treated patients (P<0.04) or SMX-TMP-treated patients (P<0.02). Initial symptom resolution occurred after approximately two days of treatment in all three groups. Secondary: Not reported
Miscellaneous				
Soheilian et al.[54] (2005) <u>Regimen A:</u> Sulfadiazine 2 g for two days, followed by sulfadiazine 500 mg every six hours, pyrimethamine 100 mg QD for two days, followed by 25 mg QD, and folinic acid 5 mg QD for six weeks; prednisone 1 mg/kg QD was started from the third day of therapy and tapered off over two	AC, PRO, RCT, SB Patients with ocular toxoplasmosis	N=59 24 months	Primary: Changes in retinochoroidal lesion size at six weeks, difference in visual acuity, adverse events, rate of recurrence Secondary: Not reported	Primary: Active toxoplasmosis retinochoroiditis resolved in all patients over the treatment phase of the study. There was no significant difference in mean reduction of retinochoroidal lesion size between the patients randomized to receive regimens A and B (61 vs 59% reduction, respectively; P=0.75). No significant difference in visual acuity between the regimen A and B groups (P=0.56). Adverse effects were similar in both groups with only one patient in each group experiencing rash as the only significant drug-related side effect. There was no significant difference in the rate of recurrence between the regimen A and B groups after 24 months of follow-up (10.3 vs 10.0%, respectively; P=0.64). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
weeks vs Regimen B: SMX-TMP 400-80 mg two tablets every 12 hours for six weeks; prednisone 1 mg/kg QD was started from the third day of therapy and tapered off over two weeks				
Bosch-Driessen et al.[55] (2002) Regimen A: Sulfadiazine 4 g QD, pyrimethamine 100 mg on day one, followed by 50 mg QD, and folinic acid 15 mg QD for four weeks; prednisone 40 mg QD was started from the third day of therapy and tapered off after 10 days vs Regimen B: Pyrimethamine 100	AC, MC, OL, RCT Patients, 16 to 80 years of age with an active toxoplasmic retinochoroidal lesion located centrally within the major temporal vascular arcades or a juxtapapillary lesion	N=46 24 months	Primary: Time of intraocular inflammation resolution, size of the retinochoroidal lesion, difference in visual acuity, side effects Secondary: Not reported	Primary: There was no significant difference in the duration of intraocular inflammation between the regimen A and B groups (P=0.96). There was no significant difference in the decrease in size of the retinochoroidal lesion between the regimen A and B groups three months after study onset (P=0.32). There was no significant difference in the decrease in visual acuity between the regimen A and B groups (P=0.72). There was no significant difference in the rate of recurrence between the regimen A and B groups during the 24 months of follow-up (56 vs 33%, respectively; P=0.10). Adverse effects were more frequent in the sulfadiazine group compared to the azithromycin group (64 vs 33%; P<0.04). Thrombocytopenia as well as an elevation in serum creatinine and liver enzymes was observed in both groups. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg on day one, followed by 50 mg QD, azithromycin 250 mg QD or 500 mg QOD, and folinic acid 15 mg QD for four weeks; prednisone 40 mg QD was started from the third day of therapy and tapered off after 10 days				
van Rossum et al.[56] (2007) Sulfasalazine 50 mg/kg/day vs placebo	PRO, SB Patients 2 to 18 years of age, with onset of JIA before the age of 16, at least one joint with active arthritis, and an insufficient response to NSAID drug therapy	N=61 7 to 10 years	Primary: Disease outcomes over time Secondary: Not reported	Primary: Active joints were present in 74% of the patients, including 30% with active polyarthritis. Compared to the end of the trial, follow-up of both groups combined showed a significant increase in joint limitation, but a stable situation in clinical parameters and acute phase reactants. The median C-HAQ for the whole group was 0.25 (range 0 to 2). None to mild disability was reported by 74% of the patients, moderate disability by 20% and severe disability by 6% of the patients. At follow up, 53% of patients in the sulfasalazine group were on DMARDs, including four still on sulfasalazine. The median duration of sulfasalazine treatment was 2.5 years. Over the follow-up period, 50% of sulfasalazine patients were switched to another DMARD treatment, including methotrexate in 47%. The median duration of methotrexate treatment was three years. The median number of DMARDs used in the follow-up period was 1.5 (range one to five). At follow-up, 72% of patients in the placebo group were on DMARDs, including four patients on sulfasalazine. The median duration of sulfasalazine treatment in the placebo group was significantly longer than

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				in the sulfasalazine group (5.2 years). Over the follow-up period, 64% of the placebo group switched to other DMARDs, including methotrexate (55% of the patients). The median duration of methotrexate treatment was four years. The median number of DMARDs used in the follow-up period by the placebo group was two (range zero to five). At follow-up, 47% of the sulfasalazine patients were classified as ACR Pedi 30 responders compared to the placebo patients (P=0.02). Secondary: Not reported
Braun et al.[57] (2011) Sulfasalazine titrated to a maximum of 3 g/day for 16 weeks vs etanercept 50 mg once weekly for 16 weeks	DB, MC, RCT Patients with active ankylosing spondylitis	N=566 16 weeks	Primary: Proportion of patients who achieved the Assessment of SpondyloArthritis international Society criteria for 20% improvement at 16 weeks Secondary: Proportion of responders according to the Assessment of SpondyloArthritis international Society criteria for 20% response criteria at prespecified visits up to week 16, as well as the	Primary: A total of 75.9% patients receiving etanercept achieved an Assessment of SpondyloArthritis international Society criteria for 20% response at week 16, compared to 52.9% of the patients in the sulfasalazine group (P<0.0001). Secondary: A significantly greater proportion of patients in the etanercept group than in the sulfasalazine group achieved an Assessment of SpondyloArthritis international Society criteria for 20% response as early as week two of treatment (P<0.0001); this difference was sustained through week 16. The proportions of patients receiving etanercept who achieved Assessment of SpondyloArthritis international Society criteria for 40% and Assessment of SpondyloArthritis international Society criteria for improvement in five of six domains at responses were significantly higher at all time points, as early as week two and through week 16, when compared to the proportions of patients receiving sulfasalazine who achieved these end points (P<0.0001). An Assessment of SpondyloArthritis international Society criteria for 40% response was achieved by 59.8% of etanercept-treated patients compared to 32.6% of sulfasalazine-treated patients at week 16 (P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			proportion of patients meeting the Assessment of SpondyloArthritis international Society criteria for 40% improvement criteria and the proportion achieving Assessment of SpondyloArthritis international Society criteria for 20% improvement in five of six domains at prespecified visits up to week 16	The percentage of patients achieving an Assessment of SpondyloArthritis international Society criteria for improvement in five of six domains at response after 16 weeks was significantly greater in the etanercept group (45.5%) compared to the sulfasalazine group (21.2%; P<0.0001). The percentage of patients achieving partial remission was significantly higher in the group receiving etanercept compared to the group receiving sulfasalazine, as early as week two through week 16 (P<0.001). At week 16, 33.3% of patients in the etanercept group and 15.5% of patients in the sulfasalazine group achieved partial remission (P<0.0001). Treatment-emergent adverse events were reported in 55.3% of patients in the study. The proportions of patients who reported a treatment-emergent adverse event or an adverse event of special interest were similar in the etanercept group and the sulfasalazine group. A significantly greater number of patients in the etanercept group than in the sulfasalazine group reported experiencing injection-site reactions (10.8 vs 1.6%, respectively; P<0.001. Other common adverse events reported in the etanercept and sulfasalazine groups were upper respiratory tract infection (8.2% and 9.1%, respectively), headache (7.7 and 11.2%, respectively), and nausea (6.6 and 9.6%, respectively).
Song et al.[58] (2011) Sulfasalazine 2 to 3 g per day vs etanercept 25 mg SC twice weekly Sulfasalazine patients could be switched to methotrexate (15 to 20 mg weekly).	MC, OL, RCT Patients 18 to 50 years of age with NSAID-refractory axial spondyloarthritis with a symptom duration of <5 years	N=76 48 weeks	Primary: Change of active inflammatory lesions in the sacroiliac joints and spine on magnetic resonance imaging Secondary: Reduction of active inflammatory lesions on the posterior elements of the spine and a reduction of	Primary: At week 48, the reduction of the sacroiliac joint score from 7.7 at baseline to 2.0 with etanercept was significantly larger than the sulfasalazine group (decrease from 5.4 at baseline to 3.5; P=0.02). Secondary: At week 48, the reduction of inflammation in the spine from 2.2 at baseline to 1.0 in the etanercept group was significantly larger than the sulfasalazine group (decrease from 1.4 at baseline to 1.3; P=0.01). The number of enthesitic sites improved significantly from 26 to 11 in the etanercept group vs 24 to 26 in the sulfasalazine group (P=0.04). At week 48, 50% of patients reached clinical remission in the etanercept group vs 19% in the sulfasalazine group.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			peripheral enthesitis on magnetic resonance imaging	
Rheumatoid Arthritis				
Suarez-Almazor et al.[59] (2000) Sulfasalazine vs placebo	MA Patients with RA	N=468 (6 trials) ≥6 months	Primary: Failure to maintain either a complete global or clinical remission, adverse effects Secondary: Not reported	Primary: In the pooled analysis, sulfasalazine was more efficacious compared to placebo in the number of tender joints (standardized weighed mean difference, -0.49; 95% CI, -0.75 to -0.36). In the pooled analysis, sulfasalazine was more efficacious compared to placebo in the number of swollen joints (standardized weighed mean difference, -0.49; 95% CI, -0.79 to -0.12). In the pooled analysis, sulfasalazine was more efficacious compared to placebo in pain severity (standardized weighed mean difference, -0.42; 95% CI, -0.72 to -0.12). In the pooled analysis, sulfasalazine was more efficacious compared to placebo in erythrocyte sedimentation rate (standardized weighed mean difference, -17.6 mm; 95% CI, -0.64 to 0.00). Withdrawals from adverse effects were significantly higher in the sulfasalazine group (OR, 3.0). Patients receiving placebo were four more times more likely to discontinue treatment because of lack of efficacy than patients receiving sulfasalazine. Secondary: Not reported
Capell et al.[60] (2007) <u>Phase I</u> Sulfasalazine enteric-coated tablets 500 mg daily, increasing by	OL (Phase I), RCT (Phase II) Patients 18 to 80 years of age and with RA, disease duration <10 years, and active disease	<u>Phase I</u> N=687 6 months <u>Phase II</u>	Primary: Reduction in DAS at 18 months Secondary: Proportion of patients achieving a good response	Primary: At 18 months, DAS was significantly lower in those who received combination treatment compared to those who received either sulfasalazine or methotrexate alone, but the two monotherapy arms were not significantly different (combination vs sulfasalazine; P=0.039, combination vs methotrexate; P=0.023, sulfasalazine vs methotrexate; P=0.79).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
500 mg weekly until the target dose of 40 mg/kg/day (or the maximum tolerated dose) Phase II Sulfasalazine at the dose achieved by six months with the addition of methotrexate initially 7.5 mg/week, increasing by 2.5 mg/month until the maximal permitted dose of 25 mg or toxicity occurred vs sulfasalazine at the dose achieved by six months, with the addition of placebo vs placebo with the addition of methotrexate initially 7.5 mg/week, increasing by 2.5 mg/month until the maximal permitted dose of 25	defined by the DAS of >2.4; patients with DAS ≥ 2.4 after six months were included in phase II	N=165 18 months	as determined by the EULAR criteria (DAS <2.4, and a fall in score from baseline by 1.2) and ACR 20, 50 and 70 responses, safety	Secondary: For change in EULAR DAS in the three groups, there was a trend for more patients to be in the remission or good DAS category in the combination group and fewer in the high DAS group at 18 months. ACR 20, 50 and 70 responses indicate that the combination group achieved a higher proportion in the 20, 50 and 70% responding groups compared to the single drugs alone, although this was not statistically significant. Radiographic examination showed no significant difference in total Sharp score and in total erosions (hands and feet), and joint space narrowing between six and 18 months in the groups was similar, with no significant difference between the three groups.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg or toxicity occurred				
Combe et al.[61] (2009) Sulfasalazine 2 to 3 g daily vs etanercept 25 mg SC twice weekly vs sulfasalazine 2 to 3 g daily plus etanercept 25 mg SC twice weekly	DB, MC, RCT Patients ≥ 18 years of age with active adult onset RA and disease duration of ≤20 years	N=260 2 years	Primary: Disease activity, disease remission, percentage of patients achieving 20% or greater improvement (ACR 20), ACR response rates (ACR 20, ACR 50 and ACR 70), DAS and morning stiffness in minutes Secondary: Not reported	Primary: Disease activity (as assessed by mean DAS) was significantly lower in the groups receiving etanercept than in the group receiving sulfasalazine from week two to week 104 (P<0.01). Significantly lower mean DAS values were observed during weeks 68 through 104 for the combination group compared to the etanercept alone group (P<0.05). A significantly higher proportion of patients receiving the combination or etanercept had a low level of disease activity compared to those receiving sulfasalazine after six months, which was maintained throughout the two years (P<0.01); at two years, 57.0% of patients receiving combination, 45.6% receiving etanercept and 4.0% receiving sulfasalazine. The proportion of patients achieving disease remission was significantly higher with the etanercept groups compared to the sulfasalazine group (P<0.01). Treatment response as assessed by ACR 20 was achieved by a significantly higher percentage of patients receiving etanercept, added to or in place of sulfasalazine, compared to those receiving sulfasalazine (P<0.01). These significant differences in treatment response among the groups were also seen using ACR 50 (P<0.01) and ACR 70 (P<0.01) criteria. Response rates were not significantly different between the two groups receiving etanercept. Secondary: Not reported
van Vollenhoven et al.[62] (2009) Sulfasalazine 1,000 mg BID or hydroxy-chloroquine 400 mg daily plus	MC, RCT Patients ≥18 years of age with early RA (symptom duration <1 year) who had received methotrexate for three to four	N=258 12 months	Primary: Achievement of a good response according to EULAR criteria at 12 months Secondary: Achievement of a	Primary: At 12 months, 25% of patients receiving sulfasalazine and hydroxychloroquine and 39% of patients receiving infliximab had a good response according to EULAR criteria (P=0.0160). Secondary: At 12 months, 49% of patients receiving sulfasalazine and hydroxychloroquine and 60% of patients receiving infliximab had a good or moderate response according to EULAR criteria (P=0.0817).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
methotrexate vs infliximab 3 mg/kg IV at weeks zero, two, six and every eight weeks thereafter plus methotrexate	months and had not achieved low disease activity		good or moderate response with EULAR criteria, and ACR 20, ACR 50, and ACR 70	At 12 months, 28% of patients receiving sulfasalazine and hydroxychloroquine and 42% of patients receiving infliximab achieved ACR 20 (P=0.0266). At 12 months, 15% of patients receiving sulfasalazine and hydroxychloroquine and 25% of patients receiving infliximab achieved ACR 50 (P=0.0424). At 12 months, 7% of patients receiving sulfasalazine and hydroxychloroquine and 12% of patients receiving infliximab achieved ACR 70 (P=0.2044). Adverse events were similar among the treatment groups and accorded with known adverse events of the drugs used. No deaths occurred in either group.
Ulcerative Colitis				
Sutherland et al.[63] (2006) Sulfasalazine vs 5-aminosalicylic acid	MA Patients with active mild-moderate ulcerative colitis	12 studies At least 4 weeks	Primary: Failure to induce either a complete global or clinical remission, endoscopic improvement, adverse effects Secondary: Not reported	Primary: There was no statistically significant difference in the failure to induce either a complete global or clinical remission between 5-aminosalicylic acid and sulfasalazine (OR, 0.83; 95% CI, 0.42 to 1.13). There was no statistically significant difference in the failure to induce endoscopic improvement between 5-aminosalicylic acid and sulfasalazine (OR, 0.66; 95% CI, 0.42 to 1.04). There were significantly more withdrawals due to side effects with sulfasalazine compared to 5-aminosalicylic acid. Secondary: Not reported
Sutherland et al.[64] (2006) Sulfasalazine	MA Patients with active mild-moderate	N=1,598 (11 studies) At least 7 months	Primary: Failure to maintain either a complete global or clinical remission, adverse	Primary: Sulfasalazine was found to be more efficacious in terms of maintaining either a complete global or clinical remission compared to 5-aminosalicylic acid (OR, 1.29; 95% CI, 1.05 to 1.57).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs 5-aminosalicylic acid	ulcerative colitis		effects Secondary: Not reported	There was no statistically significant difference in the number of withdrawals due to side effects between the two groups (OR, 1.31; 95% CI, 0.86 to 1.99). Secondary: Not reported
Sood et al.[65] (2003) Sulfasalazine 6 g daily vs azathioprine 2.5 mg/kg/day	OL, PRO, RCT Adults >18 years of age with newly diagnosed or recently relapsed ulcerative colitis	N=25 18 months	Primary: Treatment failure (either disease relapse or drug withdrawal because of adverse effects) Secondary: Not reported	Primary: Five of 12 patients in the azathioprine group and eight of 13 patients in the sulfasalazine group had sustained remission during the study period of 18 months. The difference between the two groups was not statistically significant. Two patients in the azathioprine group had to stop therapy due to adverse effects (bone marrow suppression and acute pancreatitis). All patients in the azathioprine group who had treatment failure developed it in the first half of the study while patients in the sulfasalazine group experienced treatment failure throughout the study. Secondary: Not reported
Green et al.[66] (2002) Sulfasalazine 333 mg three capsules TID vs balsalazide 750 mg three capsules TID	DB, MC, PG, RCT Adults >18 years of age with newly diagnosed or recently relapsed ulcerative colitis and a negative stool sample	N=57 12 weeks	Primary: Rate of remission, change in symptoms, sigmoidoscopic and histological assessments, patient assessment, adverse events Secondary: Not reported	Primary: There was no significant difference in the remission rate between the sulfasalazine and balsalazide groups (59 vs 75%, respectively; P=0.19). Both groups showed a significant improvement in stool frequency over time. The proportion of patients with normal sigmoidoscopic appearances increased at each visit for both groups. Rectal biopsies taken at entry and at the final visit demonstrated similar improvements in both groups. According to patient diaries, the median number of stools with blood and/or mucus decreased to zero in both treatment groups by week six and was maintained at this level through the end of the study.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Fewer patients in the balsalazide group withdrew from the study due to adverse events compared to the sulfasalazine group (7 vs 31%, respectively; P=0.041). Secondary: Not reported.
Nikfar et al.[67] (2009) Sulfasalazine vs mesalamine	MA Patients with mild-to-moderate ulcerative colitis	19 trials Variable duration	Primary: Overall improvement, relapse rate, total adverse events, and withdrawals because of adverse events Secondary: Not reported	Primary: The summary RR for overall improvement in four trials that compared sulfasalazine and mesalamine was 1.04 (95% CI, 0.89 to 1.21; P=0.63). The summary RR for relapse in six trials that compared sulfasalazine and mesalamine was 0.98 (95% CI, 0.78 to 1.23; P=0.85). Data on adverse events in studies that compared sulfasalazine and mesalamine yielded an overall RR of 0.76 (95% CI, 0.54 to 1.07; P=0.11). The summary RR for withdrawals because of adverse events in eight trials that compared sulfasalazine and mesalamine was 0.78 (95% CI 0.46 to 1.3; P=0.33). Secondary: Not reported
Loftus et al.[68] (2004) Mesalazine, olsalazine, or balsalazide vs placebo or sulfasalazine	MA Patients with active ulcerative colitis	N=6,031 (46 studies) 2 to 12 weeks	Primary: Adverse events, withdrawal due to adverse events Secondary: Not reported	Primary: One study of mesalazine vs sulfasalazine for active colitis showed significantly fewer patients with adverse events with mesalazine. Both balsalazide vs sulfasalazine studies for active disease showed significantly fewer withdrawals with balsalazide. One trial of balsalazide vs sulfasalazine for maintenance showed significantly fewer patients with adverse events with balsalazide. Otherwise, no significant differences in safety outcomes were noted. Secondary: Not reported.

Drug regimen abbreviations: BID=twice daily, IM=intramuscular, QD=once daily, QID=four times daily, SC=subcutaneous, TID=three times daily

Study design abbreviations: AC=active-controlled, CI=confidence interval, DB=double-blind, MA=meta-analysis, MC=multicenter, NS=not significant, OL=open label, OR=odds ratio, PG=parallel group, PRO=prospective, RCT=randomized trial, RETRO=retrospective, RR=relative risk, XO=crossover
Other abbreviations: ACR=American College of Rheumatology, AIDS=acquired immunodeficiency syndrome, C-HAQ=childhood health assessment questionnaire, COPD=chronic obstructive pulmonary disease, DAS=disease activity score, DMARD=disease modifying antirheumatic drug, EULAR=European League Against Rheumatism, HIV=human immunodeficiency virus, ITT=intention to treat, IV=intravenous, JIA=juvenile idiopathic arthritis, MRSA=methicillin resistant Staphylococcus aureus, NSAID=nonsteroidal antiinflammatory drug, PCP=pneumocystis pneumonia, PEF=peak expiratory flow, RA=rheumatoid arthritis, SMX-TMP=sulfamethoxazole-trimethoprim, UTI=urinary tract infection

Additional Evidence

Dose Simplification
In a meta-analysis of 22 studies, Tran et al. reported no difference in cure rates between short courses (one to three days) and long courses (seven to 14 days) of sulfamethoxazole-trimethoprim for the treatment of uncomplicated cystitis in children <18 years of age.[39]

Stable Therapy
In a randomized, double-blind, crossover trial, El-Chaar et al. evaluated the differences in taste and adherence with brand and generic antibiotic suspensions in children.[69] While there was no difference in adherence, children verbally expressed a preference for Bactrim® compared to the generic sulfamethoxazole-trimethoprim product (P=0.0342).

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 Sulfonamides

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Sulfadiazine	tablet	N/A	N/A	$$$$$
Sulfasalazine	delayed-release tablet, tablet	Azulfidine®*	$$$	$$$
Combination Products				
Sulfamethoxazole and trimethoprim	injection, suspension, tablet	Bactrim®*, Bactrim DS®*, Sulfatrim®*	$	$

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

X. Conclusions

The sulfonamides are effective for the treatment of a variety of conditions, and the Food and Drug Administration-approved indications vary depending on the agent. Sulfadiazine and sulfamethoxazole-trimethoprim are approved to treat a variety of infections, including central nervous system, dermatological,

gastrointestinal, genitourinary, respiratory, as well as several miscellaneous infections.[1-6] Sulfasalazine is approved for the treatment of ulcerative colitis and rheumatoid arthritis. [1-2,5-6] All of the sulfonamides are available in a generic formulation.

There are many guidelines that define the appropriate place in therapy for the sulfonamides. The agent that is recommended is dependent upon the infectious organism being treated and the corresponding spectrum of activity of the sulfonamide. Sulfadiazine and sulfamethoxazole-trimethoprim are recommended as specific therapy for the treatment of susceptible pathogens causing encephalitis, diabetic foot infections, urinary tract infections, sinusitis, prophylaxis/treatment of *Pneumocystis (carinii) jiroveci* pneumonia, prophylaxis/treatment of *Toxoplasma* encephalitis, as well as for the secondary prevention of rheumatic fever.[7-9,13,19,20,22,27] They are recommended as an alternative treatment option for meningitis, skin and soft-tissue infections, granuloma inguinale, and pertussis.[10,12,18,26] Sulfasalazine is recommended as one of several initial treatment options for ulcerative colitis and rheumatoid arthritis.[17,31,32] There are very few clinical studies that directly compare the efficacy and safety of the sulfonamides.[33,43,54] However, the sulfonamides been shown to be comparable in efficacy to antibacterial agents in other classes.[36,37,40-42,46,47,50-52,54,60,65,66]

The use of sulfonamides has been associated with rare cases of fatal adverse events, such as Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis, agranulocytosis, aplastic anemia and other blood dyscrasias. Sulfonamide therapy should be discontinued at the first sign of these serious adverse events.[1]

There is insufficient evidence to support that one brand sulfonamide 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 sulfonamide products 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 sulfonamide 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.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
Pharmacotherapy Review of Tetracyclines
AHFS Class 081224
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I. Overview

The tetracyclines are approved to treat a variety of infections, including central nervous system, dermatologic, gastrointestinal, genitourinary, respiratory, as well as several miscellaneous infections.[1-8] They bind reversibly to the 30S subunit of bacterial ribosomes and exert a bacteriostatic effect by blocking protein synthesis.[1-8]

The tetracyclines exhibit broad-spectrum antibacterial activity and are most active against aerobic gram-positive and gram-negative bacteria. They also have activity against many atypical pathogens. The widespread use of the tetracyclines has led to an increase in resistance. Cross-resistance has also been reported among the various agents. Tigecycline has been shown to have activity against tetracycline-resistant pathogens. It is not affected by the two major tetracycline-resistance mechanisms, ribosomal protection and efflux. There has been no cross-resistance observed between tigecycline and other antibacterials.[1-8]

The tetracyclines that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Demeclocycline, doxycycline, minocycline, and tetracycline are available in a generic formulation. This class was last reviewed in August 2014.

Table 1. Tetracyclines Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Demeclocycline	tablet	N/A	demeclocycline
Doxycycline	capsule, delayed-release capsule, delayed-release tablet, injection, suspension (reconstituted), syrup, tablet	Adoxa®*, Adoxa Pak®*, Doryx®*, Morgidox®*, Vibramycin®*	doxycycline
Minocycline	capsule, injection, tablet	Minocin®	minocycline
Tetracycline	capsule	N/A	tetracycline
Tigecycline	injection	Tygacil®	none

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

The tetracyclines 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 tetracyclines 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 Tetracyclines[1-8]

Organism	Demeclocycline	Doxycycline	Minocycline	Tetracycline	Tigecycline
Gram-Positive Organisms					
Bacillus anthracis	✔	✔	✔	✔	
Enterococcus faecalis				✔	✔
Enterococcus faecium				✔	
Listeria monocytogenes	✔	✔	✔	✔	
Staphylococcus aureus	✔	✔	✔		✔
Staphylococcus epidermidis					✔
Streptococci, viridans group				✔	
Streptococcus agalactiae					✔
Streptococcus anginosus					✔
Streptococcus pneumoniae	✔	✔	✔	✔	✔
Streptococcus pyogenes				✔	✔
Gram-Negative Organisms					
Acinetobacter species	✔	✔	✔	✔	
Bacteroides species				✔	✔
Bartonella bacilliformis	✔	✔	✔	✔	
Brucella species	✔	✔	✔	✔	
Calymmatobacterium granulomatis	✔	✔	✔	✔	
Campylobacter fetus	✔		✔	✔	
Citrobacter freundii					✔
Enterobacter aerogenes	✔	✔	✔	✔	
Enterobacter cloacae					✔
Escherichia coli	✔	✔	✔	✔	✔
Francisella tularensis	✔	✔	✔	✔	
Haemophilus ducreyi	✔	✔	✔	✔	
Haemophilus influenzae	✔	✔	✔	✔	✔
Klebsiella species	✔	✔	✔	✔	✔
Legionella pneumophila					✔
Neisseria gonorrhoeae	✔	✔	✔	✔	
Neisseria meningitidis			✔		
Shigella species	✔	✔	✔	✔	
Vibrio cholerae	✔	✔	✔	✔	
Yersinia pestis	✔	✔	✔	✔	
Miscellaneous Organisms					
Actinomyces species	✔	✔	✔	✔	
Balantidium coli		✔		✔	

Organism	Demeclocycline	Doxycycline	Minocycline	Tetracycline	Tigecycline
Borrelia recurrentis	✔	✔	✔	✔	
Chlamydophila psittaci	✔	✔	✔	✔	
Chlamydia trachomatis	✔	✔	✔	✔	
Clostridium species	✔	✔	✔	✔	✔
Entamoeba species	✔	✔	✔	✔	
Fusobacterium nucleatum	✔	✔	✔	✔	
Mycobacterium marinum			✔		
Mycoplasma pneumoniae	✔	✔	✔	✔	
Peptostreptococcus micros					✔
Plasmodium falciparum		✔			
Propionibacterium acnes	✔	✔	✔	✔	
Rickettsia species	✔	✔	✔	✔	
Treponema pallidum	✔	✔	✔	✔	
Treponema pertenue	✔	✔	✔	✔	
Ureaplasma urealyticum	✔	✔	✔	✔	

II. Evidence-Based Medicine and Current Treatment Guidelines

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

Table 3. Treatment Guidelines Using the Tetracyclines

Clinical Guideline	Recommendation(s)

European Society of Cardiology: **Guidelines for the Management of Infective Endocarditis (2015)**[9]	Main principles of prevention if infective endocarditis
	• The principle of antibiotic prophylaxis when performing procedures at risk of infective endocarditis (IE) in patients with predisposing cardiac conditions is maintained.
	• Antibiotic prophylaxis must be limited to patients with the highest risk of IE undergoing the highest risk dental procedures (dental procedures requiring manipulation of the gingival or periapical region of the teeth or perforation of the oral mucosa).
	  o Patients with a prosthetic valve, including transcatheter valve, or a prosthetic material used for cardiac valve repair.
	  o Patients with previous IE.
	  o Patients with congenital heart disease.
	• Good oral hygiene and regular dental review are more important than antibiotic prophylaxis to reduce the risk of IE.
	• Aseptic measures are mandatory during venous catheter manipulation and during any invasive procedures in order to reduce the rate of health care-associated IE.
	• Recommended prophylaxis for dental procedures at high-risk:
	  o Single-dose amoxicillin or penicillin 30 to 60 minutes before procedure.
	  o If allergy to penicillin or ampicillin, single-dose clindamycin 30 to 60 minutes before procedure.
	
	Antimicrobial therapy: principles
	• The treatment of infective endocarditis relies on the combination of prolonged antimicrobial therapy and - in about half of patients - surgical eradication of the infected tissues.
	• Prolonged therapy with a combination of bactericidal drugs is the basis of IE treatment. Drug treatment of prosthetic valve endocarditis (PVE) should last longer (at least six weeks) than that of native valve endocarditis (NVE) (two to six weeks).
	• In both NVE and PVE, the duration of treatment is based on the first day of effective antibiotic therapy, not on the day of surgery. A new full course of treatment should only start if valve cultures are positive, the choice of antibiotic being based on the susceptibility of the latest recovered bacterial isolate.
	• The indications and pattern of use of aminoglycosides have changed. They are no longer recommended in staphylococcal NVE because their clinical benefits have not been demonstrated but they can increase renal toxicity; and, when they are indicated in other conditions, aminoglycosides should be given in a single daily dose in order to reduce nephrotoxicity.
	• New antibiotic regimens have emerged in the treatment of staphylococcal IE, including daptomycin and the combination of high-doses of cotrimoxazole plus clindamycin, but additional investigations are necessary in large series before they can be recommended in all patients.
	
	Antimicrobial therapy: regimens
	• Antibiotic treatment of infective endocarditis due to oral streptococci and *Streptococcus* bovis group:
	  o Penicillin-susceptible strains:
	  ▪ Penicillin G, amoxicillin, or ceftriaxone for four weeks.
	  ▪ Penicillin G, amoxicillin, or ceftriaxone plus gentamicin or netilmicin for two weeks.
	  ▪ Vancomycin for four weeks (in beta-lactam allergic patients).

Clinical Guideline	Recommendation(s)
	o Penicillin-resistant strains: ▪ Penicillin G, amoxicillin, or ceftriaxone for four weeks plus gentamicin for two weeks. ▪ Vancomycin for four weeks plus gentamicin for two weeks (in beta-lactam allergic patients). • Antibiotic treatment of infective endocarditis due to *Staphylococcus* species: o Methicillin-susceptible strains (native valves): ▪ Flucloxacillin or oxacillin for four to six weeks. ▪ Cotrimoxazole intravenous for one week and oral for five weeks plus clindamycin for one week (for *Staphylococcus aureus*). o Penicillin-allergic patients or methicillin-resistant staphylococci (native valves): ▪ Vancomycin for four to six weeks. ▪ Alternative: Daptomycin for four to six weeks. ▪ Cotrimoxazole intravenous for one week and oral for five weeks plus clindamycin for one week (for *Staphylococcus aureus*). o Methicillin-susceptible strains (prosthetic valves): ▪ Flucloxacillin or oxacillin for at least six weeks, rifampin for at least six weeks, and gentamicin for two weeks. o Penicillin-allergic patients or methicillin-resistant staphylococci (prosthetic valves): ▪ Vancomycin for at least six weeks, rifampin for at least six weeks, and gentamicin for two weeks. • Antibiotic treatment of infective endocarditis due to *Enterococcus* species: o Beta-lactam and gentamicin susceptible strains: ▪ Amoxicillin for four to six weeks plus gentamicin for two to six weeks. ▪ Ampicillin plus gentamicin for six weeks. ▪ Vancomycin plus gentamicin for six weeks. • Antibiotic treatment of blood culture-negative infective endocarditis: o *Brucella* species: ▪ Doxycycline, cotrimoxazole, and rifampin for ≥3 months. o *Coxiella burnetii* (agent of Q fever): ▪ Doxycycline plus hydroxychloroquine for >18 months. ▪ o *Bartonella* species: ▪ Doxycycline orally for four weeks plus gentamicin for two weeks. o *Legionella* species: ▪ Levofloxacin intravenous for ≥6 weeks or clarithromycin intravenous for two weeks then orally for four weeks plus rifampin. o *Mycoplasma* species: ▪ Levofloxacin for ≥6 months. o *Tropheryma whipplei* (agent of Whipple's disease): ▪ Doxycycline plus hydroxychloroquine orally for ≥18 months. • Proposed antibiotic regimens for initial empirical treatment of infective endocarditis in acute severely ill patients (before pathogen identification): o Community-acquired native valves or late prosthetic valves (≥12 months post surgery) endocarditis: ▪ Ampicillin intravenous plus flucloxacillin or oxacillin intravenous plus gentamicin intravenous for once dose. ▪ Vancomycin intravenous plus gentamicin intravenous (for penicillin allergic patients). o Early PVE (<12 months post surgery) or nosocomial and non-nosocomial healthcare associated endocarditis:

Clinical Guideline	Recommendation(s)
	▪ Vancomycin intravenous, gentamicin intravenous, and rifampin orally.
American College of Cardiology/ American Heart Association: **2008 Focused Update Incorporated Into the American College of Cardiology/ American Heart Association 2006 Guidelines for the Management of Patients With Valvular Heart Disease (2008)[10]** American College of Cardiology/ American Heart Association: **Guideline for the Management of Patients With Valvular Heart Disease (2014)[11] (although a more current guideline more detailed information was included as part of the 2008 Focused update; as such both are summarized together)**	<u>Rheumatic fever prophylaxis</u> • Primary prevention of rheumatic heart disease: o Penicillin G benzathine intramuscular once or penicillin V orally for 10 days. o Erythromycin estolate or erythromycin ethylsuccinate orally for 10 days, or azithromycin orally for five days in patients who are allergic to penicillin. • Secondary prevention of rheumatic fever: o Penicillin G benzathine intramuscular every four weeks, or penicillin V orally twice daily, or sulfadiazine orally once daily. o Erythromycin orally twice daily for patients who are allergic to penicillin. <u>Endocarditis prophylaxis</u> • Prophylaxis against infective endocarditis is reasonable for the following patients at highest risk for adverse outcomes from infective endocarditis who undergo dental procedures that involve manipulation of either gingival tissue or the periapical region of teeth or perforation of the oral mucosa: o Patients with prosthetic cardiac valve or prosthetic material used for cardiac valve repair. o Patients with previous infective endocarditis. o Patients with congenital heart disease. o Cardiac transplant recipients with valve regurgitation due to a structurally abnormal valve. • Prophylaxis against infective endocarditis is not recommended for non-dental procedures (such as transesophageal echocardiogram, esophagogastroduodenoscopy, or colonoscopy) in the absence of active infection. • Regimens for dental procedures (single dose 30 to 60 minutes before procedure): o Oral: amoxicillin. o Unable to take oral medications: ampicillin, cefazolin or ceftriaxone. o Allergic to penicillin or ampicillin (oral): cephalexin, clindamycin, or azithromycin. o Allergic to penicillins or ampicillin and unable to take oral medication: cefazolin, ceftriaxone, or clindamycin. • Therapy of native valve endocarditis caused by highly penicillin-susceptible viridans group streptococci and *Streptococcus bovis:* o Penicillin G or ceftriaxone for four weeks. o Ceftriaxone plus gentamicin for two weeks. o Vancomycin for four weeks in patients allergic to penicillin. • Therapy of native valve endocarditis caused by strains of viridans group streptococci and *Streptococcus bovis* relatively resistant to penicillin: o Penicillin G or ceftriaxone for four weeks plus gentamicin for two weeks. o Vancomycin for four weeks in patients allergic to penicillin. • Therapy for native valve or prosthetic valve enterococcal endocarditis caused by strains susceptible to penicillin, gentamicin, and vancomycin: o Ampicillin for four to six weeks or penicillin G plus gentamicin for four to six weeks. o Vancomycin plus gentamicin for six weeks in patients allergic to penicillin. • Therapy for endocarditis caused by staphylococci in the absence of prosthetic materials: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin for six weeks plus the optional addition of gentamicin for three to five days. ▪ Cefazolin for six weeks with the optional addition of gentamicin in patients allergic to penicillin. o Oxacillin-resistant strains:

Clinical Guideline	Recommendation(s)
	▪ Vancomycin for six weeks. • Therapy for prosthetic valve endocarditis caused by staphylococci: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin, rifampin, and gentamicin for ≥6 weeks. o Oxacillin-resistant strains: ▪ Vancomycin, rifampin, and gentamicin for ≥6 weeks. • Therapy for both native and prosthetic valve endocarditis caused by *Haemophilus* species *(Haemophilus parainfluenzae, Haemophilus aphrophilus, Haemophilus paraphrophilus), Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* species microorganisms: o Ceftriaxone for four weeks. o Ampicillin-sulbactam for four weeks. o Ciprofloxacin for four weeks. • Therapy for culture-negative endocarditis including *Bartonella* endocarditis: o Native valve: ▪ Ampicillin-sulbactam plus gentamicin (or vancomycin for patients allergic to penicillin) plus ciprofloxacin for four to six weeks. o Prosthetic valve (early; ≤1 year): ▪ Vancomycin for six weeks, plus gentamicin for two weeks, plus cefepime for six weeks, plus rifampin for six weeks. o Prosthetic valve (late; >1 year): ▪ Suspected *Bartonella*, culture negative: • Ceftriaxone for six weeks plus gentamicin with/without doxycycline for six weeks. ▪ Documented *Bartonella*, culture positive: • Doxycycline for six weeks plus gentamicin for two weeks.
American Heart Association: **Infective Endocarditis in Adults: Diagnosis, Antimicrobial Therapy, and Management of Complications (2015)**[12]	• Therapy for native valve endocarditis caused by viridans group streptococci and *Streptococcus gallolyticus* (Formerly Known as *Streptococcus bovis)*: o Highly penicillin-susceptible strains: ▪ Penicillin G or ceftriaxone for four weeks. ▪ Penicillin G or ceftriaxone plus gentamicin for two weeks (in patients with uncomplicated infective endocarditis, rapid response to therapy, and no underlying renal disease). ▪ Vancomycin for four weeks (recommended only for patients unable to tolerate penicillin or ceftriaxone therapy). o Relatively penicillin-resistant strains: ▪ Penicillin for four weeks plus gentamicin for the first two weeks. ▪ If the isolate is ceftriaxone susceptible, then ceftriaxone alone may be considered. ▪ Vancomycin for four weeks (recommended only for patients unable to tolerate beta-lactam therapy). • Therapy for native valve endocarditis caused by *A defectiva* and *Granulicatella* Species and viridans group streptococci: o For patients with infective endocarditis caused by *A defectiva*, *Granulicatella* species, and viridans group streptococci with a penicillin MIC ≥0.5 µg/mL, treat with a combination of ampicillin or penicillin plus gentamicin as done for enterococcal infective endocarditis with infectious diseases consultation. o If vancomycin is used in patients intolerant of ampicillin or penicillin, then the addition of gentamicin is not needed. o Ceftriaxone combined with gentamicin may be a reasonable alternative treatment option for isolates that are susceptible to ceftriaxone. • Therapy for endocarditis of prosthetic valves or other prosthetic material caused by viridans group streptococci and *Streptococcus gallolyticus* (Formerly Known as *Streptococcus bovis)*:

Clinical Guideline	Recommendation(s)
	o Penicillin for six weeks plus gentamicin for the first two weeks. o Extend gentamicin to six weeks if the MIC is >0.12 µg/mL for the infecting strain. o Vancomycin can be used in patients intolerant of penicillin, ceftriaxone, or gentamicin. • Therapy for endocarditis of prosthetic valves or other prosthetic material caused by *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and Groups B, C, F, and G β-Hemolytic Streptococci: o Penicillin, cefazolin, or ceftriaxone for four weeks is reasonable for infective endocarditis caused by *S pneumoniae*; vancomycin can be useful for patients intolerant of β-lactam therapy. o Six weeks of therapy is reasonable for prosthetic valve endocarditis caused by *S pneumoniae*. o High-dose penicillin or a third-generation cephalosporin is reasonable in patients with infective endocarditis caused by penicillin-resistant *S pneumoniae* without meningitis; if meningitis is present, then high doses of cefotaxime (or ceftriaxone) are reasonable. o The addition of vancomycin and rifampin to cefotaxime (or ceftriaxone) may be considered in patients with infective endocarditis caused by *S pneumoniae* that are resistant to cefotaxime. o Because of the complexities of infective endocarditis caused by *S pneumoniae*, consultation with an infectious diseases specialist is recommended. o For infective endocarditis caused by *S pyogenes*, four to six weeks of therapy with aqueous crystalline penicillin G or ceftriaxone is reasonable; vancomycin is reasonable only in patients intolerant of β-lactam therapy. o For infective endocarditis caused by group B, C, or G streptococci, the addition of gentamicin to penicillin G or ceftriaxone for at least the first two weeks of a four to six week treatment course may be considered. o Consultation with an infectious diseases specialist to guide treatment is recommended in patients with infective endocarditis caused by β-hemolytic streptococci. • Therapy for endocarditis caused by staphylococci in the absence of prosthetic valves or other prosthetic material: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin for six weeks. ▪ For penicillin-allergic individuals: cefazolin for six weeks. o Oxacillin-resistant strains ▪ Vancomycin for six weeks. ▪ Daptomycin for six weeks. • Therapy for prosthetic valve endocarditis caused by staphylococci: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin plus rifampin (for at least six weeks) and gentamicin (for two weeks). o Oxacillin-resistant strains: ▪ Vancomycin plus rifampin (for at least six weeks) and gentamicin (for two weeks). • Therapy for native valve or prosthetic valve enterococcal endocarditis: o Strains susceptible to penicillin and gentamicin: ▪ Ampicillin or penicillin G plus gentamicin for four to six weeks. ▪ Double β-lactam ampicillin plus ceftriaxone for six. o Strains susceptible to penicillin and resistant to aminoglycosides or streptomycin-susceptible gentamicin-resistant in patients able to tolerate β-Lactam therapy: ▪ Ampicillin plus ceftriaxone for six weeks. ▪ Ampicillin or penicillin G plus streptomycin for four to six

Clinical Guideline	Recommendation(s)
	weeks. o Vancomycin and aminoglycoside-susceptible penicillin-resistant enterococcus species in patients unable to tolerate β-lactam : ▪ Unable to tolerate β-lactams: • Vancomycin plus gentamicin for six weeks (vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone therapy). ▪ Intrinsic penicillin resistance: • Vancomycin plus gentamicin for six weeks. o Strains Resistant to Penicillin, Aminoglycosides, and Vancomycin: ▪ Linezolid or daptomycin for at least six weeks. • Therapy for both native and prosthetic valve endocarditis caused by *Haemophilus* species *(Haemophilus parainfluenzae, Haemophilus aphrophilus, Haemophilus paraphrophilus), Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* species microorganisms: o Ceftriaxone (cefotaxime or another third- or fourth-generation cephalosporin may be substituted) or ampicillin or ciprofloxacin for four weeks. Fluoroquinolone therapy recommended only for patients unable to tolerate cephalosporin and ampicillin therapy; levofloxacin or moxifloxacin may be substituted. • Therapy for culture-negative endocarditis including *Bartonella* endocarditis: o For patients with acute (days) clinical presentations of native valve infection, coverage for *S aureus*, β-hemolytic streptococci, and aerobic Gram-negative bacilli is reasonable. o For patients with a subacute (weeks) presentation of native valve endocarditis, coverage of *S aureus*, viridans group streptococci, HACEK, and enterococci is reasonable. o For patients with culture-negative prosthetic valve endocarditis, coverage for staphylococci, enterococci, and aerobic Gram-negative bacilli is reasonable if onset of symptoms is within one year of prosthetic valve placement. o If symptom onset is >1 year after valve placement, then infective endocarditis is more likely to be caused by staphylococci, viridans group streptococci, and enterococci, and antibiotic therapy for these potential pathogens is reasonable.
Infectious Diseases Society of America: **Clinical Practice Guidelines: Management of Encephalitis (2008)**[13] **(Was reviewed and deemed current as of July 2011)**	Empirical therapy • Acyclovir should be initiated in all patients with suspected encephalitis, pending results of diagnostic studies. • Other empirical antimicrobial agents should be initiated on the basis of specific epidemiologic or clinical factors, including appropriate therapy for presumed bacterial meningitis, if clinically indicated. • In patients with clinical clues suggestive of rickettsial or ehrlichial infection during the appropriate season, doxycycline should be added to empirical treatment regimens. Bacteria • *Bartonella bacilliformis:* chloramphenicol, ciprofloxacin, doxycycline, ampicillin, or sulfamethoxazole-trimethoprim is recommended. • *Bartonella henselae:* doxycycline or azithromycin, with or without rifampin, can be considered. • *Listeria monocytogenes:* ampicillin plus gentamicin is recommended; sulfamethoxazole-trimethoprim is an alternative in the penicillin-allergic patient. • *Mycoplasma pneumoniae:* antimicrobial therapy (azithromycin, doxycycline, or a fluoroquinolone) can be considered. • *Tropheryma whipplei:* ceftriaxone, followed by either sulfamethoxazole-

Clinical Guideline	Recommendation(s)
	trimethoprim or cefixime, is recommended. Helminths • *Baylisascaris procyonis:* albendazole plus diethylcarbamazine can be considered; adjunctive corticosteroids should also be considered. • *Gnathostoma* species: albendazole or ivermectin is recommended. • *Taenia solium:* need for treatment should be individualized; albendazole and corticosteroids are recommended; praziquantel can be considered as an alternative. Rickettsioses and ehrlichiosis • *Anaplasma phagocytophilum:* doxycycline is recommended. • *Ehrlichia chaffeensis:* doxycycline is recommended. • *Rickettsia rickettsii:* doxycycline is recommended; chloramphenicol can be considered an alternative in selected clinical scenarios, such as pregnancy. • *Coxiella burnetii:* doxycycline plus a fluoroquinolone plus rifampin is recommended. Spirochetes • *Borrelia burgdorferi:* ceftriaxone, cefotaxime, or penicillin G is recommended. • *Treponema pallidum:* penicillin G is recommended; ceftriaxone is an alternative. Protozoa • *Acanthamoeba:* sulfamethoxazole-trimethoprim plus rifampin plus ketoconazole or fluconazole plus sulfadiazine plus pyrimethamine can be considered. • *Balamuthia mandrillaris:* pentamidine, combined with a macrolide (azithromycin or clarithromycin), fluconazole, sulfadiazine, flucytosine, and a phenothiazine can be considered. • *Naegleria fowleri:* amphotericin B (intravenous and intrathecal) and rifampin, combined with other agents, can be considered. • *Plasmodium falciparum:* quinine, quinidine, or artemether is recommended; atovaquone-proguanil is an alternative; exchange transfusion is recommended for patients with 110% parasitemia or cerebral malaria; corticosteroids are not recommended. • *Toxoplasma gondii:* pyrimethamine plus either sulfadiazine or clindamycin is recommended; sulfamethoxazole-trimethoprim alone and pyrimethamine plus atovaquone, clarithromycin, azithromycin, or dapsone are alternatives. • *Trypanosoma brucei gambiense:* eflornithine is recommended; melarsoprol is an alternative. • *Trypanosoma brucei rhodesiense:* melarsoprol is recommended.

Infectious Diseases Society of America: **Practice Guidelines for the Diagnosis and Management of Skin and Soft-Tissue Infections (2014)**[14]	Impetigo and ecthyma
	• Gram stain and culture of the pus or exudates from skin lesions of impetigo and ecthyma are recommended to help identify whether *Staphylococcus aureus* and/or a β-hemolytic *Streptococcus* is the cause (strong, moderate), but treatment without these studies is reasonable in typical cases.
	• Bullous and nonbullous impetigo can be treated with oral or topical antimicrobials, but oral therapy is recommended for patients with numerous lesions or in outbreaks affecting several people to help decrease transmission of infection. Treatment for ecthyma should be an oral antimicrobial.
	  o Treatment of bullous and nonbullous impetigo should be with either mupirocin or retapamulin twice daily for five days.
	  o Oral therapy for ecthyma or impetigo should be a seven-day regimen with an agent active against *S. aureus* unless cultures yield streptococci alone (when oral penicillin is the recommended agent). Because *S. aureus* isolates from impetigo and ecthyma are usually methicillin susceptible, dicloxacillin or cephalexin is recommended.

Clinical Guideline	Recommendation(s)
	When MRSA is suspected or confirmed, doxycycline, clindamycin, or sulfamethoxazole-trimethoprim is recommended. Purulent skin and soft-tissue infections (cutaneous abscesses, furuncles, carbuncles, and inflamed epidermoid cysts) • Gram stain and culture of pus from carbuncles and abscesses are recommended, but treatment without these studies is reasonable in typical cases. Gram stain and culture of pus from inflamed epidermoid cysts are not recommended. • Incision and drainage is the recommended treatment for inflamed epidermoid cysts, carbuncles, abscesses, and large furuncles. • The decision to administer antibiotics directed against *S. aureus* as an adjunct to incision and drainage should be made based upon presence or absence of systemic inflammatory response syndrome (SIRS), such as temperature >38°C or <36°C, tachypnea >24 breaths per minute, tachycardia >90 beats per minute, or white blood cell count >12 000 or <400 cells/µL. An antibiotic active against MRSA is recommended for patients with carbuncles or abscesses who have failed initial antibiotic treatment or have markedly impaired host defenses or in patients with SIRS and hypotension. Recurrent skin abscesses • A recurrent abscess at a site of previous infection should prompt a search for local causes such as a pilonidal cyst, hidradenitis suppurativa, or foreign material. • Recurrent abscesses should be drained and cultured early in the course of infection. • After obtaining cultures of recurrent abscess, treat with a five to ten day course of an antibiotic active against the pathogen isolated. • Consider a five-day decolonization regimen twice daily of intranasal mupirocin, daily chlorhexidine washes, and daily decontamination of personal items such as towels, sheets, and clothes for recurrent *S. aureus* infection. • Adult patients should be evaluated for neutrophil disorders if recurrent abscesses began in early childhood. Erysipelas and cellulitis • Cultures of blood or cutaneous aspirates, biopsies, or swabs are not routinely recommended except in patients with malignancy on chemotherapy, neutropenia, severe cell-mediated immunodeficiency, immersion injuries, and animal bites. • Typical cases of cellulitis without systemic signs of infection should receive an antimicrobial agent that is active against streptococci. For cellulitis with systemic signs of infection (moderate nonpurulent), systemic antibiotics are indicated. Many clinicians could include coverage against methicillin-susceptible *S. aureus* (MSSA). For patients whose cellulitis is associated with penetrating trauma, evidence of MRSA infection elsewhere, nasal colonization with MRSA, injection drug use, or SIRS (severe nonpurulent), vancomycin or another antimicrobial effective against both MRSA and streptococci is recommended. In severely compromised patients, broad-spectrum antimicrobial coverage may be considered. Vancomycin plus either piperacillin-tazobactam or imipenem/meropenem is recommended as a reasonable empiric regimen for severe infections. • The recommended duration of antimicrobial therapy is five days, but treatment should be extended if the infection has not improved within this time period. Surgical site infections

Clinical Guideline	Recommendation(s)

	• Suture removal plus incision and drainage should be performed for surgical site infections.
	• Adjunctive systemic antimicrobial therapy is not routinely indicated, but in conjunction with incision and drainage may be beneficial for surgical site infections associated with a significant systemic response.
	• A brief course of systemic antimicrobial therapy is indicated in patients with surgical site infections following clean operations on the trunk, head and neck, or extremities that also have systemic signs of infection.
	• A first-generation cephalosporin or an antistaphylococcal penicillin for MSSA, or vancomycin, linezolid, daptomycin, telavancin, or ceftaroline where risk factors for MRSA are high (nasal colonization, prior MRSA infection, recent hospitalization, recent antibiotics), is recommended.
	• Agents active against gram-negative bacteria and anaerobes, such as a cephalosporin or fluoroquinolone in combination with metronidazole, are recommended for infections following operations on the axilla, gastrointestinal tract, perineum, or female genital tract.
	
	Necrotizing fasciitis
	• Empiric antibiotic treatment should be broad (e.g., vancomycin or linezolid plus piperacillin-tazobactam or a carbapenem; or plus ceftriaxone and metronidazole), as the etiology can be polymicrobial (mixed aerobic–anaerobic microbes) or monomicrobial (group A streptococci, community-acquired MRSA).
	• Penicillin plus clindamycin is recommended for treatment of documented group A streptococcal necrotizing fasciitis.
	
	Pyomyositis
	• Cultures of blood and abscess material should be obtained.
	• Vancomycin is recommended for initial empirical therapy. An agent active against enteric gram-negative bacilli should be added for infection in immunocompromised patients or following open trauma to the muscles.
	• Cefazolin or antistaphylococcal penicillin (e.g., nafcillin or oxacillin) is recommended for treatment of pyomyositis caused by MSSA.
	• Antibiotics should be administered intravenously initially, but once the patient is clinically improved, oral antibiotics are appropriate for patients in whom bacteremia cleared promptly and there is no evidence of endocarditis or metastatic abscess. Two to three weeks of therapy is recommended.
	
	Clostridial gas gangrene or myonecrosis
	• Urgent surgical exploration of the suspected gas gangrene site and surgical debridement of involved tissue should be performed.
	• In the absence of a definitive etiologic diagnosis, broad-spectrum treatment with vancomycin plus either piperacillin-tazobactam, ampicillin-sulbactam, or a carbapenem antimicrobial is recommended. Definitive antimicrobial therapy with penicillin and clindamycin is recommended for treatment of clostridial myonecrosis.
	
	Animal bites
	• Preemptive early antimicrobial therapy for three to five days is recommended for patients who:
	  o are immunocompromised;
	  o are asplenic;
	  o have advanced liver disease;
	  o have preexisting or resultant edema of the affected area;
	  o have moderate to severe injuries, especially to the hand or face; or

Clinical Guideline	Recommendation(s)
	○ have injuries that may have penetrated the periosteum or joint capsule. • Oral treatment options ○ Amoxicillin-clavulanate is recommended. ○ Alternative oral agents include doxycycline, as well as penicillin VK plus dicloxacillin. ○ First-generation cephalosporins, penicillinase-resistant penicillins, macrolides, and clindamycin all have poor in vitro activity against *Pasteurella multocida* and should be avoided. • Intravenous ○ β-lactam-β-lactamase combinations, piperacillin-tazobactam, second-generation cephalosporins, and carbapenems. • Tetanus toxoid should be administered to patients without toxoid vaccination within 10 years. Tetanus, diphtheria, and tetanus (Tdap) is preferred over Tetanus and diphtheria (Td) if the former has not been previously given. Cutaneous anthrax • Oral penicillin V 500 mg four times daily for seven to 10 days is the recommended treatment for naturally acquired cutaneous anthrax. • Ciprofloxacin 500 mg by mouth twice daily or levofloxacin 500 mg intravenously/orally every 24 hours for 60 days is recommended for bioterrorism cases because of presumed aerosol exposure. Bacillary angiomatosis and cat scratch disease • Azithromycin is recommended for cat scratch disease (strong, moderate) according to the following dosing protocol: ○ Patients >45 kg: 500 mg on day one followed by 250 mg for four additional days. ○ Patients <45 kg: 10 mg/kg on day one and 5 mg/kg for four more days. • Erythromycin 500 mg four times daily or doxycycline 100 mg bid for two weeks to two months is recommended for treatment of bacillary angiomatosis. Erysipeloid • Penicillin (500 mg four times daily) or amoxicillin (500 mg three times daily [tid]) for seven to 10 days is recommended for treatment of erysipeloid. Glanders • Ceftazidime, gentamicin, imipenem, doxycycline, or ciprofloxacin is recommended based on in vitro susceptibility. Bubonic plague • Bubonic plague should be diagnosed by Gram stain and culture of aspirated material from a suppurative lymph node. Streptomycin (15 mg/kg intramuscularly every 12 hours) or doxycycline (100 mg twice daily by mouth) is recommended for treatment of bubonic plague. Gentamicin could be substituted for streptomycin. Tularemia • Streptomycin (15 mg/kg every 12 hours intramuscularly) or gentamicin (1.5 mg/kg every 8 hours intravenously) is recommended for treatment of severe cases of tularemia. • Tetracycline (500 mg four times daily) or doxycycline (100 mg twice daily by mouth) is recommended for treatment of mild cases of tularemia.
World	General considerations

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Gastroenterology Organization: **Acute Diarrhea (2012)**[15]	• 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. o Alternative: fluoroquinolones (e.g., ciprofloxacin).
Infectious Diseases Society of America: **The Practice of Travel Medicine (2006)**[16]	<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,

Clinical Guideline	Recommendation(s)
	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)**[17]	Recommendations for therapy against specific pathogens
	• *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.
	• *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: **Guideline on the Management of *Helicobacter pylori* Infection (2007)**[18]	• The recommended primary therapies for *Helicobacter pylori* infection include: a proton pump inhibitor, clarithromycin, and amoxicillin, or metronidazole (clarithromycin-based triple therapy) for 14 days or a proton pump inhibitor or histamine 2 receptor antagonist, bismuth, metronidazole, and tetracycline (bismuth quadruple therapy) for 10 to 14 days.
Canadian Helicobacter Study Group:	• A quadruple combination of a proton pump inhibitor, bismuth, tetracycline, and metronidazole or a proton pump inhibitor, amoxicillin, metronidazole, and clarithromycin for 14 days can be considered first-line therapy for the eradication of

Clinical Guideline	Recommendation(s)
The Toronto Consensus for the Treatment of *Helicobacter pylori* Infection in Adults (2016)[19]	*Helicobacter pylori*. • Proton pump inhibitor-based triple therapy is restricted to areas with known low clarithromycin resistance or high eradication success with these regimens. • Recommended rescue therapies include bismuth quadruple therapy and levofloxacin-containing therapy. • Rifabutin regimens should be restricted to patients who have failed to respond to at least three prior regimens.
European *Helicobacter pylori* Study Group: **Management of *Helicobacter pylori* Infection–The Maastricht IV Consensus Report (2012)**[20]	• First-line therapy should be with triple therapy using a proton pump inhibitor or ranitidine bismuth citrate, combined with clarithromycin and amoxicillin or metronidazole. • Second-line therapy should include bismuth-containing quadruple therapy or proton pump inhibitor, levofloxacin and amoxicillin.
Centers for Disease Control and Prevention: **Sexually Transmitted Diseases Treatment Guidelines (2015)**[21]	Arthritis and arthritis-dermatitis syndrome • Recommended regimen: o Ceftriaxone 1 g intramuscular or intravenous every 24 hours plus azithromycin 1 g orally in a single dose. • Alternative regimen: o Cefotaxime 1 g intravenous every eight hours or ceftizoxime 1 g intravenous every eight hours plus azithromycin 1 g orally in a single dose. Bacterial vaginosis • Recommended regimens: o Metronidazole 500 mg orally twice a day for seven days. o Metronidazole gel 0.75%, one full applicator (5 g) intravaginally, once a day for five days. o Clindamycin cream 2%, one full applicator (5 g) intravaginally at bedtime for seven days. • Alternative regimens: o Tinidazole 2 g orally once daily for two days. o Tinidazole 1 g 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. Cervicitis • Recommended regimens for presumptive treatment: o Azithromycin 1 g orally in a single dose. o Doxycycline 100 mg orally twice a day for seven days. Chancroid • Recommended regimens: o Azithromycin 1 g 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. Chlamydial infections • Recommended regimens: o Azithromycin 1 g orally in a single dose. o Doxycycline 100 mg orally twice a day for seven days. • Alternative regimens:

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	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. Chlamydial infections among children • 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 g orally in a single dose. • Recommended regimens for children ≥8 years of age: o Azithromycin 1 g orally in a single dose. o Doxycycline 100 mg orally twice a day for seven days. Disseminated gonococcal infection • Recommended regimen: o Ceftriaxone 1 g intramuscular or intravenous every 24 hours. • Alternative regimens: o Cefotaxime 1 g intravenous every eight hours. o Ceftizoxime 1 g intravenous every eight hours. Epididymitis • 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. Granuloma inguinale (Donovanosis) • Recommended regimen: o Azithromycin 1 g orally once per week or 500 mg daily for at least three weeks and until all lesions have completely healed. • Alternative regimens: o Doxycycline 100 mg orally twice a day 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 g intramuscular in a single dose plus azithromycin 1 g orally in a single dose. Gonococcal infections among children • Recommended regimen for children >45 kg:

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	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 25 to 50 mg/kg intravenous or intramuscular in a single dose, not to exceed 125 mg. • Recommended regimen for children who weigh ≤45 kg and who have bacteremia or arthritis: o Ceftriaxone 50 mg/kg (maximum dose: 1 g) 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 g intravenous every 12 hours plus azithromycin 1 g orally in a single dose. <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 g 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. • Alternative regimen: o Azithromycin suspension, 20 mg/kg/day orally, one dose daily for three days. <u>Pelvic inflammatory disease</u> • Recommended parenteral regimen A: o Cefotetan 2 g intravenous every 12 hours. o Cefoxitin 2 g 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.

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	• Alternative parenteral regimens:
	  o Ampicillin-sulbactam 3 g 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 g intramuscular in a single dose and probenecid, 1 g 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 g orally in a single dose.
	  o Tinidazole 2 g orally in a single dose plus azithromycin 1 g orally in a single dose (if not used for initial episode).
	
	<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>Trichomoniasis</u>

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	• Recommended regimen:
	  o Metronidazole 2 g orally in a single dose.
	  o Tinidazole 2 g orally in a single dose.
	• Alternative regimen:
	  o Metronidazole 500 mg orally twice a day for seven days.
	
	Neurosyphilis
	• 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.
	
	Uncomplicated gonococcal infections of the cervix, urethra, and rectum
	• 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 1g orally in a single dose or doxycycline 100 mg orally twice a day for seven days.
	
	Uncomplicated gonococcal infections of the pharynx
	• Recommended regimens:
	  o Ceftriaxone 250 mg intermuscular in a single dose plus azithromycin 1g orally in a single dose or doxycycline 100 mg orally twice a day for seven days.

Working Group on Civilian Biodefense: **Anthrax as a Biological Weapon, Updated Recommendations for Management (2002)**[22]	Inhalation anthrax in the contained casualty setting - adults • Ciprofloxacin 400 mg intravenous every 12 hours initially, then 500 mg by mouth twice daily when clinically appropriate; OR • Doxycycline 100 mg intravenous every 12 hours initially with either one or two of the following: rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, clindamycin, and/or clarithromycin. Switch to 100 mg by mouth twice daily when clinically appropriate. Inhalation anthrax in the contained casualty setting - children • Ciprofloxacin 10 to 15 mg/kg every 12 hours intravenous, then 10 to 15 mg/kg by mouth every 12 hours when clinically appropriate; OR • Doxycycline (if ≤45 kg–2.2 mg/kg intravenous; if > 45 kg–100 mg intravenous) every 12 hours initially with either one or two of the following: rifampin, vancomycin, penicillin, ampicillin, chloramphenicol, imipenem, clindamycin, and/or clarithromycin. Switch to oral therapy when clinically appropriate using same intravenous dose. Inhalation anthrax in a mass casualty setting - adults • Recommended treatment: ciprofloxacin 500 mg by mouth every 12 hours. • Alternative treatment option: doxycycline 100 mg by mouth every 12 hours or amoxicillin 500 mg by mouth every eight hours. Inhalation anthrax in a mass casualty setting - children • Recommended treatment: ciprofloxacin 10 to 15 mg/kg by mouth every 12 hours. • Alternative treatment option: amoxicillin 500 mg by mouth every eight hours (weight ≥20 kg) or amoxicillin 40 mg/kg by mouth every eight hours (weight <20 kg).

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	Inhalation anthrax in a mass casualty setting – pregnant women • Recommended treatment: ciprofloxacin 500 mg by mouth every 12 hours. • Alternative treatment option: amoxicillin 500 mg every eight hours.

Global Initiative for Chronic Obstructive Lung Disease: **Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2016)**[23]	• Prophylactic, continuous use of antibiotics has been shown to have no effect on the frequency of exacerbations in chronic obstructive pulmonary disease.
	• The use of antibiotics, other than for treating infectious exacerbations of chronic obstructive pulmonary disease and other bacterial infections, is currently not indicated.
	• Based on current available evidence, antibiotics should be given to:
	  o Patients with exacerbations of chronic obstructive pulmonary disease with the following three cardinal symptoms: dyspnea, sputum volume, and sputum purulence.
	  o Patients with exacerbations of chronic obstructive pulmonary disease with two of the cardinal symptoms, if the increased purulence of sputum is one of the two symptoms.
	  o Patients with a severe exacerbation of chronic obstructive pulmonary disease that requires mechanical ventilation (invasive or noninvasive).
	• The recommended length of antibiotic therapy is usually five to 10 days.
	• The choice of antibiotic should be based on local bacterial resistance patterns.
	• Initial empiric treatment may include an aminopenicillin with or without clavulanic acid, macrolide, or tetracycline. In patients with frequent exacerbations, severe airflow limitation, and/or exacerbations requiring mechanical ventilation, sputum cultures or cultures from other materials from the lung should be performed, as gram-negative bacteria or resistant pathogens that may not be sensitive to the afore-mentioned antibiotics may be present.

Infectious Diseases Society of America: **Management of Community-Acquired Pneumonia in Infants and Children Older Than 3 Months of Age (2011)**[24]
 	
Reviewed and deemed current as of 04/2013
	Outpatient treatment
	• Antimicrobial therapy is not routinely required for preschool-aged children with community-acquired pneumonia, because viral pathogens are responsible for the great majority of clinical disease.
	• Amoxicillin should be used as first-line therapy for previously healthy, appropriately immunized infants and preschool children with mild to moderate community-acquired pneumonia suspected to be of bacterial origin. Amoxicillin provides appropriate coverage for *Streptococcus pneumoniae*.
	• For patients allergic to amoxicillin, the following agents are considered alternative treatment options:
	  o Second- or third-generation cephalosporin (cefpodoxime, cefuroxime, cefprozil).
	  o Levofloxacin (oral therapy).
	  o Linezolid (oral therapy).
	• Macrolide antibiotics should be prescribed for treatment of children (primarily school-aged children and adolescents) evaluated in an outpatient setting with findings compatible with community-acquired pneumonia caused by atypical pathogens.
	
	Inpatient treatment
	• Ampicillin or penicillin G should be administered to the fully immunized infant or school-aged child admitted to a hospital ward with community-acquired pneumonia when local epidemiologic data document lack of substantial high-level penicillin resistance for invasive *Streptococcus pneumoniae*.
	• Empiric therapy with a third-generation parenteral cephalosporin (ceftriaxone or cefotaxime) should be prescribed for hospitalized infants and children who are not fully immunized, in regions where local epidemiology of invasive pneumococcal strains documents high-level penicillin resistance, or for infants and children with life-threatening infection, including those with empyema.
	• Non–β-lactam agents, such as vancomycin, have not been shown to be more

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	effective than third-generation cephalosporins in the treatment of pneumococcal pneumonia for the degree of resistance noted currently in North America. • Empiric combination therapy with a macrolide (oral or parenteral), in addition to a β-lactam antibiotic, should be prescribed for the hospitalized child for whom *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* are significant considerations. • Vancomycin or clindamycin (based on local susceptibility data) should be provided in addition to β-lactam therapy if clinical, laboratory, or imaging characteristics are consistent with infection caused by *Staphylococcus aureus*.

Infectious Diseases Society of America/American Thoracic Society: **Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults (2007)**[25]	<u>Empirical antimicrobial therapy</u>
	• Recommendations are generally for a class of antibiotics rather than for a specific drug, unless outcome data clearly favor one drug.
	• Because overall efficacy remains good for many classes of agents, the more potent drugs are given preference because of their benefit in decreasing the risk of selection for antibiotic resistance.
	• Outpatient treatment
	  o Previously healthy and no risk factors for drug-resistant *Streptococcus pneumoniae* infection:
	  ▪ Macrolide (azithromycin, clarithromycin, or erythromycin).
	  ▪ Doxycycline.
	  o Presence of comorbidities, such as chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressing conditions or use of immunosuppressing drugs; use of antimicrobials within the previous three months (in which case an alternative from a different class should be selected); or other risks for drug-resistant Streptococcus pneumoniae infection:
	  ▪ Respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin).
	  ▪ β-lactam plus a macrolide (high-dose amoxicillin or amoxicillin-clavulanate is preferred; alternatives include ceftriaxone, cefpodoxime, and cefuroxime; doxycycline is an alternative to the macrolide).
	  o In regions with a high rate of infection with high-level macrolide-resistant *Streptococcus pneumoniae,* consider the use of alternative agents listed above for any patient, including those without comorbidities.
	• Inpatient, non-intensive care unit treatment
	  o Respiratory fluoroquinolone.
	  o β-lactam plus a macrolide (preferred β-lactam agents include cefotaxime, ceftriaxone, and ampicillin; ertapenem for selected patients; with doxycycline as an alternative to the macrolide. A respiratory fluoroquinolone should be used for penicillin-allergic patients).
	• Inpatient, intensive care unit treatment
	  o β-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) plus either azithromycin or a fluoroquinolone (for penicillin-allergic patients, a respiratory fluoroquinolone and aztreonam are recommended).
	  o For *Pseudomonas* infection, use an antipneumococcal, antipseudomonal β-lactam (piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin; OR
	  o Antipneumococcal, antipseudomonal β-lactam (listed above) plus an aminoglycoside and azithromycin; OR
	  o Antipneumococcal, antipseudomonal β-lactam (listed above) plus an aminoglycoside and an antipneumococcal fluoroquinolone (for penicillin-allergic patients, substitute aztreonam for the above β-lactam).
	  o For community-acquired methicillin-resistant *Staphylococcus aureus* infection, add vancomycin or linezolid.

American Thoracic	• Select an initial empiric therapy based on the absence or presence of risk factors for

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Society/ Infectious Diseases Society of America: **Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia (2005)**[26]	multidrug-resistant pathogens. These risk factors include prolonged duration of hospitalization (five days or more), admission from a healthcare-related facility, and recent prolonged antibiotic therapy.
	• Patients with healthcare-related pneumonia should be treated for potentially drug-resistant organisms, regardless of when during the hospital stay the pneumonia begins.
	• In selecting empiric therapy for patients who have recently received an antibiotic, an effort should be made to use an agent from a different antibiotic class, because recent therapy increases the probability of inappropriate therapy and can predispose to resistance to that same class of antibiotics.
	• Initial empiric antibiotic therapy for hospital-acquired pneumonia or ventilator-associated pneumonia in patients with no known risk factors for multidrug-resistant pathogens, early onset, and any disease severity:
	  o Ceftriaxone; OR
	  o Levofloxacin, moxifloxacin, ciprofloxacin; OR
	  o Ampicillin-sulbactam; OR
	  o Ertapenem.
	• Initial empiric antibiotic therapy for hospital-acquired pneumonia, ventilator-associated pneumonia, and healthcare-associated pneumonia in patients with late-onset disease or risk factors for multidrug-resistant pathogens and all disease severity–combination antibiotic therapy is recommended as follows:
	• Antipseudomonal cephalosporin (cefepime, ceftazidime) or antipseudomonal carbapenem (imipenem or meropenem) or β-lactam-β-lactamase inhibitor (piperacillin-tazobactam) plus antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) or aminoglycoside (amikacin, gentamicin, or tobramycin) plus linezolid or vancomycin if methicillin-resistant *Staphylococcus aureus* risk factors are present or there is a high incidence locally.

Infectious Diseases Society of America: **Diagnosis and Management of Complicated Intra-abdominal Infection in Adults and Children (2010)**[27]	<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%

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	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 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. <u>Health care-associated infection:</u> • 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. <u>Cholecystitis and cholangitis:</u> • 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: **Clinical Assessment, Treatment, and Prevention of Lyme Disease, Human Granulocytic**	• Doxycycline, amoxicillin or cefuroxime axetil for 14 days is recommended for the treatment of adult patients with early localized or early disseminated Lyme disease associated with erythema migrans, in the absence of specific neurologic manifestations (see Lyme meningitis, below) or advanced atrioventricular heart block. • Each of these antimicrobial agents has been shown to be highly effective for the treatment of erythema migrans and associated symptoms in prospective studies. • Doxycycline has the advantage of being effective for treatment of Human Granulocytic Anaplasmosis (but not for babesiosis), which may occur

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Anaplasmosis, and Babesiosis (2006)[28]	simultaneously with early Lyme disease.
Infectious Diseases Society of America: **Management of Patients with Infections Caused by Methicillin-Resistant *Staphylococcus Aureus* (2011)[29]**	<u>Skin and soft-tissue infections</u> • For a cutaneous abscess, incision and drainage is the primary treatment. For simple abscesses or boils, incision and drainage alone is likely to be adequate. • Antibiotic therapy is recommended for abscesses associated with the following conditions: severe or extensive disease (e.g., involving multiple sites of infection) or rapid progression in presence of associated cellulitis, signs and symptoms of systemic illness, associated comorbidities or immunosuppression, extremes of age, abscess in an area difficult to drain (e.g., face, hand, and genitalia), associated septic phlebitis, and lack of response to incision and drainage alone. • For outpatients with purulent cellulitis, empirical therapy for community-acquired methicillin-resistant *Staphylococcus aureus* is recommended pending culture results. Empirical therapy for infection due to beta-hemolytic streptococci is likely to be unnecessary. • For outpatients with non-purulent cellulitis, empirical therapy for infection due to beta-hemolytic streptococci is recommended. Empirical coverage for community-acquired methicillin-resistant *Staphylococcus aureus* is recommended in patients who do not respond to beta-lactam therapy and may be considered in those with systemic toxicity. • For empirical coverage of community-acquired methicillin-resistant *Staphylococcus aureus* in outpatients with skin and soft-tissue infections, oral antibiotic options include the following: clindamycin, sulfamethoxazole-trimethoprim, a tetracycline (doxycycline or minocycline), and linezolid. If coverage for both beta-hemolytic streptococci and community-acquired methicillin-resistant *Staphylococcus aureus* is desired, options include the following: clindamycin alone or sulfamethoxazole-trimethoprim or a tetracycline in combination with a beta-lactam (e.g., amoxicillin) or linezolid alone. • The use of rifampin as a single agent or as adjunctive therapy for the treatment of skin and soft-tissue infections is not recommended. • For hospitalized patients with complicated skin and soft-tissue infections, in addition to surgical debridement and broad-spectrum antibiotics, empirical therapy for methicillin-resistant *Staphylococcus aureus* should be considered pending culture data. Options include the following: vancomycin intravenous, linezolid oral or intravenous, daptomycin intravenous, telavancin intravenous, and clindamycin intravenous or oral. A beta-lactam antibiotic (e.g., cefazolin) may be considered in hospitalized patients with non-purulent cellulitis with modification to methicillin-resistant *Staphylococcus aureus*-active therapy if there is no clinical response. • For children with minor skin infections (such as impetigo) and secondarily infected skin lesions (such as eczema, ulcers, or lacerations), mupirocin 2% topical ointment can be used. • Tetracyclines should not be used in children <8 years of age. • In hospitalized children with skin and soft-tissue infections, vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, empirical therapy with clindamycin intravenous is an option if the clindamycin resistance rate is low (<10%) with transition to oral therapy if the strain is susceptible. Linezolid oral or intravenous is an alternative. <u>Methicillin-resistant Staphylococcus aureus and infective endocarditis (native valve)</u> • For adults with uncomplicated bacteremia, vancomycin or daptomycin intravenous for at least two weeks is recommended. For complicated bacteremia, four to six weeks of therapy is recommended, depending on the extent of infection. • For adults with infective endocarditis, intravenous vancomycin or daptomycin for six weeks is recommended.

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	• Addition of gentamicin to vancomycin is not recommended for bacteremia or native valve infective endocarditis.
	
	Methicillin-resistant *Staphylococcus aureus* bacteremia and infective endocarditis (prosthetic valve)
	• Intravenous vancomycin plus rifampin oral or intravenous for at least six weeks plus gentamicin intravenous for two weeks.
	• In children, vancomycin intravenous is recommended for the treatment of bacteremia and infective endocarditis. Duration of therapy may range from two to six weeks depending on source, presence of endovascular infection, and metastatic foci of infection.
	• Data regarding the safety and efficacy of alternative agents in children are limited, although daptomycin intravenous may be an option. Clindamycin or linezolid should not be used if there is concern for infective endocarditis or endovascular source of infection, but may be considered in children whose bacteremia rapidly clears and is not related to an endovascular focus.
	• Data are insufficient to support the routine use of combination therapy with rifampin or gentamicin in children with bacteremia or infective endocarditis.
	
	Management of methicillin-resistant *Staphylococcus aureus* pneumonia
	• For hospitalized patients with severe community-acquired pneumonia, empirical therapy for methicillin-resistant *Staphylococcus aureus* is recommended pending sputum and/or blood culture results.
	• For health care–associated methicillin-resistant *Staphylococcus aureus* or community-acquired methicillin-resistant *Staphylococcus aureus* pneumonia, intravenous vancomycin or linezolid oral or intravenous or clindamycin oral or intravenous, if the strain is susceptible, is recommended for seven to 21 days, depending on the extent of infection.
	• In children, intravenous vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, clindamycin intravenous can be used as empirical therapy if the clindamycin resistance rate is low (<10%) with transition to oral therapy if the strain is susceptible. Linezolid oral or intravenous is an alternative.
	
	Management of methicillin-resistant *Staphylococcus aureus* bone and joint infections
	• Antibiotics available for parenteral administration include intravenous vancomycin and daptomycin.
	• Some antibiotic options with parenteral and oral routes of administration include the following: sulfamethoxazole-trimethoprim in combination with rifampin, linezolid, and clindamycin. Some experts recommend the addition of rifampin. For patients with concurrent bacteremia, rifampin should be added after clearance of bacteremia.
	• A minimum eight-week course is recommended. Some experts suggest an additional one to three months (and possibly longer for chronic infection or if debridement is not performed) of oral rifampin-based combination therapy with sulfamethoxazole-trimethoprim, doxycycline-minocycline, clindamycin, or a fluoroquinolone, chosen on the basis of susceptibilities.
	• For septic arthritis, refer to antibiotic choices for osteomyelitis. A three to four-week course of therapy is suggested.
	
	Management of methicillin-resistant *Staphylococcus aureus* infections of the central nervous system
	• Meningitis
	  o Intravenous vancomycin for two weeks is recommended. Some experts recommend the addition of rifampin.
	  o Alternatives include the following: linezolid or sulfamethoxazole-

Clinical Guideline	Recommendation(s)
	trimethoprim. o For central nervous system shunt infection, shunt removal is recommended, and it should not be replaced until cerebrospinal fluid cultures are repeatedly negative. • Brain abscess, subdural empyema, spinal epidural abscess o Intravenous vancomycin for four to six weeks is recommended. Some experts recommend the addition of rifampin. o Alternatives include the following: linezolid and sulfamethoxazole-trimethoprim. • Septic thrombosis of cavernous or dural venous sinus o Intravenous vancomycin for four to six weeks is recommended. Some experts recommend the addition of rifampin. o Alternatives include the following: linezolid and sulfamethoxazole-trimethoprim. o Intravenous vancomycin is recommended in children.
Working Group on Civilian Biodefense: **Plague as a Biological Weapon: Medical and Public Health Management Consensus Statement (2000)**[30]	• For adults with pneumonic plague in the contained casualty settings, the preferred choice is streptomycin or gentamicin and alternative choices include doxycycline, ciprofloxacin, or chloramphenicol. • For children with pneumonic plague in the contained casualty settings, the preferred choice is streptomycin or gentamicin and alternative choices include doxycycline, ciprofloxacin, or chloramphenicol. • For pregnant women with pneumonic plague in the contained casualty settings, the preferred choice is gentamicin and an alternative choice is doxycycline. • For adults with pneumonic plague in the mass casualty setting and postexposure prophylaxis, the preferred choice is doxycycline, or ciprofloxacin and the alternative choice is chloramphenicol. • For children with pneumonic plague in the mass casualty setting and postexposure prophylaxis, the preferred choice is doxycycline or ciprofloxacin and an alternative choice is chloramphenicol. • For pregnant women with pneumonic plague in the mass casualty setting and postexposure prophylaxis, the preferred choice is doxycycline or ciprofloxacin and an alternative choice is chloramphenicol.
Centers for Disease Control and Prevention: **Diagnosis and Management of Tickborne Rickettsial Diseases: Rocky Mountain Spotted Fever, Ehrlichiosis, and Anaplasmosis—United States (2016)**[31]	• The Centers for Disease Control and Prevention recommends doxycycline as the treatment of choice for all tickborne rickettsial diseases in patients of all ages, including children aged <8 years, and should be initiated immediately in persons with signs and symptoms suggestive of rickettsial disease. • Chloramphenicol is an alternative drug that has been used to treat Rocky Mountain Spotted Fever; however, epidemiologic studies in which Centers for Disease Control and Prevention case report data have been used suggested that patients with Rocky Mountain Spotted Fever treated with chloramphenicol have a higher risk of dying than persons who received a tetracycline. • Chloramphenicol is associated with adverse hematologic effects, which have resulted in its limited use in the United States, and monitoring of blood indices is required if this drug is used. • If chloramphenicol is substituted for doxycycline in the empiric treatment of tickborne rickettsial diseases, ehrlichiosis and anaplasmosis will not be covered and Rocky Mountain Spotted Fever treatment might be suboptimal. • Rifampin could be an alternative for the treatment of mild illness due to anaplasmosis in the case of pregnancy or documented allergy to tetracycline-class drugs.

III. Indications

The Food and Drug Administration (FDA)-approved indications for the tetracyclines 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 Tetracyclines[1-8]

Indication	Demeclocycline	Doxycycline	Minocycline	Tetracycline	Tigecycline
Central Nervous System Infections					
Treatment of asymptomatic *Neisseria meningitidis* carriers			✔		
Dermatological Infections					
Acne		✔	✔	✔	
Skin and skin-structure infections	✔	✔	✔	✔	✔ §#
Staphylococcus aureus infections	✔			✔	
Treponema pertenue infections	✔ †	✔ †	✔ †	✔ †	
Yaws	✔ †	✔ †	✔ †	✔ †	
Gastrointestinal Infections					
Cholera	✔	✔	✔	✔	
Intestinal amebiasis	✔	✔		✔	
Genitourinary Infections					
Chancroid	✔	✔	✔	✔	
Chlamydial infection	✔	✔	✔	✔	
Endocervical infections		✔	✔	✔	
Granuloma inguinale	✔	✔	✔	✔	
Rectal infections		✔	✔	✔	
Syphilis	✔ †	✔ †	✔ †	✔ †	
Treponema pallidum infections	✔ †	✔ †	✔ †	✔ †	
Urethritis (gonococcal)	✔ †	✔ †			
Urethritis/cervicitis (gonococcal)			✔	✔ ‡	
Urethritis/cervicitis (non-gonococcal)	✔	✔	✔	✔	
Urinary tract infections	✔	✔	✔	✔	
Respiratory Infections					
Anthrax	✔ †	✔	✔ †	✔ †	
Community-acquired bacterial pneumonia					✔ #
Haemophilus influenzae infections	✔	✔	✔	✔	
Mycoplasma pneumonia	✔	✔	✔	✔	
Respiratory tract infections	✔	✔	✔	✔	
Streptococcus pneumoniae infections	✔	✔	✔	✔	

Indication	Demeclocycline	Doxycycline	Minocycline	Tetracycline	Tigecycline
Streptococcus pyogenes infections	✔			✔	
Miscellaneous Infections					
Acinetobacter species infections	✔	✔	✔	✔	
Actinomycotic infections	✔ †	✔ †	✔ †	✔ †	
Bacteroides species infections	✔			✔	
Bartonellosis	✔	✔	✔	✔	
Brucellosis	✔ *	✔ *	✔ *	✔ *	
Campylobacter fetus infections	✔	✔	✔	✔	
Clostridial infections	✔ †	✔ †	✔ †	✔ †	
Disease caused by rickettsiae	✔	✔	✔	✔	
Escherichia coli infections	✔	✔	✔	✔	
Enterobacter aerogenes infections	✔	✔	✔	✔	
Fusobacterium fusiforme infections	✔ †	✔ †	✔ †	✔ †	
Inclusion conjunctivitis		✔	✔	✔	
Intra-abdominal infections					✔ §#
Listeriosis	✔ †	✔ †	✔ †	✔ †	
Lymphogranuloma venereum	✔	✔	✔	✔	
Malaria prophylaxis		✔			
Periodontitis			✔		
Plague		✔	✔	✔	
Psittacosis	✔	✔	✔	✔	
Q fever	✔	✔	✔	✔	
Relapsing fever	✔	✔	✔	✔	
Rickettsialpox	✔	✔	✔	✔	
Rocky Mountain spotted fever	✔	✔	✔	✔	
Shigellosis	✔	✔	✔	✔	
Spotted fevers	✔	✔	✔	✔	
Tick fevers	✔	✔	✔	✔	
Trachoma	✔	✔	✔	✔	
Tularemia	✔	✔	✔	✔	
Typhus	✔	✔	✔	✔	
Vincent's infection	✔ †	✔ †	✔ †	✔ †	

*In conjunction with streptomycin.
†Alternative therapy for the following infections when penicillin is contraindicated.
‡Tetracycline is not a recommended alternative for uncomplicated gonorrhea according to the Centers for Disease Control and Prevention sexually transmitted diseases guidelines.
§Complicated infections.
#Infections caused by susceptible isolettes of the designated microorganisms (see Table 2).

IV. Pharmacokinetics

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

Table 5. Pharmacokinetic Parameters of the Tetracyclines[2]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Demeclocycline	Not reported	41 to 91	Liver	Renal (44) Feces (13 to 46)	10 to 15
Doxycycline	100	Varies	Liver	Renal (40)	18 to 22
Minocycline	90	76	Not reported	Renal/Feces	11 to 22
Tetracycline	Readily absorbed	5	Liver	Renal (60)	8 to 10
Tigecycline	Not reported	71 to 89	Liver	Renal (33) Feces (59)	42

V. Drug Interactions

Major drug interactions with the tetracyclines are listed in Table 6.

Table 6. Major Drug Interactions with the Tetracyclines[2]

Generic Name(s)	Interaction	Mechanism
Tetracyclines	Acitretin	Concurrent use of acitretin and tetracyclines may result in an increased risk of pseudotumor cerebri (benign intracranial hypertension).
Tetracyclines	Digoxin	Co-administration may result in increased serum levels of digoxin in a small subset of patients (10%). Monitor digoxin levels and signs of toxicity.
Tetracyclines	Methoxyflurane	Co-administration may enhance the risk for renal toxicity; deaths have been reported. Do not co-administer. If possible seek alternative agents.
Tetracyclines	Penicillins	The bacteriostatic action of tetracyclines may interfere with the bactericidal activity of penicillins. Consider avoiding this combination if at all possible.
Tetracyclines	Retinoids	Acitretin may increase the risk of pseudotumor cerebri. An additive adverse effect is thought to be responsible. Avoid concomitant and subsequent monotherapy usage of these agents.
Doxycycline	Methotrexate	Concurrent use of doxycycline and methotrexate may result in an increased risk of methotrexate toxicity (leukopenia, thrombocytopenia, anemia, nephrotoxicity, mucosal ulcerations).
Minocycline	Atazanavir	Concurrent use of atazanavir and minocycline may result in decreased atazanavir exposure and plasma concentrations.

VI. Adverse Drug Events

The most common adverse drug events reported with the tetracyclines are noted in Table 7. The use of tetracyclines during the period of tooth development (from the last half of pregnancy through eight years of age) may cause permanent discoloration of teeth. Due to the risk of this discoloration, the tetracyclines should not be used in children under eight years of age (except for the treatment and postexposure prophylaxis of anthrax), unless other drugs are not likely to be effective or are contraindicated. This adverse reaction is more common during long-term use of the drugs, but has been observed following repeated short-term courses.

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

Adverse Events	Demeclocycline	Doxycycline	Minocycline	Tetracycline	Tigecycline
Cardiovascular					
Bradycardia	-	-	-	-	✔
Pericarditis	✔	✔	✔	✔	-
Central Nervous System					
Bulging fontanels	✔	✔	✔	✔	-
Dizziness	✔	-	-	-	3
Fever	-	-	-	✔	-
Headache	✔	-	✔	-	6
Intracranial hypertension	-	✔	✔	-	-
Pseudotumor cerebri	✔	-	✔	✔	✔
Dermatological					
Erythema multiforme	✔	✔	✔	-	-
Erythematous rash	✔	✔	✔	✔	-
Exfoliative dermatitis	-	✔	✔	✔	-
Maculopapular rash	✔	✔	✔	✔	-
Nail discoloration	-	-	-	✔	-
Oncolysis	-	-	-	✔	-
Photosensitivity	✔	✔	✔	✔	✔
Pruritus	-	-	-	-	<2
Rash	-	-	-	✔	3
Skin hyperpigmentation	✔	-	✔	-	-
Stevens-Johnson syndrome	✔	✔	✔	-	✔
Toxic epidermal necrolysis	-	✔	✔	-	-
Urticaria	✔	✔	✔	✔	-
Endocrine and Metabolic					
Diabetes insipidus syndrome	✔	-	-	-	-
Nephrogenic diabetes insipidus	✔	-	-	-	-
Thyroid dysfunction	✔	-	✔	-	-
Gastrointestinal					
Abdominal pain	-	-	-	-	6

Adverse Events	Demeclocycline	Doxycycline	Minocycline	Tetracycline	Tigecycline
Anorexia	✔	✔	✔	✔	<2
Black hairy tongue	-	-	-	✔	-
Diarrhea	✔	✔	✔	✔	12
Dyspepsia	-	-	-	✔	2
Dysphagia	✔	✔	✔	✔	-
Enamel hypoplasia	-	-	-	✔	-
Enterocolitis	✔	✔	✔	✔	-
Esophageal ulcerations	✔	✔	✔	✔	-
Esophagitis	-	✔	✔	✔	-
Glossitis	✔	✔	✔	✔	-
Nausea	✔	✔	✔	✔	25 to 35
Oral pigmentation	-	✔	-	-	-
Pancreatitis	✔	-	-	✔	✔
Tooth discoloration	✔	✔	✔	✔	✔
Vomiting	✔	-	✔	✔	18 to 20
Genitourinary					
Acute renal failure	✔	-	✔	✔	-
Anogenital inflammatory lesions	-	✔	-	✔	-
Azotemia	-	-	-	✔	✔
Balanitis	✔	-	✔	-	-
Leukorrhea	-	-	-	-	<2
Monilial overgrowth	✔	-	✔	✔	<2
Renal damage	-	-	✔	✔	-
Vaginitis	-	-	-	-	<2
Hepatic					
Hepatic cholestasis	-	-	-	-	✔
Hepatic dysfunction	-	-	-	-	✔
Hepatic failure	✔	-	-	✔	✔
Hepatitis	✔	-	-	-	-
Hepatotoxicity	✔	-	✔	✔	-
Jaundice	-	-	-	-	<2
Hematologic					
Anemia	-	-	-	-	5
Eosinophilia	✔	✔	✔	✔	<2
Hemolytic anemia	✔	✔	✔	✔	-
Neutropenia	✔	✔	✔	✔	-
Porphyria	-	-	✔	-	-

Adverse Events	Demeclocycline	Doxycycline	Minocycline	Tetracycline	Tigecycline
Prothrombin time increased	-	-	-	-	<2
Thrombocytopenia	✔	✔	✔	✔	<2
Thrombocytopenic purpura	-	-	-	✔	-
Thrombophlebitis	-	-	-	✔	<2
Laboratory Test Abnormalities					
Acidosis	-	-	-	-	✔
Alkaline phosphatase increase	-	-	-	-	3
Amylase increased	-	-	-	-	3
Bilirubinemia	-	-	-	-	2
Blood urea nitrogen increased	✔	✔	✔	✔	3
Creatinine increased	-	-	-	-	<2
Hyperphosphatemia	-	-	-	-	✔
Hypocalcemia	-	-	-	-	<2
Hypoglycemia	-	-	-	-	<2
Hyponatremia	-	-	-	-	2
Hypoproteinemia	-	-	-	-	5
Total bilirubin increased	-	-	-	-	✔
Transaminases increased	✔	-	-	-	4 to 5
Musculoskeletal					
Arthralgia	-	-	-	✔	-
Polyarthralgia	✔	-	✔	-	-
Respiratory					
Cough	-	-	-	-	4
Dyspnea	-	-	-	-	3
Pneumonia	-	-	-	-	2
Pulmonary infiltrates	✔	-	✔	-	-
Other					
Abnormal healing	-	-	-	-	3
Abscess	-	-	-	-	2
Allergic reaction	-	-	-	-	<2
Anaphylactoid purpura	✔	-	✔	✔	-
Anaphylaxis	✔	✔	✔	✔	✔
Angioneurotic edema	✔	✔	✔	✔	-
Chills	-	-	-	-	<2
Hypersensitivity reaction	-	-	✔	✔	-
Infection	-	-	-	-	7
Injection site reaction	-	-	-	-	<2

Adverse Events	Demeclocycline	Doxycycline	Minocycline	Tetracycline	Tigecycline
Lupus erythematosus exacerbation	✔	✔	✔	✔	-
Lupus-like syndrome	✔	-	✔	-	-
Myasthenic syndrome	✔	-	-	-	-
Phlebitis	-	-	-	-	3
Pruritus	-	-	-	-	<2
Septic shock	-	-	-	-	<2
Stools abnormal	-	-	-	-	<2
Superinfection	-	-	-	-	✔
Taste perversion	-	-	-	-	<2
Thyroid gland discoloration	✔	✔	✔	✔	-
Tinnitus	✔	✔	✔	-	-
Visual disturbances	✔	-	-	-	-

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

Table 8. Boxed Warning for Tigecycline[1,7]

WARNING
An increase in all-cause mortality has been observed in a meta-analysis of Phase 3 and 4 clinical trials in Tygacil®-treated patients vs comparator. The cause of this mortality risk difference of 0.6% (95% confidence interval, 0.1 to 1.2) has not been established. Tygacil® should be reserved for use in situations when alternative treatments are not suitable.

VII. Dosing and Administration

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

Table 9. Usual Dosing Regimens for the Tetracyclines[1-8]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Demeclocycline	Unspecified infections: Tablet: 150 mg four times daily or 300 mg twice daily Gonorrhea (patients sensitive to penicillin): Tablet: 600 mg as an initial dose, followed by 300 mg every 12 hours for four days (total of 3 g)	Unspecified infections in children >8 years of age: Tablet: 7 to 13 mg/kg/day divided into two to four doses	Tablet: 150 mg 300 mg
Doxycycline	Unspecified infections: Oral formulations: 200 mg on the first day of treatment (administered 100 mg every 12 hours or 50 mg every six hours), followed by a maintenance dose of 100 mg/day or 50 mg every 12 hours; for severe infections, 100 mg every 12 hours Acute epididymo-orchitis: Oral formulations: 100 mg daily for at least 10 days Inhalational anthrax (post-exposure): Oral formulations: 100 mg twice daily for 60 days Malaria prophylaxis: Oral formulations: 100 mg daily, beginning one to two days before travel to the malarious area; prophylaxis should be continued daily during travel in the malarious area and for four weeks after the traveler leaves the malarious area Nongonococcal urethritis: Oral formulations: 100 mg twice daily for at least seven days Syphilis: Oral delayed release formulations: 100 mg twice daily for 14 days (early, <1 year, primary or secondary infection); 100 mg twice daily for 28 days (latent, >1 year or duration unknown) Uncomplicated gonococcal infections (except anorectal infections in men): Oral formulations: 100 mg twice daily for at least seven days; alternative regimen, 300 mg immediately followed	Unspecified infections in children >8 years of age <45 kg (>45 kg see adult dose): All formulations: 4.4 mg/kg divided into two doses on the first day, followed by 2.2 mg/kg given as a single daily dose or divided into two doses, on subsequent day; for more severe infections up to 4.4 mg/kg may be used Inhalational anthrax (post-exposure) <45 kg (>45 kg see adult dose): Oral formulations: 2.2 mg/kg twice daily for 60 days Malaria prophylaxis in children >8 years of age: Oral formulations: 2.2 mg/kg daily, beginning one to two days before travel to the malarious area; prophylaxis should be continued daily during travel in the malarious area and for four weeks after the traveler leaves the malarious area; maximum dose, 100 mg daily	Capsule: 50 mg 75 mg 100 mg 150 mg Delayed release capsule: 75 mg Delayed release tablet: 75 mg 100 mg 150 mg 200 mg Injection: 100 mg Suspension (reconstituted): 25 mg/5 mL Syrup: 50 mg/5 mL Tablet: 50 mg 75 mg 100 mg 150 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	in one hour by a second 300 mg dose Uncomplicated urethral, endocervical, or rectal infection: Oral formulations: 100 mg twice daily for at least seven days		
Minocycline	Unspecified infections: Capsule, tablet: 200 mg initially, followed by 100 mg every 12 hours; alternatively, if more frequent doses are preferred, two or four 50 mg capsules may be given initially followed by one 50 mg capsule four times daily Injection: 200 mg initially, followed by 100 mg administered over 60 minutes every 12 hours Gonococcal infections (except urethritis and anorectal infections in men, uncomplicated): Capsule, tablet: 200 mg initially, followed by 100 mg every 12 hours for a minimum of four days Gonococcal urethritis (in men, uncomplicated), meningococcal carrier state : Capsule, tablet: 100 mg every 12 hours for five days *Mycobacterium marinum* infections: Capsule, tablet: 100 mg every 12 hours for six to eight weeks Syphilis: Capsule, tablet: 200 mg initially, followed by 100 mg every 12 hours for 10 to 15 days Urethral, endocervical, or rectal infections: Capsule, tablet: 100 mg every 12 hours for at least seven days	Unspecified infections in children >8 years of age: Capsule, injection, tablet: 4 mg/kg initially, followed by 2 mg/kg every 12 hours	Capsule: 50 mg 75 mg 100 mg Injection: 100 mg Tablet: 50 mg 75 mg 100 mg
Tetracycline	Unspecified infections: Capsule: 500 mg twice daily or 250 mg four times daily; for sever infections dose may be increased to 500 mg four times daily Brucellosis: Capsule: 500 mg four times daily for three weeks plus streptomycin 1 g intramuscular twice daily the first week and once daily the second week	Unspecified infections in children >8 years of age: Capsule: 25 to 50 mg/kg/day divided in four equal doses	Capsule: 250 mg 500 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	Plague: Capsule: 500 mg every 6 hours for 10 to 14 days Anthrax: Capsule: 250 to 500 mg every six hours for five to nine days Gonorrhea: Capsule: 500 mg four times daily for seven days Syphilis: Capsule: 500 mg four times daily for 14 days (early, <1 year, primary or secondary infection); 500 mg four times daily for 28 days (latent, >1 year or duration unknown) Tularemia (mild to moderate): Capsule: 500 mg four times a day for at least 14 days Urethral, endocervical, or rectal infections: Capsule: 500 mg four times a day for at least seven days		
Tigecycline	Intra-abdominal infections: Injection: 100 mg intravenous as an initial dose, followed by 50 mg intravenous every 12 hours for five to 14 days Community-acquired bacterial pneumonia: Injection: 100 mg intravenous as an initial dose, followed by 50 mg intravenous every 12 hours for seven to 14 days Skin and skin-structure infections: Injection: 100 mg intravenous as an initial dose, followed by 50 mg intravenous every 12 hours for five to 14 days	Safety and efficacy in children have not been established.	Injection: 50 mg

VIII. Effectiveness

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

Table 10. Comparative Clinical Trials with the Tetracyclines

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Dermatological Infections				
Montravers et al.[32] (2013) Tigecycline as monotherapy or in combination with other antibacterials	MA Patients with a mean age of 63.2±14.9 years of age who received tigecycline for complicated skin and soft tissue infection were included	N=254 Duration varied	Primary: Mean Acute Physiology and Chronic Health Evaluation II and Sequential Organ Failure Assessment scores Secondary: Not reported	Primary: Clinical response rates at the end of treatment were 79.6% for all patients who received the standard dosage (183/230), 86.7% for patients who received tigecycline as monotherapy (143/165), 75.0% for patients with a nosocomial infection (96/128), 75.3% for patients with an Acute Physiology and Chronic Health Evaluation II score >15 (61/81) and 58.3% for patients with a Sequential Organ Failure Assessment score >7 (7/12). Secondary: Not reported
Lauf et al.[33] (2014) Tigecycline 150 mg IV every 24 hours, with or without placebo for up to 28 days vs ertapenem 1 g IV every 24 hours, with or without adjunctive IV vancomycin for up to 28 days Patients with	DB, RCT Hospitalized men and women ≥18 years of age with diabetes mellitus who had a foot infection that did not extend above the knee, with or without osteomyelitis. The infection had to be of acute onset or a worsening within 14 days prior to the screening visit.	N=955 (without osteomyelitis) N=118 (with osteomyelitis) 12 to 92 days after the last dose for patients without osteomyelitis and 25 to 27 weeks for patients with osteomyelitis	Primary: Clinical response within the clinically evaluable and the clinically modified intent-to-treat populations at the test-of-cure visit Secondary: Microbiologic efficacy of tigecycline, in vitro susceptibility data on tigecycline	Primary: At the test-of-cure assessment in the patients without osteomyelitis, 77.5% of tigecycline-treated subjects and 82.5% of ertapenem ± vancomycin-treated subjects in the clinically evaluable population were considered cured, and 71.4% of those treated with tigecycline subjects and 77.9% of those who received ertapenem ± vancomycin in the clinically modified intent-to-treat population were considered cured. The tigecycline regimen did not meet the primary study endpoint of noninferiority to the ertapenem ± vancomycin regimen for the clinically evaluable population (true difference in efficacy of tigecycline minus ertapenem ± vancomycin regimen, −5.5%; 95% CI, −11.0 to 0.1) or clinically modified intent-to-treat population (true difference in efficacy of tigecycline minus ertapenem ± vancomycin regimen, −6.7; 95% CI, −12.3 to −1.1). Secondary: In the population without osteomyelitis, the cure rates for most baseline isolates were either slightly higher or similar for ertapenem ± vancomycin as compared with tigecycline-treated subjects. However, participants in

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osteomyelitis were treated for up to 42 days				the tigecycline regimen with *Escherichia coli* (21/28; 75.0%), MRSA (29/44; 65.9%), and *S. agalactiae* infections (35/40; 87.5%) had higher cure rates compared to subjects receiving ertapenem ± vancomycin (28/38, 73.7%; 17/26, 65.4%; and 40/48, 83.3%; respectively). The cure rates for tigecycline-treated participants with methicillin-susceptible *S. aureus* (MSSA) or *Klebsiella pneumoniae* infections were lower than expected compared with those treated with ertapenem ± vancomycin. For subjects with baseline bacteremia, excluding contaminants, in the primary study, the clinical cure rate at the test-of-cure visit was 6/7 (86%) for tigecycline-treated subjects and 14/14 (100%) for ertapenem-treated subjects.
Chuang et al.[34] (2011) Aztreonam 2 g IV every 12 hours plus vancomycin 1 g IV vs tigecycline 100 mg IV as an initial dose, followed by 50 mg IV every 12 hours	DB, MC, RCT Hospitalized patients ≥18 years of age with complicated skin and soft tissue infections	N=127 5 to 14 days	Primary: Clinical response in clinically evaluable and clinical modified intent-to-treat populations Secondary: Clinical response (cure or failure) by baseline isolate and type of infection	Primary: In India, the clinical response rates in the clinically evaluable and clinically evaluable-modified intent-to-treat populations were higher in the tigecycline group than in the vancomycin-aztreonam group. Clinically evaluable rates were 83.3% in patients treated with tigecycline and 75.8% in patients treated with vancomycin-aztreonam. The clinically evaluable-modified intent-to-treat cure rates for tigecycline vs vancomycin-aztreonam were 78.6 vs 66.7%, respectively. Small sample size prevented non-inferiority analysis. In Taiwan, the clinical response rates in the clinically evaluable populations were lower in the tigecycline group than in the vancomycin-aztreonam group. Clinically evaluable rates were 78.6% in patients treated with tigecycline and 90.0% in patients treated with vancomycin-aztreonam. The clinically evaluable-modified intent-to-treat cure rates for tigecycline vs vancomycin-aztreonam were 73.3 and 75%, respectively. Small sample size prevented any meaningful statistical analysis. Secondary: In India, the number of isolates was small and no definitive inferences are possible. However, tigecycline demonstrated antimicrobial efficacy against isolates commonly linked to complicated skin and skin structure infections. No MRSA isolates were noted among Indian patients. In Taiwan, few isolates were available. They included one patient with MRSA, which responded to tigecycline.
Gastrointestinal Infections				

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Kearney et al.[35] (2000) Tetracycline 500 mg QID, bismuth subsalicylate 2 tablets QID, metronidazole 250 mg QID, and cimetidine 400 mg BID or famotidine 20 mg BID for 14 days (BMT-H_2) vs tetracycline 500 mg QID, bismuth subsalicylate 2 tablets QID, metronidazole 250 mg QID, and lansoprazole 30 mg BID for 7 days (BMT-PPI) vs metronidazole 500 mg BID, lansoprazole 30 mg BID, and clarithromycin 250 mg BID for 7 days (MLC)	OL Patients with peptic ulcer disease or prescribed H_2-receptor antagonists or proton pump inhibitors, and who tested positive with histology, rapid urease or urea breath testing for *H pylori* infection	N=224 6 weeks	Primary: Defining treatment success rates for *H pylori* infection at end of study Secondary: Adverse events	Primary: The intent-to-treat cure rates for BMT-H_2, BMT-PPI, and MLC were 81, 87, and 90%, respectively (all; P>0.05). The per-protocol cure rates for BMT-H_2, BMT-PPI, and MLC were 84, 91, and 92% (all; P>0.05). Secondary: The side-effect profile for the three treatment groups revealed no significant differences in the frequency of the most common side effects, diarrhea and constipation. Metallic taste was significantly more severe in the MLC group (P=0.04). Nausea was significantly more common in the MLC group than the BMT-H_2 group (P=0.04). There were no significant differences in the frequency of dizziness/lightheadedness, cramping, or other side effects between the BMT-H_2 and MLC groups, and between BMT-PPI and BMT-H_2 groups. Severe headaches were significantly more frequent in the BMT-PPI group than the BMT-H_2 group (P=0.02). A significantly higher number of patients discontinued therapy due to adverse events in the BMT-H_2 and BMT-PPI treatment groups than the MLC group (P=0.049).
Magaret et al.[36] (2001)	MC, RCT	N=48	Primary: Negative ^{14}C-UBT	Primary: Per-protocol eradication rates for patients on triple therapy and quadruple

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Tetracycline 250 mg QID, bismuth subsalicylate 2 tablets QID, lansoprazole 30 mg BID, and metronidazole 250 mg QID for 14 days vs lansoprazole 30 mg BID, amoxicillin 1,000 mg BID, and clarithromycin 500 mg BID for 14 days	Patients years of age failing prior treatment for *H pylori*	6 weeks	of <50 disintegrations per minute at time of follow-up indicating cure of infection Secondary: Side effects and compliance	therapy were 82 and 80%, respectively (P=0.85). Intention-to-treat eradication rates for triple and quadruple therapy were 72 and 65%, respectively (P=0.63). Secondary: Compliance in patients receiving triple and quadruple therapy was 89% (P=0.98). Side effects were reported in 84% of patients on triple therapy and 82% of patients on quadruple therapy (P=0.85). Side effects included nausea (33%), upset stomach (25%), diarrhea (36%), abdominal pain (16%), lightheadedness/dizziness (4%), and fatigue (8%).
Miehlk et al.[37] (2003) Tetracycline 500 mg QID, bismuth citrate 107 mg QID, omeprazole 20 mg BID, and metronidazole 500 mg QID for 14 days vs omeprazole 40 mg QID and amoxicillin 750	RCT, XO Patients 18 to 80 years of age with at least one previous failure *of H pylori* therapy documented by confirmatory examinations and antimicrobial resistance to both metronidazole and clarithromycin	N=84 26 months	Primary: Two negative biopsy-based tests, histology and rapid urease test, or a validated ^{13}C-urea breath test to confirm successful treatment Secondary: Not reported	Primary: In the per-protocol analysis, patients on high-dose dual therapy and quadruple therapy achieved *H pylori* cure rates of 83.8 and 92.1%, respectively (P=0.71). Cure rates using intent-to-treat analysis were 75.6 and 81.4% for high-dose dual therapy and quadruple therapy, respectively, and were not significantly different (P=0.60). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
mg QID for 14 days				
Perri et al.[38] (2001) Tetracycline 500 mg QID, bismuth citrate 240 mg BID, pantoprazole 40 mg BID, and metronidazole 250 mg TID for 10 days (quadruple therapy group) vs pantoprazole 40 mg BID, amoxicillin 1 g BID, and rifabutin 150 mg every other day for 10 days (RIF 150 mg group) vs pantoprazole 40 mg BID, amoxicillin 1 g BID, and rifabutin 300 mg every other day for 10 days (RIF 300 mg group)	OL, PRO, RCT Patients with *H pylori* infection confirmed by ^{13}C-urea breath test after failure of one or more standard regimens	N=135 6 weeks	Primary: Eradication rates as defined by negative ^{13}C-urea breath test four weeks after end of treatment Secondary: Side effect rates reported after end of treatment	Primary: By intent-to-treat analysis, eradication rates for the pantoprazole, amoxicillin and rifabutin 150 mg treatment group (RIF 150 mg group) were 66.6%. Eradication rates for pantoprazole, metronidazole, bismuth citrate, and tetracycline (quadruple therapy group) were also 66.6%. The eradication rate for pantoprazole, amoxicillin, and rifabutin 300 mg (RIF 300 mg group) was 86.6%, which was significantly different than the other two treatment groups (P<0.025). Secondary: There was a significant difference in the side effects observed in rifabutin-treated patients compared to patients receiving quadruple therapy. The rates of side effects were 9, 11 and 47%, (P<0.0001), for the triple therapies with the RIF 150 mg group, RIF 300 mg group, and quadruple therapy group, respectively.
Katelaris et al.[39]	MC, OL, PG, RCT	N=405	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2002) Tetracycline 500 mg QID, bismuth subcitrate 108 mg QID, pantoprazole 40 mg BID, metronidazole 200 mg TID and 400 mg in the evening for 7 days (PBTM7) vs tetracycline 500 mg QID, bismuth subcitrate 108 mg QID, and metronidazole 200 mg TID and 400 mg in the evening for 14 days (BTM14) vs pantoprazole 40 mg, amoxicillin 1,000 mg, and clarithromycin 500 mg BID (PAC7)	Patients ≥18 years of age with *H pylori* infection confirmed by a positive urease test and confirmatory histology and ^{13}C-urea breath test	8 weeks	At week eight, ^{13}C-urea breath test to determine the outcome of eradication therapy Secondary: Compliance and adverse event profile	By intent-to-treat analysis, the eradication rates for the PAC7, PBTM7, and BTM14 treatment groups were 78, 82 and 69%, respectively. By per-protocol analysis, the corresponding eradication rates were 82, 88, and 74%, respectively. In both analysis, the eradication rates for PBTM7 and PAC7 were not significantly different (all P>0.05), while eradication rates for PBTM7 were significantly higher than BTM14 (P=0.01). Secondary: Adverse effects were common in all treatment groups. Adverse effects that interfered with activities of daily living were significantly higher in the BTM14 group (P<0.01). The number of patients who discontinued treatment due to adverse effects was also higher in the BTM14 group (9%) vs the PBTM7 group (3%) and the PAC7 group (2%). Noncompliance, defined as less than 90% of study drug taken, was higher in BTM14 than PBTM7 and PAC7.
Uygun et al.[40] (2007) Tetracycline 500 mg QID, bismuth	RCT, SB, SC Patients with *H pylori* infection and non-ulcer dyspepsia	N=240 14 days	Primary: *H pylori* eradication rates Secondary:	Primary: The intent to treat and per protocol populations, *H pylori* eradication rates were 70% (95% CI, 61 to 78) and 82.3% (95% CI, 74 to 89) in the BLTM group, and 57.5% (95%CI, 48 to 66) and 62.7% (95%CI, 53 to 71) in the LAC group.

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subsalicylate 300 mg QID, lansoprazole 30 mg BID, and metronidazole 500 mg TID (BLTM group) vs lansoprazole 30 mg BID, amoxicillin 1 g BID and clarithromycin 500 mg BID (LAC)			Not reported	The BLTM treatment achieved a significantly better eradication rate than the LAC treatment in per protocol analysis (82.3 vs 62.7%; P=0.002). Although a better intent to treat rate was obtained in the BLTM group than in the LAC group, the difference was not significant (70 vs 57.5%; P=0.06). Mild to severe side-effects, which were more frequent in the BLTM group, were reported in 18.2% of the patients. Although it was not statistically significant, the number of patients ceasing the treatment for side-effects was more in BLTM group than in the LAC group. Secondary: Not reported
Wu et al.[41] (2011) Tetracycline 500 mg QID, bismuth subcitrate 120 mg QID, esomeprazole 40 mg BID, and metronidazole for 7 days as rescue therapy (EBTM) vs tetracycline 500 mg QID, bismuth subcitrate120 mg QID, esomeprazole 40 mg BID, and amoxicillin 500 mg QID for 7 days	RCT Patients ≥18 years of age with persistent *H pylori* infection who failed standard first-line therapy (proton-pump inhibitor, clarithromycin and amoxicillin)	N=120 8 weeks posttreatment	Primary: Eradication rates, adverse events, resistance rates, compliance Secondary: Not reported	Primary: In the intent to treat analysis, there was a significantly lower eradication rate for the EBTA group (62%; 95% CI, 50 to 75) than for the EBTM group (81%; 95% CI, 71 to 91; P=0.02). In the per protocol analysis, *H pylori* infection was eradicated in 64% of the EBTA group (95% CI, 52 to 76) and 83% of the EBTM group (95% CI, 74 to 92; P=0.01). A total of 19% of patients in the EBTA group and 44% of patients in the EBTM group reported at least one adverse event during eradication therapy. The EBTA group had fewer adverse events than the EBTM group (P=0.004). The frequency of nausea in the EBTA group was lower than in the EBTM group (5 vs 16%, respectively). Tetracycline- and metronidazole-resistant strains were found in 2 and 53% of the patients, respectively. No strains developed resistance to amoxicillin. In the EBTA group, the *H pylori* eradication rate for the tetracycline-susceptible strains was 67% by intent to treat analysis and 68% by per protocol analysis. All the strains in the subgroup were susceptible to amoxicillin. In the EBTM group, no tetracycline-resistant

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as rescue therapy (EBTA)				strains existed. The eradication rate of tetracycline-susceptible strains was 80 and 83% by intent to treat and per protocol analyses, respectively. With respect to metronidazole resistance, eradication rates were similar between susceptible and resistant strains by either intent to treat or per protocol analyses. Compliance rates were 97% in both treatment groups (P=1.00). Secondary: Not reported
Songür et al.[42] (2009) Tetracycline 500 mg QID, bismuth subcitrate 300 mg QID, lansoprazole 30 mg BID, and metronidazole 500 mg BID for 10 days (BLTM) vs tetracycline 500 mg QID, ranitidine bismuth citrate 400 mg BID, lansoprazole 30 mg BID, and metronidazole 500 mg BID for 10 days (RBLTM) vs tetracycline 500	RCT, SC Patients with *H pylori* infection and dyspeptic symptoms	N=464 14 days	Primary: Eradication rates, compliance Secondary: Not reported	Primary: In the per protocol analysis, eradication rates in LAC, BLTM, RBLTM, and LTM groups were 35.6, 54.9, 64.4, and 60.0%, respectively. In the intent to treat analysis, eradication r rates in LAC, BLTM, RBLTM, and LTM groups were 32.7, 47.1, 57.3, and 54.8%, respectively. The BLTM, RBLTM, and LTM treatment groups achieved a significantly better eradication rate than the LAC treatment group (P<0.001). There was no significant difference between BLTM, RBLTM, and LTM treatment groups. Compliance rates with LAC, BLTM, RBLTM, and LTM therapies were 91, 87, 90, and 94%, respectively. The treatments were generally well tolerated. Secondary: Not reported

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mg QID, lansoprazole 30 mg BID, and metronidazole 500 mg BID for 10 days (LTM) vs lansoprazole 30 mg BID, amoxicillin 1,000 mg BID, and clarithromycin 500 mg BID for 14 days (LAC)				
Malfertheiner et al.[43] (2011) Tetracycline 125 mg, bismuth subcitrate potassium 140 mg, and metronidazole 125 mg (as a single three-in-one capsule) 3 capsules QID plus omeprazole 20 mg BID for 10 days (quadruple therapy) vs omeprazole 20 mg,	OL, RCT Patients ≥18 years of age with *H pylori* infection and upper gastrointestinal symptoms	N=399 56 days posttreatment	Primary: Eradication rates, resistance rates, and safety Secondary: Not reported	Primary: In the per protocol analysis, eradication rates were 93% with quadruple therapy compared to 70% with standard therapy (P<0.0001). Quadruple therapy was found to be non-inferior to standard therapy. In the intention-to-treat analysis, eradication rates were 80% with quadruple therapy compared to 55% with standard therapy (P<0.0001). Metronidazole sensitivity did not significantly affect the efficacy of quadruple therapy in the per protocol population (P=0.283). Clarithromycin sensitivity seemed to significantly affect the efficacy of standard therapy (P<0.0001). Simultaneous metronidazole and clarithromycin resistance reduced efficacy only in patients treated with standard therapy (P=0.001). The incidence of serious treatment emergent adverse events and discontinuations due to a treatment emergent adverse events were similar between groups (<2.0%). The main adverse events were gastrointestinal and central nervous system disorders. Secondary:

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amoxicillin 500 mg, and clarithromycin 500 mg BID for 7 days (standard therapy)				Not reported
Zheng et al.[44] (2010) Tetracycline 750 mg BID, colloidal bismuth subcitrate 220 mg BID, pantoprazole 40 mg BID, and metronidazole 400 mg TID for 10 days (PBMT) vs pantoprazole 40 mg BID, amoxicillin 1.0 g BID and clarithromycin 500 mg BID for 7 days (PAC)	OL, RCT, SC Patients 18 to 70 years of age with non-ulcer dyspepsia and *H pylori* infection	N=170 7 to 10 days	Primary: Eradication rates, resistance rates, safety Secondary: Not reported	Primary: In the intent to treat analysis, eradication rates were 63.5% in the PAC group and 89.4% in the PBMT groups (P<0.05). In the per protocol analysis, the eradication rates were 65.1% in the PAC group and 91.6% in the PBMT group (P<0.05). The *H pylori* primary resistance rates to metronidazole and clarithromycin were 41.6 and 20.8%, respectively, whereas all the *H pylori* isolates were sensitive to amoxicillin and tetracycline. Adverse events were similar among the treatment groups and included bitter taste, nausea, poor appetite, and occasional symptoms, such as diarrhea, vomiting, drug eruption, insomnia, constipation, and lethargy. The adverse events rates of quadruple therapy and triple therapy were 42.3 and 60.0%, respectively. Secondary: Not reported
de Boer et al.[45] (1998) Tetracycline 500 mg QID, ranitidine bismuth citrate 400 mg BID, and metronidazole 500 mg TID for 7 days	OL, PG, RCT Patients with upper gastrointestinal symptoms and infected with *H pylori*	N=168 8 weeks	Primary: Endoscopy performed six weeks after completion of treatment to determine *H pylori* infection, defined as a positive CLOtest,	Primary: Logistical regression analysis determined that there was no difference between the seven-day and 14-day treatments. Intent-to-treat analysis cure rate for the ranitidine bismuth citrate, tetracycline, and metronidazole treatment group was 86%. The cure rate for the ranitidine bismuth citrate, amoxicillin, and clarithromycin treatment group was 92%. The cure rate for the ranitidine bismuth citrate and clarithromycin treatment group was 95%. Per-protocol cure rates were 89, 93, and 96% respectively. There was no statistical difference between the three groups.

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vs ranitidine bismuth citrate 400 mg BID, amoxicillin 1,000 mg BID, and clarithromycin 500 mg BID for 7 days vs ranitidine bismuth citrate 400 mg BID, clarithromycin 500 mg BID for 14 days			confirmed by histology or culture Secondary: Safety	Secondary: Side effects were comparable among the treatment groups. Overall, 32% of patients in the ranitidine bismuth citrate, tetracycline, metronidazole treatment group, 18% of the ranitidine bismuth citrate, amoxicillin, and clarithromycin treatment group, and 23% of the ranitidine bismuth citrate and clarithromycin treatment group reported side effects during the trial period (P=0.249).
Altintas et al.[46] (2004) Tetracycline 1 g BID, ranitidine-bismuth citrate 400 mg BID, and metronidazole 500 mg TID for 14 days (triple therapy) vs ranitidine-bismuth citrate 1 g BID for 14 days and azithromycin 500 mg QD for 7 days (dual therapy)	RCT Patients ≥18 years of age who were resistant to triple therapy consisting of a proton pump inhibitor clarithromycin and amoxicillin for the treatment of *H pylori*	N=52 6 weeks	Primary: Eradication rates of *H pylori* as confirmed by endoscopy and biopsy Secondary: Improvement in symptoms of endoscopic gastritis	Primary: There was a significant difference between the treatment groups. Eradication rates for triple and dual therapy were 44.4 and 12.0%, respectively (P=0.01). Secondary: There were significant improvements in the severity of endoscopic gastritis in both groups (P=0.01), but no significant differences between the two groups (P=0.600).

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Luther et al.[47] (2010) Tetracycline, metronidazole, bismuth-containing compound, and proton-pump inhibitor (bismuth quadruple therapy) vs clarithromycin triple therapy (amoxicillin, clarithromycin, and proton-pump inhibitor)	MA Patients with *H pylori* infection	N=1,679 (9 trials) Variable duration	Primary: Eradication rate, compliance rate, adverse events Secondary: Not reported	Primary: The eradication rate with bismuth quadruple therapy was 78.3% compared to 77% with clarithromycin triple therapy (RR, 1.002; 95% CI, 0.936 to 1.073). The compliance rate with bismuth quadruple therapy was 92.6% compared to 98.9% with clarithromycin triple therapy (RR, 0.99; 95% CI, 0.938 to 1.045). The overall incidence of adverse events in patients receiving bismuth quadruple therapy was 35.5% compared to 35.4% with clarithromycin triple therapy (RR, 1.037; 95% CI, 1.037 to 1.135). Secondary: Not reported
Genitourinary Infections				
Romanowski et al.[48] (1993) Minocycline 100 mg nightly for 7 days vs doxycycline 100 mg BID for 7 days	DB, RCT Patients with nongonococcal urethritis, mucopurulent cervicitis, or whose sexual partner had either condition or a positive culture for *Chlamydia* treatments	N=253 7 weeks	Primary: Clinical cure (symptoms subsiding or resolving by day 14) Secondary: Adverse effects	Primary: The proportion with urethritis or cervicitis did not differ by treatment group at any follow-up visit (men: doxycycline, 82%; minocycline, 88%; women: doxycycline, 90%; minocycline, 91%; combined: doxycycline, 85%; minocycline, 89%; P>0.08). Unprotected sexual contact did not affect clinical or microbiological cure rates. Secondary: Adverse effects occurred more frequently in the doxycycline group (men: 43 vs 26%; P=0.05; women: 62 vs 35%; P=0.009). Although the proportion with dizziness did not differ by drug administered (P=0.1), dizziness was reported more often by women (11 vs 3%).
Kovacs et al.[49] (1989) Minocycline 100 mg BID for day 1	PRO, RCT, SB Patients with *Chlamydia trachomatis*	N=103 12 weeks	Primary: Efficacy (resolution of signs and symptoms of infections, and	Primary: Minocycline and doxycycline showed equal effectiveness in the eradication of mycoplasmas in over 80% of the treated patients. Minocycline appeared to have a slight advantage with respect to the

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
followed by 100 mg/day for days 2 to 10 vs doxycycline 100 mg BID for day 1 followed by 100 mg/day for days 2 to 10	infection of the cervix		eradication of organism) Secondary: Adverse events	resolution of the gynecological symptoms that were associated with the chlamydial infection (83.3 vs 81.2%) A 10-day course of either drug resulted in a negative result of a chlamydial culture for all patients at the follow-up assessment, which occurred between 11 days to 12 weeks after therapy. Secondary: A total of 19 patients reported adverse events and 11 of these patients received minocycline therapy while the remaining eight patients were treated with doxycycline. The adverse events were generally mild, the most frequent event being gastric upset, which was seen in both treatment groups, and giddiness/dizziness in the minocycline treatment group.
Mena et al.[50] (2009) Doxycycline 100 mg BID for 7 days vs azithromycin 1 g as a single dose	RCT, SC Men with nongonococcal urethritis	N=398 6 weeks	Primary: Persistence or recurrence of *Mycoplasma genitalium* infection Secondary: Not reported	Primary: From the initial study population enrolled, 36 men in the azithromycin group and 42 men in the doxycycline group tested positive at the initial study enrollment for *Mycoplasma genitalium*. Of those testing positive at initial follow-up (10 to 17 days post therapy), 13% (95% CI, 3 to 35) were from the azithromycin group compared to 55% in the doxycycline group (95% CI, 36 to 72; P=0.002). Of the 15 persistently *Mycoplasma genitalium* infected men who were clinically cured at the early initial follow-up visit, 47% experienced clinical relapse over the subsequent two to six weeks. Secondary: Not reported
Heystek et al.[51] (2009) Moxifloxacin 400 mg QD for 14 days vs doxycycline 100 mg BID for 14	DB, MC, RCT Women with uncomplicated pelvic inflammatory disease	N=434 14 days	Primary: Clinical success two to 14 days posttreatment (clinical cure and improvement combined) Secondary: Clinical cure rate	Primary: Clinical success rates two to 14 days following treatment were 96.6% with moxifloxacin and 98% with the comparator regimen in the per protocol population (95% CI -4.5 to 1.6) Clinical success rates were 77.0% with moxifloxacin and 76.7% with the comparator regimen in the intent to treat population (95% CI, -5.8 to 6.9). Moxifloxacin was found to be non-inferior to the comparator arm. Secondary: At two to 14 days posttreatment, clinical cure rates were 81.5% with

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days, metronidazole 400 mg TID for 14 days, ciprofloxacin 500 mg as a single dose			at two to 14 days posttreatment, clinical success rate at 21 to 35 days posttreatment (clinical failures at day two to 14 posttreatment carried forward for follow-up), bacteriological response	moxifloxacin and 83.2% with the comparator regimen in the per protocol population (95% CI -9.2 to 5.1). Clinical cure rates were 64.7% with moxifloxacin and 65.0% with the comparator regimen in the intent to treat population (95% CI, -7.5 to 7.0). Clinical success rates 21 to 35 days following treatment were 93.8% with moxifloxacin and 91.3% with the comparator regimen in the per protocol population (95% CI -3.8 to 7.4). Clinical success rates were 60.1% with moxifloxacin and 56.8% with the comparator regimen in the intent to treat (95% CI, -5.8 to 9.1).
Respiratory Infections				
Daniels et al.[52](2010) Doxycycline 200 mg/day for 7 days vs placebo All patients received systemic corticosteroids.	DB, PC, RCT Hospitalized patients ≥45 years of age with an acute exacerbation of COPD	N=223 (265 exacerbations) 30 days	Primary: Clinical response on day 30 Secondary: Clinical response on day 10, clinical cure on days 10 and 30, antibiotic treatment for lack of efficacy, lung function, time to treatment failure, symptoms, microbiological response	Primary: At 30 days, clinical success was observed in 61 (n=78) and 53% (n=72) of patients receiving doxycycline and placebo (OR, 1.3; 95% CI, 0.8 to 2.0; P=0.32). Secondary: At 10 days, doxycycline showed “superiority” over placebo in terms of clinical success (OR, 1.9; 95% CI, 1.1 to 3.2; P=0.03). At 10 days, clinical cure was observed in 67 (n=86) and 51% (n=69) of patients receiving doxycycline and placebo (OR, 1.9; 95% CI, 1.2 to 3.2; P=0.01). At 30 days, the corresponding proportions were 51 (n=65) and 41% (n=56) (OR, 1.4; 95% CI, 0.9 to 2.3; P=0.15). Time to treatment failure was not significantly longer with doxycycline compared to placebo (P=0.19). Thirty seven (n=46) and 46% (n=62) of patients had treatment failure. OL antibiotic treatment for lack of efficacy was applied in 15 (n=19) and 28% (n=38) of patients receiving doxycycline and placebo by 10 days (OR, 0.5; 95% CI, 0.03 to 0.9; P=0.01). At 30 days, the corresponding proportions were 33 (n=42) and 45% (n=61) (OR, 0.7; 95% CI, 0.1 to 1.1; P=0.13).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Paired lung function data were available for 85% (n=224) of patients on days one and 10 and in 71% (n=189) of patients on days one and 30. The mean increase in FEV_1 on day 10 was 0.16±0.26 L with doxycycline and 0.11±0.26 L with placebo (mean difference, 0.05 L; 95% CI, -0.02 to 0.12; P=0.016). On day 30, the mean increase was 0.15±0.33 and 0.08±0.25 L with doxycycline and placebo (mean difference, 0.07 L; 95% CI, -0.03 to 0.13; P=0.22). The mean change in total symptom scores on day 10 was -10.1±9.0 and -6.2±8.6 with doxycycline and placebo (mean difference, -2.3; 95% CI, -3.9 to -0.8; P=0.003). The corresponding changes at day 30 were -9.4±9.7 and -8.3±8.6 (mean difference, -1.0; 95% CI, -3.7 to 1.8; P=0.50). Separate mean symptom scores of cough and sputum purulence were significantly more reduced with doxycycline at 10 days, but not at 30 days (P value not reported). Two hundred and fourteen potential bacterial pathogens were isolated in 158 exacerbations. Bacteriological success was accomplished in 67 (52/78) and 34% (25/73) of patients receiving doxycycline and placebo (OR, 3.8; 95% CI, 1.9 to 7.5; P<0.001).
Maesen et al.[53] (1989) Doxycycline 100 mg BID for 7 days vs minocycline 100 mg BID for 7 days	DB, RCT Patients admitted to the hospital because of purulent exacerbations of chronic respiratory disease	N=41 15 days	Primary: Bacteriological and clinical assessment Secondary: Not reported	Primary: Bacteriological and clinical assessment before and immediately after treatment showed no significant differences between the doxycycline and the minocycline groups, nor did further evaluation after seven days follow-up. Secondary: Not reported
Mokabberi et al.[54] (2010) Levofloxacin 500 mg IV QD vs	DB, PRO, RCT Patients ≥18 years of age with pneumonia requiring hospitalization	N=65 two months	Primary: Response to treatment, failure to treatment and complications, length of stay	Primary: Efficacy of treatment was not significantly different between the treatment groups (P=0.844). There were two failures in the levofloxacin group and one failure in the doxycycline group (P=0.893).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
doxycycline 100 mg IV BID Patients were allowed to switch from IV to oral therapy at the discretion of the physician.			Secondary: Not reported	Two patients in the levofloxacin group had side effects (mild diarrhea), while no side effects were noted for doxycycline (P=0.375). The mean time to change from IV to oral for levofloxacin group was 2.73 and 2.88 days for doxycycline group (P=0.647). Length of stay was 5.7 days for levofloxacin and 4.0 days for doxycycline (P<0.001). Secondary: Not reported
Tanaseanu et al.[55] (2008) Levofloxacin 500 mg IV QD or BID vs tigecycline 100 mg IV as an initial dose, followed by 50 mg IV BID Patients were allowed to switch to oral levofloxacin after 3 days if specific criteria were met.	DB, MC, RCT, Patients >18 years of age hospitalized with community-acquired pneumonia	N=891 7 to 14 days	Primary: Clinical response in clinically evaluable and clinical modified intent to treat populations at test of cure Secondary: Health care resource utilization, safety	Primary: At the test of cure assessment in the clinically evaluable and clinical modified intent to treat populations, there were no significant differences in the clinical cure rates for tigecycline as compared to levofloxacin. Tigecycline cured 89.7% of patients and levofloxacin cured 86.3% of patients (95% CI, -2.2 to 9.1; P<0.001 for non-inferiority). In the study in which patients were allowed to switch to oral levofloxacin therapy after ≥3 days of IV administration of either study medication, there were no significant differences in the percentage of patients who switched to oral therapy (tigecycline, 89.9%; levofloxacin, 87.8%) or in the median duration of oral therapy in either group (3.9 days for tigecycline vs 3.32 for levofloxacin). In the clinical modified intent to treat population, tigecycline 81% of patients and levofloxacin cured 79.7% of patients (95% CI -4.5 to 7.1, P<0.001 for non-inferiority). Secondary: In the pooled studies, there was no significant difference between the two treatment groups in hospital length of stay during the primary hospitalization (tigecycline: mean [SD], 9.8 [6.0] days; levofloxacin, 9.8 [6.0] days; P=0.883). There was no difference in mean duration of study antibiotic therapy (tigecycline, 9.8 [3.1] days; levofloxacin, 10.0 [3.2] days; P=0.453).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				There were no significant differences between the treatment groups in the rate of rehospitalization, admission for intensive care unit care, admission to emergency room care, use of home health care, or nursing home admissions after discharge from the primary hospitalization. More tigecycline-treated patients than levofloxacin-treated patients reported that adverse events were considered drug related, and nausea and vomiting occurred at a significantly higher rate for tigecycline versus levofloxacin (P<0.001). Discontinuations for adverse events were low (tigecycline, 6.1% and levofloxacin, 8.1%).
Tanaseanu et al.[56] (2009) Levofloxacin 500 mg IV QD or BID vs tigecycline 100 mg IV as an initial dose, followed by 50 mg IV every 12 hours	DB, MC, RCT Patients ≥18 years of age with a community-acquired pneumonia	N=428 7 to 14 days	Primary: Clinical response in the clinically evaluable population and clinical modified intent to treat populations at the test of cure visit (10 to 21days posttreatment) Secondary: Microbiologic eradication rates	Primary: In the clinically evaluable population, clinical cure rates at the test of cure visit were 88.9% for tigecycline and 85.3% for levofloxacin (P=0.4025). In the clinical modified intent to treat population, clinical cure rates were 83.7% for tigecycline and 81.5% for levofloxacin (P<0.6269). Tigecycline was found to be non-inferior to levofloxacin (P<0.001). Secondary: In the microbiologically evaluable population, eradication rates at the test of cure visit were similar among the treatment groups for common pathogens. The most common isolate was *Streptococcus pneumoniae*, with similar eradication for tigecycline (92%) and levofloxacin (89%). Both therapies eradicated 100% of penicillin-intermediate and penicillin-resistant strains. *Mycoplasma pneumoniae* was the most commonly identified atypical organism, and was eradicated in 96% of tigecycline patients and 92% of levofloxacin patients. No obvious differences in eradication rates of other organisms were found, though the number of other isolates was small.
Miscellaneous Infections				
Wormser et al.[57] (2006) Doxycycline for 10 days	DB, RCT Patients with early Lyme disease	N=180 30 months	Primary: Complete response rate (resolution of erythema migrans and symptoms, return to pre-	Primary: No significant differences in clinical response were found at 20 days (P>0.2). No significant differences in clinical response were found at 30 months (P>0.2).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs doxycycline for 10 days with a single IV dose of ceftriaxone vs doxycycline for 20 days			Lyme-disease health) Secondary: Adverse events	Secondary: The doxycycline-ceftriaxone group had a significantly higher incidence of diarrhea than 10-day and 20-day doxycycline treatment groups (P<0.001). Patient in the doxycycline-ceftriaxone treatment group were more likely to experience an adverse drug event than patient in the 10-day doxycycline (P=0.055) and 20-day doxycycline (P=0.035) treatment groups.
Roushan et al.[58] (2010) Gentamicin 5 mg/kg QD for five days plus doxycycline 100 mg BID for eight weeks (gentamicin-doxycycline group) vs streptomycin 1 g IM for two weeks plus doxycycline 100 mg BID for 45 days (streptomycin-doxycycline group)	RCT Patients >10 years of age with brucellosis	N=164 Up to 8 weeks	Primary: Therapeutic failure due to lack of efficacy and relapse Secondary: Safety	Primary: Therapeutic failure was seen in two (2.4%) patients from the gentamicin-doxycycline group and in four (4.9%) patients from the streptomycin-doxycycline group (P=0.68). Relapse occurred in two (2.4%) patients from the gentamicin-doxycycline group and in five (6.1%) patients from the streptomycin-doxycycline group (P=0.44). Success occurred in 78 (95.12%) patients in the gentamicin-doxycycline group and in 73 (89%) patients in the streptomycin-doxycycline group (P=0.25). Secondary: The rates of adverse effects were similar in the gentamicin-doxycycline group (28%) and in the streptomycin-doxycycline group (22%; P=0.5).
Keramat et al.[59] (2009)	PRO, RCT Patients ≥18 years	N=178 8 to 12 weeks	Primary: Response and relapse rates	Primary: Response to therapy was observed in 93.7% of patients at the end of treatment for all three groups (DR, 96.7%; CR, 95.2%; CD, 87.3%). There

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Ciprofloxacin 15 mg/kg BID plus rifampin 15 mg/kg QD (CR group) vs ciprofloxacin 15 mg/kg BID plus doxycycline 200 mg QD (CD group) vs doxycycline 200 mg PO QD plus rifampin 15 mg/kg QD (DR group)	of age with acute brucellosis		Secondary: Not reported	were no significant differences among the treatment groups (P=0.09). Therapeutic failure was seen in 12 cases, though no significant differences were noted among the three groups (P=0.88). After six months, 12 patients relapsed (DR, 7.7%; CR, 8.3%; CD, 17.5%; P=0.35).
Mwengee et al.[60] (2006) Gentamicin 2.5 mg/kg IM every 12 hours for seven days vs doxycycline 100 mg (adults) or 2.2 mg/kg (children) orally every 12 hours for seven days	OL, RCT Adults and children with symptoms of bubonic, septicemic, or pneumonic plague lasting less than or equal to three days	N=65 2 weeks	Primary: Efficacy Secondary: Not reported	Primary: Three patients, two of whom were treated with gentamicin and one of whom was treated with doxycycline, died on the first or second day of treatment, and these deaths were attributed to advanced disease and complications including pneumonia, septicemia, hemorrhage, and renal failure at the start of therapy. All other patients experienced cure or an improved condition after receiving therapy, resulting in favorable response rates of 94% for gentamicin (95% CI, 81.1 to 99.0) and 97% for doxycycline (95% CI, 83.4 to 99.8). *Yersinia pestis* isolates obtained from 30 patients belonged to biotype *antiqua* and were susceptible to gentamicin and doxycycline, which had MICs of 0.13 mg/L and 0.25 to 0.5 mg/L, respectively. Serum concentrations of antibiotics were within therapeutic ranges, and adverse events were infrequent. Patients treated with gentamicin demonstrated a modest increase in the mean serum creatinine concentration after treatment (P<0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Both gentamicin and doxycycline were effective therapies for adult and pediatric plague, with high rates of favorable responses and low rates of adverse events. Secondary: Not reported
Boulanger et al.[61] (2004) Streptomycin vs gentamicin vs tetracycline vs gentamicin plus tetracycline	RETRO Patients with plague whose cases were reported in New Mexico during 1985 to 1999	N=75 Duration varied	Primary: Mean number of hospital days, fever days, complications, and deaths Secondary: Not reported	Primary: The mean number of fever days after the initiation of antimicrobial treatment was 3.5 days for the streptomycin group, 2.6 days for the gentamicin group, 1.9 days for the gentamicin-tetracycline group and 2.6 days for the tetracycline group (P=0.23). The mean duration of hospital days was 6.2 days in the streptomycin group, 7.2 days in the gentamicin group, and 6.0 days in the gentamicin-tetracycline group (P=0.57). There were no deaths among the 50 patients in the four treatment groups. The mean numbers of fever days, hospital days, and complications and the number of deaths did not differ between patients treated with streptomycin and those treated with gentamicin. Secondary: Not reported
Eckmann et al.[62] (2013) Tigecycline as monotherapy or in combination with other antibacterials	MA Patients with a mean of 63.1+14.0 years of age who received tigecycline for complicated intra-abdominal infection were included	N=785 Duration varied	Primary: Mean Acute Physiology and Chronic Health Evaluation II and Sequential Organ Failure Assessment scores Secondary: Not reported	Primary: Clinical response rates at the end of treatment were 77.4% for all patients (567/733), 80.6% for patients who received tigecycline as monotherapy (329/408), 75.2% for patients with a nosocomial infection (354/471), 75.8% for patients with an Acute Physiology and Chronic Health Evaluation II score >15 (250/330) and 54.2% (32/59) for patients with a Sequential Organ Failure Assessment score > 7. Secondary: Not reported
Guirao et al.[63] (2013)	MA	N=1,039	Primary: Adverse events,	Primary: Nausea and vomiting were reported in <2% of patients. The most common

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Tigecycline as monotherapy or in combination with other antibacterials	Patients with a mean of 63 years of age who received tigecycline for complicated skin and soft-tissue infection or complicated intra-abdominal infection were included	Duration varied	mortality, Acute Physiology and Chronic Health Evaluation II and Sequential Organ Failure Assessment scores Secondary: Not reported	serious adverse events were multi-organ failure (4.0 and 10.0% in complicated skin and soft-tissue infection and complicated intra-abdominal infection patients, respectively) and sepsis (4.0 and 6.1%, respectively). Death was recorded for 24/254 (9.4%) complicated skin and soft-tissue infection and 147/785 (18.7%) complicated intra-abdominal infection patients. Mortality rates were higher in the group with a baseline Acute Physiology and Chronic Health Evaluation II score of >15 compared with those with a score of <15 (18.7 vs 3.5% for complicated skin and soft-tissue infection patients and 23.8 vs 16.0% for complicated intra-abdominal infection patients). A similar trend was seen when complicated intra-abdominal infection patients were stratified by Sequential Organ Failure Assessment score. Secondary: Not reported
Babinchak et al.[64] (2005) Tigecycline 100 mg as an initial dose, followed by 50 mg IV every 12 hours vs imipenem-cilastatin 500 mg IV every 6 hours	MA Adults with complicated intra-abdominal infections	N=1,642 (2 trials) 47 to 56 days	Primary: Clinical response (infection and associated signs and symptoms resolved) Secondary: Safety	Primary: Clinical cure rates were 86.1% for patients in the tigecycline group, vs 86.2% for patients in the imipenem-cilastatin group (P<0.0001 for non-inferiority). Secondary: Nausea (24.4% tigecycline, 19.0% imipenem-cilastatin [P=0.01]), vomiting (19.2% tigecycline, 14.3% imipenem-cilastatin [P=0.008]), and diarrhea (13.8% tigecycline, 13.2% imipenem-cilastatin [P=0.719]) were the most frequently reported adverse events.
Fomin et al.[65] (2008) Tigecycline 100 mg as an initial dose, followed by	DB, RCT (pooled analysis) Adults with complicated intra-abdominal	N=1,259 5 to 14 days	Primary: Clinical response at the test-of-cure visit in the microbiologically evaluable and	Primary: Clinical cure rates at the test-of-cure visit were 92.4% for tigecycline vs 88.8% for imipenem-cilastatin in the microbiologically evaluable population (95% CI, 2.2 to 9.4). Clinical cure rates for the modified intent-to-treat populations were 87.3%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
50 mg IV every 12 hours vs imipenem-cilastatin 500 mg IV every 6 hours	infections		microbiological modified intent-to-treat populations Secondary: Safety	for tigecycline vs 83.5% for imipenem-cilastatin (95% CI, -2.5, 10.0) at the test-of-cure visit. Secondary: The most commonly reported treatment emergent adverse events for tigecycline and imipenem-cilastatin were nausea (14.7 and 11.8%, respectively; P=0.267) and vomiting (10.7 and 7.3%, respectively; P=0.146). The imipenem-cilastatin group had significantly higher treatment emergent adverse events of fever, hyperglycemia, and dyspnea (P=0.017, P=0.031, and P=0.011, respectively) compared to tigecycline. The tigecycline treatment group had significantly higher treatment emergent adverse events of amylase and blood urea nitrogen increase (P=0.011 and P=0.003, respectively).
Mallick et al.[66] (2007) Tigecycline 100 mg as an initial dose, followed by 50 mg IV every 12 hours vs imipenem-cilastatin 500 mg IV every 6 hours	DB, RCT (pooled analysis) Adults with complicated intra-abdominal infections	N=1005 5 to 14 days	Primary: Clinical response, safety, and health care resource utilization Secondary: Not reported	Primary: Clinical cure rates were 88.1% for tigecycline and 87.0% for imipenem–cilastatin (P=0.59). Treatment-emergent adverse events, regardless of study drug causality or severity, occurred in 73.8% of tigecycline- and 71.6% of imipenem–cilastatin-treated patients (P=0.346). Of the three most frequently reported adverse events, tigecycline was associated with a significantly higher rate of nausea (24.4%) relative to imipenem–cilastatin (19.0%; P<0.010) and a significantly higher rate of vomiting (19.2% relative to imipenem–cilastatin (14.3%; P<0.008). There were no significant differences between the groups in terms of occurrence of diarrhea (13.8% with tigecycline; 13.2% with imipenem–cilastatin; P=0.719). There were no significant differences between the tigecycline and the imipenem– cilastatin groups for any health resource utilization, clinical outcome, or antibiotic discontinuation rates.
Chen et al.[67] (2010)	MC, OL, RCT Patients ≥18 years	N=191 ≤2 weeks	Primary: Clinical response at the test-of-cure	Primary: In the microbiologically evaluable population, 86.5% of patients receiving tigecycline and 97.9% of patients receiving imipenem-cilastatin were

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Imipenem-cilastatin 500-500 mg every six hours vs tigecycline 100 mg IV as an initial dose, followed by 50 mg IV every 12 hours	of age with complicated intra-abdominal infections		visit (12 to 37 days after therapy) for the microbiologically evaluable and microbiologic modified intent-to-treat populations Secondary: Not reported	cured at the test-of-cure visit (95% CI, -23.05 to 0.7). In the microbiologic modified intent-to-treat population, 81.7% of patients receiving tigecycline and 90.9% of patients receiving imipenem-cilastatin were cured at the test-of-cure visit (95% CI, -23.4 to 4.9). In the clinically evaluable population, 87.0% of patients receiving tigecycline and 95.4% of patients receiving imipenem-cilastatin were cured at the test-of-cure visit (95% CI, -18.3 to 1.5). In the clinical microbiologic modified intent-to-treat population (those with complicated appendicitis), 80.4% of patients receiving tigecycline and 89.8% of patients receiving imipenem-cilastatin were cured at the test-of-cure visit (95% CI, -20.3 to 1.6). The overall incidence of treatment-emergent adverse events was 80.4% for tigecycline compared to 53.9% for imipenem-cilastatin (P<0.001). Adverse events were primarily gastrointestinal in nature, especially nausea (21.6 vs 3.9%; P<0.001) and vomiting (12.4 vs 2.0%; P=0.005). Secondary: Not reported
Towfigh et al.[68] (2010) Ceftriaxone 2 g IV QD plus metronidazole 1 to 2 g IV daily in divided doses for four to 14 days (CTX/MET) vs tigecycline 100 mg IV as an initial	MC, OL, RCT Patients ≥18 years of age with community-origin 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 TGC and in 74% of patients in the CTX/MET group (-4.0; 95% CI, -13.1 to 5.1; P=0.009). TCG was found to be non-inferior to CTX/MET. Secondary: Clinical cure rates for the microbiologically evaluable population were 66% with TGC and 70% with CTX/MET (-3.4; 95% CI, -14.5 to 7.8; P=0.020. TCG was found to be non-inferior to CTX/MET. In the c-mITT population, clinical cure was reported in 64% of patients receiving TGC and in 71% of patients receiving CTX/MET (-7.0; 95% CI, -15.8 to 1.08; P=0.038. TGC was found to be non-inferior to CTX/MET.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
dose, followed by 50 mg IV every 12 hours for four to 14 days (TGC)				*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 population, infections were cured in 68.0 and 67.0% of all monomicrobial and polymicrobial infections, respectively, in the TGC-treated patients, and 71.5 and 68.3% of all monomicrobial and polymicrobial infections, respectively, in the CTX/MET-treated patients. Adverse events were similar with TGC and CTX/MET. 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%).

Drug regimen abbreviations: BID=twice daily, IM=intramuscular, IV=intravenous, QD=once daily, QID=four times daily, TID=three times daily
Study abbreviations: DB=double-blind, MA=meta-analysis, MC=multicenter, OL=open-label, PC=placebo controlled, PG=parallel group, PRO=prospective, RCT=randomized controlled trial, RETRO=retrospective, SB=single-blind, SC=single center, XO=cross over
Miscellaneous abbreviations: CI=confidence interval, COPD=chronic obstructive pulmonary disease, FEV_1=forced expiratory volume in one second, *H pylori*=*Helicobacter pylori*, MRSA=Methicillin-resistant *Staphylococcus aureus*, OR=odds ratio, RR=relative risk, SD=standard deviation

Additional Evidence

Dose Simplification
Dunbar-Jacob et al. evaluated compliance with oral therapies for the treatment of pelvic inflammatory disease.[69] Patients were randomly assigned to receive either inpatient therapy (parenteral cefoxitin and doxycycline for two days, followed by doxycycline orally for 14 days) or outpatient therapy (parenteral cefoxitin as a single dose and doxycycline orally for 14 days). Patients took an average of 70% of the prescribed doses. The doses of doxycycline were taken for less than half of outpatient days of treatment, unscheduled drug holidays occurred on almost 25% of outpatient days, and only 16.9% of doses were taken within the optimal timing interval. Lee et al. evaluated compliance rates with bismuth subsalicylate, metronidazole, and tetracycline for the treatment of *Helicobacter pylori* infections.[70] The enhanced group received medication counseling from a pharmacist, along with a medication calendar and a medication box. There was no significant difference between the groups in the number of patients taking more than 60% of the medications. However, there was a significant difference in the number of patients taking more than 90% of the medications (67% of the control group vs 89% of the enhanced compliance group; P<0.01).

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 Tetracyclines

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Demeclocycline	tablet	N/A	N/A	$$$$$
Doxycycline	capsule, delayed-release capsule, delayed-release tablet, injection, suspension (reconstituted), syrup, tablet	Adoxa®*, Adoxa Pak®*, Doryx®*, Morgidox®*, Vibramycin®*	$$$-$$$$$	$
Minocycline	capsule, injection, tablet	Minocin®	$$$$$	$
Tetracycline	capsule	N/A	N/A	$$$$$
Tigecycline	injection	Tygacil®	$$$$$	N/A

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

X. Conclusions

The tetracyclines are approved to treat a variety of infections, including central nervous system, dermatologic, gastrointestinal, genitourinary, respiratory, as well as numerous miscellaneous infections.[1-8] Demeclocycline, doxycycline, minocycline, and tetracycline are available in a generic formulation.

There are many guidelines that define the appropriate place in therapy for the tetracyclines. The specific agent that is recommended is dependent upon the infectious organism being treated and the corresponding spectrum of activity of the tetracycline. The tetracyclines are recommended for the treatment of susceptible pathogens causing endocarditis, encephalitis, cholera, *Helicobacter pylori* infections, sexually transmitted diseases, anthrax, infectious exacerbations of chronic obstructive pulmonary disease, community-acquired pneumonia, intra-abdominal infections, Lyme disease, plague, and tickborne rickettsial diseases.[9-11,13,15,18,19,21-23,25,27,28,30,31]

There are few published studies that directly compare the tetracyclines. Doxycycline and minocycline have demonstrated similar efficacy and safety when used for the treatment of genitourinary and respiratory infections.[48,49,53] The tetracyclines have also been shown to be comparable in efficacy to antibacterial agents in other classes.[32-68]

There is insufficient evidence to support that one brand tetracycline 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 tetracyclines 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 tetracycline 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 Antibacterials, Miscellaneous
AHFS Class 081228
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I. Overview

The miscellaneous antibacterials are a diverse group of products that are used to treat many different types of infections.[1-14] The Food and Drug Administration-approved indications vary depending on the particular agent and antimicrobial properties. It is important to analyze current treatment guidelines and published studies when making therapeutic decisions about the miscellaneous antibacterial agents.

Bacitracin inhibits bacterial cell well synthesis and prevents the incorporation of amino acids and nucleotides into the cell wall.[15] The lincosamides (clindamycin and lincomycin) bind to the 50S subunit of bacterial ribosomes to inhibit protein synthesis.[1,2,15] Colistimethate and polymyxin B are surface active agents that penetrate and disrupt the bacterial cell membrane.[1,2,15] Daptomycin is a cyclic lipopeptide that binds to bacterial membranes and causes a rapid depolarization of membrane potential. The loss of membrane potential leads to inhibition of the synthesis of protein, which results in bacterial cell death.[2,5] Linezolid acts early in translation by binding to a site on the bacterial 23S ribosomal ribonucleic acid (RNA) of the 50S subunit. It prevents the formation of a functional 70S initiation complex, which is an essential component of the bacterial translation process.[2] Quinupristin and dalfopristin act synergistically by binding to different sites on the bacterial ribosome to disrupt protein synthesis. Dalfopristin has been shown to inhibit the early phase of protein synthesis while quinupristin inhibits the late phase of protein synthesis.[13] Rifaximin binds to bacterial deoxyribonucleic acid (DNA)-dependent RNA polymerase, thereby inhibiting bacterial RNA synthesis.[8] Telavancin inhibits bacterial cell wall synthesis by interfering with the polymerization and cross-linking of peptidoglycan.[10] Vancomycin binds to the bacterial cell wall causing immediate inhibition of cell wall synthesis and secondary damage to the cytoplasmic membrane.[1,2,15]

Three new agents have been FDA-approved since the class was last reviewed. Dalbavancin and oritavancin are semisynthetic lipoglycopeptides that interfere with cell wall synthesis and are bactericidal against *Staphylococcus aureus* and *Streptococcus pyogenes in vitro*. They are FDA-approved for the treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates.[4,7] Tedizolid phosphate is an oxazolidinone-class antibacterial that is also approved for the treatment of ABSSSI.[9] It is the second agent in its class, the first being linezolid. Tedizolid phosphate is only approved for use against susceptible isolates of *Staphylococcus aureus* (including methicillin-resistant *S. aureus* [MRSA]), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* Group and *Enterococcus faecalis*. According to the FDA, ABSSSIs are skin infections which have a minimum lesion surface area of at least 75 cm^2 and includes cellulitis, erysipelas, wound infection, and major cutaneous abscess.[9]

Previously, two combination products containing bismuth, metronidazole and tetracycline were included in this review (Helidac® and Pylera®). Helidac® was discontinued by the manufacturer in 2014.[16] Pylera® is used to eradicate *Helicobacter pylori* in patients with duodenal ulcer disease. It contains all three of the antibacterial components in a single capsule. Bismuth, metronidazole and tetracycline are all active as antibacterial agents. The antibacterial action of bismuth salts is not well understood.[12] Metronidazole is metabolized through reductive pathways into reactive intermediates that have cytotoxic actions.[12,14] Tetracycline interacts with the 30S subunit of the bacterial ribosome and inhibits protein synthesis.[12,14]

The miscellaneous antibacterials that are included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. Bacitracin, clindamycin, colistimethate, lincomycin, linezolid, polymyxin B sulfate, and vancomycin are available in a generic formulation. This class was last reviewed in August 2014.

Table 1. Antibacterials, Miscellaneous Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Single Entity Agents			
Bacitracin	injection	Baciim®*	bacitracin

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Clindamycin	capsule, injection, solution	Cleocin HCl®*, Cleocin Palmitate®*, Cleocin Phosphate®*	clindamycin
Colistimethate	injection	Coly-Mycin M Parenteral®*	colistimethate
Dalbavancin	injection	Dalvance®	none
Daptomycin	injection	Cubicin®	none
Lincomycin	injection	Lincocin®*	lincomycin
Linezolid	injection, suspension, tablet	Zyvox®*	linezolid
Oritavancin	injection	Orbactiv®	none
Polymyxin B sulfate	injection	N/A	polymyxin B sulfate
Rifaximin	tablet	Xifaxan®	none
Tedizolid	injection, tablet	Sivextro®	none
Telavancin	injection	Vibativ®	none
Vancomycin	capsule, injection	Vancocin®*	vancomycin
Combination Products			
Colloidal bismuth subcitrate, metronidazole, and tetracycline	capsule	Pylera®	none
Quinupristin and dalfopristin	injection	Synercid®	none

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

The miscellaneous antibacterials have been shown to be active against the strains of microorganisms 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 antibacterials, miscellaneous that are noted in Tables 5 to 7. 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 Single Entity Antibacterials, Miscellaneous[1-14]

Organism	Bacitracin	Clinda-mycin	Colisti-methate	Dalba-vancin	Dapto-mycin	Linco-mycin	Linezolid	Orita-vancin	Polymyxin B Sulfate	Rifaximin	Tedizolid	Telava-ncin	Vanco-mycin
Gram-Positive Aerobes													
Enterococcus faecalis				✔	✔			✔			✔	✔	
Enterococcus faecium							✔					✔	
Staphylococcus aureus	✔	✔		✔	✔	✔	✔	✔			✔	✔	✔
Staphylococcus epidermidis		✔										✔	
Streptococcus agalactiae		✔		✔	✔		✔	✔			✔	✔	
Streptococcus anginosus				✔				✔			✔	✔	
Streptococcus dysgalactia				✔	✔			✔				✔	
Streptococcus pneumoniae		✔				✔	✔						
Streptococcus pyogenes		✔		✔	✔		✔	✔			✔	✔	
Gram-Negative Aerobes													
Enterobacter species			✔						✔				
Escherichia coli			✔						✔	✔			
Haemophilus influenzae									✔				
Klebsiella species			✔						✔				
Pseudomonas aeruginosa			✔						✔				
Gram-Positive Anaerobes													
Clostridium difficile													✔
Clostridium perfringens		✔											
Peptostreptococcus species		✔											
Gram-Negative Anaerobes													
Bacteroides fragilis		✔											
Fusobacterium necrophorum		✔											
Fusobacterium nucleatum		✔											
Prevotella melaninogenica		✔											

Table 3. Microorganisms Susceptible to the Combination Antibacterials, Miscellaneous[12-14]

Organism	Colloidal Bismuth Subcitrate, Metronidazole, and Tetracycline	Quinupristin and Dalfopristin
Gram-Positive Aerobes		
Corynebacterium jeikeium		✔
Helicobacter pylori	✔	
Staphylococcus aureus		✔
Staphylococcus epidermidis		✔
Streptococcus agalactiae		✔
Streptococcus pyogenes		✔

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of the miscellaneous antibacterials are summarized in Table 4.

Table 4. Treatment Guidelines Using the Antibacterials, Miscellaneous

Clinical Guideline	Recommendation(s)

European Society of Cardiology: **Guidelines for the Management of Infective Endocarditis (2015)[17]**	Main principles of prevention if infective endocarditis
	• The principle of antibiotic prophylaxis when performing procedures at risk of infective endocarditis (IE) in patients with predisposing cardiac conditions is maintained.
	• Antibiotic prophylaxis must be limited to patients with the highest risk of IE undergoing the highest risk dental procedures (dental procedures requiring manipulation of the gingival or periapical region of the teeth or perforation of the oral mucosa).
	  o Patients with a prosthetic valve, including transcatheter valve, or a prosthetic material used for cardiac valve repair.
	  o Patients with previous IE.
	  o Patients with congenital heart disease.
	• Good oral hygiene and regular dental review are more important than antibiotic prophylaxis to reduce the risk of IE.
	• Aseptic measures are mandatory during venous catheter manipulation and during any invasive procedures in order to reduce the rate of health care-associated IE.
	• Recommended prophylaxis for dental procedures at high-risk:
	  o Single-dose amoxicillin or penicillin 30 to 60 minutes before procedure.
	  o If allergy to penicillin or ampicillin, single-dose clindamycin 30 to 60 minutes before procedure.
	
	Antimicrobial therapy: principles
	• The treatment of infective endocarditis relies on the combination of prolonged antimicrobial therapy and - in about half of patients - surgical eradication of the infected tissues.
	• Prolonged therapy with a combination of bactericidal drugs is the basis of IE treatment. Drug treatment of prosthetic valve endocarditis (PVE) should last longer (at least six weeks) than that of native valve endocarditis (NVE) (two to six weeks).
	• In both NVE and PVE, the duration of treatment is based on the first day of effective antibiotic therapy, not on the day of surgery. A new full course of treatment should only start if valve cultures are positive, the choice of antibiotic being based on the susceptibility of the latest recovered bacterial isolate.
	• The indications and pattern of use of aminoglycosides have changed. They are no longer recommended in staphylococcal NVE because their clinical benefits

Clinical Guideline	Recommendation(s)
	have not been demonstrated but they can increase renal toxicity; and, when they are indicated in other conditions, aminoglycosides should be given in a single daily dose in order to reduce nephrotoxicity. • New antibiotic regimens have emerged in the treatment of staphylococcal IE, including daptomycin and the combination of high-doses of cotrimoxazole plus clindamycin, but additional investigations are necessary in large series before they can be recommended in all patients. <u>Antimicrobial therapy: regimens</u> • Antibiotic treatment of infective endocarditis due to oral streptococci and *Streptococcus* bovis group: o Penicillin-susceptible strains: ▪ Penicillin G, amoxicillin, or ceftriaxone for four weeks. ▪ Penicillin G, amoxicillin, or ceftriaxone plus gentamicin or netilmicin for two weeks. ▪ Vancomycin for four weeks (in beta-lactam allergic patients). o Penicillin-resistant strains: ▪ Penicillin G, amoxicillin, or ceftriaxone for four weeks plus gentamicin for two weeks. ▪ Vancomycin for four weeks plus gentamicin for two weeks (in beta-lactam allergic patients). • Antibiotic treatment of infective endocarditis due to *Staphylococcus* species: o Methicillin-susceptible strains (native valves): ▪ Flucloxacillin or oxacillin for four to six weeks. ▪ Cotrimoxazole intravenous for one week and oral for five weeks plus clindamycin for one week (for *Staphylococcus aureus*). o Penicillin-allergic patients or methicillin-resistant staphylococci (native valves): ▪ Vancomycin for four to six weeks. ▪ Alternative: Daptomycin for four to six weeks. ▪ Cotrimoxazole intravenous for one week and oral for five weeks plus clindamycin for one week (for *Staphylococcus aureus*). o Methicillin-susceptible strains (prosthetic valves): ▪ Flucloxacillin or oxacillin for at least six weeks, rifampin for at least six weeks, and gentamicin for two weeks. o Penicillin-allergic patients or methicillin-resistant staphylococci (prosthetic valves): ▪ Vancomycin for at least six weeks, rifampin for at least six weeks, and gentamicin for two weeks. • Antibiotic treatment of infective endocarditis due to *Enterococcus* species: o Beta-lactam and gentamicin susceptible strains: ▪ Amoxicillin for four to six weeks plus gentamicin for two to six weeks. ▪ Ampicillin plus gentamicin for six weeks. ▪ Vancomycin plus gentamicin for six weeks. • Antibiotic treatment of blood culture-negative infective endocarditis: o *Brucella* species: ▪ Doxycycline, cotrimoxazole, and rifampin for ≥3 months. o *Coxiella burnetii* (agent of Q fever): ▪ Doxycycline plus hydroxychloroquine for >18 months. ▪ o *Bartonella* species: ▪ Doxycycline orally for four weeks plus gentamicin for two weeks.

Clinical Guideline	Recommendation(s)
	o *Legionella* species: ▪ Levofloxacin intravenous for ≥6 weeks or clarithromycin intravenous for two weeks then orally for four weeks plus rifampin. o *Mycoplasma* species: ▪ Levofloxacin for ≥6 months. o *Tropheryma whipplei* (agent of Whipple's disease): ▪ Doxycycline plus hydroxychloroquine orally for ≥18 months. • Proposed antibiotic regimens for initial empirical treatment of infective endocarditis in acute severely ill patients (before pathogen identification): o Community-acquired native valves or late prosthetic valves (≥12 months post surgery) endocarditis: ▪ Ampicillin intravenous plus flucloxacillin or oxacillin intravenous plus gentamicin intravenous for once dose. ▪ Vancomycin intravenous plus gentamicin intravenous (for penicillin allergic patients). o Early PVE (<12 months post surgery) or nosocomial and non-nosocomial healthcare associated endocarditis: ▪ Vancomycin intravenous, gentamicin intravenous, and rifampin orally.
American College of Cardiology/American Heart Association: **2008 Focused Update Incorporated Into the American College of Cardiology/American Heart Association 2006 Guidelines for the Management of Patients With Valvular Heart Disease (2008)**[18] American College of Cardiology/American Heart Association: **Guideline for the Management of Patients With Valvular Heart Disease (2014)**[19] **(although a more current guideline more detailed information was included as part of the 2008 Focused update; as such both are summarized together)**	<u>Rheumatic fever prophylaxis</u> • Primary prevention of rheumatic heart disease: o Penicillin G benzathine intramuscular once or penicillin V orally for 10 days. o Erythromycin estolate or erythromycin ethylsuccinate orally for 10 days, or azithromycin orally for five days in patients who are allergic to penicillin. • Secondary prevention of rheumatic fever: o Penicillin G benzathine intramuscular every four weeks, or penicillin V orally twice daily, or sulfadiazine orally once daily. o Erythromycin orally twice daily for patients who are allergic to penicillin. <u>Endocarditis prophylaxis</u> • Prophylaxis against infective endocarditis is reasonable for the following patients at highest risk for adverse outcomes from infective endocarditis who undergo dental procedures that involve manipulation of either gingival tissue or the periapical region of teeth or perforation of the oral mucosa: o Patients with prosthetic cardiac valve or prosthetic material used for cardiac valve repair. o Patients with previous infective endocarditis. o Patients with congenital heart disease. o Cardiac transplant recipients with valve regurgitation due to a structurally abnormal valve. • Prophylaxis against infective endocarditis is not recommended for non-dental procedures (such as transesophageal echocardiogram, esophagogastroduodenoscopy, or colonoscopy) in the absence of active infection. • Regimens for dental procedures (single dose 30 to 60 minutes before procedure): o Oral: amoxicillin. o Unable to take oral medications: ampicillin, cefazolin or ceftriaxone. o Allergic to penicillin or ampicillin (oral): cephalexin, clindamycin, or azithromycin. o Allergic to penicillins or ampicillin and unable to take oral medication: cefazolin, ceftriaxone, or clindamycin. • Therapy of native valve endocarditis caused by highly penicillin-susceptible viridans group streptococci and *Streptococcus bovis:*

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	o Penicillin G or ceftriaxone for four weeks. o Ceftriaxone plus gentamicin for two weeks. o Vancomycin for four weeks in patients allergic to penicillin. • Therapy of native valve endocarditis caused by strains of viridans group streptococci and *Streptococcus bovis* relatively resistant to penicillin: o Penicillin G or ceftriaxone for four weeks plus gentamicin for two weeks. o Vancomycin for four weeks in patients allergic to penicillin. • Therapy for native valve or prosthetic valve enterococcal endocarditis caused by strains susceptible to penicillin, gentamicin, and vancomycin: o Ampicillin for four to six weeks or penicillin G plus gentamicin for four to six weeks. o Vancomycin plus gentamicin for six weeks in patients allergic to penicillin. • Therapy for endocarditis caused by staphylococci in the absence of prosthetic materials: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin for six weeks plus the optional addition of gentamicin for three to five days. ▪ Cefazolin for six weeks with the optional addition of gentamicin in patients allergic to penicillin. o Oxacillin-resistant strains: ▪ Vancomycin for six weeks. • Therapy for prosthetic valve endocarditis caused by staphylococci: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin, rifampin, and gentamicin for ≥6 weeks. o Oxacillin-resistant strains: ▪ Vancomycin, rifampin, and gentamicin for ≥6 weeks. • Therapy for both native and prosthetic valve endocarditis caused by *Haemophilus* species *(Haemophilus parainfluenzae, Haemophilus aphrophilus, Haemophilus paraphrophilus), Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* species microorganisms: o Ceftriaxone for four weeks. o Ampicillin-sulbactam for four weeks. o Ciprofloxacin for four weeks. • Therapy for culture-negative endocarditis including *Bartonella* endocarditis: o Native valve: ▪ Ampicillin-sulbactam plus gentamicin (or vancomycin for patients allergic to penicillin) plus ciprofloxacin for four to six weeks. o Prosthetic valve (early; ≤1 year): ▪ Vancomycin for six weeks, plus gentamicin for two weeks, plus cefepime for six weeks, plus rifampin for six weeks. o Prosthetic valve (late; >1 year): ▪ Suspected *Bartonella*, culture negative: • Ceftriaxone for six weeks plus gentamicin with/without doxycycline for six weeks. ▪ Documented *Bartonella*, culture positive: • Doxycycline for six weeks plus gentamicin for two weeks.
American Heart Association: **Infective Endocarditis in Adults: Diagnosis, Antimicrobial**	• Therapy for native valve endocarditis caused by viridans group streptococci and *Streptococcus gallolyticus* (Formerly Known as *Streptococcus bovis)*: o Highly penicillin-susceptible strains: ▪ Penicillin G or ceftriaxone for four weeks. ▪ Penicillin G or ceftriaxone plus gentamicin for two weeks (in

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Therapy, and Management of Complications (2015)[20]	patients with uncomplicated infective endocarditis, rapid response to therapy, and no underlying renal disease). ▪ Vancomycin for four weeks (recommended only for patients unable to tolerate penicillin or ceftriaxone therapy). o Relatively penicillin-resistant strains: ▪ Penicillin for four weeks plus gentamicin for the first two weeks. ▪ If the isolate is ceftriaxone susceptible, then ceftriaxone alone may be considered. ▪ Vancomycin for four weeks (recommended only for patients unable to tolerate beta-lactam therapy). • Therapy for native valve endocarditis caused by *A defectiva* and *Granulicatella* Species and viridans group streptococci: o For patients with infective endocarditis caused by *A defectiva*, *Granulicatella* species, and viridans group streptococci with a penicillin MIC ≥0.5 µg/mL, treat with a combination of ampicillin or penicillin plus gentamicin as done for enterococcal infective endocarditis with infectious diseases consultation. o If vancomycin is used in patients intolerant of ampicillin or penicillin, then the addition of gentamicin is not needed. o Ceftriaxone combined with gentamicin may be a reasonable alternative treatment option for isolates that are susceptible to ceftriaxone. • Therapy for endocarditis of prosthetic valves or other prosthetic material caused by viridans group streptococci and *Streptococcus gallolyticus* (Formerly Known as *Streptococcus bovis)*: o Penicillin for six weeks plus gentamicin for the first two weeks. o Extend gentamicin to six weeks if the MIC is >0.12 µg/mL for the infecting strain. o Vancomycin can be used in patients intolerant of penicillin, ceftriaxone, or gentamicin. • Therapy for endocarditis of prosthetic valves or other prosthetic material caused by *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and Groups B, C, F, and G β-Hemolytic Streptococci: o Penicillin, cefazolin, or ceftriaxone for four weeks is reasonable for infective endocarditis caused by *S pneumoniae*; vancomycin can be useful for patients intolerant of β-lactam therapy. o Six weeks of therapy is reasonable for prosthetic valve endocarditis caused by *S pneumoniae*. o High-dose penicillin or a third-generation cephalosporin is reasonable in patients with infective endocarditis caused by penicillin-resistant *S pneumoniae* without meningitis; if meningitis is present, then high doses of cefotaxime (or ceftriaxone) are reasonable. o The addition of vancomycin and rifampin to cefotaxime (or ceftriaxone) may be considered in patients with infective endocarditis caused by *S pneumoniae* that are resistant to cefotaxime. o Because of the complexities of infective endocarditis caused by *S pneumoniae*, consultation with an infectious diseases specialist is recommended. o For infective endocarditis caused by *S pyogenes*, four to six weeks of therapy with aqueous crystalline penicillin G or ceftriaxone is reasonable; vancomycin is reasonable only in patients intolerant of β-lactam therapy. o For infective endocarditis caused by group B, C, or G streptococci, the addition of gentamicin to penicillin G or ceftriaxone for at least the first two weeks of a four to six week treatment course may be considered.

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	o Consultation with an infectious diseases specialist to guide treatment is recommended in patients with infective endocarditis caused by β-hemolytic streptococci. • Therapy for endocarditis caused by staphylococci in the absence of prosthetic valves or other prosthetic material: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin for six weeks. ▪ For penicillin-allergic individuals: cefazolin for six weeks. o Oxacillin-resistant strains ▪ Vancomycin for six weeks. ▪ Daptomycin for six weeks. • Therapy for prosthetic valve endocarditis caused by staphylococci: o Oxacillin-susceptible strains: ▪ Nafcillin or oxacillin plus rifampin (for at least six weeks) and gentamicin (for two weeks). o Oxacillin-resistant strains: ▪ Vancomycin plus rifampin (for at least six weeks) and gentamicin (for two weeks). • Therapy for native valve or prosthetic valve enterococcal endocarditis: o Strains susceptible to penicillin and gentamicin: ▪ Ampicillin or penicillin G plus gentamicin for four to six weeks. ▪ Double β-lactam ampicillin plus ceftriaxone for six. o Strains susceptible to penicillin and resistant to aminoglycosides or streptomycin-susceptible gentamicin-resistant in patients able to tolerate β-Lactam therapy: ▪ Ampicillin plus ceftriaxone for six weeks. ▪ Ampicillin or penicillin G plus streptomycin for four to six weeks. o Vancomycin and aminoglycoside-susceptible penicillin-resistant enterococcus species in patients unable to tolerate β-lactam : ▪ Unable to tolerate β-lactams: • Vancomycin plus gentamicin for six weeks (vancomycin therapy recommended only for patients unable to tolerate penicillin or ceftriaxone therapy). ▪ Intrinsic penicillin resistance: • Vancomycin plus gentamicin for six weeks. o Strains Resistant to Penicillin, Aminoglycosides, and Vancomycin: ▪ Linezolid or daptomycin for at least six weeks. • Therapy for both native and prosthetic valve endocarditis caused by *Haemophilus* species *(Haemophilus parainfluenzae, Haemophilus aphrophilus, Haemophilus paraphrophilus), Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens,* and *Kingella* species microorganisms: o Ceftriaxone (cefotaxime or another third- or fourth-generation cephalosporin may be substituted) or ampicillin or ciprofloxacin for four weeks. Fluoroquinolone therapy recommended only for patients unable to tolerate cephalosporin and ampicillin therapy; levofloxacin or moxifloxacin may be substituted. • Therapy for culture-negative endocarditis including *Bartonella* endocarditis: o For patients with acute (days) clinical presentations of native valve infection, coverage for *S aureus*, β-hemolytic streptococci, and aerobic Gram-negative bacilli is reasonable. o For patients with a subacute (weeks) presentation of native valve endocarditis, coverage of *S aureus*, viridans group streptococci, HACEK, and enterococci is reasonable.

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	o For patients with culture-negative prosthetic valve endocarditis, coverage for staphylococci, enterococci, and aerobic Gram-negative bacilli is reasonable if onset of symptoms is within one year of prosthetic valve placement. o If symptom onset is >1 year after valve placement, then infective endocarditis is more likely to be caused by staphylococci, viridans group streptococci, and enterococci, and antibiotic therapy for these potential pathogens is reasonable.
Infectious Diseases Society of America: **Clinical Practice Guidelines: Management of Encephalitis (2008)**[21] **(Was reviewed and deemed current as of July 2011)**	Empirical therapy • Acyclovir should be initiated in all patients with suspected encephalitis, pending results of diagnostic studies. • Other empirical antimicrobial agents should be initiated on the basis of specific epidemiologic or clinical factors, including appropriate therapy for presumed bacterial meningitis, if clinically indicated. • In patients with clinical clues suggestive of rickettsial or ehrlichial infection during the appropriate season, doxycycline should be added to empirical treatment regimens. Bacteria • *Bartonella bacilliformis:* chloramphenicol, ciprofloxacin, doxycycline, ampicillin, or sulfamethoxazole-trimethoprim is recommended. • *Bartonella henselae:* doxycycline or azithromycin, with or without rifampin, can be considered. • *Listeria monocytogenes:* ampicillin plus gentamicin is recommended; sulfamethoxazole-trimethoprim is an alternative in the penicillin-allergic patient. • *Mycoplasma pneumoniae:* antimicrobial therapy (azithromycin, doxycycline, or a fluoroquinolone) can be considered. • *Tropheryma whipplei:* ceftriaxone, followed by either sulfamethoxazole-trimethoprim or cefixime, is recommended. Helminths • *Baylisascaris procyonis:* albendazole plus diethylcarbamazine can be considered; adjunctive corticosteroids should also be considered. • *Gnathostoma* species: albendazole or ivermectin is recommended. • *Taenia solium:* need for treatment should be individualized; albendazole and corticosteroids are recommended; praziquantel can be considered as an alternative. Rickettsioses and ehrlichiosis • *Anaplasma phagocytophilum:* doxycycline is recommended. • *Ehrlichia chaffeensis:* doxycycline is recommended. • *Rickettsia rickettsii:* doxycycline is recommended; chloramphenicol can be considered an alternative in selected clinical scenarios, such as pregnancy. • *Coxiella burnetii:* doxycycline plus a fluoroquinolone plus rifampin is recommended. Spirochetes • *Borrelia burgdorferi:* ceftriaxone, cefotaxime, or penicillin G is recommended. • *Treponema pallidum:* penicillin G is recommended; ceftriaxone is an alternative. Protozoa • *Acanthamoeba:* sulfamethoxazole-trimethoprim plus rifampin plus ketoconazole or fluconazole plus sulfadiazine plus pyrimethamine can be considered. • *Balamuthia mandrillaris:* pentamidine, combined with a macrolide (azithromycin or clarithromycin), fluconazole, sulfadiazine, flucytosine, and a

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	phenothiazine can be considered. • *Naegleria fowleri:* amphotericin B (intravenous and intrathecal) and rifampin, combined with other agents, can be considered. • *Plasmodium falciparum:* quinine, quinidine, or artemether is recommended; atovaquone-proguanil is an alternative; exchange transfusion is recommended for patients with 110% parasitemia or cerebral malaria; corticosteroids are not recommended. • *Toxoplasma gondii:* pyrimethamine plus either sulfadiazine or clindamycin is recommended; sulfamethoxazole-trimethoprim alone and pyrimethamine plus atovaquone, clarithromycin, azithromycin, or dapsone are alternatives. • *Trypanosoma brucei gambiense:* eflornithine is recommended; melarsoprol is an alternative. • *Trypanosoma brucei rhodesiense:* melarsoprol is recommended.

European Federation of Neurological Societies: **Guideline on the Management of Community-acquired Bacterial Meningitis (2008)**[22]	Empirical therapy
	• Ceftriaxone 2 g every 12 to 24 hours or cefotaxime 2 g every six to eight hours.
	• Alternative therapy: meropenem 2 g every eight hours or chloramphenicol 1 g every six hours.
	• If penicillin or cephalosporin-resistant pneumococcus is suspected, use ceftriaxone or cefotaxime plus vancomycin 60 mg/kg every 24 hours after a loading dose of 15 mg/kg.
	• Ampicillin-amoxicillin 2 g every four hours if *Listeria* is suspected.
	
	Pathogen specific therapy
	• Penicillin-sensitive pneumococcal meningitis:
	  o Benzyl penicillin 250,000 U/kg/day, ampicillin-amoxicillin 2 g every four hours, ceftriaxone 2 g every 12 hours or cefotaxime 2 g every six to eight hours.
	  o Alternative therapy: meropenem 2 g every eight hours or vancomycin 60 mg/kg every 24 hours as a continuous infusion after a 15 mg/kg loading dose plus rifampicin 600 mg every 12 hours, or moxifloxacin 400 mg daily.
	• Pneumococcus with reduced susceptibility to penicillin or cephalosporins:
	  o Ceftriaxone or cefotaxime plus vancomycin±rifampicin.
	  o Alternative therapy: moxifloxacin, meropenem or linezolid 600 mg combined with rifampicin.
	• Meningococcal meningitis:
	  o Benzyl penicillin, ceftriaxone, or cefotaxime.
	  o Alternative therapy: meropenem, chloramphenicol, or moxifloxacin.
	• *Haemophilus influenzae* type B:
	  o Ceftriaxone or cefotaxime.
	  o Alternative therapy: chloramphenicol–ampicillin-amoxicillin.
	• Listerial meningitis:
	  o Ampicillin or amoxicillin 2 g every four hours±gentamicin 1 to 2 mg every eight hours for the first seven to 10 days.
	  o Alternative therapy: sulfamethoxazole-trimethoprim 10 to 20 mg/kg every six to 12 hours or meropenem.
	• *Staphylococcal* species:
	  o Flucloxacillin 2 g every four hours or vancomycin if penicillin allergy is suspected.
	  o Rifampicin should also be considered in addition to either agent. Linezolid should be considered for methicillin-resistant staphylococcal meningitis.
	• Gram-negative *Enterobacteriaceae*:
	  o Ceftriaxone, cefotaxime or meropenem.
	• Pseudomonal meningitis:

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	o Meropenem±gentamicin.
Infectious Diseases Society of America: **Practice Guidelines for the Management of Bacterial Meningitis (2004)**[23]	Empiric therapy • Empirical antimicrobial therapy is initiated either when the lumbar puncture is delayed or for patients with purulent meningitis and a negative cerebrospinal fluid gram stain result: o Age <1 month: ampicillin plus cefotaxime or ampicillin plus an aminoglycoside. o Age one to 23 months: vancomycin plus a third-generation cephalosporin. o Age two to 50 years: vancomycin plus a third-generation cephalosporin. o Age >50 years: vancomycin plus ampicillin plus a third-generation cephalosporin. o Basilar skull fracture: vancomycin plus a third-generation cephalosporin. o Penetrating head trauma: vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem. o Post neurosurgery: vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem. o Cerebrospinal fluid shunt: vancomycin plus cefepime, vancomycin plus ceftazidime, or vancomycin plus meropenem. Specific therapy • Recommendations for specific antimicrobial therapy in bacterial meningitis are based on isolated pathogens and susceptibility. • *Streptococcus pneumoniae* o Penicillin minimum inhibitory concentrations <0.1 µg/mL: standard therapy includes penicillin G or ampicillin; alternative therapies include ceftriaxone, cefotaxime, or chloramphenicol. o Penicillin minimum inhibitory concentrations 0.1 to 1.0 µg/mL: standard therapy includes ceftriaxone or cefotaxime; alternative therapies include cefepime or meropenem. o Penicillin minimum inhibitory concentrations ≥2 µg/mL: standard therapies include vancomycin plus ceftriaxone or cefotaxime; alternative therapies include gatifloxacin or moxifloxacin. o Cefotaxime or ceftriaxone minimum inhibitory concentrations ≥1.0 µg/mL: standard therapies include vancomycin plus ceftriaxone or cefotaxime (consider addition of rifampin if minimum inhibitory concentrations of ceftriaxone is >2 µg/mL); alternative therapies include gatifloxacin or moxifloxacin. • *Neisseria meningitides* o Penicillin minimum inhibitory concentrations <0.1 µg/mL: standard therapy includes penicillin G or ampicillin; alternative therapy includes ceftriaxone, cefotaxime or chloramphenicol. o Penicillin minimum inhibitory concentrations 0.1 to 1.0 µg/mL: standard therapy includes ceftriaxone or cefotaxime; alternative therapies include chloramphenicol, a fluoroquinolone or meropenem. • *Listeria monocytogenes* o Standard therapy includes ampicillin or penicillin G; alternative therapies include sulfamethoxazole-trimethoprim or meropenem. • *Streptococcus agalactiae* o Standard therapy includes ampicillin or penicillin G; alternative therapies include ceftriaxone or cefotaxime. • *Escherichia coli* and other Enterobacteriaceae o Standard therapy includes a third-generation cephalosporin; alternative therapies include aztreonam, fluoroquinolone, meropenem, sulfamethoxazole-trimethoprim or ampicillin.

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	• *Pseudomonas aeruginosa*
	  o Standard therapies include cefepime or ceftazidime; alternative therapies include aztreonam, ciprofloxacin, or meropenem (addition of an aminoglycoside should be considered).
	• *Haemophilus influenzae* β-lactamase negative strains
	  o Standard therapy includes ampicillin; alternative therapies include ceftriaxone, cefotaxime, cefepime, chloramphenicol or a fluoroquinolone.
	• *Haemophilus influenzae* β-lactamase positive strains
	  o Standard therapy includes a third-generation cephalosporin; alternative therapies include cefepime, chloramphenicol or a fluoroquinolone.
	• *Staphylococcus aureus* methicillin susceptible
	  o Standard therapy includes nafcillin or ofloxacin; alternative therapies include vancomycin or meropenem.
	• *Staphylococcus aureus* methicillin resistant
	  o Standard therapy includes vancomycin (consider addition of rifampin); alternative therapies include sulfamethoxazole-trimethoprim or linezolid.
	• *Staphylococcus epidermidis*
	  o Standard therapy includes vancomycin (consider addition of rifampin); alternative therapy includes linezolid.
	• *Enterococcus* species ampicillin susceptible
	  o Standard therapy includes ampicillin plus gentamicin.
	• *Enterococcus* species ampicillin resistant
	  o Standard therapy includes vancomycin plus gentamicin.
	• *Enterococcus* species ampicillin and vancomycin resistant
	  o Standard therapy includes linezolid.

Infectious Diseases Society of America: **Practice Guidelines for the Diagnosis and Management of Skin and Soft-Tissue Infections (2014)**[24]	Impetigo and ecthyma
	• Gram stain and culture of the pus or exudates from skin lesions of impetigo and ecthyma are recommended to help identify whether *Staphylococcus aureus* and/or a β-hemolytic *Streptococcus* is the cause (strong, moderate), but treatment without these studies is reasonable in typical cases.
	• Bullous and nonbullous impetigo can be treated with oral or topical antimicrobials, but oral therapy is recommended for patients with numerous lesions or in outbreaks affecting several people to help decrease transmission of infection. Treatment for ecthyma should be an oral antimicrobial.
	  o Treatment of bullous and nonbullous impetigo should be with either mupirocin or retapamulin twice daily for five days.
	  o Oral therapy for ecthyma or impetigo should be a seven-day regimen with an agent active against *S. aureus* unless cultures yield streptococci alone (when oral penicillin is the recommended agent). Because *S. aureus* isolates from impetigo and ecthyma are usually methicillin susceptible, dicloxacillin or cephalexin is recommended. When MRSA is suspected or confirmed, doxycycline, clindamycin, or sulfamethoxazole-trimethoprim is recommended.
	
	Purulent skin and soft-tissue infections (cutaneous abscesses, furuncles, carbuncles, and inflamed epidermoid cysts)
	• Gram stain and culture of pus from carbuncles and abscesses are recommended, but treatment without these studies is reasonable in typical cases. Gram stain and culture of pus from inflamed epidermoid cysts are not recommended.
	• Incision and drainage is the recommended treatment for inflamed

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	epidermoid cysts, carbuncles, abscesses, and large furuncles. • The decision to administer antibiotics directed against *S. aureus* as an adjunct to incision and drainage should be made based upon presence or absence of systemic inflammatory response syndrome (SIRS), such as temperature >38°C or <36°C, tachypnea >24 breaths per minute, tachycardia >90 beats per minute, or white blood cell count >12 000 or <400 cells/µL. An antibiotic active against MRSA is recommended for patients with carbuncles or abscesses who have failed initial antibiotic treatment or have markedly impaired host defenses or in patients with SIRS and hypotension. <u>Recurrent skin abscesses</u> • A recurrent abscess at a site of previous infection should prompt a search for local causes such as a pilonidal cyst, hidradenitis suppurativa, or foreign material. • Recurrent abscesses should be drained and cultured early in the course of infection. • After obtaining cultures of recurrent abscess, treat with a five to ten day course of an antibiotic active against the pathogen isolated. • Consider a five-day decolonization regimen twice daily of intranasal mupirocin, daily chlorhexidine washes, and daily decontamination of personal items such as towels, sheets, and clothes for recurrent *S. aureus* infection. • Adult patients should be evaluated for neutrophil disorders if recurrent abscesses began in early childhood. <u>Erysipelas and cellulitis</u> • Cultures of blood or cutaneous aspirates, biopsies, or swabs are not routinely recommended except in patients with malignancy on chemotherapy, neutropenia, severe cell-mediated immunodeficiency, immersion injuries, and animal bites. • Typical cases of cellulitis without systemic signs of infection should receive an antimicrobial agent that is active against streptococci. For cellulitis with systemic signs of infection (moderate nonpurulent), systemic antibiotics are indicated. Many clinicians could include coverage against methicillin-susceptible *S. aureus* (MSSA). For patients whose cellulitis is associated with penetrating trauma, evidence of MRSA infection elsewhere, nasal colonization with MRSA, injection drug use, or SIRS (severe nonpurulent), vancomycin or another antimicrobial effective against both MRSA and streptococci is recommended. In severely compromised patients, broad-spectrum antimicrobial coverage may be considered. Vancomycin plus either piperacillin-tazobactam or imipenem/meropenem is recommended as a reasonable empiric regimen for severe infections. • The recommended duration of antimicrobial therapy is five days, but treatment should be extended if the infection has not improved within this time period. <u>Surgical site infections</u> • Suture removal plus incision and drainage should be performed for surgical site infections. • Adjunctive systemic antimicrobial therapy is not routinely indicated, but in conjunction with incision and drainage may be beneficial for surgical site infections associated with a significant systemic response. • A brief course of systemic antimicrobial therapy is indicated in patients

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	with surgical site infections following clean operations on the trunk, head and neck, or extremities that also have systemic signs of infection.
	• A first-generation cephalosporin or an antistaphylococcal penicillin for MSSA, or vancomycin, linezolid, daptomycin, telavancin, or ceftaroline where risk factors for MRSA are high (nasal colonization, prior MRSA infection, recent hospitalization, recent antibiotics), is recommended.
	• Agents active against gram-negative bacteria and anaerobes, such as a cephalosporin or fluoroquinolone in combination with metronidazole, are recommended for infections following operations on the axilla, gastrointestinal tract, perineum, or female genital tract.
	
	<u>Necrotizing fasciitis</u>
	• Empiric antibiotic treatment should be broad (e.g., vancomycin or linezolid plus piperacillin-tazobactam or a carbapenem; or plus ceftriaxone and metronidazole), as the etiology can be polymicrobial (mixed aerobic–anaerobic microbes) or monomicrobial (group A streptococci, community-acquired MRSA).
	• Penicillin plus clindamycin is recommended for treatment of documented group A streptococcal necrotizing fasciitis.
	
	<u>Pyomyositis</u>
	• Cultures of blood and abscess material should be obtained.
	• Vancomycin is recommended for initial empirical therapy. An agent active against enteric gram-negative bacilli should be added for infection in immunocompromised patients or following open trauma to the muscles.
	• Cefazolin or antistaphylococcal penicillin (e.g., nafcillin or oxacillin) is recommended for treatment of pyomyositis caused by MSSA.
	• Antibiotics should be administered intravenously initially, but once the patient is clinically improved, oral antibiotics are appropriate for patients in whom bacteremia cleared promptly and there is no evidence of endocarditis or metastatic abscess. Two to three weeks of therapy is recommended.
	
	<u>Clostridial gas gangrene or myonecrosis</u>
	• Urgent surgical exploration of the suspected gas gangrene site and surgical debridement of involved tissue should be performed.
	• In the absence of a definitive etiologic diagnosis, broad-spectrum treatment with vancomycin plus either piperacillin-tazobactam, ampicillin-sulbactam, or a carbapenem antimicrobial is recommended. Definitive antimicrobial therapy with penicillin and clindamycin is recommended for treatment of clostridial myonecrosis.
	
	<u>Animal bites</u>
	• Preemptive early antimicrobial therapy for three to five days is recommended for patients who:
	  o are immunocompromised;
	  o are asplenic;
	  o have advanced liver disease;
	  o have preexisting or resultant edema of the affected area;
	  o have moderate to severe injuries, especially to the hand or face; or
	  o have injuries that may have penetrated the periosteum or joint capsule.
	• Oral treatment options
	  o Amoxicillin-clavulanate is recommended.
	  o Alternative oral agents include doxycycline, as well as penicillin VK plus dicloxacillin.

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	○ First-generation cephalosporins, penicillinase-resistant penicillins, macrolides, and clindamycin all have poor in vitro activity against *Pasteurella multocida* and should be avoided. • Intravenous ○ β-lactam-β-lactamase combinations, piperacillin-tazobactam, second-generation cephalosporins, and carbapenems. • Tetanus toxoid should be administered to patients without toxoid vaccination within 10 years. Tetanus, diphtheria, and tetanus (Tdap) is preferred over Tetanus and diphtheria (Td) if the former has not been previously given. Cutaneous anthrax • Oral penicillin V 500 mg four times daily for seven to 10 days is the recommended treatment for naturally acquired cutaneous anthrax. • Ciprofloxacin 500 mg by mouth twice daily or levofloxacin 500 mg intravenously/orally every 24 hours for 60 days is recommended for bioterrorism cases because of presumed aerosol exposure. Bacillary angiomatosis and cat scratch disease • Azithromycin is recommended for cat scratch disease (strong, moderate) according to the following dosing protocol: ○ Patients >45 kg: 500 mg on day one followed by 250 mg for four additional days. ○ Patients <45 kg: 10 mg/kg on day one and 5 mg/kg for four more days. • Erythromycin 500 mg four times daily or doxycycline 100 mg bid for two weeks to two months is recommended for treatment of bacillary angiomatosis. Erysipeloid • Penicillin (500 mg four times daily) or amoxicillin (500 mg three times daily [tid]) for seven to 10 days is recommended for treatment of erysipeloid. Glanders • Ceftazidime, gentamicin, imipenem, doxycycline, or ciprofloxacin is recommended based on in vitro susceptibility. Bubonic plague • Bubonic plague should be diagnosed by Gram stain and culture of aspirated material from a suppurative lymph node. Streptomycin (15 mg/kg intramuscularly [IM] every 12 hours) or doxycycline (100 mg twice daily by mouth) is recommended for treatment of bubonic plague. Gentamicin could be substituted for streptomycin. Tularemia • Streptomycin (15 mg/kg every 12 hours intramuscularly) or gentamicin (1.5 mg/kg every 8 hours intravenously) is recommended for treatment of severe cases of tularemia. • Tetracycline (500 mg four times daily) or doxycycline (100 mg twice daily by mouth) is recommended for treatment of mild cases of tularemia.
Infectious Diseases Society of America: **Diagnosis and Treatment of Diabetic**	• Empirical antibiotic regimens should be based on the clinical severity of the infection. • Current clinical data does not allow for the recommendation of any specific antibiotic regimen for diabetic foot infections.

Clinical Guideline	Recommendation(s)
Foot Infections (2012)[25]	• Suggested agents are derived from available published clinical trials and expert experience. • Definitive regimens should consider results of culture and susceptibility tests, as well as the clinical response to the empirical regimen. Similar agents of the same drug class may be substituted. Some of these regimens may not have Food and Drug Administration approval for complicated skin and skin-structure infections, and only linezolid, ertapenem and piperacillin-tazobactam are currently specifically approved for diabetic foot infections. • Suggested empirical antibiotic regimens for mild infections: dicloxacillin, clindamycin, cephalexin, sulfamethoxazole-trimethoprim, amoxicillin-clavulanate, levofloxacin and doxycycline. • Suggested empirical antibiotic regimens for moderate infections: levofloxacin, cefoxitin, ceftriaxone, ampicillin-sulbactam, moxifloxacin, tigecycline, linezolid, daptomycin, ertapenem, ticarcillin-clavulanate, piperacillin-tazobactam, levofloxacin or ciprofloxacin with clindamycin, imipenem-cilastatin, vancomycin, ceftazidime, cefepime, aztreonam. • Suggested empirical antibiotic regimens for severe infections: piperacillin-tazobactam, vancomycin, ceftazidime, cefepime, aztreonam or a carbapenem.
Society for Healthcare Epidemiology of America/Infectious Diseases Society of America: **Clinical Practice Guidelines for *Clostridium difficile* Infection in Adults (2010)**[26]	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 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**	Treatment of *Clostridium difficile* infection
	• 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

Clinical Guideline	Recommendation(s)
Document for *Clostridium difficile* Infection (2014)[27]	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 (2012)[28]**	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. • 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. Antimicrobial agents for the treatment of specific causes of diarrhea • 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.

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	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)**[29]	<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. • 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)**[30]	<u>Recommendations for therapy against specific pathogens</u> • *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.

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	o Fluoroquinolone. • *Campylobacter* species: o Erythromycin. • *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: **Guideline on the Management of *Helicobacter pylori* Infection (2007)**[31]	• The recommended primary therapies for *Helicobacter pylori* infection include: a proton pump inhibitor, clarithromycin, and amoxicillin, or metronidazole (clarithromycin-based triple therapy) for 14 days or a proton pump inhibitor or histamine 2 receptor antagonist, bismuth, metronidazole, and tetracycline (bismuth quadruple therapy) for 10 to 14 days.
Canadian Helicobacter Study Group: **The Toronto Consensus for the Treatment of *Helicobacter pylori* Infection in Adults (2016)**[32]	• A quadruple combination of a proton pump inhibitor, bismuth, tetracycline, and metronidazole or a proton pump inhibitor, amoxicillin, metronidazole, and clarithromycin for 14 days can be considered first-line therapy for the eradication of *Helicobacter pylori.* • Proton pump inhibitor-based triple therapy is restricted to areas with known low clarithromycin resistance or high eradication success with these regimens. • Recommended rescue therapies include bismuth quadruple therapy and levofloxacin-containing therapy. • Rifabutin regimens should be restricted to patients who have failed to respond to at least three prior regimens.
European *Helicobacter pylori* Study Group: **Management of *Helicobacter pylori* Infection–The Maastricht IV Consensus Report (2012)**[33]	• First-line therapy should be with triple therapy using a proton pump inhibitor or ranitidine bismuth citrate, combined with clarithromycin and amoxicillin or metronidazole. • Second-line therapy should include bismuth-containing quadruple therapy or proton pump inhibitor, levofloxacin and amoxicillin.
Centers for Disease Control and Prevention: **Sexually Transmitted Diseases Treatment Guidelines (2015)**[34]	Arthritis and arthritis-dermatitis syndrome • Recommended regimen: o Ceftriaxone 1 g intramuscular or intravenous every 24 hours plus azithromycin 1 g orally in a single dose. • Alternative regimen: o Cefotaxime 1 g intravenous every eight hours or ceftizoxime 1 g intravenous every eight hours plus azithromycin 1 g orally in a single

Clinical Guideline	Recommendation(s)
	dose. Bacterial vaginosis • Recommended regimens: o Metronidazole 500 mg orally twice a day for seven days. o Metronidazole gel 0.75%, one full applicator (5 g) intravaginally, once a day for five days. o Clindamycin cream 2%, one full applicator (5 g) intravaginally at bedtime for seven days. • Alternative regimens: o Tinidazole 2 g orally once daily for two days. o Tinidazole 1 g 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. Cervicitis • Recommended regimens for presumptive treatment: o Azithromycin 1 g orally in a single dose. o Doxycycline 100 mg orally twice a day for seven days. Chancroid • Recommended regimens: o Azithromycin 1 g 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. Chlamydial infections • Recommended regimens: o Azithromycin 1 g 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. Chlamydial infections among children • 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 g orally in a single dose. • Recommended regimens for children ≥8 years of age: o Azithromycin 1 g orally in a single dose. o Doxycycline 100 mg orally twice a day for seven days. Disseminated gonococcal infection • Recommended regimen: o Ceftriaxone 1 g intramuscular or intravenous every 24 hours. • Alternative regimens: o Cefotaxime 1 g intravenous every eight hours. o Ceftizoxime 1 g intravenous every eight hours.

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	Epididymitis
	• 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.
	
	Granuloma inguinale (Donovanosis)
	• Recommended regimen:
	  o Azithromycin 1 g orally once per week or 500 mg daily for at least three weeks and until all lesions have completely healed.
	• Alternative regimens:
	  o Doxycycline 100 mg orally twice a day 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 g intramuscular in a single dose plus azithromycin 1 g orally 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 25 to 50 mg/kg intravenous or intramuscular in a single dose, not to exceed 125 mg.
	• Recommended regimen for children who weigh ≤45 kg and who have bacteremia or arthritis:
	  o Ceftriaxone 50 mg/kg (maximum dose: 1 g) 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 g intravenous every 12 hours plus azithromycin 1 g orally in a single dose.
	
	Lymphogranuloma venereum
	• Recommended regimen:

Clinical Guideline	Recommendation(s)
	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 g 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. • Alternative regimen: o Azithromycin suspension, 20 mg/kg/day orally, one dose daily for three days. <u>Pelvic inflammatory disease</u> • Recommended parenteral regimen A: o Cefotetan 2 g intravenous every 12 hours. o Cefoxitin 2 g 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 g 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 g intramuscular in a single dose and probenecid, 1 g 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 g orally in a single dose.

Clinical Guideline	Recommendation(s)
	o Tinidazole 2 g orally in a single dose plus azithromycin 1 g orally in a single dose (if not used for initial episode). Primary and secondary syphilis • 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. Early latent syphilis • 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. Late latent syphilis or latent syphilis of unknown duration • 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. Tertiary syphilis • 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. Trichomoniasis • Recommended regimen: o Metronidazole 2 g orally in a single dose. o Tinidazole 2 g orally in a single dose. • Alternative regimen: o Metronidazole 500 mg orally twice a day for seven days. Neurosyphilis • 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. Uncomplicated gonococcal infections of the cervix, urethra, and rectum • 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 1g orally in a single dose or doxycycline 100 mg orally twice a day for

Clinical Guideline	Recommendation(s)
	seven days. Uncomplicated gonococcal infections of the pharynx • Recommended regimens: o Ceftriaxone 250 mg intermuscular in a single dose plus azithromycin 1g orally in a single dose or doxycycline 100 mg orally twice a day for seven days.
American Academy of Otolaryngology–Head and Neck Surgery Foundation: **Clinical Practice Guideline: Adult Sinusitis (2015)**[35]	Symptomatic relief of viral rhinosinusitis • Management of viral rhinosinusitis is primarily symptomatic, with an analgesic or antipyretic provided for pain or fever, respectively. • Nasal saline may be palliative and cleansing with low risk of adverse reactions. • Oral decongestants may provide symptomatic relief and should be considered barring any medical contraindications, such as hypertension or anxiety. The use of topical decongestant is likely to be palliative, but continuous duration of use should not exceed three to five days, as recommended by the manufacturers, to avoid rebound congestion and rhinitis medicamentosa. • Clinical experience suggests oral antihistamines may provide symptomatic relief of excessive secretions and sneezing, although there are no clinical studies supporting the use of antihistamines in acute viral rhinosinusitis. • Guaifenesin (an expectorant) and dextromethorphan (a cough suppressant) are often used for symptomatic relief of viral rhinosinusitis symptoms, but evidence of clinical efficacy is lacking. Symptomatic relief of acute bacterial rhinosinusitis • Symptomatic treatments for acute bacterial rhinosinusitis include analgesics, topical intranasal steroids, and/or nasal saline irrigation. None of these products has been specifically approved by the FDA for use in acute rhinosinusitis (as of March 2014), and only some have data from controlled clinical studies supporting this use. • Over-the-counter analgesics, such as nonsteroidal anti-inflammatory drugs or acetaminophen, are usually sufficient to relieve facial pain associated with acute bacterial rhinosinusitis. • Antihistamines have no role in the symptomatic relief of acute bacterial rhinosinusitis in nonatopic patients. No studies support their use in an infectious setting, and antihistamines may worsen congestion by drying the nasal mucosa. Initial management of acute bacterial rhinosinusitis • Offer watchful waiting (without antibiotics) or prescribe initial antibiotic therapy for adults with uncomplicated acute bacterial rhinosinusitis. Watchful waiting should be offered only when there is assurance of follow-up, such that antibiotic therapy is started if the patient's condition fails to improve by seven days after acute bacterial rhinosinusitis diagnosis or if it worsens at any time. Choice of antibiotic for acute bacterial rhinosinusitis • If a decision is made to treat acute bacterial rhinosinusitis with an antibiotic, the clinician should prescribe amoxicillin with or without clavulanate as first-line therapy for five to ten days for most adults. • For penicillin-allergic patients, either doxycycline or a respiratory fluoroquinolone (levofloxacin or moxifloxacin) is recommended as an alternative agent for empiric antimicrobial therapy. Treatment failure for acute bacterial rhinosinusitis • If the patient worsens or fails to improve with the initial management option by seven days after diagnosis or worsens during the initial management, the clinician should reassess the patient to confirm acute bacterial rhinosinusitis,

Clinical Guideline	Recommendation(s)
	exclude other causes of illness, and detect complications. • If acute bacterial rhinosinusitis is confirmed in the patient initially managed with observation, the clinician should begin antibiotic therapy. • If the patient was initially managed with an antibiotic, the clinician should change the antibiotic.
American Academy of Allergy, Asthma, and Immunology/ American College of Allergy, Asthma and Immunology/ Joint Council on Allergy, Asthma and Immunology: **The Diagnosis and Management of Sinusitis: A Practice Parameter Update (2014)**[36]	• Treat acute bacterial rhinosinusitis if symptoms last longer than 10 days or with recrudescence of symptoms after progressive improvement. • The most commonly reported bacterial pathogens in acute bacterial rhinosinusitis are *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Staphylococcus aureus*. • The antibiotics currently approved by the FDA for acute bacterial rhinosinusitis are azithromycin, clarithromycin, amoxicillin-clavulanate, cefprozil, cefuroxime axetil, loracarbef, levofloxacin, trimethoprim-sulfamethoxazole, and moxifloxacin. Although some studies have reported comparisons of different antibiotics for adult acute bacterial rhinosinusitis, not one was found to be superior. • Owing to concerns over bacterial resistance, the Infectious Diseases Society of America no longer recommends the use of macrolides for empiric treatment of acute bacterial rhinosinusitis. That organization recommends amoxicillin-clavulanate as first-line therapy and doxycycline, levofloxacin, and moxifloxacin in patients allergic to penicillin. • The Infectious Diseases Society of America recommends five to seven days of treatment with antibiotics for uncomplicated acute bacterial rhinosinusitis in adults and 10 to 14 days in children. • Use intranasal steroids for treatment of acute rhinosinusitis as monotherapy or with antibiotics.
American Academy of Pediatrics: **Clinical Practice Guideline for the Diagnosis and Management of Acute Bacterial Sinusitis in Children Aged 1 to 18 years (2013)**[37]	• Antibiotic therapy should be prescribed for acute bacterial sinusitis in children with severe onset or worsening course (signs, symptoms or both). • Antibiotic therapy or additional outpatient observation for three days should be utilized for children with persistent illness (nasal discharge of any quality, cough or both for at least 10 days). • When a decision has been made to initiate antibiotic therapy for the treatment of acute bacterial sinusitis, amoxicillin with or without clavulanate is considered first-line. • For children ≥2 years of age with uncomplicated acute bacterial sinusitis that is mild to moderate in severity who do not attend child care and have not received antibiotics in the previous four weeks, amoxicillin 45 mg/kg/day in two divided doses is recommended. In communities with high prevalence of *Streptococcus pneumoniae* (>10%, including intermediate and high level resistance), amoxicillin may be initiated at 80 to 90 mg/kg/day in two divided doses with a maximum of 2 g per dose. • Patients with moderate to severe illness and those <2 years of age who are attending child care or have recently received antibiotics, amoxicillin-clavulanate (80 to 90 mg/kg/day of amoxicillin with 6.4 mg/kg/day of clavulanate to a maximum of 2 g per dose) may be used. • A single dose of ceftriaxone 50 mg/kg intravenous or intramuscular may be used for children who are vomiting, unable to tolerate oral medication or unlikely to adhere to initial doses of antibiotic.
Infectious Diseases Society of America: **Management of Community-Acquired Pneumonia in Infants and Children Older Than 3 Months of Age**	<u>Outpatient treatment</u> • Antimicrobial therapy is not routinely required for preschool-aged children with community-acquired pneumonia, because viral pathogens are responsible for the great majority of clinical disease. • Amoxicillin should be used as first-line therapy for previously healthy, appropriately immunized infants and preschool children with mild to moderate community-acquired pneumonia suspected to be of bacterial origin. Amoxicillin

Clinical Guideline	Recommendation(s)

(2011)[38]
 	
Reviewed and deemed current as of 04/2013
	provides appropriate coverage for *Streptococcus pneumoniae*.
	• For patients allergic to amoxicillin, the following agents are considered alternative treatment options:
	  o Second- or third-generation cephalosporin (cefpodoxime, cefuroxime, cefprozil).
	  o Levofloxacin (oral therapy).
	  o Linezolid (oral therapy).
	• Macrolide antibiotics should be prescribed for treatment of children (primarily school-aged children and adolescents) evaluated in an outpatient setting with findings compatible with community-acquired pneumonia caused by atypical pathogens.
	
	<u>Inpatient treatment</u>
	• Ampicillin or penicillin G should be administered to the fully immunized infant or school-aged child admitted to a hospital ward with community-acquired pneumonia when local epidemiologic data document lack of substantial high-level penicillin resistance for invasive *Streptococcus pneumoniae*.
	• Empiric therapy with a third-generation parenteral cephalosporin (ceftriaxone or cefotaxime) should be prescribed for hospitalized infants and children who are not fully immunized, in regions where local epidemiology of invasive pneumococcal strains documents high-level penicillin resistance, or for infants and children with life-threatening infection, including those with empyema.
	• Non–β-lactam agents, such as vancomycin, have not been shown to be more effective than third-generation cephalosporins in the treatment of pneumococcal pneumonia for the degree of resistance noted currently in North America.
	• Empiric combination therapy with a macrolide (oral or parenteral), in addition to a β-lactam antibiotic, should be prescribed for the hospitalized child for whom *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* are significant considerations.
	• Vancomycin or clindamycin (based on local susceptibility data) should be provided in addition to β-lactam therapy if clinical, laboratory, or imaging characteristics are consistent with infection caused by *Staphylococcus aureus*.

Infectious Diseases Society of America/American Thoracic Society: **Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults (2007)**[39]	<u>Empirical antimicrobial therapy</u>
	• Recommendations are generally for a class of antibiotics rather than for a specific drug, unless outcome data clearly favor one drug.
	• Because overall efficacy remains good for many classes of agents, the more potent drugs are given preference because of their benefit in decreasing the risk of selection for antibiotic resistance.
	• Outpatient treatment
	  o Previously healthy and no risk factors for drug-resistant *Streptococcus pneumoniae* infection:
	  ▪ Macrolide (azithromycin, clarithromycin, or erythromycin).
	  ▪ Doxycycline.
	  o Presence of comorbidities, such as chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressing conditions or use of immunosuppressing drugs; use of antimicrobials within the previous three months (in which case an alternative from a different class should be selected); or other risks for drug-resistant Streptococcus pneumoniae infection:
	  ▪ Respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin).
	  ▪ β-lactam plus a macrolide (high-dose amoxicillin or amoxicillin-clavulanate is preferred; alternatives include ceftriaxone, cefpodoxime, and cefuroxime; doxycycline is an alternative to the macrolide).
	  o In regions with a high rate of infection with high-level macrolide-

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	resistant *Streptococcus pneumoniae,* consider the use of alternative agents listed above for any patient, including those without comorbidities.
	• Inpatient, non-intensive care unit treatment
	  o Respiratory fluoroquinolone.
	  o β-lactam plus a macrolide (preferred β-lactam agents include cefotaxime, ceftriaxone, and ampicillin; ertapenem for selected patients; with doxycycline as an alternative to the macrolide. A respiratory fluoroquinolone should be used for penicillin-allergic patients).
	• Inpatient, intensive care unit treatment
	  o β-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) plus either azithromycin or a fluoroquinolone (for penicillin-allergic patients, a respiratory fluoroquinolone and aztreonam are recommended).
	  o For *Pseudomonas* infection, use an antipneumococcal, antipseudomonal β-lactam (piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin; OR
	  o Antipneumococcal, antipseudomonal β-lactam (listed above) plus an aminoglycoside and azithromycin; OR
	  o Antipneumococcal, antipseudomonal β-lactam (listed above) plus an aminoglycoside and an antipneumococcal fluoroquinolone (for penicillin-allergic patients, substitute aztreonam for the above β-lactam).
	  o For community-acquired methicillin-resistant *Staphylococcus aureus* infection, add vancomycin or linezolid.

American Thoracic Society/ Infectious Diseases Society of America: **Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia (2005)**[40]	• Select an initial empiric therapy based on the absence or presence of risk factors for multidrug-resistant pathogens. These risk factors include prolonged duration of hospitalization (five days or more), admission from a healthcare-related facility, and recent prolonged antibiotic therapy.
	• Patients with healthcare-related pneumonia should be treated for potentially drug-resistant organisms, regardless of when during the hospital stay the pneumonia begins.
	• In selecting empiric therapy for patients who have recently received an antibiotic, an effort should be made to use an agent from a different antibiotic class, because recent therapy increases the probability of inappropriate therapy and can predispose to resistance to that same class of antibiotics.
	• Initial empiric antibiotic therapy for hospital-acquired pneumonia or ventilator-associated pneumonia in patients with no known risk factors for multidrug-resistant pathogens, early onset, and any disease severity:
	  o Ceftriaxone; OR
	  o Levofloxacin, moxifloxacin, ciprofloxacin; OR
	  o Ampicillin-sulbactam; OR
	  o Ertapenem.
	• Initial empiric antibiotic therapy for hospital-acquired pneumonia, ventilator-associated pneumonia, and healthcare-associated pneumonia in patients with late-onset disease or risk factors for multidrug-resistant pathogens and all disease severity–combination antibiotic therapy is recommended as follows:
	  o Antipseudomonal cephalosporin (cefepime, ceftazidime) or antipseudomonal carbapenem (imipenem or meropenem) or β-lactam-β-lactamase inhibitor (piperacillin-tazobactam) plus antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) or aminoglycoside (amikacin, gentamicin, or tobramycin) plus linezolid or vancomycin if methicillin-resistant *Staphylococcus aureus* risk factors are present or there is a high incidence locally.

National Institutes of Health, the Centers for Disease Control and	Primary prophylaxis of *Pneumocystis jiroveci* pneumonia • Sulfamethoxazole-trimethoprim is the recommended prophylactic agent. One double-strength tablet daily is the preferred regimen. However, one single-

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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 (2016)**[41]	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 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 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 jiroveci* despite sulfamethoxazole-trimethoprim prophylaxis are usually effectively treated with standard doses of sulfamethoxazole-trimethoprim. • Patients with documented or suspected *Pneumocystis 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 jiroveci* therapy. • The recommended duration of therapy for *Pneumocystis jiroveci* is 21 days. • Patients who have a history of *Pneumocystis 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 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 is recommended as the preferred regimen for *Pneumocystis jiroveci* prophylaxis and is effective against *Toxoplasma* encephalitis and is therefore recommended.

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	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 jiroveci* pneumonia. • Atovaquone with or without pyrimethamine-leucovorin can also be considered. • 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. 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. 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

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	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. • Ethambutol is the recommended second drug.
Infectious Diseases Society of America: **Diagnosis and Management of Complicated Intra-abdominal Infection in Adults and Children (2010)**[42]	Community-acquired infection in adults: mild to moderate severity • 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. Community-acquired infection in adults: high severity • 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. Community-acquired infection in pediatric patients • 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 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

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	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: **Management of Patients with Infections Caused by Methicillin-Resistant *Staphylococcus Aureus* (2011)**[43]	Skin and soft-tissue infections • For a cutaneous abscess, incision and drainage is the primary treatment. For simple abscesses or boils, incision and drainage alone is likely to be adequate. • Antibiotic therapy is recommended for abscesses associated with the following conditions: severe or extensive disease (e.g., involving multiple sites of infection) or rapid progression in presence of associated cellulitis, signs and symptoms of systemic illness, associated comorbidities or immunosuppression, extremes of age, abscess in an area difficult to drain (e.g., face, hand, and genitalia), associated septic phlebitis, and lack of response to incision and drainage alone. • For outpatients with purulent cellulitis, empirical therapy for community-acquired methicillin-resistant *Staphylococcus aureus* is recommended pending culture results. Empirical therapy for infection due to beta-hemolytic streptococci is likely to be unnecessary. • For outpatients with non-purulent cellulitis, empirical therapy for infection due to beta-hemolytic streptococci is recommended. Empirical coverage for community-acquired methicillin-resistant *Staphylococcus aureus* is recommended in patients who do not respond to beta-lactam therapy and may be considered in those with systemic toxicity. • For empirical coverage of community-acquired methicillin-resistant *Staphylococcus aureus* in outpatients with skin and soft-tissue infections, oral antibiotic options include the following: clindamycin, sulfamethoxazole-trimethoprim, a tetracycline (doxycycline or minocycline), and linezolid. If coverage for both beta-hemolytic streptococci and community-acquired methicillin-resistant *Staphylococcus aureus* is desired, options include the following: clindamycin alone or sulfamethoxazole-trimethoprim or a tetracycline in combination with a beta-lactam (e.g., amoxicillin) or linezolid alone. • The use of rifampin as a single agent or as adjunctive therapy for the treatment of

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	skin and soft-tissue infections is not recommended. • For hospitalized patients with complicated skin and soft-tissue infections, in addition to surgical debridement and broad-spectrum antibiotics, empirical therapy for methicillin-resistant *Staphylococcus aureus* should be considered pending culture data. Options include the following: vancomycin intravenous, linezolid oral or intravenous, daptomycin intravenous, telavancin intravenous, and clindamycin intravenous or oral. A beta-lactam antibiotic (e.g., cefazolin) may be considered in hospitalized patients with non-purulent cellulitis with modification to methicillin-resistant *Staphylococcus aureus*-active therapy if there is no clinical response. • For children with minor skin infections (such as impetigo) and secondarily infected skin lesions (such as eczema, ulcers, or lacerations), mupirocin 2% topical ointment can be used. • Tetracyclines should not be used in children <8 years of age. • In hospitalized children with skin and soft-tissue infections, vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, empirical therapy with clindamycin intravenous is an option if the clindamycin resistance rate is low (<10%) with transition to oral therapy if the strain is susceptible. Linezolid oral or intravenous is an alternative. <u>Methicillin-resistant Staphylococcus aureus and infective endocarditis (native valve)</u> • For adults with uncomplicated bacteremia, vancomycin or daptomycin intravenous for at least two weeks is recommended. For complicated bacteremia, four to six weeks of therapy is recommended, depending on the extent of infection. • For adults with infective endocarditis, intravenous vancomycin or daptomycin for six weeks is recommended. • Addition of gentamicin to vancomycin is not recommended for bacteremia or native valve infective endocarditis. <u>Methicillin-resistant *Staphylococcus aureus* bacteremia and infective endocarditis (prosthetic valve)</u> • Intravenous vancomycin plus rifampin oral or intravenous for at least six weeks plus gentamicin intravenous for two weeks. • In children, vancomycin intravenous is recommended for the treatment of bacteremia and infective endocarditis. Duration of therapy may range from two to six weeks depending on source, presence of endovascular infection, and metastatic foci of infection. • Data regarding the safety and efficacy of alternative agents in children are limited, although daptomycin intravenous may be an option. Clindamycin or linezolid should not be used if there is concern for infective endocarditis or endovascular source of infection, but may be considered in children whose bacteremia rapidly clears and is not related to an endovascular focus. • Data are insufficient to support the routine use of combination therapy with rifampin or gentamicin in children with bacteremia or infective endocarditis. <u>Management of methicillin-resistant *Staphylococcus aureus* pneumonia</u> • For hospitalized patients with severe community-acquired pneumonia, empirical therapy for methicillin-resistant *Staphylococcus aureus* is recommended pending sputum and/or blood culture results. • For health care–associated methicillin-resistant *Staphylococcus aureus* or community-acquired methicillin-resistant *Staphylococcus aureus* pneumonia, intravenous vancomycin or linezolid oral or intravenous or clindamycin oral or intravenous, if the strain is susceptible, is recommended for seven to 21 days, depending on the extent of infection.

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	• In children, intravenous vancomycin is recommended. If the patient is stable without ongoing bacteremia or intravascular infection, clindamycin intravenous can be used as empirical therapy if the clindamycin resistance rate is low (<10%) with transition to oral therapy if the strain is susceptible. Linezolid oral or intravenous is an alternative.
	
	Management of methicillin-resistant *Staphylococcus aureus* bone and joint infections
	• Antibiotics available for parenteral administration include intravenous vancomycin and daptomycin.
	• Some antibiotic options with parenteral and oral routes of administration include the following: sulfamethoxazole-trimethoprim in combination with rifampin, linezolid, and clindamycin. Some experts recommend the addition of rifampin. For patients with concurrent bacteremia, rifampin should be added after clearance of bacteremia.
	• A minimum eight-week course is recommended. Some experts suggest an additional one to three months (and possibly longer for chronic infection or if debridement is not performed) of oral rifampin-based combination therapy with sulfamethoxazole-trimethoprim, doxycycline-minocycline, clindamycin, or a fluoroquinolone, chosen on the basis of susceptibilities.
	• For septic arthritis, refer to antibiotic choices for osteomyelitis. A three to four-week course of therapy is suggested.
	
	Management of methicillin-resistant *Staphylococcus aureus* infections of the central nervous system
	• Meningitis
	  o Intravenous vancomycin for two weeks is recommended. Some experts recommend the addition of rifampin.
	  o Alternatives include the following: linezolid or sulfamethoxazole-trimethoprim.
	  o For central nervous system shunt infection, shunt removal is recommended, and it should not be replaced until cerebrospinal fluid cultures are repeatedly negative.
	• Brain abscess, subdural empyema, spinal epidural abscess
	  o Intravenous vancomycin for four to six weeks is recommended. Some experts recommend the addition of rifampin.
	  o Alternatives include the following: linezolid and sulfamethoxazole-trimethoprim.
	• Septic thrombosis of cavernous or dural venous sinus
	  o Intravenous vancomycin for four to six weeks is recommended. Some experts recommend the addition of rifampin.
	  o Alternatives include the following: linezolid and sulfamethoxazole-trimethoprim.
	  o Intravenous vancomycin is recommended in children.

Infectious Diseases Society of America: **Clinical Practice Guideline for the Use of Antimicrobial Agents in Neutropenic Patients with Cancer (2010)**[44]
 	
Reviewed and deemed current as of 04/2013
	Initial antibiotic therapy
	• Oral route:
	  o For low-risk adults only; use ciprofloxacin plus amoxicillin-clavulanate.
	• Monotherapy with vancomycin not indicated:
	  o Choose therapy with one of the following agents: cefepime or ceftazidime, or imipenem or meropenem.
	• Two drugs without vancomycin:
	  o Choose an aminoglycoside plus antipseudomonal penicillin, cephalosporin (cefepime or ceftazidime), or carbapenem.
	• Vancomycin plus one or two antibiotics:
	  o Choose cefepime or ceftazidime plus vancomycin, with or without an

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	aminoglycoside; carbapenem plus vancomycin, with or without an aminoglycoside; or antipseudomonal penicillin plus an aminoglycoside and vancomycin.
	
	Modification of therapy during the first week of treatment
	• Patient becomes afebrile in three to five days:
	  o Adjust therapy to the most appropriate drug(s). If no etiologic agent is identified and if the patient is at low risk initially, and oral antibiotic treatment was begun with no subsequent complications, continue use of the same drugs.
	  o If the patient was at low risk initially and therapy with intravenous drugs was begun with no subsequent complications, the regimen may be changed after 48 hours to oral ciprofloxacin plus amoxicillin-clavulanate for adults or cefixime for children.
	  o If the patient is at high risk initially with no subsequent complications, continue use of the same intravenous drugs.
	• Persistent fever throughout the first three to five days:
	  o Reassess therapy on day three. If there is no clinical worsening, continue use of the same antibiotics; stop vancomycin use if cultures do not yield organisms.
	  o If there is progressive disease, change antibiotics.
	  o If the patient is febrile after five days, consider adding an antifungal drug.
	
	Antibiotic prophylaxis for afebrile neutropenic patients
	• Use of antibiotic prophylaxis is not routine because of emerging antibiotic resistance, except for the use of sulfamethoxazole-trimethoprim to prevent *Pneumocystis carinii* pneumonitis.

National Comprehensive Cancer Network: **Prevention and Treatment of Cancer-Related Infections (2016)**[45]	Low infection risk prophylaxis • Antimicrobial prophylaxis is not recommended in patients with low infection risk. Intermediate infection risk prophylaxis • Consider using fluoroquinolone prophylaxis. High infection risk prophylaxis • Consider using fluoroquinolone prophylaxis. • Additional prophylaxis may be necessary. *Pneumocystis jirovecii* prophylaxis • Sulfamethoxazole-trimethoprim is the preferred treatment. Sulfamethoxazole-trimethoprim has the additional benefit of activity against other pathogens including Nocardia, Toxoplasma, and Listeria. • Atovaquone, dapsone, and pentamidine are potential alternatives as prophylaxis for patients intolerant to sulfamethoxazole-trimethoprim. • Consider sulfamethoxazole-trimethoprim desensitization or atovaquone, dapsone, or pentamidine when *Pneumocystis* prophylaxis is required in patients who are sulfamethoxazole-trimethoprim intolerant. For patients receiving dapsone, consider assessing G6PD levels. Pneumococcal infection prophylaxis • Prophylaxis for pneumococcal infection should begin three months after patients undergo hematopoietic stem cell transplantation with penicillin, and prophylaxis should continue for at least one year after the transplant. • In regions that have pneumococcal isolates with intermediate or high-level

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	resistance to penicillin, sulfamethoxazole-trimethoprim will likely be adequate for pneumococcal prophylaxis. Initial empiric antibiotic therapy • Patients with neutropenia should begin empiric treatment with broad spectrum antibiotics at the first sign of infection. • Intravenous antibiotic monotherapy for uncomplicated infections (choose one): o Cefepime. o Imipenem-cilastatin. o Meropenem. o Piperacillin-tazobactam. o Ceftazidime. • Oral antibiotic combination therapy for low-risk patients with uncomplicated infections: o Ciprofloxacin plus amoxicillin-clavulanate. o Moxifloxacin. o Oral antibiotic regimen recommended should not be used if quinolone prophylaxis was used. • Complicated infections (choose based on local antibiotic susceptibility patterns): o Intravenous antibiotic monotherapy is preferred. o Intravenous combination therapy could be considered especially in cases of resistance. Antibacterial agents: empiric gram-positive activity • Vancomycin o Gram-positive organisms with the exception of VRE and a number of rare organisms. o Should not be considered as routine therapy for neutropenia and fever unless certain risk factors present. o Dosing individualized with monitoring of levels; loading dose may be considered. • Daptomycin o Has in vitro activity against VRE but is not FDA-approved for this indication. o Weekly creatine phosphokinase (CPK) to monitor for rhabdomyolysis. o Not indicated for pneumonia due to inactivation by pulmonary surfactant. • Linezolid o Gram-positive organisms including VRE. o Hematologic toxicity (typically with prolonged cases over two weeks) may occur. o Not routinely use in fever and neutropenia, although may impair neutrophil and platelet recovery for extended use. o Treatment option for VRE and MRSA. o Peripheral/optic neuropathy with long-term use. Antibacterial agents: anti-pseudomonal • Cefepime o Broad-spectrum activity against most gram-positive and negative organisms (not active against most anaerobes and *Enterococcus* species). o Use for suspected/proven CNS infection with susceptible organism. o Empiric therapy for neutropenic fever. • Ceftazidime o Relatively poor gram-positive activity (not active against most

Clinical Guideline	Recommendation(s)
	anaerobes and *Enterococcus* species). o Use for suspected/proven CNS infection with susceptible organism. o Empiric therapy for neutropenic fever (resistance among gram-negative rods at some centers). • Imipenem-cilastatin/ meropenem/ doripenem o Broad spectrum activity against most gram-positive, gram-negative, and anaerobic organisms. o Preferred against extended spectrum beta-lactamase and serious *Enterobacter* infections. o Carbapenem-resistant gram-negative rod infections are an increasing problem at a number of centers. o Use for suspected intra-abdominal source. o Meropenem is preferred over imipenem for suspected/proven CNS infection. o Effective in nosocomial pneumonia and intra-abdominal infections. • Piperacillin-tazobactam o Broad spectrum activity against most gram-positive, gram-negative, and anaerobic organisms. o Use for suspected intra-abdominal source. <u>Antibacterial agents: other</u> • Aminoglycosides o Activity primarily against gram-negative organisms. o Often used as empiric therapy in seriously ill or hemodynamically unstable patients. • Ciprofloxacin in combination with amoxicillin-clavulanate o Good activity against gram-negative and atypical organisms. Less active than "respiratory" fluoroquinolones against gram-positive organisms. o Ciprofloxacin alone has no activity against anaerobes. o Avoid for empiric therapy if patient recently treated with fluoroquinolone prophylaxis. • Levofloxacin/ moxifloxacin o Good activity against gram-negative and atypical organisms. o Levofloxacin has no activity against anaerobes. Moxifloxacin has limited activity against Pseudomonas. o Prophylaxis may increase bacterial resistance and superinfection. • Metronidazole o Good activity against anaerobic organisms. • Sulfamethoxazole-trimethoprim o Highly effective as prophylaxis against *Pneumocystis jiroveci* in high-risk patients. o Monitor for myelosuppression, hepatotoxicity, and hyperkalemia.
American Society of Health-System Pharmacists/ Infectious Diseases Society of America/ Surgical Infection Society/ Society for Healthcare Epidemiology of America: **Clinical practice guidelines for antimicrobial prophylaxis in surgery**	<u>Common principles</u> • The optimal time for administration of preoperative doses is within 60 minutes before surgical incision. Some agents, such as fluoroquinolones and vancomycin, require administration over one to two hours; therefore, the administration of these agents should begin within 120 minutes before surgical incision. • The selection of an appropriate antimicrobial agent for a specific patient should take into account the characteristics of the ideal agent, the comparative efficacy of the antimicrobial agent for the procedure, the safety profile, and the patient's medication allergies. • For most procedures, cefazolin is the drug of choice for prophylaxis because it is the most widely studied antimicrobial agent, with proven efficacy. It has a

Clinical Guideline	Recommendation(s)
(2013)[46]	desirable duration of action, spectrum of activity against organisms commonly encountered in surgery, reasonable safety, and low cost. • There is little evidence to suggest that broad-spectrum antimicrobial agents (i.e., agents with broad in vitro antibacterial activity) result in lower rates of postoperative SSI compared with older antimicrobial agents with a narrower spectrum of activity. However, comparative studies are limited by small sample sizes, resulting in difficulty detecting a significant difference between antimicrobial agents. Cardiac procedures • For patients undergoing cardiac procedures, the recommended regimen is a single preincision dose of cefazolin or cefuroxime with appropriate intraoperative redosing. • For patients with serious allergy or adverse reaction to β-lactams, vancomycin or clindamycin may be an acceptable alternative. • Vancomycin should be used for prophylaxis in patients known to be colonized with MRSA. • Mupirocin should be given intranasally to all patients with documented *S. aureus* colonization. Thoracic procedures • In patients undergoing thoracic procedures, a single dose of cefazolin or ampicillin–sulbactam is recommended. • For patients with serious allergy or adverse reaction to β-lactams, vancomycin or clindamycin may be an acceptable alternative. • Vancomycin should be used for prophylaxis in patients known to be colonized with MRSA. Gastroduodenal procedures • Antimicrobial prophylaxis in gastroduodenal procedures should be considered for patients at highest risk for postoperative infections, including risk factors such as increased gastric pH (e.g., patients receiving acid-suppression therapy), gastroduodenal perforation, decreased gastric motility, gastric outlet obstruction, gastric bleeding, morbid obesity, ASA classification of ≥3, and cancer. • A single dose of cefazolin is recommended in procedures during which the lumen of the intestinal tract is entered. A single dose of cefazolin is recommended in clean procedures, such as highly selective vagotomy, and antireflux procedures only in patients at high risk of postoperative infection due to the presence of the above risk factors. • Alternative regimens for patients with β -lactam allergy include clindamycin or vancomycin plus gentamicin, aztreonam, or a fluoroquinolone. • Higher doses of antimicrobials are uniformly recommended in morbidly obese patients undergoing bariatric procedures. Higher doses of antimicrobials should be considered in significantly overweight patients undergoing gastroduodenal and endoscopic procedures. Biliary tract procedures • A single dose of cefazolin should be administered in patients undergoing open biliary tract procedures. • Alternatives include ampicillin–sulbactam and other cephalosporins (cefotetan, cefoxitin, and ceftriaxone). Alternative regimens for patients with β -lactam allergy include clindamycin or vancomycin plus gentamicin, aztreonam, or a fluoroquinolone; or metronidazole plus gentamicin or a fluoroquinolone.

Clinical Guideline	Recommendation(s)

	Appendectomy procedures
	• For uncomplicated appendicitis, the recommended regimen is a single dose of a cephalosporin with anaerobic activity (cefoxitin or cefotetan) or a single dose of a first-generation cephalosporin (cefazolin) plus metronidazole.
	• For β -lactam-allergic patients, alternative regimens include clindamycin plus gentamicin, aztreonam, or a fluoroquinolone; and metronidazole plus gentamicin or a fluoroquinolone (ciprofloxacin or levofloxacin).
	
	Small intestine procedures
	• For small bowel surgery without obstruction, the recommended regimen is a first generation cephalosporin (cefazolin). For small bowel surgery with intestinal obstruction, the recommended regimen is a cephalosporin with anaerobic activity (cefoxitin or cefotetan) or the combination of a first-generation cephalosporin (cefazolin) plus metronidazole.
	• For β -lactam-allergic patients, alternative regimens include clindamycin plus gentamicin, aztreonam, or a fluoroquinolone; and metronidazole plus gentamicin or a fluoroquinolone (ciprofloxacin or levofloxacin).
	
	Hernia repair procedures
	• For hernioplasty and herniorrhaphy, the recommended regimen is a single dose of a first-generation cephalosporin (cefazolin). For patients known to be colonized with MRSA, it is reasonable to add a single preoperative dose of vancomycin to the recommended agent. For β –lactam-allergic patients, alternative regimens include clindamycin and vancomycin.
	
	Colorectal procedures
	• A single dose of second-generation cephalosporin with both aerobic and anaerobic activities (cefoxitin or cefotetan) or cefazolin plus metronidazole is recommended for colon procedures.
	• In institutions where there is increasing resistance to first- and second-generation cephalosporins among gram-negative isolates from SSIs, a single dose of ceftriaxone plus metronidazole is recommended over routine use of carbapenems. An alternative regimen is ampicillin–sulbactam.
	• In most patients, mechanical bowel preparation combined with a combination of oral neomycin sulfate plus oral erythromycin base or oral neomycin sulfate plus oral metronidazole should be given in addition to intravenous prophylaxis. The oral antimicrobial should be given as three doses over approximately 10 hours the afternoon and evening before the operation and after the mechanical bowel preparation.
	• Alternative regimens for patients with β–lactam allergies include (1) clindamycin plus an aminoglycoside, aztreonam, or a fluoroquinolone and (2) metronidazole plus an aminoglycoside or a fluoroquinolone. Metronidazole plus aztreonam is not recommended as an alternative because this combination has no aerobic gram-positive activity.
	
	Head and neck procedures
	• Clean procedures:
	  o Antimicrobial prophylaxis is not required.
	• Clean-contaminated procedures:
	  o Antimicrobial prophylaxis has not been shown to benefit patients undergoing tonsillectomy or functional endoscopic sinus procedures.
	  o The preferred regimens for patients undergoing other clean-contaminated head and neck procedures are (1) cefazolin or cefuroxime plus metronidazole and (2) ampicillin–sulbactam.
	  o Clindamycin is a reasonable alternative in patients with a documented β-lactam allergy. The addition of an aminoglycoside to clindamycin may be

Clinical Guideline	Recommendation(s)
	appropriate when there is an increased likelihood of gram-negative contamination of the surgical site. Neurosurgery procedures • A single dose of cefazolin is recommended for patients undergoing clean neurosurgical procedures, CSF-shunting procedures, or intrathecal pump placement. Clindamycin or vancomycin should be reserved as an alternative agent for patients with a documented β-lactam allergy (vancomycin for MRSA-colonized patients). Cesarean delivery procedures • The recommended regimen for all women undergoing cesarean delivery is a single dose of cefazolin administered before surgical incision. For patients with β-lactam allergies, an alternative regimen is clindamycin plus gentamicin. Hysterectomy procedures • The recommended regimen for women undergoing vaginal or abdominal hysterectomy, using an open or laparoscopic approach, is a single dose of cefazolin. • Cefoxitin, cefotetan, or ampicillin–sulbactam may also be used. Alternative agents for patients with a b-lactam allergy include (1) either clindamycin or vancomycin plus an aminoglycoside, aztreonam, or a fluoroquinolone and (2) metronidazole plus an aminoglycoside or a fluoroquinolone. Ophthalmic procedures • Due to the lack of robust data from trials, specific recommendations cannot be made regarding choice, route, or duration of prophylaxis. • As a general principle, the antimicrobial prophylaxis regimens used in ophthalmic procedures should provide coverage against common ocular pathogens, including *Staphylococcus* species and gram-negative organisms, particularly *Pseudomonas* species. Orthopedic procedures • Antimicrobial prophylaxis is not recommended for patients undergoing clean orthopedic procedures, including knee, hand, and foot procedures, arthroscopy, and other procedures without instrumentation or implantation of foreign materials. • Antimicrobial prophylaxis is recommended for orthopedic spinal procedures with and without instrumentation. The recommended regimen is cefazolin. • The recommended regimen in hip fracture repair or other orthopedic procedures involving internal fixation is cefazolin. Clindamycin and vancomycin should be reserved as alternative agents. • The recommended regimen for patients undergoing total hip, elbow, knee, ankle, or shoulder replacement is cefazolin. Clindamycin and vancomycin should be reserved as alternative agents. Urologic procedures • No antimicrobial prophylaxis is recommended for clean urologic procedures in patients without risk factors for postoperative infections. • Patients with preoperative bacteriuria or UTI should be treated before the procedure, when possible, to reduce the risk of postoperative infection. • For patients undergoing lower urinary tract instrumentation with risk factors for infection, the use of a fluoroquinolone or trimethoprim– sulfamethoxazole (oral or intravenous) or cefazolin (intravenous or intramuscular) is recommended.

Clinical Guideline	Recommendation(s)
	Vascular procedures • The recommended regimen for patients undergoing vascular procedures associated with a higher risk of infection, including implantation of prosthetic material, is cefazolin. Heart, lung, heart-lung, liver, pancreas, and kidney transplantation • Antimicrobial prophylaxis is indicated for all patients undergoing heart transplantation. The recommended regimen is a single dose of cefazolin. Alternatives include vancomycin or clindamycin with or without gentamicin, aztreonam, or a single fluoroquinolone dose. • Adult patients undergoing lung transplantation should receive antimicrobial prophylaxis, because of the high risk of infection. Patients with negative pretransplantation cultures should receive antimicrobial prophylaxis as appropriate for other types of cardiothoracic procedures. The recommended regimen is a single dose of cefazolin. • The recommended agents for patients undergoing liver transplantation are (1) piperacillin–tazobactam and (2) cefotaxime plus ampicillin. The duration of prophylaxis should be restricted to 24 hours or less. • The recommended regimen for patients undergoing pancreas or SPK transplantation is cefazolin. • The recommended agent for patients undergoing kidney transplantation is cefazolin. Plastic surgery and breast procedures • Antimicrobial prophylaxis is not recommended for most clean procedures in patients without additional postoperative infection risk factors. • Although no studies have demonstrated antimicrobial efficacy in these procedures, expert opinion recommends that patients with risk factors undergoing clean plastic procedures receive antimicrobial prophylaxis. The recommendation for clean-contaminated procedures, breast cancer procedures, and clean procedures with other risk factors is a single dose of cefazolin or ampicillin–sulbactam.
American College of Gastroenterology: **Practice Guidelines: Hepatic Encephalopathy (2001)**[47]	Bowel cleansing • Bowel cleansing is a standard therapeutic measure in hepatic encephalopathy. • 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. Nonabsorbable disaccharides • 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). Antibiotics • 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 g/day) should be given for one to two weeks. • For chronic encephalopathy, neomycin (1 to 2 g/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 miscellaneous antibacterials are noted in Tables 5 to 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 5. FDA-Approved Indications for the Single Entity Antibacterials, Miscellaneous (Drugs B-L)[1-11]

Indication	Bacitracin	Clindamycin	Colistimethate	Dalbavancin	Daptomycin	Lincomycin
Dermatological Infections						
Skin and skin-structure infections		✔ *§		✔	✔	
Genitourinary Infections						
Endometritis		✔ *§				
Gynecologic infections		✔ *§				
Nongonococcal tubo-ovarian abscess		✔ *§				
Pelvic cellulitis		✔ *§				
Postsurgical vaginal cuff infection		✔ *§				
Respiratory Infections						
Empyema	✔	✔ *§				
Lung abscess		✔ *§				
Pneumonia	✔	✔ §				
Pneumonitis		✔ *				
Respiratory tract infection		✔ *§				
Miscellaneous Infections						
Bone and/or joint infections		✔ §				
Endocarditis					✔	
Intra-abdominal infections		✔ *§				
Septicemia		✔ *			✔	
Serious infections due to susceptible organisms			✔			✔

§Injection formulation.
*Oral formulation.

Table 6. FDA-Approved Indications for the Single Entity Antibacterials, Miscellaneous (Drugs L-V)[1-11]

Indication	Linezolid	Oritavancin	Polymyxin B Sulfate	Rifaximin	Tedizolid	Telavancin	Vancomycin
Central Nervous System Infections							
Meningeal infections			✔				
Dermatological Infections							
Diabetic foot infections	✔						
Skin and skin-structure infections	✔	✔			✔	✔	
Gastrointestinal Infections							

Indication	Linezolid	Oritavancin	Polymyxin B Sulfate	Rifaximin	Tedizolid	Telavancin	Vancomycin
Enterocolitis							✔ *
Pseudomembranous colitis due to *Clostridium difficile*							✔ *
Travelers' diarrhea				✔			
Urinary tract infections			✔				
Respiratory Infections							
Hospital-acquired and ventilator-associated bacterial pneumonia						✔	
Pneumonia (community-acquired)	✔						
Pneumonia (nosocomial)	✔						
Respiratory tract infections (lower)							✔ §
Miscellaneous Infections							
Endocarditis							✔ §
Hepatic encephalopathy				✔			
Septicemia			✔				
Serious infections due to susceptible organisms			✔				✔ §
Vancomycin-resistant *Enterococcus faecium* infections	✔						

§Injection formulation
*Oral formulation

Table 7. FDA-Approved Indications for the Combination Antibacterials, Miscellaneous[12-14]

Indication	Bismuth, Metronidazole and Tetracycline	Quinupristin and Dalfopristin
Central Nervous System Infections		
Meningeal infections	✔	
Dermatological Infections		
Skin and skin-structure infections		✔
Gastrointestinal Infections		
Treatment of patients with *Helicobacter pylori* infection and duodenal ulcer disease (active or history within the past five years) to eradicate *Helicobacter pylori* (in combination with omeprazole)	✔	
Urinary tract infections	✔	
Miscellaneous Infections		
Septicemia	✔	
Serious infections due to susceptible organisms	✔	

IV. Pharmacokinetics

The pharmacokinetic parameters of the single entity agents miscellaneous antibacterials and the components of the combination products are listed in Table 8.

Table 8. Pharmacokinetic Parameters of the Antibacterials, Miscellaneous[1-14]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Bacitracin	Minimal	Not reported	Not reported	Renal (10 to 40)	1.5
Bismuth	Not reported	>90	Not reported	Renal	>120
Clindamycin	Oral: 90	60 to 95	Liver	Renal (10) Feces (4)	2 to 4
Colistimethate	Not reported	Not reported	Not reported	Not reported	2 to 3
Dalbavancin	Not reported	93 to 99	Not reported	Renal (33) Feces (20)	204
Dalfopristin	Not reported	50 to 56	Not reported	Renal (20) Feces (75)	0.4 to 1.0
Daptomycin	Not reported	83 to 93	Not reported	Renal (78.0) Feces (5.7)	7.7 to 8.3
Lincomycin	Not reported	28 to 86	Liver	Renal (1.8 to 24.8) Feces (30 to 40)	5.4
Linezolid	100	31	Liver	Renal (30) Feces (9)	Oral: 4.26 to 5.40 Intravenous: 4.4 to 4.8
Metronidazole	Well absorbed	<20	Liver	Renal (60 to 80) Feces (6 to 15)	8
Oritavancin	Not reported	85	Not metabolized	Renal/Feces	245
Polymyxin B sulfate	Not reported	79 to 92	Not reported	Renal (0 to 4)	6
Quinupristin	Not reported	23 to 32	Not reported	Renal (20) Feces (75)	0.6 to 1.0
Rifaximin	Not reported	62 to 67.5	Not reported	Renal (<1.00) Feces (96.62)	6
Tedizolid	91	70 to 90	Not reported	Renal (18) Feces (82)	12
Telavancin	Not reported	90	Not reported	Renal (64 to 76)	6 to 8
Tetracycline	Readily absorbed	65	Liver	Renal/Feces	8 to 11
Vancomycin	Oral: negligible	55	Not reported	Intravenous: Renal (40 to 100)	4 to 6

V. Drug Interactions

Major drug interactions with the miscellaneous antibacterials are listed in Table 9.

Table 9. Major Drug Interactions with the Antibacterials, Miscellaneous[2]

Generic Name(s)	Interaction	Mechanism
Bacitracin	Non-depolarizing muscle relaxants	Neuromuscular blockage may be enhanced. The polypeptide antibiotics may affect pre-synaptic and post-synaptic myoneural function and act synergistically with nondepolarizing muscle relaxants.
Colistimethate	Aminoglycosides	Concurrent use of colistimethate and aminoglycosides may result in

Generic Name(s)	Interaction	Mechanism
		respiratory depression.
Daptomycin	Statins	Coadministration of daptomycin and statins may increase the risk of rhabdomyolysis. The mechanism for this interaction is currently unknown.
Lincomycin	Aluminum salts	Gastrointestinal absorption is decreased for lincomycin and delayed for clindamycin when they are administered with kaolin-pectin antidiarrheals.
Lincomycin	Nondepolarizing muscle relaxants	The lincosamides may enhance the actions of the nondepolarizing muscle relaxants, possibly contributing to profound and severe respiratory depression.
Linezolid	Anorexiants	Toxicity of anorexiants may be increased by coadministration of linezolid. Headache, hyperpyrexia, elevated blood pressure, and bradycardia may occur. Anorexiants can liberate large quantities of intraneuronal norepinephrine that have accumulated during treatment with linezolid.
Linezolid	Norepinephrine reuptake inhibitors	Toxic effects may be increased with concurrent administration of norepinephrine reuptake inhibitors and linezolid. Serious and sometimes fatal reactions have occurred. Pharmacologic effects of norepinephrine reuptake inhibitors and linezolid may be additive.
Linezolid	Serotonin–norepinephrine reuptake inhibitors	Linezolid and serotonin–norepinephrine reuptake inhibitors may exert additive pharmacologic activity potentially leading to severe central nervous system toxicity.
Linezolid	Serotonin reuptake blockers	Serotonin reuptake blockers and linezolid increase central nervous system serotonin activity, perhaps synergistically. This may cause central nervous system toxicity.
Linezolid	Sympathomimetics	Pharmacologic effects of sympathomimetics may be increased by linezolid. Headache, hyperpyrexia, and hypertension may occur. The mechanism differs depending on the type of sympathomimetics involved.
Linezolid	Tetracyclic antidepressants	The mechanism is unknown. Tetracyclic antidepressants are thought to act by blocking reuptake of neurotransmitters, including norepinephrine. The concomitant use of monoamine oxidase inhibitors could potentiate sympathomimetic activity.
Linezolid	Tricyclic antidepressants	Severe, sometimes lethal, toxicity may occur. The mechanism for this interaction in currently unknown.
Linezolid	Triptans	Inhibition of monoamine oxidase by linezolid may decrease the metabolic elimination of triptans. Other mechanisms may exist. The potential for development of serotonin syndrome is a possibility.
Linezolid	Bupropion	Use of bupropion with linezolid is contraindicated due to the potential for hypertensive crisis. The inhibitory effects of bupropion on norepinephrine and dopamine reuptake may be enhanced by concomitant use of linezolid.
Linezolid	Buspirone	The risk of linezolid-induced hypertension may be increased by coadministration of buspirone. The mechanism for this interaction is currently unknown.
Linezolid	Cyclobenzaprine	Cyclobenzaprine is a tricyclic amine structurally related to tricyclic antidepressants. Though the mechanism of action is unknown, it is likely that adrenergic activity is enhanced with concurrent administration.
Linezolid	Dextromethorphan	A severe and potentially fatal toxic reaction may occur when dextromethorphan is administered to patients receiving linezolid. The mechanism for this interaction is currently unknown.
Linezolid	Levodopa	Linezolid may decrease the enzymatic degradation of dopamine and norepinephrine formed from levodopa.

Generic Name(s)	Interaction	Mechanism
Linezolid	Meperidine	A severe and potentially fatal reaction may occur shortly after administering meperidine to patients receiving linezolid. The excitatory interaction may be due to additive increases of central nervous system serotonin activity. The depressive form may result from inhibition of hepatic metabolism of meperidine.
Linezolid	Methylphenidate	Pharmacologic effects of methylphenidate may be increased by linezolid. Headache, gastrointestinal symptoms and hypertension may occur.
Linezolid	Nefazodone	Unexpected toxicity may occur in some patients. The mechanism for this interaction is currently unknown.
Linezolid	Tramadol	A severe reaction potentially involving the respiratory, cardiovascular, and central nervous systems may occur shortly after administering tramadol to patients receiving linezolid. The seizure threshold may also be reduced.
Linezolid	Catechol O-methyltransferase inhibitors	The combination of linezolid with Catechol O-methyltransferase inhibitors may result in inhibition of the majority of pathways responsible for normal catecholamine metabolism.
Linezolid	Monoamine oxidase inhibitors	Adverse effects may be increased with concurrent administration of linezolid and monoamine oxidase inhibitors.
Linezolid	Narcotic analgesics	A severe reaction potentially involving the respiratory, cardiac and central nervous systems may occur shortly after administering narcotic analgesics to patients receiving linezolid.
Linezolid	Apraclonidine	Hypertension may be potentiated. The mechanism is unknown.
Linezolid	Sibutramine	Use of high-dose sibutramine with linezolid has been reported by the manufacturer of sibutramine to increase the potential risk for serotonin syndrome.
Linezolid	Tryptophan	The combination of linezolid and tryptophan may produce severe unexpected toxicity in some patients.
Linezolid	Trazodone	Linezolid and trazodone may increase central nervous system serotonin activity, perhaps synergistically.
Metronidazole	Anticoagulants	The anticoagulant effect of warfarin may be enhanced and hemorrhage could occur due to decreased metabolism of warfarin by metronidazole.
Metronidazole	Busulfan	Busulfan trough concentrations may be elevated, increasing risk of serious toxicity. Avoid coadministration of busulfan and metronidazole.
Metronidazole	Disulfiram	Acute toxic psychosis may occur during the coadministration of metronidazole and disulfiram.
Metronidazole	Human immunodeficiency virus protease inhibitors	Coadministration of metronidazole and human immunodeficiency virus protease inhibitors may cause an alcohol intolerance reaction. The alcohol and aldehyde dehydrogenase-mediated metabolic pathway of propylene glycol or alcohol, an excipient in human immunodeficiency virus protease inhibitors, may be blocked by metronidazole.
Oritavancin	Heparin	Concurrent use of heparin and oritavancin may result in falsely elevated aPTT test results.
Oritavancin	Warfarin	Concurrent use of oritavancin and warfarin may result in increased warfarin exposure.
Polymyxin B Sulfate	Non-depolarizing muscle relaxants	Neuromuscular blockage may be enhanced. The polypeptide antibiotics may affect pre-synaptic and post-synaptic myoneural function and act synergistically with nondepolarizing muscle relaxants.
Quinupristin-dalfopristin	Macrolide immuno-suppressive	Pharmacologic and toxic effects of macrolide immunosuppressives may be increased by quinupristin-dalfopristin. Inhibition of cytochrome P450 3A4 isoenzymes by quinupristin-dalfopristin may

Generic Name(s)	Interaction	Mechanism
		decrease the metabolic elimination of macrolide immunosuppressives.
Quinupristin-dalfopristin	Statins	Pharmacologic and toxic effects of statins may be increased by quinupristin-dalfopristin. Inhibition of cytochrome P450 3A4 isoenzymes by quinupristin-dalfopristin may decrease the metabolic elimination of statins.
Quinupristin-dalfopristin	Vinca alkaloids	Pharmacologic and toxic effects of vinca alkaloids may be increased by quinupristin-dalfopristin. Inhibition of cytochrome P450 3A4 isoenzymes by quinupristin-dalfopristin may decrease the metabolic elimination of vinca alkaloids.
Quinupristin-dalfopristin	Haloperidol	Concurrent use of haloperidol and quinupristin/dalfopristin may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
Quinupristin-dalfopristin	Astemizole	Concurrent use of astemizole and quinupristin/dalfopristin may result in an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, cardiac arrest).
Telavancin	5-HT_3 receptor antagonists	Concurrent use of 5-HT_3 receptor antagonists and telavancin may result in an increased risk of QT interval prolongation.
Telavancin	Azole antifungals	Concurrent use of telavancin and azole antifungals may result in increased risk of QT interval prolongation.
Telavancin	Class I and III antiarrhythmics	Concurrent use of antiarrhythmics and telavancin may result in an increased risk of QT interval prolongation.
Telavancin	Gonadotropin releasing hormone agonists	Concurrent use may result in increased risk of QT-interval prolongation.
Telavancin	Tyrosine kinase inhibitors	Concurrent use of tyrosine kinase inhibitors and telavancin may result in an increased risk of QT interval prolongation.
Telavancin	Quinolones	Concurrent use of quinolones and telavancin may result in an increased risk of QT interval prolongation.
Telavancin	Phenothiazines	Concurrent use of telavancin and phenothiazines may result in an increased risk of QT interval prolongation.
Telavancin	Tricyclic antidepressants	Concurrent use of tricyclic antidepressants and telavancin may result in an increased risk of QT interval prolongation.
Telavancin	Alfuzosin	Concurrent use of alfuzosin and telavancin may result in an increased risk of QT interval prolongation.
Telavancin	Apomorphine	Concurrent use of apomorphine and telavancin may result in an increased risk of QT interval prolongation.
Telavancin	Asenapine	Concurrent use of asenapine and telavancin may result in an increased risk of QT interval prolongation.
Telavancin	Astemizole	Concurrent use of astemizole and telavancin may result in increased risk of QT interval prolongation.
Telavancin	Clozapine	Concurrent use of clozapine and telavancin may result in an increased risk of QT interval prolongation.
Telavancin	Erythromycin	Concurrent use of erythromycin and telavancin may result in an increased risk of QT interval prolongation.
Telavancin	Fingolimod	Concurrent use of fingolimod and telavancin may result in an increased risk of QT interval prolongation.
Telavancin	Heparin	Concurrent use of heparin and telavancin may result in artificial prolongation of aPTT test results.
Telavancin	Lopinavir	Concurrent use of lopinavir/ritonavir and telavancin may result in an increased risk of QT interval prolongation.
Telavancin	Lumefantrine	Concurrent use of artemether/lumefantrine and telavancin may result in an increased risk of QT interval prolongation.
Telavancin	Mefloquine	Concurrent use of mefloquine and telavancin may result in an increased risk of QT interval prolongation.

Generic Name(s)	Interaction	Mechanism
Telavancin	Methadone	Concurrent use of methadone and telavancin may result in increased risk of QT interval prolongation.
Telavancin	Mifepristone	Concurrent use of mifepristone and telavancin may result in an increased risk of QT interval prolongation.
Telavancin	Octreotide	Concurrent use of octreotide and telavancin may result in an increased risk of QT interval prolongation.
Telavancin	Quinine	Concurrent use of quinine and telavancin may result in an increased risk of QT interval prolongation.
Telavancin	Salmeterol	Concurrent use of salmeterol and telavancin may result in an increased risk of QT interval prolongation.
Telavancin	Solifenacin	Concurrent use of solifenacin and telavancin may result in an increased risk of QT interval prolongation.
Telavancin	Telithromycin	Concurrent use of telavancin and telithromycin may result in increased risk of QT interval prolongation.
Telavancin	Tetrabenazine	Concurrent use of telavancin and tetrabenazine may result in an increased risk of QT interval prolongation.
Telavancin	Toremifene	Concurrent use of telavancin and toremifene may result in an increased risk of QT interval prolongation.
Tetracyclines	Acitretin	Concurrent use of acitretin and tetracyclines may result in an increased risk of pseudotumor cerebri (benign intracranial hypertension).
Tetracyclines	Digoxin	Co-administration may result in increased serum levels of digoxin in a small subset of patients (10%). Monitor digoxin levels and signs of toxicity.
Tetracyclines	Methoxyflurane	Co-administration may enhance the risk for renal toxicity; deaths have been reported. Do not co-administer. If possible seek alternative agents.
Tetracyclines	Penicillins	The bacteriostatic action of tetracyclines may interfere with the bactericidal activity of penicillins. Consider avoiding this combination if at all possible.
Tetracyclines	Retinoids	Acitretin may increase the risk of pseudotumor cerebri. An additive adverse effect is thought to be responsible. Avoid concomitant and subsequent monotherapy usage of these agents.
Vancomycin	Piperacillin-Tazobactam	Concurrent use of piperacillin-tazobactam and vancomycin may result in increased risk of acute kidney injury.
Vancomycin	Amikacin	Concurrent use of amikacin and vancomycin may result in additive ototoxicity and/or nephrotoxicity.
Vancomycin	Gentamicin	Concurrent use of gentamicin and vancomycin may result in nephrotoxicity.
Vancomycin	Tobramycin	Concurrent use of tobramycin and vancomycin may result in additive ototoxicity and/or nephrotoxicity.

VI. Adverse Drug Events

The most common adverse drug events reported with the miscellaneous antibacterials are listed in Tables 10 to 11. The boxed warnings for bacitracin, clindamycin, lincomycin, metronidazole, polymyxin B sulfate, and telavancin are listed in Tables 12 to 17.

Table 10. Adverse Drug Events (%) Reported with the Single Entity Antibacterials, Miscellaneous[1-14]

Adverse Events	Baci-tracin	Clinda-mycin	Colistim-ethate	Dalba-vancin	Dapto-mycin	Linco-mycin	Linez-olid	Orita-vancin	Polymyxin B Sulfate	Rifax-imin	Tedi-zolid	Tela-vancin	Vanco-mycin
Cardiovascular													
Atrial fibrillation	-	-	-	-	<1	-	-	-	-	-	-	-	-
Atrial flutter	-	-	-	-	<1	-	-	-	-	-	-	-	-
Cardiac arrest	-	✔	-	-	<1	-	-	-	-	-	-	-	-
Cardiopulmonary arrest	-	✔	-	-	-	✔	-	-	-	-	-	-	-
Cerebral ischemia	-	-	-	-	-	-	-	-	-	-	-	-	-
Chest pain	-	-	-	-	7	-	-	-	-	>2 to 5	-	-	-
Edema	✔	-	-	-	7	-	✔	<2	-	15	-	-	-
Flattening T-wave	-	-	-	-	-	-	-	-	-	-	-	-	-
Hypertension	-	-	-	-	1 to 6	-	<1	-	-	-	<2	-	-
Hypotension	✔	✔	-	-	2 to 5	✔	-	-	-	>2 to 5	-	-	✔
Myocardial infarction	-	-	-	-	-	-	-	-	-	-	-	-	-
Palpitation	-	-	-	-	-	-	-	-	-	-	<2	-	-
Tachycardia	-	-	-	-	-	-	-	<1	-	-	<2	-	-
Central Nervous System													
Anxiety	-	-	-	-	5	-	-	-	-	-	-	-	-
Ataxia	-	-	-	-	-	-	-	-	✔	-	-	-	-
Depression	-	-	-	-	-	-	-	-	-	7	-	-	-
Dizziness	-	-	✔	<2	2 to 6	✔	<2	<1	✔	13	2	6	✔
Fatigue	-	-	-	-	<1	-	-	-	-	12	-	-	-
Fever	✔	-	✔	-	2 to 7	-	2	-	-	6	-	-	✔
Hallucinations	-	-	-	-	<1	-	-	-	-	-	-	-	-
Headache	-	-	✔	5	5 to 7	-	1 to 11	<1	-	10	6	11	-
Incoordination	-	-	-	-	-	-	-	-	-	-	-	-	-
Insomnia	-	-	-	-	5 to 9	-	3	-	-	13	<2	13	-
Irritability	-	-	-	-	-	-	-	-	✔	-	-	-	-
Mental status change	-	-	-	-	<1	-	-	-	-	-	-	-	-
Paresthesia	-	-	✔	-	<1	-	-	-	✔	-	<2	-	-

Adverse Events	Baci-tracin	Clinda-mycin	Colistim-ethate	Dalba-vancin	Dapto-mycin	Linco-mycin	Linez-olid	Orita-vancin	Polymyxin B Sulfate	Rifax-imin	Tedi-zolid	Tela-vancin	Vanco-mycin
Peripheral neuropathy	-	-	-	-	-	-	<1	-	-	-	<2	-	-
Pseudotumor cerebri	-	-	-	-	-	-	-	-	-	-	-	-	-
Seizure	-	-	✔	-	-	-	<1	-	-	-	-	5	-
Somnolence	-	-	-	-	-	-	-	-	-	-	-	-	-
Syncope	-	-	-	-	-	-	-	-	-	<2	-	-	-
Tingling of extremities	✔	-	✔	-	-	-	-	-	-	-	-	-	-
Tinnitus	-	-	-	-	<1	✔	-	-	-	<2	-	-	✔
Vertigo	-	-	-	-	-	✔	-	-	-	-	-	-	-
Visual disturbances	-	-	-	-	-	-	-	-	-	-	<2	-	-
Weakness	-	-	✔	-	-	-	-	-	-	-	-	-	-
Dermatologic													
Dermatitis	-	-	-	-	-	-	-	-	-	-	<2	-	-
Eczema	-	-	-	-	<1	-	-	-	-	-	-	-	-
Erythema	-	-	-	-	5	-	-	-	-	-	-	-	-
Erythema multiforme	-	✔	-	-	-	✔	-	<2	-	-	-	-	-
Exfoliative dermatitis	-	✔	-	-	-	✔	-	-	-	-	-	-	-
Flushing	-	-	-	<2	<1	-	-	-	-	-	<2	-	-
Heat rash	-	-	-	-	<1	-	-	-	-	-	-	-	-
Petechia	-	-	-	<2	-	-	-	-	-	-	-	-	-
Photosensitivity	-	-	-	-	-	-	-	-	-	<2	-	-	-
Pruritus	✔	✔	✔	2	3 to 6	✔	<1	<2	-	9	<2	36	-
Rash	✔	✔	✔	3	4 to 7	✔	2	<2	✔	5	-	4	✔
Stevens-Johnson syndrome	-	✔	-	-	-	✔	<1	-	-	-	-	-	✔
Urticaria	-	✔	✔	<2	-	✔	-	<2	-	-	<2	-	✔
Gastrointestinal													
Abdominal distention	-	-	-	-	<1	-	-	-	-	<2	-	-	-
Abdominal pain	-	✔	-	<2	6	✔	✔	-	-	2 to 9	-	2	-
Anal discomfort	-	-	-	-	-	-	-	-	-	-	-	-	-
Anorexia	✔	-	-	-	-	-	-	-	-	2 to 5	-	-	-
Appetite decreased	✔	-	-	-	<1	-	-	-	-	-	-	3	-
Black stool	-	-	-	-	-	-	-	-	-	<2	-	-	-

Adverse Events	Baci-tracin	Clinda-mycin	Colistim-ethate	Dalba-vancin	Dapto-mycin	Linco-mycin	Linez-olid	Orita-vancin	Polymyxin B Sulfate	Rifax-imin	Tedi-zolid	Tela-vancin	Vanco-mycin
Colitis	-	✔	-	-	-	✔	-	-	-	-	-	-	-
Constipation	-	-	-	-	6 to 11	-	2	-	-	3	-	-	-
Diarrhea	✔	✔	-	4	5 to 12	✔	3 to 11	<1	-	2 to 6	4	7	-
Dry mouth	-	-	-	-	<1	-	-	-	-	2 to 5	-	-	-
Duodenal ulcer	-	-	-	-	-	-	-	-	-	-	-	-	-
Dyspepsia	-	-	-	-	1 to 4	-	<1	-	-	-	-	-	-
Dysphagia	-	-	-	-	<1	-	-	-	-	-	-	-	-
Enamel hypoplasia	-	-	-	-	-	-	-	-	-	-	-	-	-
Enterocolitis	-	-	-	-	-	✔	-	-	-	-	-	-	-
Epigastric distress	-	-	-	-	<1	-	-	-	-	-	-	-	-
Esophagitis	-	✔	-	-	-	-	-	-	-	-	-	-	-
Flatulence	-	-	-	-	<1	-	-	-	-	11	-	-	-
Gastrointestinal hemorrhage	-	-	-	<2	2	-	-	-	-	-	-	-	-
Gastrointestinal upset	✔	-	✔	-	✔	-	-	-	-	<2	-	-	-
Gingival pain	-	-	-	-	<1	-	-	-	-	-	-	-	-
Glossitis	-	-	-	-	-	✔	-	-	-	-	-	-	-
Hematochezia	-	-	-	<2	-	-	-	-	-	-	-	-	-
Loose stools	-	-	-	-	4	-	-	-	-	-	-	-	-
Melena	-	-	-	<2	-	-	-	-	-	-	-	-	-
Nausea	✔	✔	-	6	6 to 10	✔	3 to 10	<1	-	14	8	27	✔
Oral candidiasis	-	-	-	<2	-	-	-	-	-	-	<2	-	-
Oral moniliasis	-	-	-	-	-	-	<1	-	-	-	-	-	-
Pseudomembranous colitis	-	✔	-	<2	-	✔	-	-	-	-	<2	-	✔
Rectal hemorrhage	-	-	-	-	-	-	-	-	-	-	-	-	-
Rectal itching/burning	✔	-	-	-	-	✔	-	-	-	-	-	-	-
Stomatitis	-	-	-	-	<1	✔	-	-	-	-	-	-	-
Stool abnormality	-	-	-	-	-	-	-	-	-	-	-	-	-
Taste alteration	-	✔	-	-	<1	-	1	-	-	<2	-	-	-
Tooth disorder	-	-	-	-	-	-	-	-	-	-	-	-	-
Tongue discoloration	-	-	-	-	-	-	✔	-	-	-	-	33	✔
Vomiting	✔	✔	-	3	3 to 12	✔	1 to 4	<1	-	2	3	14	-
Genitourinary													

Adverse Events	Baci-tracin	Clinda-mycin	Colistim-ethate	Dalba-vancin	Dapto-mycin	Linco-mycin	Linez-olid	Orita-vancin	Polymyxin B Sulfate	Rifax-imin	Tedi-zolid	Tela-vancin	Vanco-mycin
Abnormal kidney function	✔	✔	✔	-	<1	✔	-	-	✔	<2	-	-	✔
Acute kidney failure	-	-	-	-	2 to 3	-	-	-	✔	-	-	-	✔
Urinary tract infections	-	-	-	-	2 to 7	-	-	-	-	-	-	-	-
Vaginitis	-	✔	-	-	-	✔	-	-	-	-	-	-	-
Vulvovaginal infection	-	-	-	<2	-	-	-	-	-	-	<2	-	-
Hematologic													
Agranulocytosis	-	✔	-	-	-	✔	-	-	-	-	-	-	✔
Anemia	-	-	-	<2	2 to 13	✔	✔	<2	-	8	<2	-	-
Bone marrow toxicity	✔	-	-	-	-	✔	-	-	-	-	-	-	-
Eosinophilia	-	✔	-	<2	2	-	✔	<2	✔	-	-	-	✔
Hematoma	-	-	-	✔	-	-	-	-	-	-	-	-	-
Leukocytosis	-	-	-	-	<1	-	-	-	✔	-	-	-	-
Leukopenia	-	✔	-	<2	-	✔	1 to 2	-	-	-	<2	-	-
Neutropenia	-	✔	-	<2	-	✔	<1	-	-	<2	-	-	✔
Pancytopenia	-	-	-	-	-	✔	<1	-	-	-	-	-	-
Thrombocythemia	-	-	-	<2	<1	-	-	-	-	-	-	-	-
Thrombocytopenia	-	✔	-	<2	<1	✔	1 to 10	-	-	-	-	7	✔
Thrombocytosis	-	-	-	-	<1	-	-	-	-	-	-	-	-
Hepatic													
Hepatotoxicity	-	-	-	<2	-	-	-	-	-	-	-	-	-
Jaundice	-	✔	-	-	<1	✔	-	-	-	-	-	-	-
Laboratory Test Abnormalities													
Abnormal liver function tests	-	✔	-	<2	1 to 3	✔	1	-	-	-	<2	-	-
Alanine aminotransferase increased	-	-	-	✔	2 to 3	2 to 10	-	<1	-	-	-	-	-
Alkaline phosphatase increased	-	-	-	<2	2	1 to 4	-	-	-	-	-	-	-
Aspartate aminotransferase increased	-	-	-	-	2 to 3	2 to 5	-	<1	-	<2	-	-	-

Adverse Events	Baci-tracin	Clinda-mycin	Colistim-ethate	Dalba-vancin	Dapto-mycin	Linco-mycin	Linez-olid	Orita-vancin	Polymyxin B Sulfate	Rifax-imin	Tedi-zolid	Tela-vancin	Vanco-mycin
Blood urea nitrogen increased	-	-	✔	-	-	-	<2	-	-	-	-	-	✔
Electrolyte disturbance	-	-	-	-	<6	-	-	-	-	-	-	-	-
Hemoglobin decreased	-	-	-	-	-	-	-	-	-	-	3	-	-
Hyperbilirubinemia	-	-	-	-	-	<1	-	<2	-	-	-	-	-
Hyperuricemia	-	-	-	-	-	-	-	<2	-	-	-	-	-
Hypoglycemia	-	-	-	<2	-	-	-	<2	-	-	-	-	-
International normalized ratio increased	-	-	-	<2	2	-	-	-	-	-	-	-	-
Phosphorus increased	-	-	-	-	2	-	-	-	-	-	-	-	-
Platelet count decreased	-	-	-	-	-	-	-	-	-	-	2	-	-
Prothrombin time prolonged	-	-	-	-	<1	-	-	✔	-	-	-	-	-
Serum creatinine increased	-	-	✔	-	3 to 7	-	<1	-	-	-	-	8	✔
Serum lactate dehydrogenase increased	-	-	-	-	<1	-	-	-	-	-	-	-	-
Musculoskeletal													
Arthralgia	-	-	-	-	1 to 3	-	-	-	-	6	-	-	-
Back pain	-	-	-	-	7	-	-	-	-	-	-	-	-
Muscle cramps/weakness	-	-	-	-	<1	-	-	-	-	-	-	-	-
Myalgia	-	-	-	-	<1	-	-	<2	-	2 to 5	-	-	-
Tendonitis	-	-	-	-	-	-	-	-	-	-	-	-	-
Tenosynovitis	-	-	-	-	-	-	-	<2	-	-	-	-	-
Weakness	-	-	-	-	5	-	-	-	-	<2	-	-	-
Respiratory													
Apnea	-	-	✔	-	-	-	✔	-	-	-	-	-	-
Bronchospasm	-	-	-	<2	-	-	-	<2	-	-	-	-	-
Cough	-	-	-	-	3	-	-	-	-	-	-	-	-
Dyspnea	-	-	-	-	2 to 3	-	✔	-	✔	6	-	8	-

Adverse Events	Baci-tracin	Clinda-mycin	Colistim-ethate	Dalba-vancin	Dapto-mycin	Linco-mycin	Linez-olid	Orita-vancin	Polymyxin B Sulfate	Rifax-imin	Tedi-zolid	Tela-vancin	Vanco-mycin
Pharyngitis	-	-	-	-	-	-	-	-	-	<2	-	-	-
Pharyngolaryngeal pain	-	-	-	-	8	-	-	-	-	<2	-	-	-
Pleural effusion	-	-	-	-	6	-	-	-	-	-	-	-	-
Pneumonia	-	-	-	-	3	-	-	-	-	2 to 5	-	-	-
Polyarthritis	-	✔	-	-	-	-	-	-	-	-	-	-	-
Respiratory arrest	✔	-	✔	-	-	-	-	-	✔	-	-	-	-
Rhinitis	-	-	-	-	-	-	-	-	-	2 to 5	-	-	-
Upper respiratory tract infection	-	-	-	-	-	-	-	-	-	2 to 5	-	-	-
Wheezing	-	-	-	-	-	-	-	<2	-	-	-	-	-
Other													
Anaphylaxis	✔	✔	-	<2	<1	✔	<1	-	✔	<2	-	-	-
Angioedema	-	-	-	-	-	✔	-	<2	-	-	-	-	-
Angioneurotic edema	-	-	-	-	-	-	-	-	-	<2	-	-	-
Asthenia	-	-	-	-	5	-	-	-	-	-	-	-	-
Ataxia	-	-	✔	-	-	-	-	-	✔	-	-	-	-
Bacteremia	-	-	-	-	5	-	-	-	-	-	-	-	-
Blurred vision	-	-	-	-	<1	-	-	-	✔	-	<2	-	-
Conjunctivitis	-	-	-	-	-	-	-	-	-	-	-	-	-
Dyskinesia	-	-	-	-	<1	-	-	-	-	-	-	-	-
Extravasation	-	-	-	-	-	-	-	<2	-	-	-	-	-
Flu syndrome	-	-	-	-	-	-	-	-	-	2 to 5	-	-	-
Fungal infections	-	-	-	-	2 to 3	-	1 to 2	-	-	-	-	-	-
Hypoesthesia oral	-	-	-	-	<1	-	-	-	-	2 to 5	-	-	-
Injection site reactions	-	✔	-	<2	3 to 6	-	-	<1	-	-	-	3	-
Jitteriness	-	-	-	-	<1	-	-	-	-	-	-	-	-
Limb abscess	-	-	-	-	-	-	-	≤4	-	-	-	-	-
Limb pain	-	-	-	-	2 to 9	-	-	-	-	-	-	-	-
Lymphadenopathy	-	-	-	-	<1	-	-	-	-	-	-	-	-
Neoplasm	-	-	-	-	-	-	-	-	-	-	-	-	-
Neuromuscular blockade	✔	-	-	-	-	-	-	-	-	-	-	-	-
Osteomyelitis	-	-	-	-	6	-	-	<2	-	-	-	-	-
Pain	✔	-	-	-	-	-	-	-	-	2 to 5	-	-	-

Adverse Events	Baci-tracin	Clinda-mycin	Colistim-ethate	Dalba-vancin	Dapto-mycin	Linco-mycin	Linez-olid	Orita-vancin	Polymyxin B Sulfate	Rifax-imin	Tedi-zolid	Tela-vancin	Vanco-mycin
Pain at injection site	✔	✔	-	-	-	✔	-	-	-	-	-	4	✔
Phlebitis	-	-	-	<2	-	-	-	<1	-	-	-	-	-
Redman syndrome	-	-	-	-	-	-	-	-	-	-	-	-	✔
Rigors	-	-	-	-	<1	-	-	-	-	-	-	4	-
Sepsis	-	-	-	-	5	-	✔	-	-	-	-	-	-
Serum sickness-like reaction	-	-	-	-	-	✔	-	-	-	-	-	-	-
Sinusitis	-	-	-	-	-	-	-	-	-	-	-	-	-
Slurred speech	-	-	✔	-	-	-	-	-	-	-	-	-	-
Sweating increased	✔	-	-	-	5	-	-	-	-	-	-	-	-
Thrombophlebitis	-	✔	-	-	-	-	-	-	-	-	-	-	✔

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

Table 11. Adverse Drug Events (%) Reported with the Combination Antibacterials, Miscellaneous[1-3,12-14]

Adverse Events	Bismuth, Metronidazole and Tetracycline	Quinupristin and Dalfopristin
Cardiovascular		
Cardiac arrest	-	<1
Chest pain	1	-
Edema	-	17 to 18
Hypertension	<1	-
Hypotension	-	-
Myocardial infarction	-	-
Palpitations	<1	-
Pericarditis	1	<1
Shock	-	<1
Central Nervous System		
Abnormal dreams	-	-
Anxiety	1	-
Ataxia	✔	-
Chills	-	-
Confusion	-	-
Depression	✔	-
Dizziness	✔	-
Drowsiness	-	-
Dysautonomia	-	<1
Encephalopathy	-	<1
Fatigue	✔	-
Fever	✔	-
Headache	✔	2
Insomnia	✔	-
Irritability	✔	-
Meningeal signs	-	-
Migraine	-	-
Nervousness	✔	-
Neuropathy	-	<1
Paresthesia	-	<1
Peripheral neuropathy	✔	-
Seizure	✔	<1
Syncope	✔	<1
Tinnitus	✔	-
Tremor	-	-
Vertigo	✔	-
Visual disturbance	✔	-
Weakness	✔	-
Dermatologic		
Photosensitivity	✔	-
Pruritus	✔	2
Rash	✔	3
Stevens-Johnson syndrome	✔	-
Urticaria	✔	<1
Gastrointestinal		
Abdominal distention	-	-
Abdominal pain/discomfort	✔	-
Anorexia	2	-
Appetite decrease	-	-
Blood in stool	✔	-
Constipation	✔	-
Defecation urgency	-	-

Adverse Events	Bismuth, Metronidazole and Tetracycline	Quinupristin and Dalfopristin
Diarrhea	✔	3
Discoloration of teeth	✔	-
Dry mouth	1	-
Duodenal ulcer	1	-
Dyspepsia	✔	-
Dysphagia	✔	-
Enamel hypoplasia	✔	-
Enterocolitis	✔	-
Epigastric distress	✔	-
Eructation	<1	-
Esophageal ulceration	✔	-
Esophagitis	✔	-
Extraintestinal cancer	✔	-
Fecal abnormality	-	-
Flatulence	<1	-
Gastrointestinal hemorrhage	1	-
Gastrointestinal upset	-	-
Gingival disorder	-	-
Glossitis	<1	-
Inguinal hernia	-	-
Intestinal obstruction	<1	-
Melena	3	-
Nausea	12	3 to 5
Oral moniliasis	✔	-
Pancreatitis	-	<1
Pseudomembranous colitis	-	-
Rectal hemorrhage	<1	-
Stomatitis	-	<1
Stool abnormality	1	-
Taste alteration	1	-
Tongue discoloration	2	-
Tooth disorder	<1	-
Vomiting	✔	3 to 4
Weight decreased	-	-
Genitourinary		
Abnormal kidney function	-	-
Acute kidney failure	-	-
Albuminuria	-	-
Choluria	-	-
Cylindruria	-	-
Dysuria	✔	-
Hematuria	-	<1
Incontinence	✔	-
Leukocyturia	-	-
Pyuria	-	-
Urinary tract infections	<1	-
Vaginitis	4	<1
Hematologic		
Agranulocytosis	-	-
Anemia	-	-
Eosinophilia	-	-
Hemolytic anemia	-	<1
Leukopenia	-	-
Lymphocytosis	-	-

Adverse Events	Bismuth, Metronidazole and Tetracycline	Quinupristin and Dalfopristin
Monocytosis	-	-
Neutropenia	-	-
Pancytopenia	-	<1
Thrombocytopenia	-	<1
Laboratory Test Abnormalities		
Alanine aminotransferase increased	✔	-
Aspartate aminotransferase increased	✔	-
Hyperbilirubinemia	-	3 to 35
Hypoglycemia	-	-
Serum creatinine increased	-	-
Musculoskeletal		
Arthralgia	-	≤47
Arthritis	✔	-
Back pain	2	-
Myalgia	-	≤47
Myasthenia	-	<1
Neck pain	-	-
Neuromuscular blockade	-	-
Rheumatoid arthritis	<1	-
Tendonitis	<1	-
Weakness	4	-
Respiratory		
Apnea	-	-
Cough	<1	
Dyspnea	-	<1
Nasal passage irritation	-	-
Nasopharyngitis	-	-
Pharyngitis	2	-
Pharyngolaryngeal pain	-	-
Pleural effusion	-	<1
Pneumonia	-	-
Respiratory arrest	-	-
Respiratory distress syndrome	-	<1
Respiratory tract infection	-	-
Rhinitis	1	-
Rhinorrhea	-	-
Upper respiratory tract infection	2	-
Wheezing	-	-
Other		
Allergic reaction	-	<1
Anaphylaxis	✔	-
Angioneurotic edema	✔	-
Ataxia	-	-
Blurred vision	-	-
Clamminess	-	-
Conjunctivitis	✔	
Dehydration	-	-
Dry lips	-	-
Flu syndrome	-	-
Fungal infections	-	-

Adverse Events	Bismuth, Metronidazole and Tetracycline	Quinupristin and Dalfopristin
Gout	-	<1
Hearing loss	-	-
Hypoesthesia oral	-	-
Injection site reactions	-	12 to 13
Motion sickness	-	-
Neoplasm	✔	
Pain	✔	40 to 44
Pain at injection site	-	38 to 42
Redman syndrome	-	-
Rigors	-	-
Sepsis	-	-
Thrombophlebitis	-	-
Vasculitis	-	-

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

Table 12. Boxed Warning for Bacitracin[1]

WARNING
Nephrotoxicity: Bacitracin in parenteral (intramuscular) therapy may cause renal failure due to tubular and glomerular necrosis. Its use should be restricted to infants with staphylococcal pneumonia and empyema when due to organisms shown to be susceptible to bacitracin. It should be used only where adequate laboratory facilities are available and when constant supervision of the patient is possible. Renal function should be carefully determined prior to and daily during therapy. The recommended daily dose should not be exceeded, and fluid intake and urinary output should be maintained at proper levels to avoid kidney toxicity. If renal toxicity occurs the drug should be discontinued. The concurrent use of other nephrotoxic drugs, particularly streptomycin, kanamycin, polymyxin B, polymyxin E (colistin), and neomycin should be avoided.

Table 13. Boxed Warning for Clindamycin[1]

WARNING
Clostridium difficile–associated diarrhea has been reported with use of nearly all antibacterial agents, including clindamycin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon, leading to overgrowth of *Clostridium difficile*–associated diarrhea. Because clindamycin therapy has been associated with severe colitis, which may end fatally, reserve it for serious infections for which less toxic antimicrobial agents are inappropriate. Do not use clindamycin in patients with nonbacterial infections, such as most upper respiratory tract infections. *Clostridium difficile* produces toxins A and B, which contribute to the development of *Clostridium difficile*–associated diarrhea. Hypertoxin-producing strains of *Clostridium difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. *Clostridium difficile*–associated diarrhea must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary because *Clostridium difficile*–associated diarrhea has been reported to occur more than two months after the administration of antibacterial agents. If *Clostridium difficile*–associated diarrhea is suspected or confirmed, ongoing antibiotic use not directed against *Clostridium difficile* may need to be discontinued. Institute appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *Clostridium difficile*, and surgical evaluation as clinically indicated.

Table 14. Boxed Warning for Lincomycin[1]

WARNING
Clostridium difficile associated diarrhea has been reported with use of nearly all antibacterial agents, including Lincomycin and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *Clostridium difficile*. Because lincomycin therapy has been associated with severe colitis which may end fatally, it should be reserved for serious infections where less toxic antimicrobial agents are inappropriate. It should not be used in patients with nonbacterial infections such as most upper respiratory tract infections. *Clostridium difficile* produces toxins A and B which contribute to the development of *Clostridium difficile* associated diarrhea. Hypertoxin producing strains of *Clostridium difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. *Clostridium difficile* associated diarrhea must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since *Clostridium difficile* associated diarrhea has been reported to occur over two months after the administration of antibacterial agents. If *Clostridium difficile* associated diarrhea is suspected or confirmed, ongoing antibiotic use not directed against *Clostridium difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *Clostridium difficile*, and surgical evaluation should be instituted as clinically indicated

Table 15. Boxed Warning for the Polymyxin B Sulfate[1]

WARNING
When this drug is given intramuscularly or intrathecally, it should be given only to hospitalized patients, so as to provide constant supervision by a physician. Nephrotoxicity: Renal function should be carefully determined, and patients with renal damage and nitrogen retention should have reduced dosage. Patients with nephrotoxicity due to polymyxin B sulfate usually show albuminuria, cellular casts, and azotemia. Diminishing urine output and a rising blood urea nitrogen are indications for discontinuing therapy with this drug. Neurotoxicity: Neurotoxic reactions may be manifested by irritability, weakness, drowsiness, ataxia, perioral paresthesia, numbness of the extremities, and blurring of vision. These are usually associated with high serum levels found in patients with impaired renal function or nephrotoxicity. Concurrent therapy: The concurrent or sequential use of other neurotoxic or nephrotoxic drugs with polymyxin B sulfate, particularly bacitracin, streptomycin, neomycin, kanamycin, gentamicin, tobramycin, amikacin, cephaloridine, paromomycin, viomycin, and colistin should be avoided. Neuromuscular blockade: The neurotoxicity of polymyxin B sulfate can result in respiratory paralysis from neuromuscular blockade, especially when the drug is given soon after anesthesia or muscle relaxants. Use in pregnancy: The safety of this drug in human pregnancy has not been established.

Table 16. Boxed Warning for Telavancin[1]

WARNING
Patients with pre-existing moderate/severe renal impairment (creatinine clearance ≤ 50 mL/minute) who were treated with telavancin for hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia had increased mortality observed vs vancomycin. Use of telavancin in patients with pre-existing moderate/severe renal impairment (creatinine clearance ≤ 50 mL/minute) should be considered only when the anticipated benefit to the patient outweighs the potential risk.

Nephrotoxicity: New onset or worsening renal impairment has occurred. Monitor renal function in all patients.

Women of childbearing potential should have a serum pregnancy test prior to administration of telavancin.

Avoid use of telavancin during pregnancy unless the potential benefit to the patient outweighs the potential risk to the fetus.

Adverse developmental outcomes observed in three animal species at clinically relevant doses raise concerns about potential adverse developmental outcomes 21 in humans.

Table 17. 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.

VII. Dosing and Administration

The usual dosing regimens for the miscellaneous antibacterials are listed in Table 18.

Table 18. Usual Dosing Regimens for the Antibacterials, Miscellaneous[1-17]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Single Entity Agents			
Bacitracin	Dosing information for adults is not included in the prescribing information.	Unspecified infections: Injection: Infants <2,500 g, 900 units/kg/day in two to three divided doses; infants >2,500 g, 1,000 units/kg/day in two to three divided doses	Injection: 50,000 units
Clindamycin	Serious infections: Capsule: 150 to 300 mg every six hours Injection: 600 to 1,200 mg/day IM/IV in two to four equal doses More severe infections: Capsule: 300 to 450 mg every six hours Injection: 1,200 to 2,700 mg/day IM/IV in two to four equal doses	Serious infections: Capsule: 8 to 16 mg/kg/day divided into three or four equal doses Solution: 8 to 12 mg/kg/day divided into three or four equal doses Severe infections: Solution: 13 to 16 mg/kg/day divided into three or four equal doses More severe infections: Capsule: 16 to 20 mg/kg/day divided into three or four equal doses Solution: 17 to 25 mg/kg/day divided into three or four equal doses Unspecified infections in neonates <1 month of age: Injection: 15 to 20 mg/kg/day in three to four equal doses	Capsule: 75 mg 150 mg 300 mg Injection: 150 mg/mL Solution: 75 mg/5 mL

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
		Unspecified infections in patients one month to 16 years of age: Injection: 20 to 40 mg/kg/day in three to four equal doses	
Colistimethate	Serious infections due to susceptible organisms: Injection: 2.5 to 5 mg/kg per day in two to four divided doses	Serious infections due to susceptible organisms: Injection: 2.5 to 5 mg/kg per day in two to four divided doses	Injection: 150 mg
Dalbavancin	Skin and skin-structure infections: Injection: 1500 mg as a single dose, or 1000 mg dose followed by 500 mg dose one week later	Safety and efficacy in children have not been established.	Injection: 500 mg
Daptomycin	Bacteremia, endocarditis: Injection: 6 mg/kg IV once daily for two to six weeks Skin and skin-structure infections: Injection: 4 mg/kg IV once daily for seven to 14 days	Safety and efficacy in children have not been established.	Injection: 500 mg
Lincomycin	Serious infections: Injection: 600 IM every 24 hours; 600 mg to 1 g IV every eight to 12 hours More severe infections: Injection: 600 mg IM every 12 hours or more often; 600 mg to 1 g IV every eight to 12 hours	Serious infections in patients >1 month of age: Injection: 10 mg/kg IM every 24 hours; 10 to 20 mg/kg IV in divided doses More severe infections in patients ≥1 month of age: Injection: 10 mg/kg IM every 12 hours; 10 to 20 mg/kg IV in divided doses	Injection: 300 mg/mL
Linezolid	Pneumonia (community-acquired): Injection, suspension, tablet: 600 mg every 12 hours for 10 to 14 days Pneumonia (nosocomial): Injection, suspension, tablet: 600 mg every 12 hours for 10 to 14 days Skin and skin-structure infections (complicated): Injection, suspension, tablet: 600 mg every 12 hours for 10 to 14 days Skin and skin-structure infections (uncomplicated): Suspension, tablet: 400 mg orally every 12 hours for 10	Pneumonia (community-acquired) in patients from birth to 11 years of age: Injection, suspension, tablet: 10 mg/kg every eight hours for 10 to 14 days Pneumonia (community-acquired) in patients ≥12 years of age: Injection, suspension, tablet: 600 mg every 12 hours for 10 to 14 days Pneumonia (nosocomial) in patients from birth to 11 years of age: Injection, suspension, tablet: 10 mg/kg every eight hours for 10 to 14 days Pneumonia (nosocomial) in patients ≥12 years of age: Injection, suspension, tablet: 600 mg	Injection: 200 mg/100 mL 600 mg/300 mL Suspension: 100 mg/5 mL Tablet: 600 mg

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	to 14 days (adults) or 600 mg orally every 12 hours (adolescents) Vancomycin-resistant *Enterococcus faecium* infections: Injection, suspension, tablet: 600 mg every 12 hours for 14 to 28 days	every 12 hours for 10 to 14 days Skin and skin-structure infections (complicated) in patients from birth to 11 years of age: Injection, suspension, tablet: 10 mg/kg every eight hours for 10 to 14 days Skin and skin-structure infections (complicated) in patients ≥12 years of age: Injection, suspension, tablet: 600 mg every 12 hours for 10 to 14 days Skin and skin-structure infections (uncomplicated) in patients <5 years of age: Injection, suspension, tablet: 10 mg/kg orally every eight hours for 10 to 14 days Skin and skin-structure infections (uncomplicated) in patients five to 11 years of age: Injection, suspension, tablet: 10 mg/kg orally every 12 hours for 10 to 14 days Skin and skin-structure infections (uncomplicated) in patients >12 years of age: Injection, suspension, tablet: 600 mg orally every 12 hours Vancomycin-resistant *Enterococcus faecium* infections in patients from birth to 11 years of age: Injection, suspension, tablet: 10 mg/kg every eight hours for 14 to 28 days Vancomycin-resistant *Enterococcus faecium* infections in patients≥12 years of age: Injection, suspension, tablet: 600 mg every 12 hours for 14 to 28 days	
Oritavancin	Skin and skin-structure infections: Injection: one 1200 mg dose IV infused over three hours	Safety and efficacy in children have not been established.	Injection: 400 mg
Polymyxin B sulfate	Meningitis: Injection: Intrathecal, 50,000 units/day for three to four days, then every other day for ≥2 weeks after cerebral	Meningitis in patients <2 years of age: Injection: Intrathecal, 20,000 units/day for three to four days, then 25,000 units/day every other day for	Injection: 500,000 units

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	spinal fluid cultures are negative Unspecified infections: Injection: IM, 25,000 to 30,000 units/kg/day divided every four to six hours; IV, 15,000 to 25,000 units/kg/day divided every 12 hours	≥2 weeks after cerebral spinal fluid cultures are negative Meningitis in patients >2 years of age: Injection: Intrathecal, 50,000 units/day for three to four days, then every other day for ≥2 weeks after cerebral spinal fluid cultures are negative Unspecified infections in infants: Injection: IM, up to 40,000 units/kg/day divided every four to six hours; IV, up to 40,000 units/kg/day divided every 12 hours Unspecified infections in children: Injection: IM, 25,000 to 30,000 units/kg/day divided every four to six hours; IV, 15,000 to 25,000 units/kg/day divided every 12 hours	
Rifaximin	Hepatic encephalopathy: Tablet: 550 mg twice daily Traveler's diarrhea: Tablet: 200 mg three times daily for three days	Traveler's diarrhea in patients ≥12 years of age: Tablet: 200 mg three times daily for three days	Tablet: 200 mg 550 mg
Tedizolid	Skin and skin-structure infections: Injection: 200 mg administered once daily as an IV infusion over one hour for six days Tablet: 200 mg administered once daily orally for six days	Safety and efficacy in children have not been established.	Injection: 200 mg Tablet: 200 mg
Telavancin	Skin and skin-structure infections: Injection: 10 mg/kg IV every 24 hours for seven to 14 days Hospital-acquired and ventilator-associated bacterial pneumonia: Injection: 10 mg/kg IV every 24 hours for seven to 21 days	Safety and efficacy in children have not been established.	Injection: 250 mg 750 mg
Vancomycin	Pseudomembranous colitis and enterocolitis: Capsule: 500 mg to 2 g per day divided in three or four doses for seven to 10 days Unspecified infections: Injection: 500 mg IV every six hours or 1 g IV every 12	Pseudomembranous colitis and enterocolitis in children: Capsule: 40 mg/kg/day in three to four divided doses for seven to 10 days Unspecified infections in patients <1 month of age: Injection: 15 mg/kg IV as an initial	Capsule: 125 mg 250 mg Injection: 500 mg 750 mg 1 g 5 g

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	hours	dose, followed by 10 mg/kg every 12 hours for neonates in the 1st week of life and every eight hours thereafter up to the age of one month Unspecified infections in patients ≥1 month of age: Injection: 10 mg/kg IV per dose every six hours	10 g
Combination Products			
Colloidal bismuth subcitrate, metronidazole, and tetracycline	Treatment of patients with *Helicobacter pylori* infection and duodenal ulcer disease (active or history within the past five years) to eradicate *Helicobacter pylori* (in combination with omeprazole): Capsule: Three capsules four times daily for 10 days; administer with 20 mg twice daily of omeprazole	Safety and efficacy in children have not been established.	Capsule: 140-125-125 mg
Quinupristin and dalfopristin	Skin and skin-structure infections: Injection: 7.5 mg/kg IV every 12 hours for at least seven days	Skin and skin-structure infections in patients ≥12 years of age: Injection: 7.5 mg/kg IV every 12 hours for at least seven days	Injection: 500 mg

IM= intramuscular, IV=intravenous

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of the miscellaneous antibacterials are summarized in Table 19.

Table 19. Comparative Clinical Trials with the Antibacterials, Miscellaneous

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Dermatological Infections				
Boucher et al.[48] (2014) DISCOVER 1 Dalbavancin 1 g IV on day one, followed by 500 mg IV on day eight vs vancomycin 1 g (or 15 mg/kg) IV every 12 hours for ≥3 days with option to switch to oral linezolid 600 mg every 12 hours to complete 10 to 14 days of therapy	DB, DD, MC, RCT Adult patients with an acute bacterial SSSI who were thought to require ≥3 days of IV therapy who had ≥1 systemic sign of infection within 24 hours before randomization	N=573 10 to 14 days	Primary: Early clinical response (cessation of spread of infection-related erythema, absence of fever at 48 to 72 hours) Secondary: Clinical status at end of therapy	Primary: Early clinical response indicating treatment success was noted in 240 of 288 patients (83.3%) treated with dalbavancin compared to 233 of 285 patients (81.8%) in the vancomycin-linezolid group (difference, 1.5%; 95% CI, -4.6 to 7.9). Secondary: Clinical status indicating treatment success at the end of treatment was documented in a similar proportion of patients in the dalbavancin and vancomycin-linezolid groups in a pooled analysis of data from DISCOVER1 and DISCOVER2 (90.7 vs 92.1%, respectively; difference, -1.5; 95% CI, -4.8 to 1.9).
Boucher et al.[48] (2014) DISCOVER 2 Dalbavancin 1 g IV on day one, followed by 500 mg IV on day eight vs	DB, DD, MC, RCT Adult patients with an acute bacterial SSSI who were thought to require ≥3 days of IV therapy who had ≥1 systemic sign of infection within 24 hours before	N=739 10 to 14 days	Primary: Early clinical response (cessation of spread of infection-related erythema, absence of fever at 48 to 72 hours) Secondary: Clinical status at	Primary: Early clinical response indicating treatment success was noted in 285 of 371 patients (76.8%) treated with dalbavancin and 288 of 368 patients (78.3%) in the vancomycin-linezolid group (difference, -1.5; 95% CI, -7.4 to 4.6). Secondary: Clinical status indicating treatment success at the end of treatment was documented in a similar proportion of patients in the dalbavancin and vancomycin-linezolid groups in a pooled analysis of data from DISCOVER1 and DISCOVER2 (90.7 vs 92.1%, respectively; difference, -

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vancomycin 1 g (or 15 mg/kg) IV every 12 hours for ≥3 days with option to switch to oral linezolid 600 mg every 12 hours to complete 10 to 14 days of therapy	randomization		end of therapy	1.5; 95% CI, -4.8 to 1.9).
Loeffler et al.[49] (2002) Quinupristin-dalfopristin 7.5 mg/kg IV every 8 to 12 hours	RETRO Patients <18 years of age with signs and symptoms of serious invasive infection	N=127 2 to 73 days	Primary: Clinical responses (cure, improved, failure, or indeterminate), microbiologic response (eradication, presumed eradication, presumed persistence, persistence, or indeterminate), adverse events Secondary: Not reported	Primary: Overall favorable clinical response rate (either cure or improved) was 69% and similar across all age groups. The overall favorable microbiologic response rate (either eradicated or presumed eradicated) was 78%. A total of 8% of patients experienced treatment-related non-venous adverse events. Pain (2%) and maculopapular rash (2%) were the most frequently reported drug-related adverse events. Five patients discontinued treatment due to adverse laboratory events (three of the five were related to treatment: gamma-glutamyl transferase, total bilirubin, and eosinophils). Forty-six patients died due to reasons unrelated to quinupristin-dalfopristin toxicities. Secondary: Not reported
Davis et al.[50] (2007) Daptomycin 4 mg/kg IV once daily for 3 to 14 days	OL, PRO Adult patients with complicated SSSIs at risk for MRSA infection	N=53 14 days	Primary: Clinical resolution and duration of therapy Secondary: Not reported	Primary: The most common diagnoses were cellulitis (31%), abscess (22%), and both cellulitis with abscess (37%). Microbiology differed significantly between groups, with *Staphylococcus aureus* found in 27 patients (51%) in the daptomycin group and 167 patients (79%) in the vancomycin group and MRSA in 22 (42%) and 159 (75%), respectively (P<0.001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs vancomycin historical controls				The proportions of patients with clinical improvement or resolution of their infections on days three and five were 90 vs 70% and 98 vs 81% in the daptomycin vs vancomycin groups, respectively (P<0.01 for both comparisons), and 100% at the EOT in both groups. Among patients with complete resolution of their infections (41 patients [77%] with daptomycin vs 89 patients [42%] with vancomycin, P<0.05), median duration of IV therapy was four and seven days, respectively, (P<0.001). Secondary: Not reported
Pertel et al.[51] (2009) Daptomycin 4 mg/kg IV once daily for 7 to 14 days vs vancomycin according to standard of care for 7 to 14 days	MC, RCT, SB Adults diagnosed with cellulitis or erysipelas requiring hospitalization and IV antibiotic therapy	N=103 7 to 14 days	Primary: Clinical success rate Secondary: Not reported	Primary: The clinical success rates were 94.0% for daptomycin and 90.2% for vancomycin (95% CI, -6.7 to 14.3). Of the 50 patients in the daptomycin group, 36 (72.0%) were assessed as cured, 11 (22.0%) were improved and three (6.0%) had no follow-up data. Of the 51 patients in the vancomycin group, 28 (54.9%) were assessed as cured, 18 (35.3%) were improved, one (2.0%) had worsened and four (7.8%) had no follow-up data. Among the patients with cellulitis clinical success rates were also similar for daptomycin-treated (78.6%) and comparator-treated patients (72.7%). The mean durations of study drug administration were 6.1 days for daptomycin- and 6.2 days for vancomycin-treated patients (P=0.847). There were no significant differences between treatments in the time to achievement of any of the predefined endpoints. The median time to stabilization of infection was similar for daptomycin and vancomycin (P=0.875; 86.5 vs 85.5 hours). No differences were observed between daptomycin- and vancomycin-treated patients in the median time to defervescence (P=0.690; 12.4 vs 16.3

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				hours), cessation of erythema advancement (P=0.833; 21.0 vs 22.0 hours), or readiness for hospital discharge (P=0.993; 84.0 vs 85.5 hours). No differences were seen between the groups in the median time to 50% improvement for investigator-assessed composite scores (P=0.755; 39.9 vs 41.2 hours) as well as patient-reported pain (P=0.632; 37.3 vs 40.0 hours) or tightness/swelling scores (P=0.307; 31.0 vs 31.5 hours). Secondary: Not reported
Kauf et al.[52] (2015) Daptomycin 4 mg/kg IV QD vs vancomycin dosed at the investigator's discretion according to institutional protocol	MC, OL, PRO, RCT Patients ≥18 years of age hospitalized for complicated SSSI caused by suspected or documented MRSA infection that necessitated IV antibiotics	N=250 30 days after discharge	Primary: Infection-related length of stay Secondary: Clinical response, and patient-reported outcomes	Primary: For the primary end point, there was no significant difference between the daptomycin and vancomycin arms. Secondary: Although the unadjusted differences in clinical success were not significant, logistic regression analysis showed that vancomycin treatment, relative to daptomycin treatment, was associated with a decreased chance of achieving clinical success within two days (OR, 0.498; 95% CI, 0.249 to 0.997; P=0.049). Significant variables in the two-day response included count of Systemic Inflammatory Response Syndrome (P=0.041), Gram-negative infection (P=0.006), and baseline vancomycin use (P=0.031). Similarly, clinical success rates were not significantly different within two and three days of treatment when analyzed by infection type or pathogen. No notable differences in patient-reported outcomes (pain, health-related quality of life, or infection status) by group were observed.
Yogev et al.[53] (2003) Linezolid 10 mg/kg IV/oral every 8 hours vs vancomycin 10 to 15 mg/kg IV every	RCT Hospitalized children <12 years of age with complicated SSSIs caused by resistant gram-positive bacteria	N=120 10 to 28 days	Primary: Patient clinical outcome and pathogen eradication rates Secondary: Not reported	Primary: Clinical cure rate was 93.2% with linezolid vs 90% with vancomycin (P=0.594). Patients with a diagnosis of skin abscess had a significantly higher cure rate in the linezolid group compared to vancomycin (100 vs 60%, respectively; P=0.005). Patients with cellulitis or other types of infection had similar cure rates (P=NS for all). There was no statistically significant difference in eradication rates between treatment groups for all types of infections (P=NS for all).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
6 to 24 hours (based on age) After 3 days of treatment, linezolid group was permitted to switch to oral linezolid, and vancomycin group was permitted to switch to an oral appropriate agent based on susceptibility tests.				Fewer patients experienced adverse events with linezolid therapy compared to vancomycin (23 vs 48%, respectively; P=0.006). Vancomycin-treated patients experienced a greater incidence (statistically significant) of red man syndrome, pruritus, and rash. All other adverse events were not significantly different between treatment groups. The authors did not indicate the rate at which vancomycin was being infused. Secondary: Not reported
Li et al.[54] (2003) Linezolid 600 mg IV/oral BID vs vancomycin 1 g IV BID	MC, OL, RCT Patients with complicated skin and soft tissue infections as the primary site of MRSA infection	N=144 Treatment: ≤4 weeks Observation: ≤4 weeks	Primary: Length of hospital stay Secondary: Not reported	Primary: In the clinically evaluable population, the unadjusted mean length of hospital stay was 5.3 days shorter with linezolid vs vancomycin (15.7 vs 21 days, respectively; P=0.0025). After adjusting for baseline variables, the between-treatment difference in mean length of hospital stay increased to 6.5 days with linezolid vs vancomycin (14.3 vs 20.8 days, respectively; P<0.001). Mean duration of IV therapy was shorter in the linezolid group (5.8 vs 12.6 days; P<0.0001). Clinically evaluable patients had to be treated for ≥7 days, which may have extended the length of hospital stay for patients receiving vancomycin IV as compared to the linezolid group that had the option to switch to oral therapy. Secondary: Not reported
Itani et al.[55] (2005) Linezolid 600 mg	MC, OL, RCT Hospitalized patients with	N=1,200 7 days	Primary: Length of stay, duration of IV treatment, and	Primary: Linezolid was associated with a shorter length of stay (P<0.01), decreased duration of IV antibiotic therapy (P<0.0001), and higher rates of hospital discharge (P<0.05) as compared to vancomycin therapy.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
IV/oral every 12 hours vs vancomycin 1 g IV every 12 hours	complicated skin and soft tissue infections due to MRSA		hospital discharge rates Secondary: Not reported	Secondary: Not reported
Itani et al.[56] (2010) Linezolid 600 mg IV/oral every 12 hours for 7 to 14 days vs vancomycin 15 mg/kg mg IV every 12 hours for 7 to 14 days	OL, RCT Patients ≥18 years of age with complicated skin and soft-tissue infections due to MRSA	N=1,077 7 to 10 days posttreatment	Primary: Clinical response, microbiologic outcome, length of stay, duration of IV therapy, safety Secondary: Not reported	Primary: In the per protocol population, clinical success was reported in 92% of patients receiving linezolid compared to 88% of patients receiving vancomycin at the end of treatment (P=0.168). At the end of the study, clinical success rates were similar among the treatment groups (84% with linezolid and 80% with vancomycin; P=0.249). In the modified intent to treat population, clinical success was reported in 89% of patients receiving linezolid compared to 85% of patients receiving vancomycin at the end of treatment (P=0.090). At the end of the study, clinical success rates were similar among the treatment groups (81% with linezolid and 74% with vancomycin; P=0.048). In the per protocol population at the end of treatment, linezolid achieved a significantly higher rate of microbiologic success than vancomycin (85.4 vs 68.8%, respectively; P<0.001). At the end of the study, linezolid was comparable with vancomycin (75.0 vs 68.4%, respectively; P=0.127). In the modified intent-to-treat population, linezolid had a numerically higher success rate than vancomycin (74 vs 66%; 95% CI, -0.1 to 15.2; P=0.055). In the per protocol population, the median and mean lengths of stay were 6.0 and 7.6 days, respectively, in the linezolid group, compared to 7.0 and 8.9 days, respectively, in the vancomycin group (P=0.022). The mean duration of IV therapy was significantly shorter in the linezolid group than in the vancomycin group (5.6 vs 10.4 days; P<0.001). In the modified intent-to-treat population, the median and mean lengths of stay were 5.0 and 7.7 days, respectively, in the linezolid group, as

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				compared to 7.0 and 8.9 days, respectively, in the vancomycin group (P=0.016). The mean duration of IV therapy was significantly shorter in the linezolid group than in the vancomycin group (5.3 vs 9.8 days; P<0.001). The percentage of patients who experienced ≥1 adverse event was similar in both treatment groups (linezolid, 48%; vancomycin, 51%). Treatment-related adverse events occurred in 23% of patients in the linezolid arm and 22% of patients in the vancomycin arm. Treatment- related nephrotoxic adverse events occurred more often in the vancomycin group. There were 11 deaths in the linezolid group and seven deaths in the vancomycin group. Secondary: Not reported
Sharpe et al.[57] (2005) Linezolid 600 mg oral every 12 hours vs vancomycin 1 g IV every 12 hours All patients received perioperative cefazolin.	OL, RCT Patients ≥18 years of age with MRSA-related complicated skin and soft-tissue infections of the lower extremities	N=60 Treatment: 7 to 21 days Tests of cure: 10 days posttreatment	Primary: Clinical cure, improvement, or failure; microbiological eradication, persistence, or recurrence; duration of hospitalization and drug treatment Secondary: Not reported	Primary: Linezolid was associated with a greater incidence of cure (50 vs 20% for vancomycin) and improvement (47 vs 23% for vancomycin; P=0.015 for both comparisons). Microbiological outcomes were similar overall between treatment groups (P=0.052). Median length of therapy was 10 days for both treatment arms; of these, seven days of treatment were administered on an outpatient basis for the linezolid group compared to four outpatient days of treatment with vancomycin. Secondary: Not reported
Wilcox et al.[58] (2009) Linezolid 600 mg IV every 12 hours for 7 to 28 days	MC, OL Adults >13 years of age who had a central venous, pulmonary artery, or arterial catheter	N=739 6 to 8 weeks	Primary: Microbiologic outcome at test of cure Secondary: Clinical outcomes	Primary: Microbiologic outcomes at test of cure met non-inferiority criteria in the two primary analysis populations. In the subset with complicated SSSIs, success occurred in 146 (89.6%) of 163 linezolid patients and in 134 (89.9%) of 149 control patients (95% CI, -7.1 to 6.4).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs vancomycin 1 g IV every 12 hours for 7 to 28 days	in place for 13 days and suspected catheter-related infection		and safety	In the subset with suspected catheter-related infection, microbiologic success occurred in 82 (86.3%) of 95 linezolid recipients and in 67 (90.5%) of 74 control patients (95% CI, -13.8 to 5.4). Secondary: In the subset of patients with complicated SSSIs, clinical success occurred in 123 (77.8%) of 158 linezolid recipients and in 113 (77.9%) of 145 control patients at test-of-cure. In the subset with suspected catheter-related infection, success occurred in 70 (75.3%) of 93 linezolid recipients and in 59 (80.8%) of 73 control patients. Sensitivity analysis did not alter clinical outcomes in the subsets with complicated SSSIs (linezolid group, 75.0%; control group, 74.8%) or suspected catheter-related infection (linezolid group, 73.7%; control group, 79.7%). Adverse events, including those unrelated to treatment, occurred in 244 linezolid recipients (67.2%) and were similar between groups. Mortality rates were 10.4% for linezolid recipients (28 of 269 patients) and 10.1% for control subjects (26 of 257) in the modified intent-to-treat population through test of cure, and they were 21.5% for linezolid recipients (78 of 363) and 16.0% for the control group (58 of 363; 95% CI, -0.2 to 11.2) for all treated patients through post-study treatment day 84.
Itani et al.[59] (2012) Vancomycin IV 15 mg/kg every 12 hours vs linezolid oral 600 mg every 12 hours	RETRO Adults with complicated skin and soft tissue infections caused by MRSA	N=305 7 to 14 days	Primary: Efficacy and tolerability Secondary: Not reported	Primary: At end of study, the OR for clinical success of oral linezolid therapy vs IV vancomycin therapy was 4.0 (95% CI, 1.3 to 12.0; P=0.01), and the OR for microbiologic success at end of study was 2.7 (95% CI, 1.2 to 5.7; P=0.01). Overall rates of adverse events in each group were consistent with reported safety profiles for each drug. Secondary: Not reported
Yue et al.[60]	MA	N=3,144	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(2013) Vancomycin vs linezolid	9 RCTs comparing linezolid with vancomycin in the treatment of skin and soft tissue infections	Duration varied	clinical cure, microbiological cure, and skin and soft tissue infections -related and treatment-related mortality Secondary: Not reported	Linezolid was associated with a significantly better clinical (RR, 1.09; 95% CI, 1.03 to 1.16) and microbiological cure rate in adults (RR, 1.08; 95% CI, 1.01 to 1.16). For those infections due to MRSA, linezolid was significantly more effective than vancomycin in clinical (RR, 1.09; 95% CI, 1.03 to 1.17) and microbiological cure rates (RR, 1.17; 95% CI, 1.04 to 1.32). No RCT reported skin and soft tissue infections-related and treatment-related mortality. There was no significant difference in all-cause mortality between linezolid and vancomycin (RR, 1.44; 95% CI, 0.75 to 2.80). There were fewer incidents of red man syndrome (RR, 0.04; 95% CI, 0.01 to 0.29), pruritus (RR, 0.36; 95% CI, 0.17 to 0.75) and rash (RR, 0.27; 95% CI, 0.12 to 0.58) in the linezolid group compared to vancomycin, however, more people reported thrombocytopenia (RR, 13.06; 95% CI, 1.72 to 99.22), and nausea (RR, 2.45; 95% CI, 1.52 to 3.94) when treated with linezolid.
Corey et al.[61] (2015) SOLO II Oritavancin 1,200 mg IV once, followed by placebo every 12 hours vs vancomycin 1 g or 15 mg/kg IV every 12 hours	AC, DB, MC, RCT Patients ≥18 years of age with acute bacterial SSSI suspected or proven to be due to a gram-positive pathogen, with erythema, edema and/or induration surrounding each lesion of ≥75 cm^2, presenting with signs and symptoms of systemic inflammation and would require ≥7 days of therapy	N=1,019 7 to 10 days	Primary: Composite outcome at ECE Secondary: Investigator-assessed clinical cure at PTE, lesion area decrease of ≥20% from baseline at ECE	Primary: A total of 403 (80.1%) patients in the oritavancin group and 416 (82.9%) patients in the vancomycin group achieved a primary efficacy outcome at ECE (difference, -2.7; 95% CI, -7.5 to 2.0; P value not reported). Secondary: Oritavancin was noninferior to vancomycin for the investigator assessed clinical cure endpoint at PTE (82.7 vs 80.5%, respectively; difference, 2.2; 95% CI, -2.6 to 7.0; P value not reported) and ≥20% reduction in lesion size endpoint at ECE (85.9 vs 85.3%, respectively; difference, 0.6; 95% CI, -3.7 to 5.0; P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Corey et al.[62] (2014) SOLO I Oritavancin 1,200 mg IV once, followed by placebo every 12 hours vs vancomycin 1 g or 15 mg/kg IV every 12 hours	AC, DB, MC, RCT Patients ≥18 years of age with acute bacterial SSSI suspected or proven to be due to a gram-positive pathogen, with erythema, edema and/or induration surrounding each lesion of ≥75 cm^2, presenting with signs and symptoms of systemic inflammation and would require ≥7 days of therapy	N=968 7 to 10 days	Primary: Composite outcome at ECE Secondary: Investigator-assessed clinical cure at PTE, lesion area decrease of ≥20% from baseline at ECE	Primary: A total of 391 (82.3%) patients in the oritavancin group and 378 (78.9%) patients in the vancomycin group achieved a primary efficacy outcome at ECE (difference, 3.4; 95% CI, -1.6 to 8.4; P value not reported). Secondary: Oritavancin was noninferior to vancomycin for the investigator assessed clinical cure endpoint at PTE (79.6 vs 80.0%, respectively; difference, -0.4; 95% CI, -5.5 to 4.7; P value not reported) and ≥20% reduction in lesion size endpoint at ECE (86.9 vs 82.9%, respectively; difference, 4.1; 95% CI, -0.5 to 8.6; P value not reported).
Moran et al.[63] (2014) ESTABLISH-2 Tedizolid phosphate 200 mg IV QD vs linezolid 600 mg IV BID	AC, DB, DD, MC, RCT Patients ≥12 years of age with acute bacterial SSSIs that had a minimum lesion area of 75 cm^2, were suspected or documented to be associated with a gram-positive pathogen and had at least one systemic or regional sign of infection	N=666 Patients randomized to tedizolid phosphate received treatment for six days and patients randomized to linezolid received treatment for 10 days, with the option to step down to oral therapy	Primary: Early clinical response 48 to 72 hours after start of treatment Secondary: Response at day 7, programmatic and investigator-assessed EOT response, investigator assessed post therapy response seven to 14 days after EOT, changes in patient-reported	Primary: Early clinical response was achieved in 283 (85%) patients in the tedizolid phosphate group and 276 (83%) patients in the linezolid group, demonstrating non-inferiority of tedizolid phosphate to linezolid (2.6% difference; 95% CI, -3.0 to 8.2; P value not reported). There were no meaningful differences between groups in rates of early clinical response, irrespective of type of acute bacterial SSSI, geographic region, baseline pathogen and timing of oral step-down. Secondary: There was no significant difference between the linezolid group and the tedizolid group with regards to response at day seven (0.9% difference; 95% CI, -3.2 to 4.9; P value not reported), programmatic assessed EOT response (-4.1% difference; 95% CI,-8.8 to 0.3; P value not reported), investigator assessed EOT response (-2.0% difference; 95% CI, -5.7 to 1.2; P value not reported), and post therapy assessment (0.3%; 95% CI, -4.8 to 5.3; P value not reported).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
		after receiving ≥2 IV doses of active treatment or placebo	pain, investigator-assessed response at late follow-up, favorable microbiologic response	Improvements in patient reported pain were similar between treatment groups (P value not reported). There was no significant difference between treatment groups with regards to investigator assessed response at late follow-up (-1.1% difference; 95% CI, -3.8 to 1.3; P value not reported) and favorable microbiological response to gram-positive pathogens (-1.4 % difference; 95% CI, -8.0 to 5.1; P value not reported).
Prokocimer et al.[64] (2013) ESTABLISH-1 Tedizolid phosphate 200mg PO QD vs linezolid 600 mg PO BID	AC, DB, DD, MC, RCT Adults ≥18 years with cellulitis/erysipelas, major cutaneous abscess, or wound infection surrounded by erythema with a minimum total lesion area of 75 cm^3, accompanied by at least one local and one regional or one systemic sign of infection, and a gram-positive pathogen was suspected or documented	N=667 Patients randomized to tedizolid phosphate received treatment for six days and patients randomized to linezolid received treatment for 10 days	Primary: Early clinical response assessed at 48 to 72 hours in the intent-to-treat analysis set Secondary: Objective sustained clinical response at EOT in the intent-to-treat and clinically evaluable EOT analysis set, investigators assessment of clinical success at the PTE in the intent-to-treat and clinically evaluable PTE analysis set	Primary: Response rates at the 48 to 72 hour assessment were 79.5% (95% CI, 74.8 to 83.7; P value not reported) of 332 patients in the tedizolid phosphate group and 79.4% (95% CI, 74.7 to 83.6; P value not reported) of 335 patients in the linezolid group; a treatment difference of 0.1% (95% CI, -6.1 to 6.2; P value not reported). Response rates in patients with cellulitis/erysipelas treated with tedizolid phosphate (74.8%, N=135) were lower than for all infections combined (79.5%, N=332) as well as in patients treated with linezolid (71.9%, N=139 vs 79.4%, N=335). P values were not reported. Secondary: Absolute treatment difference with regards to sustained clinical response at EOT in the ITT analysis set was -2.6% (95% CI, -9.6 to 4.2; P value not reported) and -0.9% (95% CI, -7.7 to 5.4; P value not reported) in the clinically evaluable EOT analysis set. Absolute treatment difference with regards to investigators assessment of clinical success at the PTE in the ITT analysis set was -0.5% (95% CI, -5.8 to 4.9) and -0.8% (95% CI, -4.6 to 3.0) in the clinically evaluable PTE analysis set. In patients treated with tedizolid phosphate, response rates for cellulitis/erysipelas (63.9%, N=133) were lower than for all infections combined (69.3%, N=332) in the ITT analysis set as well as the clinically evaluable EOT analysis set (68.8%, N=112; cellulitis/erysipelas group vs 80.2%, N=273; all infections combined).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				In patients treated with linezolid, similar results were observed in the intent-to-treat analysis set (62.2%, N=135 vs 71.9%, N=335) and the clinically evaluable EOT analysis set (68.4%, N=117 vs 81.1%, N=286).
Stryjewski et al.[65] (2012) Vancomycin vs telavancin	PostHoc Patients with various complicated SSSIs	N=1,794 Duration varied	Primary: Efficacy Secondary: Not reported	Primary: Among clinically evaluable patients with major abscesses (n = 619), cure rates were 91% for telavancin and 90% for vancomycin (95% CI for the difference, -3.6 to 5.7). In patients with infective cellulitis (n = 519), cure was achieved in 87% and 88% of telavancin- and vancomycin-treated patients, respectively (95% CI for the difference, -6.2 to 5.2). Cure rates in patients with wound infections were 85% in the telavancin group and 86% in the vancomycin group (95% CI for the difference, -10.5 to 9.0). Cure rates for each type of complicated SSSIs in patients infected with MRSA were also similar between the two treatment arms. Among clinically evaluable patients infected with Panton-Valentine leucocidin-positive MRSA (n = 447), cure rates were 93% for telavancin and 90% for vancomycin (95% CI for the difference, -2.2 to 8.2). Secondary: Not reported
Stryjewski et al.[66] (2008) Telavancin 10 mg/kg IV once daily for 7 to 14 days vs vancomycin 1 g IV BID for 7 to 14 days	AC, DB, RCT (2 trials) Patients ≥18 years of age with complicated skin and soft-tissue infections caused by gram-positive organisms	N=1,867 7 to 14 days posttreatment	Primary: Clinical response at the test-of-cure visit (seven to 14 days after the last dose of study medication), microbiological response, safety Secondary: Not reported	Primary: In all treated patients at the test-of-cure visit (study 0017), cure rates were 75.8% with telavancin and 74.8% with vancomycin (95% CI, -4.8 to 6.8). In study 0018, cure rates were 77.1% with telavancin and 73.7% with vancomycin (95% CI, -1.9 to 8.7). In the clinically evaluable population at the test-of-cure visit (study 0017), cure rates were 87.9% with telavancin and 86.5% with vancomycin (95% CI, -3.6 to 6.3). In study 0018, cure rates were 88.7% with telavancin and 87.6% with vancomycin (95% CI, -3.4 to 5.6). In the pooled analysis of all treated patients (study 0017 and 0018), cure rates were 76.5% with telavancin and 74.2% with vancomycin (95% CI,

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				-1.6 to 6.2). In the clinically evaluable population (pooled analysis), cure rates were 88.3% with telavancin and 87.1% with vancomycin (95% CI, -2.1 to 4.6). Among the microbiologically evaluable patients, baseline pathogens were eradicated at the test-of-cure visit in 89.8 and 87.3% of patients who received telavancin and vancomycin, respectively (95% CI, -1.4 to 6.2). Among patients with MRSA infection at baseline, cure rates were 91% with telavancin and 86% with vancomycin (95% CI, -1.1 to 9.3). Microbiologic eradication in patients with MRSA was 90% in the telavancin group and 85% in the vancomycin group (95% CI, -0.9 to 9.8). Overall therapeutic response was also evaluated. Patients were cured and pathogens were eradicated at the test-of-cure visit in 88.6 and 86.2% of patients in the telavancin and vancomycin treatment groups, respectively (95% CI, -1.6 to 6.4). Adverse events were reported in 79 and 72% of patients who received telavancin and vancomycin, respectively. The incidence of serious adverse events was higher in the telavancin treatment group than in the vancomycin treatment group (7 vs 4%). More patients discontinued telavancin therapy than discontinued vancomycin therapy because of an adverse event (8 vs 6%). Except for taste disturbance, mild nausea, vomiting, and foamy urine in the telavancin group, adverse events were of similar type and severity between the treatment groups. Secondary: Not reported
Chen et al.[67] (2011) Cephalexin 40 mg/kg/day orally in divided doses TID for seven days	RCT Patients six months to 18 years of age with uncomplicated skin and soft tissue infections not requiring	N=200 3 months	Primary: Clinical improvement at 48 to 72 hours from the initiation of treatment Secondary:	Primary: A total of 94% of patients in the cephalexin group and 97% of patients in the clindamycin group showed improvement or resolution in their infection at 48 to 72 hours from the initial of treatment (P=0.50). The primary infection had worsened in 6% of patients in the cephalexin group and in 3% of patients in the clindamycin group. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs clindamycin 20 mg/kg/day orally in divided doses TID for seven days	hospitalization		Resolution of disease at seven days	A total of 97% of patients in the cephalexin group and 94% of patients in the clindamycin group had clinical resolution by seven days (P=0.33). Only one patient developed a new skin and soft tissue infection while on therapy. Compliance with taking medications as directed was 88% in the cephalexin group and 85% in the clindamycin group (P=0.66). According to data obtained from telephone contact (73%) and chart review (100%) at the three-month follow-up, 18% of patients had a recurrent skin and soft tissue infection. The risk of new skin and soft tissue infection did not differ according to isolation of MRSA vs MSSA from initial wound culture (21% MRSA vs 16% MSSA; P=0.51) or by cephalexin or clindamycin assignment (20 vs 16%; P=0.46). There were no serious adverse events related to study treatment.
Khawcharoenporn et al.[68] (2010) SMX-TMP one double strength tablet BID vs cephalexin 500 mg QID vs clindamycin 300 mg QID	RETRO Patients ≥18 years of age with cellulitis	N=405 Variable duration	Primary: Treatment success rate, compliance, safety Secondary: Not reported	Primary: The overall treatment success rate with SMX-TMP was significantly higher than the success rate with cephalexin (91 vs 74%; P<0.001). Clindamycin success rate was higher than that of cephalexin but did not reach statistical significance (85 vs 74%; P=0.22). The success rates of SMX-TMP and clindamycin were comparable. The treatment success rate with SMX-TMP was significantly more successful than cephalexin in patients who were male (P=0.001), were Pacific Islanders (P=0.001), had diabetes mellitus (P=0.001), were obese (P=0.002), had positive cultures for MRSA (P=0.01), and were cigarette smokers (P=0.04). The treatment success rate with clindamycin was higher than with cephalexin in patients who had MRSA infections (P<0.01), had moderately severe cellulitis (P<0.03), and were obese (P<0.04). MRSA was recovered in 62% of positive culture specimens. Compliance and adverse drug reaction rates were not significantly different among patients who received these three antibiotics.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Factors associated with treatment failure included therapy with an antibiotic that was not active against community-associated MRSA (P<0.001) and severity of cellulitis (P<0.001). Secondary: Not reported
Stevens et al.[69] (2000) Oxacillin 2 g IV every six hours followed by dicloxacillin 500 mg orally every six hours vs linezolid 600 mg IV every 12 hours	DB, DD, MC, RCT Hospitalized patients ≥18 years of age with a suspected gram-positive complicated skin and soft tissue infection	N=819 10 to 21 days	Primary: Clinical outcome and microbiological outcome based on resolution or improvement of clinical signs/ symptoms of skin and soft tissue infections at the end of treatment compared to baseline Secondary: Not reported	Primary: Of clinically evaluable patients (N=600), clinical cure rate was 88.6% in the linezolid group compared to 85.8% in the oxacillin and dicloxacillin group (P=0.300). Of microbiologically evaluable patients (N=294), the cure rate was 88.1% in the linezolid group compared to 86.1% in the oxacillin and dicloxacillin group (P=0.606). No statistically significant differences were noted in the frequency of adverse events between treatment groups. Secondary: Not reported
Stryjewski et al.[70] (2005) Telavancin 7.5 mg/kg IV once daily vs standard therapy (nafcillin or oxacillin 2 g IV every 6 hours,	AC, DB, RCT Patients ≥18 years of age with complicated skin and soft-tissue infections caused by gram-positive organisms	N=167 7 to 14 days posttreatment	Primary: Clinical response, microbiological response, safety Secondary: Not reported	Primary: The median duration of treatment was seven days in both groups. At the test-of-cure visit (seven to 14 days after the last dose of study medication), cure rates were 79% with telavancin and 80% with standard therapy (P=0.53). At the test-of-cure visit, 7% of patients receiving telavancin failed treatment compared to 4% of patients in the standard therapy group (no P value reported). For patients with S. *aureus* infection at baseline, 80% of patients in the telavancin group were cured and 77% of patients in the standard therapy

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
cloxacillin 0.5 to 1 g IV every 6 hours, or vancomycin 1 g IV BID)				group were cured (P=0.80). For patients with MRSA infection at baseline, cure rates were 82% for the telavancin group and 69% for the standard therapy group (P=1.00). A similar percentage of patients in each group (5%) discontinued therapy due to adverse events. Fewer serious adverse events were reported in the telavancin group than were for the standard therapy group. Secondary: Not reported
Stryjewski et al.[71] (2006) Telavancin 10 mg/kg IV once daily vs standard therapy (nafcillin or oxacillin 2 g IV every 6 hours, cloxacillin 0.5 to 1 g IV every 6 hours, or vancomycin 1 g IV BID)	AC, DB, RCT Patients ≥18 years of age with complicated skin and soft-tissue infections caused by gram-positive organisms	N=195 7 to 14 days posttreatment	Primary: Clinical cure in the clinically evaluable population, microbiological response, safety Secondary: Not reported	Primary: Overall, at the test-of-cure visit (seven to 14 days after the last dose of study medication), cure rates were 82% with telavancin and 85% with standard therapy (P=0.37). Overall, at the test-of-cure visit, 3% of patients receiving telavancin failed treatment compared to 6% of patients in the standard therapy group (no P value reported). In the clinically evaluable population at the test-of-cure visit, 96% of patients in the telavancin group and 94% of patients in the standard therapy group were cured (P=0.53). In the microbiologically evaluable population at the test-of-cure visit, 97% of patients in the telavancin group and 93% of patients in the standard therapy group were cured (P=0.37). In the microbiologically evaluable patients with *Staphylococcus aureus* at baseline, 96% of patients in the telavancin group and 90% of patients in the standard therapy group were cured (P=0.36). In the microbiologically evaluable patients with MRSA at baseline, 96% of patients in the telavancin group and 90% of patients in the standard therapy group were cured (P=0.42). Among the microbiologically evaluable population, baseline pathogens

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				were considered eradicated at the EOT in 89% of patients in the telavancin group and in 77% of patients in the standard-therapy group (P=0.09). At test-of-cure, pathogen eradication was higher, although not significantly, in those patients receiving telavancin (94 vs 83%; P=0.06). In patients with *Staphylococcus aureus* at baseline, eradication at test-of-cure was obtained in 92% of the patients receiving telavancin and 78% of the patients receiving standard therapy (P=0.07). In patients infected with MRSA, eradication rates were significantly higher in the telavancin group (92 vs 68%; P=0.04). Adverse events were reported in 56 and 57% of the patients receiving telavancin and standard therapy, respectively. Similar percentages of patients in both groups experienced severe adverse events (6 and 4% for the telavancin and standard therapy groups, respectively). Secondary: Not reported
Chuang et al.[72] (2011) Aztreonam 2 g IV every 12 hours plus vancomycin 1 g IV vs tigecycline 100 mg IV as an initial dose, followed by 50 mg IV every 12 hours	DB, MC, RCT Hospitalized patients ≥18 years of age with complicated SSSIs	N=127 5 to 14 days	Primary: Clinical response in clinically evaluable and clinical modified intent-to-treat populations Secondary: Clinical response (cure or failure) by baseline isolate and type of infection	Primary: In India, the clinical response rates in the clinically evaluable and clinically evaluable-modified intent-to-treat populations were higher in the tigecycline group than in the vancomycin-aztreonam group. Clinically evaluable rates were 83.3% in patients treated with tigecycline and 75.8% in patients treated with vancomycin-aztreonam. The clinically evaluable-modified intent-to-treat cure rates for tigecycline vs vancomycin-aztreonam were 78.6 vs 66.7%, respectively. Small sample size prevented non-inferiority analysis. In Taiwan, the clinical response rates in the clinically evaluable populations were lower in the tigecycline group than in the vancomycin-aztreonam group. Clinically evaluable rates were 78.6% in patients treated with tigecycline and 90.0% in patients treated with vancomycin-aztreonam. The clinically evaluable-modified intent-to-treat cure rates for tigecycline vs vancomycin-aztreonam were 73.3 and 75%, respectively. Small sample size prevented any meaningful statistical analysis. Secondary: In India, the number of isolates was small and no definitive inferences are

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				possible. However, tigecycline demonstrated antimicrobial efficacy against isolates commonly linked to complicated SSSIs. No MRSA isolates were noted among Indian patients. In Taiwan, few isolates were available. They included one patient with MRSA, which responded to tigecycline.
Corey et al.[73] (2010) Aztreonam 1 g plus vancomycin 1 g every 12 hours for 5 to 14 days vs ceftaroline 600 mg every 12 hours for 5 to 14 days	AC, DB, MC, RCT Patients ≥18 years of age with complicated skin and complicated skin and soft tissue infections who required ≥5 days of parenteral antibacterial therapy	N=702 Variable duration	Primary: Clinical cure rate at the test-of-cure visit (eight to 15 days after administration of the last dose of study medication) in the clinically evaluable and modified intent-to-treat populations Secondary: Microbiological success rate, safety	Primary: Clinical cure rates were similar for ceftaroline and vancomycin plus aztreonam in the clinically evaluable (91.1 vs 93.3%; 95% CI, -6.6 to 2.1) and modified intent-to-treat (86.6 vs 85.6%; 95% CI, -4.2 to 6.2) populations, respectively. Secondary: The clinical cure rate for MRSA complicated skin and soft tissue infections was 95.1% for ceftaroline and 95.2% for vancomycin plus aztreonam. Similar cure rates were found in patients with MSSA (91.3 and 94.6%), as well as in the patients from whom Gram-negative pathogens were isolated. The microbiological success rate was similar for ceftaroline and vancomycin overall, and for MRSA. Among the microbiologically evaluable patients, the baseline pathogen(s) was eradicated or presumed eradicated at similar rates in both the microbiologically evaluable and modified intent-to-treat populations (91.8 and 86.3% for ceftaroline; 92.5 and 83.7% for vancomycin plus aztreonam; 95% CI, -5.7 to 4.4 and 95% CI, -3.4 to 8.9, respectively). The incidence of adverse events was similar in both study groups. The majority of adverse events were mild in severity and similar in type among study groups. Diarrhea occurred in 3.4 vs 3.2% of patients in the ceftaroline and vancomycin plus aztreonam treatment groups, respectively.
Wilcox et al.[74] (2010) Aztreonam 1 g plus vancomycin 1 g	AC, DB, MC, RCT Patients ≥18 years of age with complicated skin	N=694 Variable duration	Primary: Clinical cure rate at the test-of-cure visit (eight to 15 days after	Primary: Cure rates at test-of-cure were comparable in both treatment groups across all study populations. In the clinically evaluable population, cure rates were 92.2 and 92.1% for ceftaroline and vancomycin plus aztreonam, respectively (95% CI, -4.4 to 4.5). In the modified intent-to-treat

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every 12 hours for 5 to 14 days vs ceftaroline 600 mg every 12 hours for 5 to 14 days	and soft tissue infections who required ≥5 days of parenteral antibacterial therapy		administration of the last dose of study medication) in the clinically evaluable and modified intent-to-treat populations Secondary: Microbiological success rate, safety	population, clinical cure rates for ceftaroline and vancomycin plus aztreonam were similar (85.1 vs 85.5%, respectively; 95% CI, -5.8 to 5.0). Secondary: In patients with MRSA isolated at baseline, cure rates were 91.4 and 93.3% for ceftaroline and vancomycin plus aztreonam, respectively. Similar cure rates were found in patients with MSSA (94.4% in both groups) as well as in the patients from whom a Gram-negative pathogen was isolated. Baseline pathogens were eradicated or presumed eradicated at similar rates in both the microbiologically evaluable and modified intent-to-treat populations among Gram-positive and a limited number of Gram-negative pathogens (92.9 and 86.6% for ceftaroline; 95.0 and 88.4% for vancomycin plus aztreonam; 95% CI, -6.9 to 2.5 and 95% CI, -7.5 to 3.9, respectively). There were no microbiological reinfections or recurrences at the late follow-up visit in either treatment group. The incidence of adverse events was similar in both study groups. The majority of adverse events were mild in severity and similar in type among study groups. Diarrhea occurred in 6.5 vs 4.4% in the ceftaroline and vancomycin plus aztreonam treatment groups, respectively. Adverse events considered related to the study drug and occurring in ≥3% of patients were diarrhea and pruritus.
Corey et al.[75] (2010) Aztreonam 1 g plus vancomycin 1 g every 12 hours for 5 to 14 days vs ceftaroline 600 mg	Pooled analysis (2 trials) Patients ≥18 years of age with complicated skin and soft tissue infections who required ≥5 days of parenteral antibacterial therapy	N=1,378 Variable duration	Primary: Clinical cure rate at the test-of-cure visit (eight to 15 days after administration of the last dose of study medication) in the clinically evaluable and modified intent-to-	Primary: Clinical cure rates were similar for ceftaroline and vancomycin plus aztreonam in the clinically evaluable (91.6 vs 92.7%) and modified intent-to-treat (85.9 vs 85.5%) populations, respectively. Secondary: Clinical cure rates were similar for ceftaroline and vancomycin plus aztreonam in patients infected with MRSA (93.4 vs 94.3%). The efficacy of ceftaroline and vancomycin plus aztreonam against polymicrobial and monomicrobial infections was similar.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
every 12 hours for 5 to 14 days			treat populations Secondary: Microbiological success rate, safety	Clinical relapse at the late follow-up visit was noted in 1.1% of patients in the ceftaroline group compared to 0.9% of patients in the vancomycin plus aztreonam group (clinically evaluable). Favorable microbiological response (microbiologically evaluable) was observed in 92.3% of patients in the ceftaroline group compared to 93.7% of patients in the vancomycin plus aztreonam group (95% CI, -4.8 to 2.0). Incidences of treatment-emergent adverse events were similar among the treatment groups. Diarrhea occurred in 4.9% of patients in the ceftaroline group and in 3.8% of patients in the vancomycin plus aztreonam group (modified intent-to-treat population). Adverse events considered to be related to study drug in ≥3% of patients were pruritus, nausea, and diarrhea.
Gastrointestinal Infections				
Kearney et al.[76] (2000) Tetracycline 500 mg QID, bismuth subsalicylate 2 tablets QID, metronidazole 250 mg QID, and cimetidine 400 mg BID or famotidine 20 mg BID for 14 days (BMT-H2) vs tetracycline 500 mg QID, bismuth subsalicylate 2 tablets QID, metronidazole 250	OL Patients with peptic ulcer disease or prescribed H2-receptor antagonists or proton pump inhibitors, and who tested positive with histology, rapid urease or urea breath testing for *H pylori* infection	N=224 6 weeks	Primary: Defining treatment success rates for *H pylori* infection at end of study Secondary: Adverse events	Primary: The intent-to-treat cure rates for BMT-H2, BMT-PPI, and MLC were 81, 87, and 90%, respectively (all; P>0.05). The per-protocol cure rates for BMT-H2, BMT-PPI, and MLC were 84, 91, and 92% (all; P>0.05). Secondary: The side-effect profile for the three treatment groups revealed no significant differences in the frequency of the most common side effects, diarrhea and constipation. Metallic taste was significantly more severe in the MLC group (P=0.04). Nausea was significantly more common in the MLC group than the BMT-H2 group (P=0.04). There were no significant differences in the frequency of dizziness/lightheadedness, cramping, or other side effects between the BMT-H2 and MLC groups, and between BMT-PPI and BMT-H2 groups. Severe headaches were significantly more frequent in the BMT-PPI group than the BMT-H2 group (P=0.02). A significantly higher number of patients discontinued therapy due to adverse events in the BMT-H2 and BMT-PPI treatment groups than the MLC group (P=0.049).

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mg QID, and lansoprazole 30 mg BID for 7 days (BMT-PPI) vs metronidazole 500 mg BID, lansoprazole 30 mg BID, and clarithromycin 250 mg BID for 7 days (MLC)				
Magaret et al.[77] (2001) Tetracycline 250 mg QID, bismuth subsalicylate 2 tablets QID, lansoprazole 30 mg BID, and metronidazole 250 mg QID for 14 days vs lansoprazole 30 mg BID, amoxicillin 1,000 mg BID, and clarithromycin 500 mg BID for 14 days	MC, RCT Patients years of age failing prior treatment for *H pylori*	N=48 6 weeks	Primary: Negative 14C-UBT of <50 disintegrations per minute at time of follow-up indicating cure of infection Secondary: Side effects and compliance	Primary: Per-protocol eradication rates for patients on triple therapy and quadruple therapy were 82 and 80%, respectively (P=0.85). Intention-to-treat eradication rates for triple and quadruple therapy were 72 and 65%, respectively (P=0.63). Secondary: Compliance in patients receiving triple and quadruple therapy was 89% (P=0.98). Side effects were reported in 84% of patients on triple therapy and 82% of patients on quadruple therapy (P=0.85). Side effects included nausea (33%), upset stomach (25%), diarrhea (36%), abdominal pain (16%), lightheadedness/dizziness (4%), and fatigue (8%).
Miehlk et al.[78] (2003)	RCT, XO	N=84	Primary: Two negative	Primary: In the per-protocol analysis, patients on high-dose dual therapy and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Tetracycline 500 mg QID, bismuth citrate 107 mg QID, omeprazole 20 mg BID, and metronidazole 500 mg QID for 14 days vs omeprazole 40 mg QID and amoxicillin 750 mg QID for 14 days	Patients 18 to 80 years of age with at least one previous failure of *H pylori* therapy documented by confirmatory examinations and antimicrobial resistance to both metronidazole and clarithromycin	26 months	biopsy-based tests, histology and rapid urease test, or a validated 13C-urea breath test to confirm successful treatment Secondary: Not reported	quadruple therapy achieved *H pylori* cure rates of 83.8 and 92.1%, respectively (P=0.71). Cure rates using intent-to-treat analysis were 75.6 and 81.4% for high-dose dual therapy and quadruple therapy, respectively, and were not significantly different (P=0.60). Secondary: Not reported
Perri et al.[79] (2001) Tetracycline 500 mg QID, bismuth citrate 240 mg BID, pantoprazole 40 mg BID, and metronidazole 250 mg TID for 10 days (quadruple therapy group) vs pantoprazole 40 mg BID, amoxicillin 1 g BID, and rifabutin 150 mg every other day for 10 days	OL, PRO, RCT Patients with *H pylori* infection confirmed by 13C-urea breath test after failure of one or more standard regimens	N=135 6 weeks	Primary: Eradication rates as defined by negative 13C-urea breath test four weeks after end of treatment Secondary: Side effect rates reported after end of treatment	Primary: By intent-to-treat analysis, eradication rates for the pantoprazole, amoxicillin and rifabutin 150 mg treatment group (RIF 150 mg group) were 66.6%. Eradication rates for pantoprazole, metronidazole, bismuth citrate, and tetracycline (quadruple therapy group) were also 66.6%. The eradication rate for pantoprazole, amoxicillin, and rifabutin 300 mg (RIF 300 mg group) was 86.6%, which was significantly different than the other two treatment groups (P<0.025). Secondary: There was a significant difference in the side effects observed in rifabutin-treated patients compared to patients receiving quadruple therapy. The rates of side effects were 9, 11 and 47%, (P<0.0001), for the triple therapies with the RIF 150 mg group, RIF 300 mg group, and quadruple therapy group, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(RIF 150 mg group) vs pantoprazole 40 mg BID, amoxicillin 1 g BID, and rifabutin 300 mg every other day for 10 days (RIF 300 mg group)				
Katelaris et al.[80] (2002) Tetracycline 500 mg QID, bismuth subcitrate 108 mg QID, pantoprazole 40 mg BID, metronidazole 200 mg TID and 400 mg in the evening for 7 days (PBTM7) vs tetracycline 500 mg QID, bismuth subcitrate 108 mg QID, and metronidazole 200 mg TID and 400 mg in the evening for 14 days	MC, OL, PG, RCT Patients ≥18 years of age with *H pylori* infection confirmed by a positive urease test and confirmatory histology and 13C-urea breath test	N=405 8 weeks	Primary: At week eight, 13C-urea breath test to determine the outcome of eradication therapy Secondary: Compliance and adverse event profile	Primary: By intent-to-treat analysis, the eradication rates for the PAC7, PBTM7, and BTM14 treatment groups were 78, 82 and 69%, respectively. By per-protocol analysis, the corresponding eradication rates were 82, 88, and 74%, respectively. In both analysis, the eradication rates for PBTM7 and PAC7 were not significantly different (all P>0.05), while eradication rates for PBTM7 were significantly higher than BTM14 (P=0.01). Secondary: Adverse effects were common in all treatment groups. Adverse effects that interfered with activities of daily living were significantly higher in the BTM14 group (P<0.01). The number of patients who discontinued treatment due to adverse effects was also higher in the BTM14 group (9%) vs the PBTM7 group (3%) and the PAC7 group (2%). Noncompliance, defined as less than 90% of study drug taken, was higher in BTM14 than PBTM7 and PAC7.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(BTM14) vs pantoprazole 40 mg, amoxicillin 1,000 mg, and clarithromycin 500 mg BID (PAC7)				
Uygun et al.[81] (2007) Tetracycline 500 mg QID, bismuth subsalicylate 300 mg QID, lansoprazole 30 mg BID, and metronidazole 500 mg TID (BLTM group) vs lansoprazole 30 mg BID, amoxicillin 1 g BID and clarithromycin 500 mg BID (LAC)	RCT, SB, SC Patients with *H pylori* infection and non-ulcer dyspepsia	N=240 14 days	Primary: *H pylori* eradication rates Secondary: Not reported	Primary: The intent to treat and per protocol populations, *H pylori* eradication rates were 70% (95% CI, 61 to 78) and 82.3% (95% CI, 74 to 89) in the BLTM group, and 57.5% (95%CI, 48 to 66) and 62.7% (95%CI, 53 to 71) in the LAC group. The BLTM treatment achieved a significantly better eradication rate than the LAC treatment in per protocol analysis (82.3 vs 62.7%; P=0.002). Although a better intent to treat rate was obtained in the BLTM group than in the LAC group, the difference was NS (70 vs 57.5%; P=0.06). Mild to severe side-effects, which were more frequent in the BLTM group, were reported in 18.2% of the patients. Although it was not statistically significant, the number of patients ceasing the treatment for side-effects was more in BLTM group than in the LAC group. Secondary: Not reported
Wu et al.[82] (2011) Tetracycline 500 mg QID, bismuth subcitrate 120 mg QID, esomeprazole	RCT Patients ≥18 years of age with persistent *H pylori* infection who failed standard first-line	N=120 8 weeks posttreatment	Primary: Eradication rates, adverse events, resistance rates, compliance Secondary:	Primary: In the intent to treat analysis, there was a significantly lower eradication rate for the EBTA group (62%; 95% CI, 50 to 75) than for the EBTM group (81%; 95% CI, 71 to 91; P=0.02). In the per protocol analysis, *H pylori* infection was eradicated in 64% of the EBTA group (95% CI, 52 to 76) and 83% of the EBTM group (95%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
40 mg BID, and metronidazole for 7 days as rescue therapy (EBTM) vs tetracycline 500 mg QID, bismuth subcitrate120 mg QID, esomeprazole 40 mg BID, and amoxicillin 500 mg QID for 7 days as rescue therapy (EBTA)	therapy (proton-pump inhibitor, clarithromycin and amoxicillin)		Not reported	CI, 74 to 92; P=0.01). A total of 19% of patients in the EBTA group and 44% of patients in the EBTM group reported at least one adverse event during eradication therapy. The EBTA group had fewer adverse events than the EBTM group (P=0.004). The frequency of nausea in the EBTA group was lower than in the EBTM group (5 vs 16%, respectively). Tetracycline- and metronidazole-resistant strains were found in 2 and 53% of the patients, respectively. No strains developed resistance to amoxicillin. In the EBTA group, the *H pylori* eradication rate for the tetracycline-susceptible strains was 67% by intent to treat analysis and 68% by per protocol analysis. All the strains in the subgroup were susceptible to amoxicillin. In the EBTM group, no tetracycline-resistant strains existed. The eradication rate of tetracycline-susceptible strains was 80 and 83% by intent to treat and per protocol analyses, respectively. With respect to metronidazole resistance, eradication rates were similar between susceptible and resistant strains by either intent to treat or per protocol analyses. Compliance rates were 97% in both treatment groups (P=1.00). Secondary: Not reported
Songür et al.[83] (2009) Tetracycline 500 mg QID, bismuth subcitrate 300 mg QID, lansoprazole 30 mg BID, and metronidazole 500 mg BID for 10 days (BLTM) vs	RCT, SC Patients with *H pylori* infection and dyspeptic symptoms	N=464 14 days	Primary: Eradication rates, compliance Secondary: Not reported	Primary: In the per protocol analysis, eradication rates in LAC, BLTM, RBLTM, and LTM groups were 35.6, 54.9, 64.4, and 60.0%, respectively. In the intent to treat analysis, eradication r rates in LAC, BLTM, RBLTM, and LTM groups were 32.7, 47.1, 57.3, and 54.8%, respectively. The BLTM, RBLTM, and LTM treatment groups achieved a significantly better eradication rate than the LAC treatment group (P<0.001). There was no significant difference between BLTM, RBLTM, and LTM treatment groups. Compliance rates with LAC, BLTM, RBLTM, and LTM therapies were 91, 87, 90, and 94%, respectively.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
tetracycline 500 mg QID, ranitidine bismuth citrate 400 mg BID, lansoprazole 30 mg BID, and metronidazole 500 mg BID for 10 days (RBLTM) vs tetracycline 500 mg QID, lansoprazole 30 mg BID, and metronidazole 500 mg BID for 10 days (LTM) vs lansoprazole 30 mg BID, amoxicillin 1,000 mg BID, and clarithromycin 500 mg BID for 14 days (LAC)				The treatments were generally well tolerated. Secondary: Not reported
Malfertheiner et al.[84] (2011) Tetracycline 125 mg, bismuth subcitrate potassium 140 mg,	OL, RCT Patients ≥18 years of age with *H pylori* infection and upper gastrointestinal symptoms	N=399 56 days posttreatment	Primary: Eradication rates, resistance rates, and safety Secondary: Not reported	Primary: In the per protocol analysis, eradication rates were 93% with quadruple therapy compared to 70% with standard therapy (P<0.0001). Quadruple therapy was found to be non-inferior to standard therapy. In the intention-to-treat analysis, eradication rates were 80% with quadruple therapy compared to 55% with standard therapy (P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
and metronidazole 125 mg (as a single three-in-one capsule) 3 capsules QID plus omeprazole 20 mg BID for 10 days (quadruple therapy) vs omeprazole 20 mg, amoxicillin 500 mg, and clarithromycin 500 mg BID for 7 days (standard therapy)				Metronidazole sensitivity did not significantly affect the efficacy of quadruple therapy in the per protocol population (P=0.283). Clarithromycin sensitivity seemed to significantly affect the efficacy of standard therapy (P<0.0001). Simultaneous metronidazole and clarithromycin resistance reduced efficacy only in patients treated with standard therapy (P=0.001). The incidence of serious treatment emergent adverse events and discontinuations due to a treatment emergent adverse events were similar between groups (<2.0%). The main adverse events were gastrointestinal and central nervous system disorders. Secondary: Not reported
Zheng et al.[85] (2010) Tetracycline 750 mg BID, colloidal bismuth subcitrate 220 mg BID, pantoprazole 40 mg BID, and metronidazole 400 mg TID for 10 days (PBMT) vs pantoprazole 40 mg BID, amoxicillin 1.0 g BID and	OL, RCT, SC Patients 18 to 70 years of age with non-ulcer dyspepsia and *H pylori* infection	N=170 7 to 10 days	Primary: Eradication rates, resistance rates, safety Secondary: Not reported	Primary: In the intent to treat analysis, eradication rates were 63.5% in the PAC group and 89.4% in the PBMT groups (P<0.05). In the per protocol analysis, the eradication rates were 65.1% in the PAC group and 91.6% in the PBMT group (P<0.05). The *H pylori* primary resistance rates to metronidazole and clarithromycin were 41.6 and 20.8%, respectively, whereas all the *H pylori* isolates were sensitive to amoxicillin and tetracycline. Adverse events were similar among the treatment groups and included bitter taste, nausea, poor appetite, and occasional symptoms, such as diarrhea, vomiting, drug eruption, insomnia, constipation, and lethargy. The adverse events rates of quadruple therapy and triple therapy were 42.3 and 60.0%, respectively. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
clarithromycin 500 mg BID for 7 days (PAC)				
de Boer et al.[86] (1998) Tetracycline 500 mg QID, ranitidine bismuth citrate 400 mg BID, and metronidazole 500 mg TID for 7 days vs ranitidine bismuth citrate 400 mg BID, amoxicillin 1,000 mg BID, and clarithromycin 500 mg BID for 7 days vs ranitidine bismuth citrate 400 mg BID, clarithromycin 500 mg BID for 14 days	OL, PG, RCT Patients with upper gastrointestinal symptoms and infected with *H pylori*	N=168 8 weeks	Primary: Endoscopy performed six weeks after completion of treatment to determine *H pylori* infection, defined as a positive CLOtest, confirmed by histology or culture Secondary: Safety	Primary: Logistical regression analysis determined that there was no difference between the seven-day and 14-day treatments. Intent-to-treat analysis cure rate for the ranitidine bismuth citrate, tetracycline, and metronidazole treatment group was 86%. The cure rate for the ranitidine bismuth citrate, amoxicillin, and clarithromycin treatment group was 92%. The cure rate for the ranitidine bismuth citrate and clarithromycin treatment group was 95%. Per-protocol cure rates were 89, 93, and 96% respectively. There was no statistical difference between the three groups. Secondary: Side effects were comparable among the treatment groups. Overall, 32% of patients in the ranitidine bismuth citrate, tetracycline, metronidazole treatment group, 18% of the ranitidine bismuth citrate, amoxicillin, and clarithromycin treatment group, and 23% of the ranitidine bismuth citrate and clarithromycin treatment group reported side effects during the trial period (P=0.249).
Altintas et al.[87] (2004) Tetracycline 1 g BID, ranitidine-bismuth citrate 400 mg BID, and	RCT Patients ≥18 years of age who were resistant to triple therapy consisting of a proton pump	N=52 6 weeks	Primary: Eradication rates of *H pylori* as confirmed by endoscopy and biopsy	Primary: There was a significant difference between the treatment groups. Eradication rates for triple and dual therapy were 44.4 and 12.0%, respectively (P=0.01). Secondary: There were significant improvements in the severity of endoscopic gastritis

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
metronidazole 500 mg TID for 14 days (triple therapy) vs ranitidine-bismuth citrate 1 g BID for 14 days and azithromycin 500 mg QD for 7 days (dual therapy)	inhibitor clarithromycin and amoxicillin for the treatment of *H pylori*		Secondary: Improvement in symptoms of endoscopic gastritis	in both groups (P=0.01), but no significant differences between the two groups (P=0.600).
Luther et al.[88] (2010) Tetracycline, metronidazole, bismuth-containing compound, and proton-pump inhibitor (bismuth quadruple therapy) vs clarithromycin triple therapy (amoxicillin, clarithromycin, and proton-pump inhibitor)	MA Patients with *H pylori* infection	N=1,679 (9 trials) Variable duration	Primary: Eradication rate, compliance rate, adverse events Secondary: Not reported	Primary: The eradication rate with bismuth quadruple therapy was 78.3% compared to 77% with clarithromycin triple therapy (RR, 1.002; 95% CI, 0.936 to 1.073). The compliance rate with bismuth quadruple therapy was 92.6% compared to 98.9% with clarithromycin triple therapy (RR, 0.99; 95% CI, 0.938 to 1.045). The overall incidence of adverse events in patients receiving bismuth quadruple therapy was 35.5% compared to 35.4% with clarithromycin triple therapy (RR, 1.037; 95% CI, 1.037 to 1.135). Secondary: Not reported
Hu et al.[89] (2012) Rifaximin	MA RCTs of rifaximin for the prevention of travelers' diarrhoea	N=502 Duration varied	Primary: Occurrence of travelers' diarrhoea over a two-week treatment period.	Primary: Rifaximin treatment showed a significant protection against travelers' diarrhoea (RR, 0.41; 95% CI, 0.30 to 0.56; P<0.00001). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	published in PubMed, the Cochrane Central Register of Controlled Trials, Embase, and the Science Citation Index were searched		Secondary: Requirement for antibiotic treatment, occurrence of mild diarrhea, occurrence of travelers' diarrhoea in the third week after drug withdrawal, incidence of travelers' diarrhoea associated with isolation of diarrheagenic *Escherichia coli* and adverse events	Rifaximin treatment resulted in less antibiotic-treated travelers' diarrhoea (RR, 0.30; 95% CI, 0.18 to 0.49; P<0.00001). There was no significant difference between rifaximin and placebo in the occurrence of mild diarrhoea (RR, 1.11; 95% CI, 0.78 to 1.59; P=0.55) and the occurrence of travelers' diarrhoea in the third week after drug withdrawal (RR, 0.73; 95% CI, 0.30 to 1.73; P=0.47). Enterotoxigenic *Escherichia coli* was the major cause of travelers' diarrhoea, and all trials reported no differences in adverse events between rifaximin and placebo.
Pimentel et al.[90] (2011) TARGET 1 TARGET 2 Rifaximin 550 mg TID daily for 14 days vs placebo	DB, PC, RCT (2 trials) Patients ≥18 years of age with irritable bowel syndrome without constipation	N=1,260 12 weeks	Primary: Proportion of patients who had adequate relief of global irritable bowel syndrome symptoms (weeks three through six) Secondary: Proportion of patients who had adequate relief of irritable bowel syndrome related bloating, percentage of patients who had a	Primary: Significantly more patients in the rifaximin group than in the placebo group experienced adequate relief of global irritable bowel syndrome symptoms during at least 2 of the first 4 weeks after treatment (40.8 vs 31.2%; P=0.01, in TARGET 1; 40.6 vs 32.2%; P=0.03, in TARGET 2; 40.7 vs 31.7%; P<0.001, in the two studies combined). The proportion of patients with a response to treatment was significantly greater in the rifaximin group than in the placebo group (42.7 vs 30.6%; P<0.001, in TARGET 1; 37.8 vs 28.4%; P=0.007, in TARGET 2; 40.2 vs 29.5%; P<0.001, in the two studies combined). Secondary: More patients in the rifaximin group than in the placebo group had adequate relief of bloating during at least two of the first four weeks after treatment (39.5 vs 28.7%; P=0.005, in TARGET 1; 41.0 vs 31.9%; P=0.02, in TARGET 2; 40.2 vs 30.3%; P<0.001, in the two studies combined).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			response to treatment as assessed by daily self-ratings of global irritable bowel syndrome symptoms and individual symptoms of bloating, abdominal pain, and stool consistency	A significantly greater proportion of patients in the rifaximin group than in the placebo group had relief of irritable bowel syndrome-related bloating (39.2 vs 32.5%; P=0.05, in TARGET 1; 43.5 vs 30.9%; P<0.001, in TARGET 2; 41.3 vs 31.7%; P<0.001, in the two studies combined). A significantly greater proportion of patients in the rifaximin group than in the placebo group had relief of irritable bowel syndrome-related abdominal pain and discomfort during the primary evaluation period (44.3 vs 36.3%; P=0.03, in TARGET 1; 42.9 vs 34.4%; P=0.02, in TARGET 2). In an assessment of the composite end point of abdominal pain or discomfort and loose or watery stools, significantly more patients in the rifaximin group than in the placebo group had relief during the primary evaluation period (46.6 vs 38.5%; P=0.04, in TARGET 1; 46.7 vs 36.3%; P=0.008, in TARGET 2), and a significantly greater proportion of patients in the rifaximin group had relief with respect to the individual components of this end point. More patients in the rifaximin group than in the placebo group in both studies had adequate relief of global irritable bowel syndrome symptoms within the first month, with continued relief during the first two months and during all three months in both studies (P=0.05 in TARGET 1, P=0.005 in TARGET 2, and P<0.001 in the two studies combined, for relief during all three months). Patients treated with rifaximin had adequate relief of global irritable bowel syndrome symptoms during the entire three months of the study compared to placebo (P=0.003 in TARGET 1, P=0.01 in TARGET 2, and P<0.001 in the two studies combined) and of IBS-related bloating compared to placebo (P=0.01 in TARGET 1, P<0.001 in TARGET 2, and P<0.001 in the two studies combined). The incidence of adverse events was similar in the two groups.
Martinez-Sandoval et al.[91] (2010)	DB, MC, RCT Healthy students ≥18 years of age	N=210 2 weeks	Primary: Occurrence of travelers' diarrhea	Primary: Prophylactic treatment with rifaximin significantly reduced the risk of developing travelers' diarrhea compared to placebo (15 vs 47%, respectively; P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Rifaximin 600 mg once daily for 2 weeks vs placebo	attending classes in Guadalajara, Mexico who ingested the study drug within 72 hours of arrival in Mexico		Secondary: Incidence of travelers' diarrhea resulting from all causes; incidence of travelers' diarrhea associated with diarrheagenic *Escherichia coli*; incidence of travelers' diarrhea associated with invasive bacterial pathogens; incidence of travelers' diarrhea occurring in the seven-day follow-up period; protection rates against travelers' diarrhea, travelers' diarrhea associated with diarrheagenic *Escherichia coli*, and travelers' diarrhea associated with invasive bacterial pathogens; number of participants with symptoms of enteric infection and mild diarrhea without travelers' diarrhea	Secondary: A smaller percentage of patients who received rifaximin developed travelers' diarrhea (20%) compared to those who received placebo (48%; P<0.0001). A smaller percentage of patients who developed travelers' diarrhea in the rifaximin group received rescue therapy compared to placebo (14 vs 32%, respectively; P=0.003). There was no significant difference in the percentage of patients who developed travelers' diarrhea associated with diarrheagenic *Escherichia coli* with rifaximin compared to placebo (9 vs 18%, respectively; P=0.098). Travelers' diarrhea was not associated with invasive bacterial pathogens in any patient. The percentage of individuals who developed travelers' diarrhea associated with unidentified pathogens was significantly lower in the rifaximin vs placebo group (11 vs 30%, respectively; P=0.01). A greater percentage of patients who received rifaximin completed the 14-day treatment course without developing travelers' diarrhea (76%) compared to those who received placebo (51%; P=0.0004). The percentage of patients who experienced mild diarrhea, but did not develop travelers' diarrhea, was similar between the rifaximin and placebo groups (29 vs 21%, respectively). During the seven-day post-treatment period, the percentage of patients who developed travelers' diarrhea was similar for rifaximin (16%) vs placebo (15%). The protection rates achieved with rifaximin prophylaxis were similar for travelers' diarrhea (58%; 95% CI, 35 to 73) and travelers' diarrhea requiring rescue antibiotic therapy (56%; 95% CI, 23 to 75).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Zanger et al.[92] (2013) Rifaximin 200 mg tablets BID vs placebo	DB, PC, PG, SC Individuals 18 to 64 years of age who were planning a 6 to 28 day journey to south and southeast Asia	N=239 Duration varied	Primary: Time to the first episode of classic travelers' diarrhoea, defined as three or more loose stools in 24 hours, accompanied by one or more enteric symptoms. Secondary: Not reported	Primary: Forty eight (41%) of 117 participants in the placebo group and 30 (25%) of 122 in the rifaximin group reported classic episodes of travelers' diarrhoea. From departure to seven days after return, rifaximin provided 48% protection (95% CI, 16 to 68) by lowering the incidence of travelers' diarrhoea from 199 (150 to 264) per 100 person-days in the placebo group to 104 (072 to 148) in the intervention group (incidence rate ratio, 052; 95% CI, 032 to 084; P=0005). The number needed to treat was 570 (95% CI, 344 to 1,669) to prevent one case of classic travelers' diarrhoea during the first three weeks of follow-up. Secondary: Not reported
Steffen et al.[93] (2003) Rifaximin 600 mg TID vs rifaximin 1,200 mg TID vs placebo	DB, MC, PG, RCT Adult travelers affected by acute diarrhea with at least one sign of enteric infection	N=380 Treatment: 3 days Follow-up: 5 days	Primary: Time elapsed from ingestion of first dose to passage of the last unformed stool; wellness (clinical cure) Secondary: Number of subjects with improvement of diarrhea during 24 hour intervals, number of unformed stools passed per time interval, number of subjects declared "well," treatment failures, and microbiological	Primary: Median time to last unformed stool was 32.5 and 32.9 hours for rifaximin 600 and 1,200 mg, respectively, compared to 60 hours for placebo (P=0.0001 for each treatment group vs placebo). Clinical cure within 120 hours was noted at a greater rate with rifaximin 600 and 1,200 mg (79.2 and 81.0%, respectively) compared to placebo (60.5%; P=0.001 for each treatment group vs placebo). Secondary: Improvement of diarrhea was greater in the rifaximin 600 mg group compared to placebo. In the 24 to 48 hour interval, improvement was seen in 87% of patients given rifaximin 600 mg and 72% in placebo-treated patients (P=0.007); in the 48 to 72 hour interval, improvement was seen in 91% of patients given rifaximin 600 mg and 78% in placebo-treated patients (P=0.008). Although the rate of improvement was greater than placebo overall, the differences did not reach statistical significance. Mean number of unformed stools passed was 3.1 for rifaximin groups vs 3.8 for placebo (day one), 1.6 for rifaximin groups vs 2.6 for placebo (day 2), 0.5 for rifaximin groups vs 0.9 for placebo (final day; P=0.001, repeated measures analysis of variance).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			cure	Treatment failures were noted 16.0 to 16.7% of the time with both rifaximin groups vs 34.8% with placebo-treated patients (P=0.001). Rate of microbiological cure was not significantly different across treatment groups. The most common adverse events were gastrointestinal related. Headache was also frequently reported, though with no difference between groups. Fatigue was reported more often with rifaximin 1,200 mg (1.1%; P=0.023).
Dupont et al.[94] (2005) Rifaximin 200 mg once daily vs rifaximin 200 mg BID vs rifaximin 200 mg TID vs placebo	DB, PC, RCT Healthy students ≥18 years of age attending classes in Guadalajara, Mexico who ingested the study drug within 72 hours of arrival in Mexico	N=210 2 weeks	Primary: Occurrence of diarrhea Secondary: Occurrence of mild diarrhea (defined as passage of one to two unformed stools plus a symptom) and number of days of occurrences of moderate to severe enteric symptoms per 100 person-days of observation	Primary: Over the two week treatment period, diarrhea developed in 53.7% of patients in the placebo group, 12% of patients in the once-daily rifaximin group (RR, 0.22; 95% CI, 0.10 to 0.49), 19.23% of patients in the rifaximin BID group (RR, 0.36; 95% CI, 0.19 to 0.66), 12.96% of patients in the rifaximin TID group (RR, 0.24; 95% CI, 0.12 to 0.50), and 14.74% of the combined rifaximin groups (RR, 0.27; 95% CI, 0.17 to 0.43). Diarrhea was prevented in all of the rifaximin groups (P<0.001 for each rifaximin group vs placebo). The protection rates were 72 and 77% against travelers' diarrhea and antibiotic-treated diarrhea, respectively (P<0.001 for both). Secondary: Rifaximin reduced the occurrence of mild diarrhea compared to placebo (P=0.02). In those who did not develop diarrhea, rifaximin significantly reduced the occurrence of moderate and severe intestinal problems (P=0.009 for pain or cramps; P=0.02 for excessive gas) compared to placebo. The incidence of adverse events was comparable between the rifaximin groups and the placebo group.
DuPont et al.[95] (2007)	RCT Adults with acute	N=310 5 days	Primary: Median time from beginning therapy	Primary: Rifaximin and rifaximin-loperamide significantly reduced the median time until passage of the last unformed stool (32.5 and 27.3 hours, respectively)

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Rifaximin 200 mg TID for 3 days vs loperamide 4 mg initially, followed by 2 mg after each unformed stool vs rifaximin 200 mg TID for 3 days plus loperamide 4 mg initially, followed by 2 mg after each unformed stool	diarrhea (≥3 unformed stools in 24 hours) with ≥ 1 symptom of enteric infection		until passing the last unformed stool Secondary: Not reported	compared to loperamide (69 hours; P=0.0019). The mean number of unformed stools passed during illness was lower with rifaximin-loperamide (3.99) compared to rifaximin (6.23; P=0.004) or loperamide alone (6.72; P=0.002). All treatments were well tolerated with a low incidence of adverse events. Secondary: Not reported
Louie et al.[96] (2011) Fidaxomicin 200 mg BID for 10 days vs vancomycin 125 mg orally QID for 10 days	DB, MC, RCT Patients ≥16 years of age with diarrhea and a diagnosis of *Clostridium difficile* infection, as well as the presence of *Clostridium difficile* toxin A, B, or both in the stool	N=629 28 days posttreatment	Primary: Clinical cure (resolution of symptoms and no need for further therapy for *Clostridium difficile* infection as of the second day after the end of the course of therapy) Secondary: Recurrence of *Clostridium difficile* infection (diarrhea and a	Primary: Clinical cure rates in the modified intent to treat analysis were 88.2% with fidaxomicin and 85.8% with vancomycin. Clinical cure rates in the per protocol analysis were 92.1% for fidaxomicin and 89.8% for vancomycin. The rates of clinical cure with fidaxomicin were non-inferior to those with vancomycin. Secondary: Recurrence in the modified intent to treat analysis was 15.4% with fidaxomicin compared to 25.3% with vancomycin (P=0.005). Recurrence in the per protocol analysis was 13.3% with fidaxomicin compared to 24% with vancomycin (P=0.004). Significantly fewer patients in the fidaxomicin group than in the vancomycin group had a recurrence of the infection.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			positive result on a stool toxin test within four weeks after treatment)	
Cornely, Crook et al.[97] (2012) Fidaxomicin 200 mg every 12 hours for 10 days vs vancomycin 125 mg orally every 6 hours daily for 10 days	DB, MC, PRO, RCT Patients ≥16 years of age with *Clostridium difficile* infection and either *Clostridium difficile* toxin A or B in the stool	N=535 28 days posttreatment	Primary: Clinical cure (resolution of symptoms and no need for further therapy for *Clostridium difficile* infection as of the second day after the end of the course of therapy) Secondary: Recurrence of *Clostridium difficile* infection (diarrhea and a positive result on a stool toxin test within 30days of treatment completion)	Primary: In the per protocol population, clinical cure rates in the fidaxomicin group (91.7%) were non-inferior to the rates in the vancomycin group (90.6%; one-sided 97.5% CI, -4.3). In the modified intent to treat population, clinical cure rates in the fidaxomicin group (87.7%) were non-inferior to the rates in the vancomycin group (86.8%; treatment difference, 0.9; 95% CI, -4.9 to 6.7; P=0.754). Secondary: In the modified intent to treat population, significantly more patients in the vancomycin group had a recurrence compared to the fidaxomicin group (26.9 vs 12.7%; treatment difference, -14.2; 95% CI, -21.4 to -6.8; P=0.0002). In this population, there was a significantly higher rate of sustained clinical response in the fidaxomicin group compared to the vancomycin group (76.6 vs 63.4%; treatment difference, 13.2; 95% CI, 5.3 to 21.0; P=0.001).
Cornely, Miller et al.[98] (2012) Fidaxomicin 200 mg BID for 10 days vs	DB, MC, PRO, RCT Patients >15 years of age with *Clostridium difficile* infection and either *Clostridium difficile* toxin A or B in the stool	N=178 28 days posttreatment	Primary: Recurrence of *Clostridium difficile* infection (diarrhea and a positive result on a stool toxin test within 30 days of treatment completion)	Primary: In patients with no prior episode of *Clostridium difficile* infection, there was a significantly greater proportion of patients in the vancomycin group (24.8%) that had a recurrence compared to the fidaxomicin group (12.9%; treatment difference, -11.8; 95% CI, 17.1 to 6.5; P<0.001). In patients with one prior episode of *Clostridium difficile* infection, there was no significant difference in recurrence between the vancomycin and fidaxomicin groups (32.3 vs 20.3%; treatment difference -12.3; 95% CI, -25.4 to 1.5; P=0.08).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vancomycin 125 mg orally QID for 10 days			Secondary: Not reported	Secondary: Not reported
McFarland et al.[99] (2002) Vancomycin ≤1 g to ≥2 g orally per day; taper, pulse, or combination with another antimicrobial vs metronidazole ≤1 g to 2 g PO per day; taper or pulse	DB, PC, RCT (2 trials) Patients 18 to 91 years of age with recurrent episodes of *Clostridium difficile* disease; ≥1 prior episode within 1 year	N=163 2-4 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.[100] (2005) Vancomycin oral vs metronidazole or bacitracin or fusidic acid* or teicoplanin* or rifaximin vs placebo	MA of RCTs Patients with diarrhea who recently received antibiotics for an infection other than *Clostridium difficile*	N=582 Variable duration	Primary: Initial resolution of diarrhea, initial conversion of stool 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	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). 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

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			cessation of prior antibiotic therapy Secondary: Rates of sepsis, emergent surgery, fecal diversion or colectomy, and death	(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 9 deaths, 5 of which were specified to be due to underlying illness and not related to treatment. Secondary: These end points occurred infrequently in all of the studies.
Zar et al.[101] (2007) Vancomycin 125 mg orally QID for 10 days vs metronidazole 250 mg orally QID 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
Nelson[102] (2007) Vancomycin vs metronidazole, fusidic acid, nitazoxanide, teicoplanin, rifampin, rifaximin,	MA Patients with *Clostridium difficile*-associated diarrhea	N=1157 (12 RCT) Variable duration	Primary: Clinical cure Secondary: Not reported	Primary: No single antibiotic was clearly superior to others. Teicoplanin showed in some outcomes significant benefit over vancomycin and fusidic acid, and a trend towards benefit compared to metronidazole. Only one placebo controlled trial was done and no conclusions can be drawn from it due to small size and classification error. Only one study investigated synergistic antibiotic combination, metronidazole and rifampin, and there was no advantage to the drug combination. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
bacitracin				Not reported
Song et al.[103] (1998) Gentamicin plus metronidazole vs cefuroxime plus metronidazole vs first generation or second generation cephalosporin vs third generation cephalosporin vs other antibiotic agents as monotherapy or combination therapy	MA Patients scheduled to undergo elective surgery of the colon	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 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
Genitourinary Infections				
Ugwumadu et al.[104] (2003) Clindamycin 300 mg orally BID	DB, PC, RCT Pregnant women ≥12 to 22 weeks gestation with abnormal vaginal	N=485 5 days	Primary: Spontaneous preterm delivery (birth ≥24 but <37 weeks) and late miscarriage	Primary: Incidence of spontaneous preterm delivery was 11/244 (5%) in the clindamycin group vs 28/241(12%) in the placebo group; incidence of miscarriage was 2/244 (1%) in the clindamycin group vs 10/241(4%) in the placebo group (P=0.001 for both).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs placebo	flora or bacterial vaginosis		(pregnancy loss ≥13 but <24 weeks) Secondary: Not reported	Overall, women receiving clindamycin had significantly fewer miscarriages or spontaneous preterm deliveries than did those in the placebo group. Adverse events included gastrointestinal upset (five patients receiving clindamycin vs 10 receiving placebo), rash (one patient receiving clindamycin vs two receiving placebo), vulvovaginal candidiasis (one patient receiving clindamycin vs one receiving placebo), throat irritation (one patient receiving placebo), and headache (four patients receiving clindamycin vs one receiving placebo). Overall, there was no statistically significant difference in reported adverse events (P=0.10). Secondary: Not reported
Hepatic Encephalopathy				
Sidhu et al.[105] (2011) Rifaximin 400 mg TID for 8 weeks vs placebo	DB, PC, RCT Patients 18 to 65 years of age with cirrhosis and minimal hepatic encephalopathy	N=284 8 weeks	Primary: Reversal of minimal hepatic encephalopathy at eight weeks Secondary: Not reported	Primary: In the intent-to-treat analysis, the percentage of patients showing reversal of minimal hepatic encephalopathy was significantly higher in rifaximin group than in the placebo group (75.5 vs 20.0%, respectively; P<0.0001). Secondary: Not reported
Bass et al.[106] (2010) Rifaximin 550 mg BID vs placebo Concomitant use	DB, PC, RCT Patients ≥18 years of age who had ≥2 episodes of overt hepatic encephalopathy (Conn score, ≥2) associated with hepatic cirrhosis during the previous	N=299 6 months	Primary: Time to the first breakthrough episode of hepatic encephalopathy Secondary: Time to the first hospitalization involving hepatic	Primary: Breakthrough episodes of hepatic encephalopathy were reported in 22.1% of patients receiving rifaximin and 45.9% of patients in the placebo group (HR, 0.42; 95% CI, 0.28 to 0.64; P<0.001). Four patients would need to be treated with rifaximin for 6 months to prevent one episode of overt hepatic encephalopathy. Secondary: Hospitalization involving hepatic encephalopathy occurred in 13.6% of patients receiving rifaximin and 22.6% of patients receiving placebo (HR, 0.50; 95% CI, 0.29 to 0.87; P=0.01). Nine patients would need to be

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
of lactulose was allowed throughout the study.	6 months, remission (Conn score, 0 or 1) at enrollment, and a score of ≤25 on the Model for End-Stage Liver Disease scale		encephalopathy and safety	treated with rifaximin for six months to prevent one hospitalization involving hepatic encephalopathy. The incidence of adverse events reported during the study was similar in the rifaximin group (80.0%) and the placebo group (79.9%). A total of 20 patients died during the study (9 in the rifaximin group and 11 in the placebo group). Most of the deaths were attributed to conditions associated with disease progression.
Williams et al.[107] (2000) Rifaximin 200 mg TID vs rifaximin 400 mg TID vs rifaximin 800 mg TID	DB, MC, PG, RCT Patients with cirrhosis and mild to moderate hepatic encephalopathy who had experienced recent deterioration in their neuropsychiatric status	N=54 7 days	Primary: Change in the portal-systemic encephalopathy index (calculated on the basis of asterixis, number connection test time Secondary: Not reported	Primary: There was a significant reduction in the mean portal-systemic encephalopathy index in the rifaximin 1,200 and 2,400 mg/day groups (95% CI, -17.4 to -3.1 and -17.8 to -3.6, respectively). Mean values for blood ammonia levels on days one and seven, respectively, were 132.8 and 107.1 in the rifaximin 600 mg/day group, 143.5 and 143.0 in the 1,200 mg/day group, and 183.3 and 188.6 in the 2,400 mg/day group. Rifaximin was well tolerated. Nausea and gastrointestinal system disorders were the most frequent adverse events. Secondary: Not reported
Bucci et al.[108] (1993) Rifaximin 400 mg TID vs lactulose 10 g TID	DB, RCT Patients 42 to 60 years of age with cirrhosis and signs/symptoms of portosystemic encephalopathy	N=58 15 days	Primary: Mental status using Parsons-Smith point scale, presence of asterixis, 'A' cancellation test, Reitan test, electro-encephalographic irregularities, adverse events Secondary:	Primary: There was an improvement in cognitive function in both groups. Patients receiving rifaximin had a significant improvement starting on day six (P<0.05), and those receiving lactulose had a significant improvement starting on day 12 (P<0.01). Starting on day nine, the comparison between the two groups was significantly in favor of rifaximin (P<0.01). The presence of asterixis decreased in both groups. There was a significant difference for both treatments starting on day nine compared to baseline (P<0.01). There was no significant difference between the groups. The 'A' cancellation test showed a progressive improvement in the two groups. The difference became significant starting on day six with rifaximin and day nine with lactulose compared to baseline.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			Not reported	The Reitan test showed good recovery of manipulation. There was no significant difference between the treatment groups. Improvement was noted starting on day nine in both groups. There was a significant improvement in electroencephalographic irregularities at day six with rifaximin and day nine with lactulose. The difference between the two treatment groups was significant on day six (P<0.05), as well as days 12 and 15 (P<0.01). There was a significant reduction in fasting ammonia levels beginning on day five. Levels were normal after seven days with both treatments. The comparison between the two treatments was significantly in favor of rifaximin on days three, five and 12 (P<0.05). Diarrhea, flatulence and dyspepsia appeared in 50% of patients treated with lactulose. In those treated with rifaximin, the frequency and severity of the adverse events was minimal. Body weight decreased in 28.6% of those treated with lactulose and in 6.7% of those treated with rifaximin.
Paik et al.[109] (2005) Rifaximin 400 mg TID vs lactulose 90 mL/day	OL, RCT In-patients with episodic hepatic encephalopathy who had decompensated liver cirrhosis and stage 1 to 3 hepatic encephalopathy (according to Conn's modification of Parsons-Smith classification) and serum ammonia levels >75 µmol/L	N=54 7 days	Primary: Grade of mental state, severity of flapping tremor, number connection test, blood ammonia levels, hepatic encephalopathy index, and efficacy of treatment Secondary: Not reported	Primary: Mean blood levels and grades of blood NH_3 significantly decreased with rifaximin (P<0.01) and lactulose (P<0.01). Mean blood NH_3 concentrations were similar after both treatments. Mental state was significantly improved by rifaximin and by lactulose (P<0.01 and P<0.01, respectively). Grades of flapping tremor and number connection test were improved to a similar degree by rifaximin and lactulose. Mean hepatic encephalopathy indexes improved in the rifaximin group (P=0.000) and in the lactulose group (P=0.000). There was no significant difference between the treatment groups. Blood NH_3 and hepatic encephalopathy grades improved in 78.1% and 81.3%, respectively, of the patients in the rifaximin group. In the lactulose group, 59.1% of the patients showed reduced blood ammonia grades and

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				72.7% showed improved hepatic encephalopathy grades. There was no significant difference between the treatment groups. Rifaximin was considered effective in 84.4% of patients and lactulose was considered effective in 95.4% of patients (P=0.315). One patient treated with rifaximin complained of abdominal pain, and one patient treated with lactulose experienced severe diarrhea. Secondary: Not reported
Neff et al.[110] (2006) Rifaximin 1,200 mg/day vs lactulose 60 g/day, titrated as necessary	RETRO Patients with end-stage liver disease and stage 1 or 2 hepatic encephalopathy	N=39 Variable duration	Primary: Hospitalizations and length of stay Secondary: Not reported	Primary: There were 19 total hospitalizations in the lactulose group (nine patients) and three hospitalizations in the rifaximin group. The average length of stay was shorter in the rifaximin group at 3.5 days compared to 5.0 days in the lactulose group (P<0.0001). Secondary: Not reported
Leevy et al.[111] (2007) Lactulose 30 mL BID for ≥6 months, then rifaximin 400 mg TID for ≥6 months	RETRO Patients with hepatic encephalopathy	N=146 ≥6 months	Primary: Mean number of hospitalizations during each treatment period Secondary: Average length of hospitalization, mean total time hospitalized, clinical status	Primary: There were fewer hospitalizations during the rifaximin period compared to the lactulose period (0.5 vs 1.6; P<0.001). Secondary: There were fewer days of hospitalization (2.5 vs 7.3; P<0.001) and fewer total weeks hospitalized (0.4 vs 1.8; P<0.001) during the rifaximin period compared to the lactulose period. Hepatic encephalopathy grade at the end of each treatment period reflected less severe illness with rifaximin than with lactulose (P<0.001). The percentage of patients with stage 3 or 4 hepatic encephalopathy was 6% with rifaximin and 25%with lactulose. Significantly fewer patients had asterixis at the end of the rifaximin period

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				(63%) than the lactulose period (93%; P<0.001). The percentages of patients with diarrhea, flatulence, and abdominal pain were significantly higher during the lactulose period than the rifaximin period (all, P<0.001). The percentage of patients with headache did not differ between treatment periods (P=0.718).
Mas et al.[112] (2003) Rifaximin 400 mg TID vs lactitol 20 g TID	DB, RCT Patients with grade I to III acute hepatic encephalopathy for <2 days duration and a portal-systemic encephalopathy index higher than zero	N=103 5 to 10 days	Primary: Efficacy and safety Secondary: Not reported	Primary: There were significant improvements in hepatic encephalopathy endpoints and ammonemia levels following treatment with rifaximin and lactitol. There was no significant difference between the treatment groups at the EOT (hepatic encephalopathy grade, P=0.9211; mental state, P=0.8480; asterixis, P=0.3177). The overall portal-systemic encephalopathy index decreased more progressively in the rifaximin group than in the lactitol group (P<0.01). With regards to the global assessment of efficacy at the end of treatment; both groups showed a similar clinical efficacy without significant differences. After grouping the responses into two classes (resolution/improvement vs unchanged/failure), the results were similar in both groups: 81.6 vs 18.4%, respectively, in the rifaximin group and 80.4 vs 19.6%, respectively, in the lactitol group. The percentage of patients with complete hepatic encephalopathy resolution was higher in the rifaximin group (53.1%) than in the lactitol group (37.2%). Both treatments were well tolerated. In the rifaximin group, two patients reported mild diarrhea and one patient reported abdominal pain. In the lactitol group, one patient reported mild diarrhea and one described vomiting.
Jiang et al.[113] (2008) Rifaximin vs	MA Patients ≥18 years of age with serum ammonia levels ≥75 µmol/L, signs and	N=264 (5 trials) Variable duration	Primary: Clinical efficacy Secondary: Adverse events	Primary: There was no significant difference in clinical efficacy for hepatic encephalopathy between rifaximin and nonabsorbable disaccharides (RR, 1.08; 95% CI, 0.85 to 1.38; P=0.53). Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
nonabsorbable disaccharides	symptoms of acute, chronic, or minimal hepatic encephalopathy			Diarrhea and abdominal pain were the most frequently reported adverse events. There was no difference in diarrhea between the treatment groups (RR, 0.90; 95% CI, 0.17 to 4.70; P=0.90). A significant difference on abdominal pain was noted (RR, 0.28; 95% CI, 0.08 to 0.95; P=0.04).
Festi et al.[114] (1993) Study 1 Rifaximin 1,200 mg/day for 21 days Study 2 Rifaximin 1,200 mg/day for 21 days vs neomycin 3,000 mg/day for 21 days Study 3 Rifaximin 1,200 mg/day for 21 days vs lactulose 40 g/day for 21 days	OL (Study 1), RCT (Study 2 and 3) Patients 40 to 75 years of age with clinical and biochemical signs of mild hepatic encephalopathy and liver cirrhosis	N=136 21 days	Primary: Neurological signs, electro-encephalographic abnormalities, ammonia levels Secondary: Not reported	Primary: Study 1 Rifaximin significantly reduced the frequency of neurologic signs. After five days of treatment, the percentage of patients who exhibited asterixis was significantly lower than at baseline; after 15 days of treatment, no patients showed this neurologic sign. After seven days, a significantly lower percentage of patients exhibited electroencephalography abnormalities. Blood ammonia levels were significantly improved with rifaximin after five days. Blood ammonia concentrations reached normal values and remained within the normal range throughout the study. Study 2 Both rifaximin and neomycin reduced the neurologic signs of hepatic encephalopathy, but at different rates. Treatment with rifaximin led to a significant reduction in the frequency of asterixis after three days compared to five days with neomycin. A significantly lower percentage of patients exhibited electro-encephalographic abnormalities with rifaximin and neomycin compared to baseline (P<0.001). Ammonia levels were significantly reduced by rifaximin and neomycin. Normal values were achieved after seven days of treatment. Study 3 Both rifaximin and lactulose reduced the neurologic signs of hepatic encephalopathy compared to baseline (P<0.05). Electro-encephalographic abnormalities significantly decreased in frequency with rifaximin and lactulose compared to baseline.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Ammonia levels were significantly decreased with both treatments (P<0.01). Secondary: Not reported
Miglio et al.[115] (1997) Rifaximin 400 mg TID for 14 days each month vs neomycin 1 g TID for 14 days each month	DB, RCT Patients with cirrhosis and chronic hepatic encephalopathy of grade 1 or 2	N=60 6 months	Primary: Improvement of at least one grade of hepatic encephalopathy, neurological signs, Reitan test, ammonia levels, liver function tests Secondary: Not reported	Primary: There was a progressive reduction in hepatic encephalopathy grade with rifaximin and neomycin. There was no significant difference between the two treatment groups. The improvement in hepatic encephalopathy was significant after 30 days (P<0.001 for each group). In both groups, the disturbances in speech, memory, behavior and mood, gait, asterixis, writing, serial subtraction of 7s and five-pointed star tests showed the highest improvement (P<0.001). The Reitan test only showed a significant improvement in the rifaximin group (P<0.02). Blood ammonia levels were decreased from 210.2 to 88.9 µg/100 mL in the rifaximin group (P<0.001) and from 202.1 to 86.2 µg/100 mL in the neomycin group (P<0.001). There was no significant difference between the treatment groups. There were significant decreases in aspartate aminotransferase (P<0.02) and alanine transaminase (P<0.01 in the rifaximin group and P<0.03 in the neomycin group). Secondary: Not reported
Respiratory Infections				
Rubinstein et al.[116] (2001) Linezolid 600 mg IV every 12 hours vs	DB, MC, RCT Patients ≥18 years of age with nosocomial pneumonia	N=396 Treatment: 7 to 21 days Follow-up: 12 to 28 days posttreatment	Primary: Cure, failure, microbiological success or failure Secondary: Not reported	Primary: Rates of clinical cure for the intent-to-treat population were 53.4% (86/161) vs 52.1% (74/142) with linezolid and vancomycin, respectively (P=0.79). In the clinically evaluable population, clinical cure rate was 66.4% (71/107) with linezolid and 68.1% (62/91) with vancomycin (P=0.79).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vancomycin 1 g IV every 12 hours Both regimens included aztreonam 1 to 2 g IV every 8 hours.				Microbiological success rate was 67.9% (36/53) with linezolid and 71.8% (28/39) with vancomycin (P=0.69). Safety assessments were done for the intent-to-treat population. Diarrhea was more frequent in linezolid recipients (4.4 vs 2.6%); however, abnormal liver function tests were more common with vancomycin (1.6 vs 1.0%) as was incidence of rash (1.6 vs 0%). There were 36 deaths in the linezolid group and 49 with vancomycin (17.7 vs 25.4%, respectively; P=0.06). Secondary: Not reported
Wunderink et al.[117] (2003) Linezolid 600 mg IV every 12 hours vs vancomycin 1 g IV every 12 hours Patients could have also received aztreonam 1 to 2 g IV every 8 hours.	DB, MC, RCT Patients >18 years of age with pneumonia acquired 48 hours after admission to an inpatient facility	N=345 Treatment: 7 to 21 days Follow-up: 15 to 21 days posttreatment	Primary: Clinical outcomes (cure or failure) and microbiologic outcomes (success and failure) at follow-up visit Secondary: Not reported	Primary: 55.4% of total enrolled patients (345/623) were clinically evaluable. Clinical cure rates were equivalent between linezolid- and vancomycin-treated patients (67.9 and 64.9%, respectively; P=NS). 25.5% of total patients (159/623) were microbiologically evaluable. Microbiological success rates were similar between linezolid- and vancomycin-treated patients (61.8 and 53.2%, respectively; P=NS). More patients had multiple-lobe involvement in the linezolid group vs the vancomycin group (56.1 vs 44.3%; P=0.004).
Wunderink et al.[118] (2008) Linezolid 600 mg every 12 hours vs vancomycin 1 g	MC, OL, RCT Patients with MRSA ventilator-associated pneumonia	N=149 30 days	Primary: Microbiological response and clinical cure Secondary: Clinical outcome, mortality, ventilator use at	Primary: Due to the limited number of patients per treatment group, the study did not have sufficient power to establish non-inferiority between linezolid and vancomycin for the primary end point. Overall, 56.5% of linezolid-treated patients achieved a microbiological cure compared to 47.4% of vancomycin-treated patients (P=0.757; 95% CI, -21.1 to 39.4).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
every 12 hours			the EOT and follow-up visits, health resource outcomes (duration of mechanical ventilation, hospitalization, and intensive care unit stay)	Clinical cure was demonstrated in 66.7% of linezolid-treated patients compared to 52.9% of vancomycin-treated patients (P=0.375). Secondary: The survival rate (86.7 vs 70.0%, respectively) mean duration of ventilation (10.4 vs 14.3 days, respectively), hospitalization (18.8 vs 20.1 days, respectively), intensive care unit stay (12.2 vs 16.2 days, respectively), and time spent alive and not receiving mechanical ventilation (15.5 vs 11.1 days, respectively) were not significantly different between linezolid-treated patients and vancomycin-treated patients.
Kaplan et al.[119] (2003) Linezolid IV then orally vs vancomycin IV then appropriate orally agent	RCT Hospitalized children (birth to 12 years of age) with antibiotic-resistant gram-positive infections (nosocomial pneumonia, complicated SSSIs, catheter-related bacteremia, and other infections)	N=321 10 to 28 days	Primary: Clinical cure rate and pathogen eradication rate Secondary: Not reported	Primary: Clinical cure rate was 74% with vancomycin and 79% with linezolid in the intent-to-treat population (P=0.36). The cure rate in the clinically evaluable population was 85 and 89% with vancomycin and linezolid, respectively (P=0.31). Eradication rates for MRSA were similar for both groups (P=0.89). Patients receiving linezolid required fewer days of IV therapy (P<0.001) and experienced fewer adverse drug events (P=0.003). Secondary: Not reported
Wunderink et al.[120] (2012) Vancomycin IV 15 mg/kg every 12 hours vs linezolid IV 600 mg every 12 hours	DB, MC, PRO Hospitalized adult patients with hospital-acquired or healthcare-associated MRSA pneumonia	N=1,184 7 to 14 days	Primary: Clinical outcome at end of study in evaluable per-protocol patients Secondary: Response in the modified intent-to-treat population at end of treatment and end of study	Primary: In the Per protocol population, 95 (57.6%) of 165 linezolid-treated patients and 81 (46.6%) of 174 vancomycin-treated patients achieved clinical success at end of study (95% CI, 0.5 to 21.6; P=0.042). Secondary: All-cause 60-day mortality was similar (linezolid, 15.7%; vancomycin, 17.0%), as was incidence of adverse events. Nephrotoxicity occurred more frequently with vancomycin (18.2%; linezolid, 8.4%).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			and microbiologic response in the per protocol and modified intent-to-treat population at end of treatment and end of study, survival and safety	
Fagon et al.[121] (2000) Quinupristin-dalfopristin 7.5 mg/kg IV every 8 hours vs vancomycin 1 g IV every 12 hours Aztreonam, imipenem, or tobramycin were added if determined clinically necessary.	MC, OL, RCT Patients ≥18 years developing sufficiently severe nosocomial pneumonia that required ≥5 days of parenteral antibiotics	N=171 5 to 14 days	Primary: Clinical response at test-of-cure assessment (seven to 13 days after end of treatment if cure/improvement; 13 days after end of treatment if failure) in the bacteriologically evaluable population (by-pathogen bacteriologic response, by-patient bacteriologic response) Secondary: Clinical response for the all-treated population	Primary: Therapy was clinically successful in 58.3% of patients receiving vancomycin and 56.3% of patients receiving quinupristin-dalfopristin (-2% difference [95% CI, -16.8 to 12.8]). The by-pathogen bacteriologic response was similar between treatment groups (for *Streptococcus pneumoniae, Staphylococcus aureus*, MRSA). The by-patient bacteriologic success rate was 64.3 and 58.6% in the vancomycin and quinupristin-dalfopristin groups, respectively (-5.7% difference [-20.2 to 8.9%]). 32 patients died in the vancomycin group compared to 38 patients in the quinupristin-dalfopristin group (P=0.45). Secondary: The clinical success rate was similar between groups in the all-treated population (45.3% for vancomycin and 43.3% for quinupristin-dalfopristin (-1.9% difference [-13.2 to 9.3%]). There was no statistically significant difference between groups in reported adverse events (P=NS).
Rubinstein et al.[122] (2011) Telavancin 10 mg/kg IV once	AC, DB, RCT (2 trials) Patients ≥18 years of age with	N=1,503 7 to 14 days posttreatment	Primary: Clinical response at the follow-up/test-of-cure visit (seven to 14	Primary: In all treated patients at the follow-up/test-of-cure visit (study 0015), cure rates were 57.5% with telavancin and 59.1% with vancomycin (95% CI, -8.6 to 5.5). In study 0019, cure rates were 60.2% with telavancin and 60.0% with vancomycin (95% CI, -6.8 to 7.2).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
daily for 7 to 21 days vs vancomycin 1 g IV BID for 7 to 21 days	hospital-acquired pneumonia due to gram-positive pathogens, including MRSA		days after treatment) Secondary: Not reported	In the clinically evaluable population at the follow-up/test-of-cure visit (study 0015), cure rates were 83.7% with telavancin and 80.2% with vancomycin (95% CI, -5.1 to 12.0). In study 0019, cure rates were 81.3% with telavancin and 81.2% with vancomycin (95% CI, -8.2 to 8.4). In the pooled all treated population, cure rates with telavancin were 58.9% compared to 59.5% with vancomycin (95% CI, –5.6 to 4.3). In the pooled clinically evaluable population, cure rates were 82.4% with telavancin and 80.7% with vancomycin (95% CI, –4.3 to 7.7). In patients with pneumonia due to *Staphylococcus aureus*, the clinical response at the follow-up/test-of-cure visit was 78.1% with telavancin compared to 75.2% with vancomycin; 95% CI, -9.5 to 10.4). In patients with pneumonia due to MRSA, with or without other pathogens, the clinical response at the follow-up/test-of-cure visit was 74.8% with telavancin compared to 74.7% with vancomycin; 95% CI, -9.5 to 10.4). The incidence and types of adverse events were comparable between the treatment groups. Mortality rates with telavancin were 21.5% compared to 16.6% with vancomycin (95% CI, –0.7 to 10.6) for study 0015. Mortality rates were 18.5% with telavancin compared to 20.6% with vancomycin (95% CI, –7.8 to 3.5) for study 0019. Increases in serum creatinine level were more common in the telavancin group (16 vs 10%).
Toma et al.[123] (1998) SMX-TMP 1,600-320 mg (≥60 kg) or 1,200-240 mg (<60 mg) QID for 21 days vs	DB, MC, RCT Patients ≥16 years of age with HIV-related PCP	N=116 21 days	Primary: Treatment success (>2-point improvement in the PCP score, calculated on the basis of body temperature, respiratory rate, cough, chest tightness, dyspnea,	Primary: There was no statistically significant difference in the duration of therapy between the treatment groups (P=0.68). The treatment success rates for SMX-TMP and clindamycin-primaquine were 76% and 74%, respectively. There were no statistically significant differences between the treatment regimens with respect to dyspnea scores, PCP scores and lactate dehydrogenase values at any time. There was no statistically significant difference between treatment groups with respect to the use of steroids (12 patients per group; P=0.74).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
clindamycin 450 mg QID and primaquine 15 mg once daily for 21 days			supplemental oxygen requirements, and chest radiograph), steroid use, duration of therapy, adverse events Secondary: Not reported	There was no significant difference in the rate of PCP recurrence between the two treatment arms (P=0.99). There was no significant difference in the rate of adverse effects experienced by the two treatment groups (P=0.57). Rash was the most frequent side effect in both groups. The incidence of rash was similar in both groups (P=0.78). Secondary: Not reported
Allewelt et al.[124] (2004) Ampicillin-sulbactam vs clindamycin with or without cephalosporin Dosing varied per patient	MC, OL, PRO, RCT Patients with aspiration pneumonia and lung abscess	N=70 Mean 23.4 days	Primary: Clinical response Secondary: Not reported	Primary: Clinical response at EOT in the ampicillin-sulbactam group was 73.0 vs 66.7% in the clindamycin group (P=0.06 and P=0.02, respectively). Clinical response at seven to 14 days after therapy was 65.7% in the ampicillin-sulbactam group vs 63.5% in the clindamycin group (P=0.10 and P=0.04). Duration of therapy was 22.7 days in the ampicillin-sulbactam group vs 24.1 days in the clindamycin group. Secondary: Not reported
Miscellaneous Infections				
Linden et al.[125] (2003) Colistin (colistimethate) dose based on weight	PRO Critically ill patients (organ recipients as well as other non-transplant general surgery patients) with multi-drug resistant *Pseudomonas aeruginosa*	N=23 7 to 36 days	Primary: Favorable response, defined as complete or partial resolution of signs and symptoms at end of treatment; unfavorable response, defined as persistence or	Primary: Favorable clinical response was observed in 14 patients (61%). Seven patients died during therapy (30.4%). Majority of patients enrolled had pneumonia (n=18) or intra-abdominal infection (n=5). *Pseudomonas aeruginosa* bacteremia was associated with clinical failure (P=0.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
	infection		worsening of signs and symptoms or death Secondary: Not reported	
Kasakou et al.[126] (2005) Colistin (colistimethate) 1.5 to 9 million IU IV per day Colistin was used as monotherapy or in combination with other antimicrobials.	RETRO Hospitalized patients with multi-drug resistant gram-negative bacilli managed with colistin for ≥72 hours	N=50 4 to 72 days	Primary: Mortality Secondary: Clinical outcome of infection, occurrence of renal dysfunction	Primary: In-hospital mortality was 24% (12/50); age and temperature upon hospital admission were independent predictors of mortality. Secondary: Four patients developed two episodes of infection and were treated as two different cases. A total of 53.7% (29/54) had a cure and 13% (7/54) showed improvement and 33.3% (18/54) were unresponsive. Deterioration of renal function was noted in 8% (4/50) of patients receiving colistin. A total of 6/50 patients received colistin by an alternate route in addition to IV (intraventricular, nebulized, or irrigation solution). A total of 31/50 patients had concurrent administration with one or two additional agents such as, meropenem (60%), ampicillin-sulbactam (34%), ciprofloxacin (20%), piperacillin-clavulanic acid (20%), imipenem (16%), or amikacin plus gentamicin (14%).
El-Khoury et al.[127] (2003) Linezolid 600 mg IV/oral BID (<40 kg received 10 mg/kg BID)	MC, OL Solid organ transplant patients with vancomycin-resistant *Enterococcus faecium*	N=85 Variable duration	Primary: Clinical resolution of infection Secondary: Not reported	Primary: A total of 53 patients (62.4%) survived with linezolid treatment (clinical resolution), whereas death occurred in 32 patients (32.9%). Documented negative cultures post-therapy were obtained in 47 of patients that survived. Mean duration of therapy for cured patients was 23.5 days. Adverse reactions included thrombocytopenia (four patients),

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				leukocytopenia (three patients), and increase in blood pressure (one patient). Secondary: Not reported
Linden et al.[128] (2001) Quinupristin-dalfopristin 7.5 mg/kg IV every 8 hours	MC, PRO Patients with signs and symptoms of active infection caused by vancomycin-resistant *Enterococcus faecium*	N=396 20 days (mean)	Primary: Clinical response rate, bacteriological response rate, overall response rate combined clinical and bacteriological responses Secondary: Not reported	Primary: Clinical response rate was 68.8% in evaluable population; 51% in all-treated population (including indeterminate). Bacteriologic response rate was 68% in evaluable population; 59.8% in all-treated population. Overall response rate was 65.6% in evaluable population; 48.2% in all-treated population. Overall mortality rate in the all-treated group was 28.8% while receiving treatment and 56.6% at 30 days after therapy discontinuation. Arthralgia and myalgia were common adverse events and reasons for therapy discontinuation; however, reversible after treatment discontinuation. A total of 11 patients in the all-treated population experienced superinfection caused by gram-positive pathogens. Secondary: Not reported
Winston et al.[129] (2000) Quinupristin-dalfopristin, either 7.5 mg/kg IV every 8 hours or 5 mg/kg IV every 8 hours; infused over 60 minutes	PRO Hospitalized patients with signs and symptoms of infection confirmed by cultures that are positive for vancomycin-resistant *Enterococcus faecium*	N=24 3 to 36 days	Primary: Clinical responses and bacteriological response Secondary: Not reported	Primary: Eighty-three percent of patients experienced a clinical response (80% of patients given the 7.5 mg/kg dose and 88% of patients given the 5 mg/kg dose. Bacterial eradication occurred in 74% (17/23) of patients. Four patients failed to response to therapy and four patients experienced clinical and bacteriologic relapse of vancomycin-resistant *Enterococcus faecium* 22 to 67 days after treatment was discontinued. Two patients had persistent vancomycin-resistant *Enterococcus faecium*. Sixty-nine percent of patients died during hospitalization; four due to vancomycin-resistant *Enterococcus faecium* infection and 12 due to other causes, including liver failure, invasive fungal infection, cardiac failure, *Citrobacter freundii* bacteremia, acute leukemia and fungal infection, pancreatic carcinoma, and graft-vs-host disease.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				Thirty-three percent of patients experienced arthralgias and myalgias (a higher incidence with the use of high dose [eight patients experienced arthralgias and myalgias with 7.5 mg/kg and none in 5 mg/kg dose]). Six patients experienced superinfection due to *Candida* fungemia, *Enterobacter cloacae* pneumonia, and *Enterococcus faecalis*. Secondary: Not reported
Rehm et al.[130] (2001) Quinupristin-dalfopristin 7.5 mg/kg every 8 or 12 hours diluted in 100 mL (if using central venous catheter) or 240 mL (if using peripheral venous catheter) of D5W; as 1 hour infusion	MC, PRO Patients who participated in clinical trials with quinupristin/ dalfopristin for either emergency use or for assessment of safety and efficacy in Phase III studies and continued to receive quinupristin/ dalfopristin after hospital discharge	N=37 9 days inpatient & 22 days as outpatient (mean)	Primary: Clinical responses, bacteriological response, adverse events Secondary: Not reported	Primary: Overall clinical success rate was 89.2% and bacteriological success rate was also 89.2%. 86.5% completed study without hospital readmission. Five patients required hospital readmission due to recurrent MRSA, central catheter-related bacteremia, chest pain, elevated liver enzymes, and neutropenic fever. Nineteen patients (51.4%) experienced non-venous clinical adverse events (most common: myalgia (18.9%), nausea (18.9%), arthralgia (13.5%), diarrhea, headache, and vomiting). Sixteen patients (43.2%) experienced venous access adverse events (most common: drug infusion pain, local edema, phlebitis). Five (13.5%) patients experienced abnormal lab results (anemia, azotemia, and elevated transaminase). Secondary: Not reported
Raad et al.[131] (2004) Linezolid 600 mg every 12 hours vs quinupristin-dalfopristin 7.5 mg/kg every 8 hours	OL, PRO, RCT Patients ≥18 years of age with infections caused by vancomycin-resistant *Enterococcus faecium*	N=40 39 months	Primary: Safety Secondary: Efficacy	Primary: The rate of myalgias/arthralgias in patients receiving quinupristin-dalfopristin was 33% as compared to 0% in patients receiving linezolid (P<0.01). All other reports of adverse effects were found to be NS (P>0.05). Secondary: Clinical response at the EOT were not significantly different between patients receiving quinupristin-dalfopristin and patients receiving linezolid (P=0.6). There was no statistically significant difference between the number of deaths caused by infection, relapse, or microbiological response between the two treatment arms (all P>0.05).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Kohno et al.[132] (2007) Linezolid 600 mg every 12 hours vs vancomycin 1 g every 12 hours	RCT Patients with nosocomial pneumonia, complicated skin and soft-tissue infections or sepsis caused by MRSA	N=151 7 to 14 days	Primary: Clinical success rates Secondary: Not reported	Primary: Clinical success rates in the MRSA microbiologically evaluable population were 62.9% and 50.0% for the linezolid and vancomycin groups, respectively (P=NS). Microbiological eradication rates were 79.0 and 30.0% for the linezolid and vancomycin groups, respectively (P<0.0001). At follow-up, the clinical success rates were 36.7% for both groups and the microbiological eradication rates were 46.8 and 36.7%, respectively. Reversible anemia (13%) and thrombocytopenia (19%) were reported more frequently in linezolid patients. Significantly low platelet counts were observed more frequently in patients receiving vancomycin than in linezolid patients (6 vs 3%). Mean changes in hemoglobin levels between the two groups were not different. Secondary: Not reported
Stevens et al.[133] (2002) Vancomycin 1 g IV once daily vs linezolid 600 mg IV BID Upon clinical improvement, linezolid-treated patients could be	MC, OL, RCT Hospitalized/ institutionalized patients with MRSA infections	N=460 7 to 28 days	Primary: Clinical outcomes and microbiological outcomes Secondary: Not reported	Primary: Clinical cure rate was 73.2% with linezolid vs 73.1% with vancomycin (P=0.99) in evaluable patients with MRSA (N=116) at the test-of-cure visit. There were no differences in clinical response between vancomycin and linezolid for other population subgroups (P=NS). Microbiological success rate was 58.9% with linezolid vs 63.2% with vancomycin (P=0.65) in evaluable patients with MRSA at the test-of-cure visit. Adverse event rates were similar between groups (P=0.143). A total of 61% of the linezolid group received oral administration. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
changed to linezolid 600 mg orally BID.				Not reported
Shorr et al.[134] (2005) Vancomycin 1 g IV every 12 hours vs linezolid 600 mg IV every 12 hours	MA (PRO, RCT) Patients with *Staphylococcus aureus* bacteremia (pneumonia 48 hours after hospital admission, complicated skin and soft tissue infections, or MRSA infections)	N=144 7 to 35 days	Primary: Clinical cure of primary infection at EOT, microbiological eradication of *Staphylococcus aureus* bacteremia, and overall survival Secondary: Not reported	Primary: In clinically evaluable patients, incidence of cure was 55% (28/51) in patients given linezolid and 52% (25/48) in patients given vancomycin (1.12; 95% CI, 0.51 to 2.47). In the intent-to-treat population, clinical cure occurred in 28/74 (38%) patients given linezolid and 25/70 (36%) patients given vancomycin. In patients with MRSA bacteremia, 56% (14/25) of linezolid-treated patients and 46% (13/28) of vancomycin treated patients had a cure (1.47; 95% CI, 0.50 to 4.34). Microbiological success occurred in 69% of linezolid-treated patients and 73% of vancomycin-treated patients (OR, 0.83; 95% CI, 0.37 to 1.87). The survival rate was similar for both treatment groups in patients with MRSA bacteremia as well as overall *Staphylococcus aureus* bacteremia. Mean duration of therapy was shorter with IV linezolid than with vancomycin (8.6 vs 11.7; P=0.004). Linezolid was given IV for >7 days after which it could be switched to oral.
An et al.[135] (2013) Vancomycin vs linezolid	MA 9 RCTs comparing linezolid with vancomycin for MRSA infection	N=5,249 Duration varied	Primary: Efficacy, safety Secondary: Not reported	Primary: Linezolid was associated with greater efficacy compared to vancomycin for MRSA-related infection in terms of clinical treatment success (OR, 1.77; 95% CI, 1.22 to 2.56) and microbiological treatment success (OR, 1.78; 95% CI, 1.22 to 2.58). Although no difference was found regarding the overall incidence of drug-related adverse events and serious adverse events between the linezolid and vancomycin therapy groups (drug-related adverse events: OR, 1.20; 95% CI, 0.98 to 1.48; serious adverse events: OR, 1.00; 95% CI, 0.74 to 1.36), the linezolid therapy group was associated with significantly fewer patients experiencing abnormal renal function (OR, 0.39; 95% CI, 0.28 to

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				0.55). Secondary: Not reported
Fu et al.[136] (2013) Vancomycin or teicoplanin (glycopeptides) vs linezolid	MA 13 RCTs that assess the effectiveness and safety of linezolid in comparison with glycopeptides (vancomycin and teicoplanin) for the treatment of Staphylococcus aureus infections	N=3,863 Duration varied	Primary: Efficacy and safety Secondary: Not reported	Primary: Linezolid was slightly more effective than glycopeptides in the intent-to-treat population (OR, 1.05; 95% CI, 1.01 to 1.10), was more effective in clinically assessed patients (OR, 1.38; 95% CI, 1.17 to 1.64) and in all microbiologically assessed patients (OR, 1.38; 95% CI, 1.15 to 1.65). Linezolid was associated with better treatment in skin and soft-tissue infections patients (OR, 1.61; 95% CI, 1.22 to 2.12), but not in bacteriemia (OR, 1.24; 95% CI, 0.78 to 1.97) or pneumonia (OR, 1.25; 95% CI, 0.97 to 1.60) patients. No difference of mortality between linezolid and glycopeptides was seen in the pooled trials (OR, 0.98; 95% CI, 0.83 to 1.15). While linezolid was associated with more hematological (OR, 2.23; 95% CI, 1.07 to 4.65) and gastrointestinal events (OR, 2.34; 95% CI, 1.53 to 3.59), a significantly fewer events of skin adverse effects (OR, 0.27; 95% CI, 0.16 to 0.46) and nephrotoxicity (OR, 0.45; 95% CI, 0.28 to 0.72) were recorded in linezolid. Secondary: Not reported
Chong et al.[137] (2010) Quinupristin - dalfopristin 7.5 mg/kg IV every 8 hours for ≥48 hours vs linezolid 600 mg	RETRO Patients ≥16 years of age with vancomycin-resistant *Enterococcus faecium*	N=113 Variable duration	Primary: Rates of 30-day mortality, microbiological response, and development of resistance Secondary: Not reported	Primary: The 30-day mortality rate was 48% in patients who received quinupristin-dalfopristin compared to 41% of patients who received linezolid (P=0.45). Microbiological response was observed in 60% of patients receiving quinupristin-dalfopristin compared to 66% of patients receiving linezolid (P=0.51). The development of resistance to quinupristin-dalfopristin in vancomycin-resistant *Enterococcus faecium* blood isolates was observed in 11% of patients for whom follow-up culture data were available. None of the patients developed resistance to linezolid (P=0.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
IV every 12 hours for ≥48 hours				There were no significant differences in these relapse rates between the treatment groups (P=0.8). Antibiotic-induced thrombocytopenia was observed in 5% of patients in the linezolid group. Platelet counts of all patients recovered after discontinuation of linezolid therapy.
Polyzos et al.[138] (2012) Vancomycin vs telavancin	MA 6 RCTs evaluating telavancin in the treatment of patients with infections due to Gram-positive organisms	N=2,220 Duration varied	Primary: Efficacy and safety Secondary; Not reported	Primary: Regarding complicated skin and soft tissue infections, telavancin and vancomycin showed comparable efficacy in clinically evaluable patients (OR, 1.10; 95% CI, 0.82 to 1.48). Among patients with MRSA infection, telavancin showed higher eradication rates (OR, 1.71; 95% CI, 1.08 to 2.70) and a trend towards better clinical response (OR, 1.55; 95% CI, 0.93 to 2.58). Regarding hospital-acquired pneumonia, telavancin was non-inferior to vancomycin in terms of clinical response; mortality rates for the pooled trials were comparable with telavancin (20.0%) and vancomycin (18.6%). Pooled data from complicated skin and soft tissue infections and hospital-acquired pneumonia studies on telavancin 10 mg/kg indicated higher rates of serum creatinine increases (OR, 2.22; 95% CI, 1.38 to 3.57), serious adverse events (OR, 1.53; 95% CI, 1.05 to 2.24), and adverse event-related withdrawals (OR, 1.49; 95% CI, 1.14 to 1.95) among telavancin recipients. Secondary: Not reported
Solomkin et al.[139] (2009) Ceftriaxone 2 g IV once daily plus metronidazole 500 mg IV BID for three to 14 days	DB, MC, RCT Patients ≥18 years of age with community-origin complicated intra-abdominal infections with an expected duration of	N=364 Up to 28 days	Primary: Clinical success rate at the test-of-cure visit (10 to 14 days after the EOT) Secondary: Clinical and	Primary: At the test-of-cure visit, cure rates were 90.2% for moxifloxacin and 96.5% for ceftriaxone plus metronidazole (95% CI, −11.7 to −1.7). In the intention-to-treat population, the clinical cure rates were 87.2% for moxifloxacin and 91.2% for ceftriaxone plus metronidazole (95% CI, −10.7 to 1.9). Moxifloxacin was found to be non-inferior to ceftriaxone plus metronidazole in the per protocol and intention-to-treat populations. Secondary:

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs moxifloxacin 400 mg IV once daily for three to 14 days	treatment with IV antimicrobials of 3 to 14 days		bacteriological success rates on days three and five during treatment and at the EOT; bacteriological 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	During treatment, clinical improvement occurred in similar proportions of per protocol patients in the moxifloxacin group (31.0%) and the ceftriaxone plus metronidazole group (28.1%). In the intention-to-treat population, clinical improvement occurred in 30.6% of patients receiving moxifloxacin and 27.1% of patients receiving ceftriaxone plus metronidazole. In the per protocol population, clinical resolution at EOT occurred in 92.5% of patients receiving moxifloxacin and in 97.1% of patients receiving ceftriaxone plus metronidazole (95% CI, −9.8 to −0.2). In the intention-to-treat population, clinical resolution at E occurred in 91.1% of patients receiving moxifloxacin and in 94.5% of patients receiving ceftriaxone plus metronidazole. The overall incidence of treatment-emergent adverse events was similar between the two treatment groups (31.7% with moxifloxacin vs 24.3% with ceftriaxone plus metronidazole; P=0.129).
Towfigh et al.[140] (2010) Ceftriaxone 2 g IV once daily plus metronidazole 1 to 2 g IV daily in divided doses for four to 14 days (CTX/MET) vs tigecycline 100 mg IV as an initial dose, followed by 50 mg IV every 12 hours for four to 14 days (TGC)	MC, OL, RCT, Patients ≥18 years of age with community-origin 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 TGC and in 74% of patients in the CTX/MET group (-4.0; 95% CI, -13.1 to 5.1; P=0.009). TCG was found to be non-inferior to CTX/MET. Secondary: Clinical cure rates for the microbiologically evaluable population were 66% with TGC and 70% with CTX/MET (-3.4; 95% CI, -14.5 to 7.8; P=0.020. TCG was found to be non-inferior to CTX/MET. In the c-mITT population, clinical cure was reported in 64% of patients receiving TGC and in 71% of patients receiving CTX/MET (-7.0; 95% CI, -15.8 to 1.08; P=0.038. TGC was found to be non-inferior to CTX/MET. *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 population, infections were cured in 68.0 and 67.0% of all monomicrobial

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
				and polymicrobial infections, respectively, in the TGC-treated patients, and 71.5 and 68.3% of all monomicrobial and polymicrobial infections, respectively, in the CTX/MET-treated patients. Adverse events were similar with TGC and CTX/MET. 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%).
Gentry et al.[141] (1997) Nafcillin vs vancomycin	RETRO Patients with staphylococcal endocarditis	N=56 Duration not specified	Primary: Clinical response Secondary: Not reported	Primary: In patients with methicillin-sensitive *Staphylococcus aureus* infection, complete response rate was 74% in the nafcillin group compared to 50% in the vancomycin group (P=0.12); however these differences were not statistically significant. Mortality rate was 22% in the nafcillin group and 28% in the vancomycin group (P=0.73). Secondary: Not reported

Drug regimen abbreviations: BID=twice daily, IV=intravenous, TID=three times daily, QID=four times daily
Study abbreviations: AC=active control, CI=confidence interval, DB=double-blind, DD=double-dummy, 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, RR=relative risk, SC=single center, SB=single-blind
Miscellaneous abbreviations: ECE=early clinical evaluation, EOT=end of therapy, HIV=human immunodeficiency virus, *H pylori=Helicobacter pylori*, HRQOL=health related quality of life, IV=intravenous, MRSA=methicillin-resistant *Staphylococcus aureus*, MSSA=methicillin-susceptible *Staphylococcus aureus*, PCP=*Pneumocystis carinii* pneumonia, PTE=post-therapy evaluation, SMX-TMP=sulfamethoxazole-trimethoprim, SSSI= skin and skin structure infection

Additional Evidence

Dose Simplification
Carroll et al. evaluated the efficacy of clindamycin administered for three doses (short-course) vs 15 doses (long-course) for the prophylaxis of wound infections in patients with head and neck cancer undergoing reconstructive surgery.[142] The incidence of wound infections and other complications was not significantly different among the treatment groups. Livingston et al. compared the efficacy of gentamicin and clindamycin given once daily vs every eight hours for the treatment of postpartum endometritis.[143] There was no significant different in the treatment success rates among the treatment groups (82 vs 69%, respectively; P=0.12). Cohen et al. evaluated the efficacy of vancomycin administered once-daily vs twice-daily in hospitalized patients.[144] There was no significant difference in clinical response rates among the treatment groups (92.1 vs 94.2%, respectively; P=0.72).

Stable Therapy
McCollum et al. evaluated converting patients from intravenous vancomycin to oral linezolid for the treatment of methicillin-resistant *Staphylococcus* species.[145] Of 177 patients treated with vancomycin, 58% were eligible for conversion to oral therapy with linezolid and 31% were eligible for early hospital discharge with continuation of oral therapy. Early discharge was associated with a decrease in the length of stay by 3.3 days. Li et al. assessed the use of linezolid or vancomycin for the treatment of complicated skin and soft-tissue infections on hospital length of stay.[54] Patients received intravenous linezolid followed by oral linezolid, or monotherapy with intravenous vancomycin for up to four weeks. Length of hospital stay was eight days in the linezolid group compared to 16 days in the vancomycin group (P=0.0025).

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 20. Relative Cost of the Antibacterials, Miscellaneous

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Single Entity Agents				
Bacitracin	injection	Baciim®*	$$$$$	$$$$$
Clindamycin	capsule, injection, solution	Cleocin HCl®*, Cleocin Palmitate®*, Cleocin Phosphate®*, Cleocin Phosphate in D5W®*	$$-$$$$$	$$
Colistimethate	injection	Coly-Mycin M Parenteral®*	$$$$$	$$$$$

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Dalbavancin	injection	Dalvance®	$$$$$	N/A
Daptomycin	injection	Cubicin®	$$$$$	N/A
Lincomycin	injection	Lincocin®*	$$$$$	$$$$$
Linezolid	injection, suspension, tablet	Zyvox®*	$$$$$	$$$$$
Oritavancin	injection	Orbactiv®	$$$$$	N/A
Polymyxin B sulfate	injection	N/A	N/A	$$$$$
Rifaximin	tablet	Xifaxan®	$$$$$	N/A
Tedizolid	injection, tablet	Sivextro®	$$$$$	N/A
Telavancin	injection	Vibativ®	$$$$$	N/A
Vancomycin	capsule, injection	Vancocin®*	$$$$$	$$$$$
Combination Products				
Colloidal bismuth subcitrate, metronidazole, and tetracycline	capsule	Pylera®	$$$$$	N/A
Quinupristin and dalfopristin	injection	Synercid®	$$$$$	N/A

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

X. Conclusions

The miscellaneous antibacterials are a diverse group of products that are used to treat many different types of infections.[1-14] The Food and Drug administration (FDA)-approved indications vary depending on the particular agent and antimicrobial properties. It is important to analyze current treatment guidelines and published studies when making therapeutic decisions about the miscellaneous antibacterial agents. Bacitracin, clindamycin, colistimethate, lincomycin, linezolid, polymyxin B sulfate, and vancomycin are available in a generic formulation.

The use of bacitracin is limited to the treatment of infants with pneumonia and empyema caused by susceptible strains of staphylococci. Treatment may cause renal failure due to tubular and glomerular necrosis; therefore, renal function should be carefully determined prior to and daily during therapy. The concurrent use of other nephrotoxic drugs should be avoided.[1,2,14] Polymyxin B sulfate and colistimethate are approved for the treatment of serious infections caused by susceptible gram-negative bacteria when less toxic drugs are ineffective or contraindicated.[1,2,14] The use of these agents has resulted in nephrotoxicity and neurotoxicity. Guidelines do not discuss the use of bacitracin, polymyxin B sulfate or colistimethate and published clinical trials are limited.

The lincosamide antibacterials include clindamycin and lincomycin. Guidelines recommended the use of clindamycin for the treatment of skin and soft-tissue infections and pelvic inflammatory disease. Lincomycin is not discussed in the available guidelines and has no therapeutic advantage over clindamycin. Although there are many FDA-approved indications for clindamycin, the increased risk of *Clostridium difficile*-associated diarrhea (which may end fatally) limits the use of this agent. The lincosamides should be reserved for the treatment of serious infections for which less toxic antimicrobial agents are inappropriate.[1,2,14]

Daptomycin is approved for the treatment of complicated skin and skin-structure infections, *Staphylococcus aureus* bacteremia, and right-sided infective endocarditis.[5] The spectrum of activity with daptomycin is similar to that of vancomycin. Guidelines recommend daptomycin as one of several options for the initial treatment of soft-tissue infections caused by methicillin-resistant *Staphylococcus aureus*.[43] Published studies have demonstrated similar clinical response rates when daptomycin was compared to vancomycin or penicillinase-resistant penicillins.[51,52]

Linezolid is approved for the treatment of skin and skin-structure infections, pneumonia, and vancomycin-resistant *Enterococcus faecium* infections. Guidelines recommend the use of linezolid as an initial treatment option for endocarditis (due to vancomycin-resistant *Enterococcus faecium*), meningitis (due to methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus faecium*), skin and soft-tissue infections (due to methicillin-resistant *Staphylococcus aureus*), diabetic foot infections, as well as community-acquired and

nosocomial pneumonia (due to methicillin-resistant *Staphylococcus aureus*). Several trials have demonstrated similar clinical response rates when linezolid was compared to vancomycin.[53,56,116-119,132-134] Linezolid can be administered either orally or parenterally when treating serious infections. Vancomycin is also available in an oral and injectable formulation; however, oral vancomycin has only been shown to be effective for the treatment of enterocolitis and *Clostridium difficile*-associated diarrhea. The intravenous formulation must be used for the treatment of serious infections caused by staphylococci, including methicillin-resistant strains. Studies have demonstrated a shorter length of hospital stay and duration of intravenous therapy with the use of linezolid compared to vancomycin.[54-57] Myelosuppression (including anemia, leukopenia, pancytopenia, and thrombocytopenia) has been reported in patients receiving linezolid. Complete blood counts should be monitored weekly in patients who receive linezolid, particularly in those who receive linezolid for longer than two weeks, those with pre-existing myelosuppression, those receiving concomitant drugs that produce bone marrow suppression, or those with a chronic infection who have received previous or concomitant antibiotic therapy.[6]

Tedizolid phosphate is the second agent in the oxazolidinone class, the first being linezolid. It was FDA-approved in 2014 for the treatment of acute bacterial skin and skin structure infections (ABSSSI) caused by designated susceptible bacteria.[9] FDA approval of tedizolid phosphate was based on two clinical trials, ESTABLISH-1 and ESTABLISH-2, that evaluated the safety and efficacy of the drug for treatment of ABSSSIs.[63,64] Both trials were randomized, double-blind, double-dummy, multinational, phase III, parallel group, non-inferiority studies comparing tedizolid to linezolid. In ESTABLISH-2, the primary endpoint of early clinical response (48 to 72 hours after treatment initiation) was achieved in 283 (85%) patients in the tedizolid phosphate group and 276 (83%) patients in the linezolid group, demonstrating non-inferiority of tedizolid phosphate to linezolid.[63] In ESTABLISH-1, the primary endpoint of early clinical response (48 to 72 hours after treatment initiation) was achieved in 79.5% of patients in the tedizolid phosphate group and 79.4% of patients in the linezolid group; a treatment difference of 0.1% (95% CI, -6.1 to 6.2; P value not reported).[64]

Quinupristin-dalfopristin is approved for the treatment of complicated skin and skin-structure infections.[13] Guidelines recommend the use of quinupristin-dalfopristin as one of several options for the treatment of skin and soft-tissue infections (due to methicillin-resistant *Staphylococcus aureus*) and endocarditis (due to vancomycin-resistant *Enterococcus faecium*). Studies have demonstrated similar clinical response rates when quinupristin-dalfopristin was compared to cefazolin, linezolid, oxacillin, and vancomycin.[90,121,131]

Telavancin is approved for the treatment of complicated skin and skin-structure infections caused by susceptible gram-positive bacteria (including methicillin-resistant *Staphylococcus aureus*).[10] For hospitalized patients with complicated skin and skin-structure infections, empirical therapy for methicillin-resistant *Staphylococcus aureus* should be considered. Treatment options include telavancin, vancomycin, linezolid, daptomycin, and clindamycin. Two studies compared telavancin to standard therapy (penicillinase-resistant penicillin or vancomycin) in patients with complicated skin and skin-structure infections caused by gram-positive organisms.[70,71] Cure rates were similar among the treatment groups, including in patients with methicillin-resistant *Staphylococcus aureus* at baseline. Telavancin was also compared to vancomycin in patients with hospital-acquired pneumonia due to gram-positive organisms.[122] Cure rates were similar among the treatment groups, including in patients with methicillin-resistant *Staphylococcus aureus* at baseline. Increases in serum creatinine (up to 1.5 times baseline) have occurred more frequently in patients receiving telavancin (15%) compared to patients receiving vancomycin (7%).[10] Renal function should be monitored in patients receiving telavancin prior to the start of therapy, during treatment, and at the end of therapy.

Dalbavancin and oritavancin are recently approved semisynthetic lipoglycopeptides that interfere with cell wall synthesis and are bactericidal against *Staphylococcus aureus* and *Streptococcus pyogenes in vitro*. They are FDA-approved for the treatment of adult patients with ABSSSI caused by susceptible isolates.[4,7] FDA approval of oritavancin was based on two clinical trials, SOLO I and SOLO II, that evaluated the safety and efficacy of the drug for treatment of ABSSSIs. Both trials compared oritavancin to vancomycin and found that similar proportions of patients in each treatment group achieved the primary efficacy outcome at early clinical evaluation of cessation of spreading or reduction in size of baseline lesion, absence of fever, or absence of a need rescue for antibiotic medication at 48 to 72 hours.[61,62] Dalbavancin approval was based on the DISCOVER1 and DISCOVER2 trials, which compared treatment with dalbavancin to treatment with vancomycin with the option to switch to oral linezolid in adult patients with ABSSSI. In the DISCOVER1 trial, an early clinical response indicating treatment success was documented in 83.3% and 81.8% of patients in the dalbavancin and vancomycin-linezolid groups, respectively (difference, 1.5%; 95% CI, -4.6 to 7.9).[48] Similarly, in the DISCOVER2 trial, an

early clinical response was documented in 76.8% and 78.3% of patients in the dalbavancin and vancomycin-linezolid groups, respectively (difference, -1.5; 95% CI, -7.4 to 4.6).[48]

Intravenous vancomycin is approved for the treatment of serious infections caused by susceptible strains of methicillin-resistant staphylococci, for penicillin-allergic patients, for patients who cannot receive or who have failed to respond to other drugs, and for infections caused by vancomycin-susceptible organisms that are resistant to other antimicrobial drugs.[11,14] Vancomycin is also effective for the treatment of staphylococcal endocarditis, septicemia, bone infections, lower respiratory tract infections, as well as skin and skin-structure infections. As discussed previously, several studies have demonstrated similar clinical response rates when vancomycin was compared to daptomycin, linezolid, and quinupristin-dalfopristin.[51-52,90,116,117,120,132-134] Ototoxicity and nephrotoxicity have been reported with the use of intravenous vancomycin.[11] Ototoxicity may be transient or permanent and has been reported mostly in patients who have been given excessive doses, who have an underlying hearing loss, or who are receiving concomitant therapy with another ototoxic agent, such as an aminoglycoside. Vancomycin should be used with caution in patients with renal insufficiency because the risk of toxicity is appreciably increased by high, prolonged blood concentrations.

Rifaximin is approved for the treatment of travelers' diarrhea and to reduce the risk of overt hepatic encephalopathy recurrence.[8] For travelers' diarrhea, guidelines recommend empirical treatment with one of several antibiotics, including quinolones, azithromycin, sulfamethoxazole-trimethoprim, and rifaximin.[29] For the treatment of hepatic encephalopathy, guidelines recommend lactulose as initial therapy. Antibiotics are considered an alternative treatment option for acute and chronic encephalopathy.[47] Clinical trials have evaluated the short-term use of rifaximin for the treatment of acute hepatic encephalopathy.[107-115] Rifaximin was found to be as effective, or more effective, than lactulose and neomycin.[111,112,115-117] Bass et al. evaluated the long-term efficacy and safety of rifaximin in patients who were in remission from hepatic encephalopathy.[106] Over a six-month period, breakthrough episodes of hepatic encephalopathy were reported in 22% of patients receiving rifaximin compared to 46% of patients receiving placebo ($P<0.001$). Hospitalizations occurred in 14% of patients receiving rifaximin and in 23% of patients receiving placebo ($P=0.01$). This study did not directly compare rifaximin to other standard treatments for hepatic encephalopathy. Lactulose was used concomitantly by 91% of the patients in both treatment arms.

Pylera® (bismuth, metronidazole, and tetracycline) is used to eradicate *Helicobacter pylori* in patients with duodenal ulcer disease. Pylera® contains all three of the antibacterial components in a single capsule. It should be used in combination with omeprazole for the treatment of *Helicobacter pylori* infections. Guidelines recommend either proton-pump inhibitor-based triple therapy or quadruple therapy (proton-pump inhibitor or H_2-receptor antagonist, bismuth, tetracycline, and metronidazole) for the eradication of *Helicobacter pylori*. Several clinical trials comparing quadruple therapy to triple therapy have demonstrated comparable efficacy, although this has not been consistently demonstrated.[77,79-81,83,88] There were no published studies found that directly compared Pylera® combination products with bismuth, metronidazole and tetracycline administered as separate formulations.

There is insufficient evidence to support that one brand miscellaneous antibacterial is safer or more efficacious than another within its given indication. Since the majority of 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 miscellaneous antibacterials 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 antibacterial 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
New Drug Review: Praluent®
AHFS Class 240624
November 9, 2016

I. Overview

Praluent® (alirocumab) is Food and Drug Administration (FDA)-approved as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C). Proprotein convertase subtilisin kexin 9 (PCSK9) is a serine protease produced predominantly in the liver that leads to the degradation of hepatocyte LDL receptors and increased LDL-C levels. Alirocumab works to inhibit the action of this enzyme leading to a decrease in LDL-C levels.[1]

Although the agent has demonstrated a benefit in reducing various measures of cholesterol, the extent of benefit on cardiovascular morbidity and mortality has not been determined. In addition, the agent was only approved as adjunctive therapy to maximally-dosed statin therapy, not in statin intolerant patients.[1]

The alirocumab products 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.

Table 1. Alirocumab Products Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Alirocumab	injection	Praluent®	none

PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the treatment of use of alirocumab are summarized in Table 2.

Table 2. Treatment Guidelines Using Alirocumab

Clinical Guideline	Recommendation(s)
American College of Cardiology/American Heart Association Task Force on Practice Guidelines: **Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults (2013)**[2]	Statin treatment • The panel makes no recommendations for or against specific LDL-C or non-HDL-C targets for the primary or secondary prevention of ASCVD. • High-intensity statin therapy should be initiated or continued as first-line therapy in women and men ≤75 years of age that have clinical ASCVD, unless contraindicated. • In individuals with clinical ASCVD in whom high-intensity statin therapy would otherwise be used, when high-intensity statin therapy is contraindicated or when characteristics predisposing to statin-associated adverse effects are present, moderate-intensity statin should be used as the second option if tolerated. • In individuals with clinical ASCVD >75 years of age, it is reasonable to evaluate the potential for ASCVD risk-reduction benefits and for adverse effects, drug-drug interactions and to consider patient preferences, when initiating a moderate- or high-intensity statin. It is reasonable to continue statin therapy in those who are tolerating it. • Adults ≥21 years of age with primary LDL-C ≥190 mg/dL should be treated with statin therapy (ten-year ASCVD risk estimation is not required): use high-intensity statin therapy unless contraindicated. For individuals unable to tolerate high-intensity statin therapy, use the maximum tolerated statin intensity. • For individual's ≥21 years of age with an untreated primary LDL-C ≥190

Clinical Guideline	Recommendation(s)

	mg/dL, it is reasonable to intensify statin therapy to achieve at least a 50% LDL-C reduction.
	• For individual's ≥21 years of age with an untreated primary LDL-C ≥190 mg/dL, after the maximum intensity of statin therapy has been achieved, addition of a non-statin drug may be considered to further lower LDL-C. Evaluate the potential for ASCVD risk reduction benefits, adverse effects, drug-drug interactions and consider patient preferences.
	• Moderate-intensity statin therapy should be initiated or continued for adults 40 to 75 years of age with diabetes mellitus.
	• High-intensity statin therapy is reasonable for adults 40 to 75 years of age with diabetes mellitus with a ≥7.5% estimated ten-year ASCVD risk unless contraindicated.
	• In adults with diabetes mellitus, who are <40 or >75 years of age, it is reasonable to evaluate the potential for ASCVD benefits and for adverse effects, for drug-drug interactions and to consider patient preferences when deciding to initiate, continue, or intensify statin therapy.
	• Adults 40 to 75 years of age with LDL-C 70 to 189 mg/dL, without clinical ASCVD or diabetes and an estimated ten-year ASCVD risk ≥7.5% should be treated with moderate- to high-intensity statin therapy.
	• It is reasonable to offer treatment with a moderate intensity statin to adults 40 to 75 years of age, with LDL-C 70 to 189 mg/dL, without clinical ASCVD or diabetes and an estimated ten-year ASCVD risk of 5.0 to <7.5%.
	• Before initiating statin therapy for the primary prevention of ASCVD in adults with LDL-C 70 to 189 mg/dL without clinical ASCVD or diabetes it is reasonable for clinicians and patients to engage in a discussion which considers the potential for ASCVD risk reduction benefits and for adverse effects, for drug-drug interactions and patient preferences for treatment.
	• In adults with LDL-C <190 mg/dL who are not otherwise identified in a statin benefit group, or for whom after quantitative risk assessment a risk based treatment decision is uncertain, additional factors may be considered to inform treatment decision making. In these individuals, statin therapy for primary prevention may be considered after evaluating the potential for ASCVD risk reduction benefits, adverse effects, drug-drug interactions, and discussion of patient preference.
	
	<u>Statin safety</u>
	• To maximize the safety of statins, selection of the appropriate statin and dose in men and non-pregnant/non-nursing women should be based on patient characteristics, level of ASCVD risk, and potential for adverse effects.
	• Moderate-intensity statin therapy should be used in individuals in whom high-intensity statin therapy would otherwise be recommended when characteristics predisposing them to statin associated adverse effects are present.
	• Characteristics predisposing individuals to statin adverse effects include, but are not limited to:
	  o Multiple or serious comorbidities, including impaired renal or hepatic function.
	  o History of previous statin intolerance or muscle disorders.
	  o Unexplained alanine transaminase elevations >3 times upper limit of normal.
	  o Patient characteristics or concomitant use of drugs affecting statin metabolism.
	  o >75 years of age.
	• Additional characteristics that may modify the decision to use higher statin intensities may include, but are not limited to:
	  o History of hemorrhagic stroke.

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	o Asian ancestry. • Creatinine kinase should not be routinely measured in individuals receiving statin therapy. • Baseline measurement of creatinine kinase is reasonable for individuals believed to be at increased risk for adverse muscle events based on a personal or family history of statin intolerance or muscle disease, clinical presentation, or concomitant drug therapy that might increase the risk for myopathy. • During statin therapy, it is reasonable to measure creatinine kinase in individuals with muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or generalized fatigue. • Baseline measurement of hepatic transaminase levels should be performed before initiating statin therapy. • During statin therapy, it is reasonable to measure hepatic function if symptoms suggesting hepatotoxicity arise (e.g., unusual fatigue or weakness, loss of appetite, abdominal pain, dark colored urine or yellowing of the skin or sclera). • Decreasing the statin dose may be considered when two consecutive values of LDL-C levels are <40 mg/dL. • It may be harmful to initiate simvastatin at 80 mg daily or increase the dose of simvastatin to 80 mg daily. • Individuals receiving statin therapy should be evaluated for new-onset diabetes mellitus according to the current diabetes screening guidelines. Those who develop diabetes mellitus during statin therapy should be encouraged to adhere to a heart healthy dietary pattern, engage in physical activity, achieve and maintain a healthy body weight, cease tobacco use, and continue statin therapy to reduce their risk of ASCVD events. • For individuals taking any dose of statins, it is reasonable to use caution in individuals >75 years of age, as well as in individuals that are taking concomitant medications that alter drug metabolism, taking multiple drugs, or taking drugs for conditions that require complex medication regimens (e.g., those who have undergone solid organ transplantation or are receiving treatment for HIV) . A review of the manufacturer's prescribing information may be useful before initiating any cholesterol-lowering drug). • It is reasonable to evaluate and treat muscle symptoms, including pain, tenderness, stiffness, cramping, weakness, or fatigue, in statin-treated patients according to the following management algorithm: o To avoid unnecessary discontinuation of statins, obtain a history of prior or current muscle symptoms to establish a baseline before initiating statin therapy. o If unexplained severe muscle symptoms or fatigue develop during statin therapy, promptly discontinue the statin and address the possibility of rhabdomyolysis by evaluating creatinine kinase, creatinine, and a urinalysis for myoglobinuria. • If mild to moderate muscle symptoms develop during statin therapy: o Discontinue the statin until the symptoms can be evaluated. o Evaluate the patient for other conditions that might increase the risk for muscle symptoms (e.g., hypothyroidism, reduced renal or hepatic function, rheumatologic disorders such as polymyalgia rheumatica, steroid myopathy, vitamin D deficiency, or primary muscle diseases). o If muscle symptoms resolve, and if no contraindication exists, give the patient the original or a lower dose of the same statin to establish a causal relationship between the muscle symptoms and statin therapy. o If a causal relationship exists, discontinue the original statin. Once muscle symptoms resolve, use a low dose of a different statin. o Once a low dose of a statin is tolerated, gradually increase the dose as tolerated. o If, after two months without statin treatment, muscle symptoms or

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	elevated creatinine kinase levels do not resolve completely, consider other causes of muscle symptoms listed above. o If persistent muscle symptoms are determined to arise from a condition unrelated to statin therapy, or if the predisposing condition has been treated, resume statin therapy at the original dose. • For individuals presenting with a confusional state or memory impairment while on statin therapy, it may be reasonable to evaluate the patient for non-statin causes, such as exposure to other drugs, as well as for systemic and neuropsychiatric causes, in addition to the possibility of adverse effects associated with statin drug therapy. <u>Monitoring and optimizing statin therapy</u> • Adherence to medication and lifestyle, therapeutic response to statin therapy, and safety should be regularly assessed. This should also include a fasting lipid panel performed within four to 12 weeks after initiation or dose adjustment, and every three to 12 months thereafter. Other safety measurements should be measured as clinically indicated. • The maximum tolerated intensity of statin should be used in individuals for whom a high- or moderate-intensity statin is recommended, but not tolerated. • Individuals who have a less-than anticipated therapeutic response or are intolerant of the recommended intensity of statin therapy, the following should be performed: o Reinforce medication adherence. o Reinforce adherence to intensive lifestyle changes. o Exclude secondary causes of hyperlipidemia. • It is reasonable to use the following as indicators of anticipated therapeutic response to the recommended intensity of statin therapy. Focus is on the intensity of the statin therapy. As an aid to monitoring: o High-intensity statin therapy generally results in an average LDL-C reduction of ≥50% from the untreated baseline; o Moderate-intensity statin therapy generally results in an average LDL-C reduction of 30 to <50% from the untreated baseline; o LDL-C levels and percent reduction are to be used only to assess response to therapy and adherence. They are not to be used as performance standards. • Individuals at higher ASCVD risk receiving the maximum tolerated intensity of statin therapy who continue to have a less than-anticipated therapeutic response, addition of a non-statin cholesterol-lowering drug(s) may be considered if the ASCVD risk-reduction benefits outweigh the potential for adverse effects. • Higher-risk individuals include: o Individuals with clinical ASCVD <75 years of age. o Individuals with baseline LDL-C ≥190 mg/dL. o Individuals 40 to 75 years of age with diabetes mellitus. o Preference should be given to non-statin cholesterol-lowering drugs shown to reduce ASCVD events in controlled trials. • In individuals who are candidates for statin treatment but are completely statin intolerant, it is reasonable to use non-statin cholesterol lowering drugs that have been shown to reduce ASCVD events in controlled trials if the ASCVD risk-reduction benefits outweigh the potential for adverse effects. <u>Non statin safety</u> • Baseline hepatic transaminases, fasting blood glucose or hemoglobin A1c, and uric acid should be obtained before initiating niacin, and again during up-titration to a maintenance dose and every six months thereafter. • Niacin should not be used if: o Hepatic transaminase elevations are higher than two to three times

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	upper limit of normal. o Persistent severe cutaneous symptoms, persistent hyperglycemia, acute gout or unexplained abdominal pain or gastrointestinal symptoms occur. o New-onset atrial fibrillation or weight loss occurs. • In individuals with adverse effects from niacin, the potential for ASCVD benefits and the potential for adverse effects should be reconsidered before reinitiating niacin therapy. • To reduce the frequency and severity of adverse cutaneous symptoms, it is reasonable to: o Start niacin at a low dose and titrate to a higher dose over a period of weeks as tolerated. o Take niacin with food or premedicating with aspirin 325 mg 30 minutes before niacin dosing to alleviate flushing symptoms. o If an extended-release preparation is used, increase the dose of extended-release niacin from 500 mg to a maximum of 2,000 mg/day over four to eight weeks, with the dose of extended release niacin increasing not more than weekly. o If immediate-release niacin is chosen, start at a dose of 100 mg three times daily and up-titrate to 3 g/day, divided into two or three doses. • Bile acid sequestrants should not be used in individuals with baseline fasting TG levels ≥300 mg/dL or type III hyperlipoproteinemia, because severe TG elevations might occur. • A fasting lipid panel should be obtained before bile acid sequestrants are initiated, three months after initiation, and every six to 12 months thereafter. • It is reasonable to use bile acid sequestrants with caution if baseline triglyceride levels are 250 to 299 mg/dL, and evaluate a fasting lipid panel in four to six weeks after initiation. Discontinue the bile acid sequestrants if triglycerides exceed 400 mg/dL. • It is reasonable to obtain baseline hepatic transaminases before initiating ezetimibe. When ezetimibe is coadministered with a statin, monitor transaminase levels as clinically indicated, and discontinue ezetimibe if persistent alanine transaminase elevations >3 times upper limit of normal occur. • Gemfibrozil should not be initiated in patients on statin therapy because of an increased risk for muscle symptoms and rhabdomyolysis. • Fenofibrate may be considered concomitantly with a low- or moderate-intensity statin only if the benefits from ASCVD risk reduction or triglyceride lowering when triglycerides are >500 mg/dL, are judged to outweigh the potential risk for adverse effect. • Renal status should be evaluated before fenofibrate initiation, within three months after initiation, and every six months thereafter. Assess renal safety with both a serum creatinine level and an estimated glomerular filtration rate based on creatinine. • Fenofibrate should not be used if moderate or severe renal impairment, defined as estimated glomerular filtration rate <30 mL/min per 1.73 m^2, is present. • If estimated glomerular filtration rate is between 30 and 59 mL/min per 1.73 m^2, the dose of fenofibrate should not exceed 54 mg/day. • If, during follow-up, the estimated glomerular filtration rate decreases persistently to ≤30 mL/min per 1.73 m^2, fenofibrate should be discontinued. • If eicosapentaenoic acid and/or docosahexanoic acid are used for the management of severe hypertriglyceridemia, defined as triglycerides ≥500 mg/dL, it is reasonable to evaluate the patient for gastrointestinal disturbances, skin changes, and bleeding.
American College of Cardiology:	Patients ≥21 Years of Age with Stable Clinical ASCVD without Comorbidities, on Statin for Secondary Prevention

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2016 ACC Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk (2016)[3]	• These patients should be treated first with maximally tolerated statin intensity. If patients have a ≥50% reduction in LDL-C from baseline (and may consider LDL-C <100 mg/dL), it is reasonable to continue the statin therapy and continue to monitor adherence to medications and lifestyle, and ongoing LDL-C response to therapy. • If a patient has a less-than-anticipated response (<50% reduction in LDL-C and may consider LDL-C ≥100 mg/dL): o Assess statin adherence. o If an adherent patient has not been tried on a high-intensity statin, the dose should be increased to a high-intensity dose at this time. o Intensify lifestyle modifications. o Consider adding ezetimibe 10 mg daily as the first non-statin agent. o A bile acid sequestrant (BAS) may be considered as a second-line agent for those with ezetimibe intolerance and with triglycerides <300 mg/dL, but there is no evidence for benefit of BAS in addition to statins in this population. • If ASCVD patients without comorbidities, who are on maximally tolerated statin–ezetimibe or non-statin combination therapy in the setting of documented statin intolerance, achieve a less-than-anticipated response with <50% reduction in LDL-C (and may consider LDL-C ≥100 mg/dL): o It is reasonable to consider the net benefit of alirocumab or evolocumab (in addition to or in place of ezetimibe) as a second step to achieve further LDL-C reduction. o If a PCSK9 inhibitor is prescribed, clinicians should continue maximally tolerated statin and monitoring for adherence to medications and lifestyle, side effects, and ongoing LDL-C response to therapy. <u>Clinical ASCVD with comorbidities, on statin for secondary prevention</u> • These patients should be treated first with maximally tolerated statin intensity. • If patients have a ≥50% reduction in LDL-C from baseline (and may consider LDL-C <70 mg/dL or non–HDL-C <100 mg/dL for patients with diabetes), it is reasonable to continue the statin therapy and continue to monitor adherence to medications and lifestyle, and ongoing LDL-C response to therapy. • If a patient has a less-than-anticipated response: o Address statin intolerance. o Intensify lifestyle modifications (may consider phytosterols). o Increase to high-intensity statin if not already taking. o Evaluate for statin intolerance if unable to tolerate moderate-intensity statin. Consider referral to lipid specialist if statin intolerant. o Control other risk factors. o Consider ezetimibe first. o Consider adding or replacing with PCSK9 inhibitor second. <u>Clinical ASCVD and baseline LDL-C ≥190 mg/dL not due to secondary causes, on statin for secondary prevention</u> • Patients with LDL-C ≥190 mg/dL are more likely to have heterozygous (HeFH) or homozygous (HoFH) familial hypercholesterolemia. • In patients who have a less-than-anticipated response on maximally tolerated statin therapy with <50% reduction in LDL-C (and may consider LDL-C ≥70 mg/dL): o Address statin intolerance. o Intensify lifestyle modifications (may consider phytosterols). o Increase to high-intensity statin if not already taking. o Evaluate for statin intolerance if unable to tolerate moderate-intensity statin. Consider referral to lipid specialist if statin intolerant. o Control other risk factors.

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	○ Consider ezetimibe (or BAS second line) first. ○ Consider adding or replacing with PCSK9 inhibitor second. Adults aged 40 to 75 years without ASCVD, but with diabetes • In patients with diabetes who achieve inadequate lowering of LDL-C or non-HDL-C despite adherence to lifestyle recommendations and moderate-intensity statin therapy, the recommended threshold for consideration of the net benefit of increasing to high-intensity statin therapy is failure to achieve 30 to <50% reduction in LDL-C (and may consider on -treatment LDL-C ≥100 mg/dL or non-HDL-C ≥130 mg/dL). • If a patient with diabetes and 10-year ASCVD risk <7.5% without high-risk features has a less-than-anticipated response, with <30% reduction in LDL-C (and may consider LDL-C ≥100 mg/dL or non-HDL-C ≥130 mg/dL), additional clinical approaches may be warranted. • Ezetimibe is the preferred initial non-statin therapy due to tolerability, convenience, and single-tablet daily dose. • BAS may have a modest hypoglycemic effect that may be of benefit in some diabetic patients if fasting triglycerides are <300 mg/dL. BAS may also be considered if patients have an inadequate response to ezetimibe or if patients are ezetimibe intolerant. • In the absence of ASCVD or baseline LDL-C ≥190 mg/dL not due to secondary causes, the PCSK9 inhibitors do not have an established role for primary prevention of ASCVD in patients with diabetes.
National Cholesterol Education Program: **Implications of Recent Clinical Trials for the National Cholesterol Education Program Adult Treatment Panel III Guidelines (2004)**[4]	• TLC remains an essential modality in clinical management. • When LDL-C lowering drug therapy is employed in high risk or moderately high risk patients, it is advised that intensity of therapy be sufficient to achieve ≥30 to 40% reduction in LDL-C levels. If drug therapy is a component of cholesterol management for a given patient, it is prudent to employ doses that will achieve at least a moderate risk reduction. • Standard HMG-CoA reductase inhibitors (statins) doses are defined as those that lower LDL-C levels by 30 to 40%. The same effect may be achieved by combining lower doses of statins with other drugs or products (e.g., bile acid sequestrants, ezetimibe, nicotinic acid, plant stanols/sterols). • When LDL-C level is well above 130 mg/dL (e.g., ≥160 mg/dL), the dose of statin may have to be increased or a second agent (e.g., a bile acid sequestrant, ezetimibe, nicotinic acid) may be required. Alternatively, maximizing dietary therapy (including use of plant stanols/sterols) combined with standard statin doses may be sufficient to attain goals. • Fibrates may have an adjunctive role in the treatment of patients with high TG and low HDL-C, especially in combination with statins. • In high risk patients with high TG or low HDL-C levels, consideration can be given to combination therapy with fibrates or nicotinic acid and a LDL lowering agent. • Several clinical trials support the efficacy of nicotinic acid, which raises HDL-C, for reduction of CHD risk, both when used alone and in combination with statins. The combination of a statin with nicotinic acid produces a marked reduction of LDL-C and a striking rise in HDL-C. Treatment of heterozygous familial hypercholesterolemia • Begin LDL-C lowering drugs in young adulthood. • TLC indicated for all persons. • Statins, first line of therapy (start dietary therapy simultaneously). • Bile acid sequestrants (if necessary in combination with statins). • If needed, consider triple drug therapy (statins and bile acid sequestrants and nicotinic acid).

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	Treatment of homozygous familial hypercholesterolemia • Statins may be moderately effective in some persons. • LDL-pheresis currently employed therapy (in some persons, statin therapy may slow down rebound hypercholesterolemia). Treatment of familial defective apolipoprotein B-100 • TLC indicated. • All LDL-C lowering drugs are effective. • Combined drug therapy required less often than in heterozygous familial hypercholesterolemia. Treatment of polygenic hypercholesterolemia • TLC indicated for all persons. • All LDL-C lowering drugs are effective. • If necessary to reach LDL-C goals, consider combined drug therapy.

III. Indications

The Food and Drug Administration (FDA)-approved indications for alirocumab are noted in Table 3.

Table 3. FDA-Approved Indications for Alirocumab[1,5,6]

Indication	Alirocumab
Adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-cholesterol	✔

IV. Pharmacokinetics

The pharmacokinetic parameters of alirocumab are listed in Table 4.

Table 4. Pharmacokinetic Parameters of Alirocumab[5]

Generic Name	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (days)
Alirocumab	85	Not reported	Protein degradation	Proteolytic pathway	17 to 20

V. Drug Interactions

There are no known clinically significant drug interactions with alirocumab. However, the median apparent half-life of alirocumab is reduced to 12 days when administered with a statin. This difference is not clinically meaningful and does not impact dosing recommendations.[1]

VI. Adverse Drug Events

The most common adverse drug events reported with alirocumab are listed in Table 5.

Table 5. Adverse Drug Events (%) Reported with Alirocumab[1]

Adverse Events	Alirocumab
Nasopharyngitis	11.3
Injection site reactions	7.2

Adverse Events	Alirocumab
Influenza	5.7
Urinary tract infection	4.8
Diarrhea	4.7
Bronchitis	4.3
Myalgia	4.2
Muscle spasms	3.1
Sinusitis	3.0
Cough	2.5
Contusion	2.1
Musculoskeletal pain	2.1

VII. Dosing and Administration

The usual dosing regimens for alirocumab are listed in Table 6.

Table 6. Usual Dosing Regimens for Alirocumab[1]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Alirocumab	HeFH or clinical atherosclerotic cardiovascular disease: Injection: initial, 75 mg SQ every two weeks; maintenance and maximum, 150 mg SQ every two weeks	Safety and efficacy in children have not been established.	Single-dose prefilled pen or syringe: 75 mg 150 mg

HeFH=heterozygous familial hypercholesterolemia, SQ=subcutanous

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of alirocumab are summarized in Table 7.

Table 7. Comparative Clinical Trials with Alirocumab

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Kereiakes et al.[7,8] (2015) ODYSSEY COMBO I Alirocumab 75 mg SQ every two weeks (dose increased to 150 mg at week 12 if LDL ≥70 mg/dL) vs placebo Patients continued to take statin therapy with or without other lipid lowering therapy.	DB, MC, PG, RCT Patients ≥18 years of age with established heart disease or CHD equivalent, with LDL-C ≥70 mg/dL and established heart disease or LDL-C ≥100 mg/dL and no established heart disease but at a high risk for CVE[†] and elevated LDL-C despite maximal doses of statins at maximum tolerated dosage for at least four weeks before screening	N=316 52 weeks	Primary: Percent change in calculated LDL-C from baseline to week 24 Secondary: Percentage of patients achieving LDL-C <70 mg/dL, other lipid parameters and safety evaluations	Primary: Alirocumab was associated with a significantly greater reduction in LDL-C from baseline to week 24 compared with placebo (48.2% vs 2.3%; P<0.0001). At week 12, 83.2% of evaluable alirocumab-treated patients remained on the 75 mg dose. In patients with a dose increase, LDL-C was reduced by an additional mean 22.8% at week 24 compared with week 12. These patients achieved similar reductions in LDL-C as those not requiring a dose increase (N=32). Secondary: LDL-C <70 mg/dL was achieved by 75% of the alirocumab group compared to 9% of the placebo group at week 24. Significant reductions from baseline to week 24 after therapy with alirocumab (P<0.0001 vs placebo) were observed in non–HDL-C (−39.1% vs −1.6%), apoB (−36.7% vs −0.9%), TC (−27.9% vs −2.9%), and lipoprotein(a) (−20.5% vs −5.9%). No significant change was observed in TG levels; whereas, a significant increase in HDL-C was observed in the alirocumab group (3.5% vs −3.8%; P<0.0001). The frequency of treatment-emergent adverse events and study medication discontinuations were generally comparable between treatment groups.
Cannon et al.[8,9] (2015) ODYSSEY COMBO II Alirocumab 75 mg injected SQ every two weeks (dose increased to 150 mg at week 12 if LDL ≥1.8 mmol/L)	AC, DB, DD, MC, PG, RCT Patients ≥18 years of age with established heart disease or CHD equivalent, LDL-C ≥70 mg/dL and	N=720 104 weeks	Primary: Percent change in calculated LDL-C from baseline to week 24 Secondary: Absolute	Primary: Alirocumab was associated with a significantly greater reduction in mean LDL-C from baseline at week 24 compared to ezetimibe (50.6 ± 1.4% vs 20.7 ± 1.9%; 29.8% ± 2.3% difference; P<0.0001). Secondary: Seventy seven percent of alirocumab and 45.6% of ezetimibe patients achieved LDL-C <1.8 mmol/L (P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs ezetimibe 10 mg QD Patients continued to take statin therapy. Other lipid lowering therapy was not permitted. All patients were instructed to follow a stable Therapeutic Lifestyle Changes diet, as outlined by the ATP III or an equivalent diet for the duration of the study.	established heart disease or LDL-C ≥ 100 mg/dL and no established heart disease but at a high risk for CVE[†] and elevated LDL-C despite maximal doses of statins at maximum tolerated dosage for at least four weeks before screening		cholesterol change, percent of patients achieving goal of LDL-C <70 mg/dL, other lipoprotein evaluations and safety evaluations	As compared with the ezetimibe group, the alirocumab group had greater reductions from baseline to week 24 in levels of non–HDL-C, apoB, TC, lipoprotein(a) and had a modest increase in levels of HDL-C (P<0.0001 for all comparisons). TG were reduced from baseline to week 24 by 13.0 ± 1.5% in the alirocumab group and by 12.8 ± 2.0% in the ezetimibe group, but the difference between treatment arms was not statistically significant. Alirocumab was generally well tolerated, with no evidence of an excess of treatment-emergent adverse events. Adjudicated cardiovascular events were infrequent, occurring in 4.8% (n=23) of the alirocumab group vs 3.7% (n=9) in the ezetimibe group. Treatment-emergent local injection site reactions occurred in 2.5% of patients in the alirocumab arm vs 0.8% for ezetimibe arm.
Robinson et al.[10] (2015) ODYSSEY LONG TERM Alirocumab 150 mg injected SQ every two weeks vs placebo Patients continued to take statin therapy with or without other lipid lowering agents. All patients were instructed to follow a stable Therapeutic Lifestyle Changes diet, as outlined by the ATP III or an equivalent diet for the duration of the study.	DB, MC, PC, RCT Patients ≥18 years of age at a high risk for CVE[†] (with HeFH or with established heart disease or CHD equivalent) with LDL ≥70 mg/dL receiving statins at maximum tolerated dosage for at least four weeks before screening	N=2,341 78 weeks	Primary: Percent change from baseline in LDL-C at week 24 Secondary: Absolute cholesterol change, percent of patients achieving goal of LDL-C <70 mg/dL, other lipoprotein evaluations, major cardiovascular events (death from CHD, nonfatal MI, fatal or nonfatal	Primary: There was a significantly greater decrease in LDL-C with alirocumab from baseline at week 24 compared to placebo (−61.0% vs 0.08%; −62% placebo-corrected difference; P<0.0001). This effect remained consistent over 78 weeks. Secondary: The mean absolute LDL-C level at week 24 was 48 mg/dL in the alirocumab group and 119 mg/dL in the placebo group, corresponding to a mean absolute change from baseline of −74 mg/dL and −4 mg/dL, respectively (P<0.0001). The goal of an LDL-C level of <70 mg/dL at week 24 was met by 79.3% of the patients in the alirocumab group compared to 8.0% of the patients in the placebo group (P<0.001). As compared with the placebo group, the alirocumab group had greater reductions from baseline to week 24 in levels of non–HDL-C, apoB, TC, lipoprotein(a) and triglycerides and had a modest increase in levels of HDL-C and apolipoprotein A1 (P<0.001 for all comparisons).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
			ischemic stroke, or unstable angina requiring hospitalization), adherence rates and safety evaluations	In a post hoc analysis, the rate of major adverse cardiovascular events was lower with alirocumab than with placebo (1.7% vs 3.3%; HR, 0.52; 95% CI, 0.31 to 0.90; P=0.02). Adherence was 98.0% and 97.6% in the alirocumab group and the placebo group, respectively. The alirocumab group, as compared with the placebo group, had higher rates of injection-site reactions (5.9% vs 4.2%), myalgia (5.4% vs 2.9%), neurocognitive events (1.2% vs 0.5%), and ophthalmologic events (2.9% vs 1.9%).
Roth et al.[11] (2015) ODYSSEY MONO Alirocumab 75 mg injected SQ every two weeks (dose increased to 150 mg at week 8 if LDL ≥70 mg/dL) vs ezetimibe 10 mg QD	DB, MC, PC, RCT Patients with primary hyper-cholesterolemia and moderate risk for CVE[†] and LDL-C ≥100mg/dL and ≤190mg/dL	N=103 34 weeks	Primary: Percent change in calculated LDL-C from baseline to week 24 Secondary: Safety evaluations	Primary: There was a significantly greater decrease in LDL-C with alirocumab from baseline at week 24 compared to ezetimibe (47.2% vs 15.6%; P<0.0001). Secondary: Safety parameters and adverse events were similar between the two groups. The most common class of adverse events was infections (39.2% with ezetimibe vs 42.3% with alirocumab), which included nasopharyngitis, influenza, and upper respiratory tract infection. Injection-site reactions occurred in less than 2% of patients in both groups. Muscle-related adverse events occurred in 3.9% of patients treated with ezetimibe and 3.8% of patients treated with alirocumab.
Bays et al.[12,13] (2015) ODYSSEY OPTIONS I Alirocumab 75 mg injected SQ every two weeks (dose increased to 150 mg at week 12 if LDL ≥70 mg/dL) vs ezetimibe 10 mg QD	AC, DB, MC, PG, RCT Patients ≥18 years of age with LDL-C ≥70 mg/dL and established heart disease or LDL-C ≥ 100 mg/dL and risk factors for CVE[†]	N=355 24 weeks	Primary: Percent change in calculated LDL-C from baseline to week 24 Secondary: Safety evaluations	Primary: Among atorvastatin 20 and 40 mg regimens respectively, there was a significantly greater decrease in LDL-C with alirocumab add-on from baseline at week 24 compared to add-on ezetimibe, double dose atorvastatin and switching to rosuvastatin (44.1% and 54.0% vs 20.5% and 22.6%, 5.0% and 4.8%, and 21.4%; P<0.001 vs all comparators). Most alirocumab-treated patients (86%) maintained their 75 mg every two weeks regimen. Secondary: Treatment-emergent adverse events occurred in 65.4% of alirocumab patients, compare to 64.4% ezetimibe and 63.8% double atorvastatin/switch to rosuvastatin (data pooled).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs atorvastatin (at double baseline dose) vs rosuvastatin 40 mg QD (atorvastatin 40 mg baseline dose cohort only) Prior to randomization, patients were stabilized on atorvastatin 20 mg to 40 mg QD.				

Drug regimen abbreviations: QD=once daily, SQ=subcutaneously
Study abbreviations: AC=active-controlled, DB=double-blind, DD=double-dummy, MC=multicenter, PC=placebo-controlled, PG=parallel-group, RCT=randomized controlled trial
apoB=apolipoprotein B, ATP=Adult Treatment Program, CHD=coronary heart disease, CI=confidence interval, CVE=cardiovascular events, HDL-C=high density lipoprotein, HeFH=heterozygous familial hypercholesterolemia, HR=hazard ratio, LDL-C=low density lipoprotein cholesterol, TC=total cholesterol, TG=triglyceride

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 Alirocumab

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Alirocumab	injection	Praluent®	$$$$$	N/A

N/A=Not available

X. Conclusions

Praluent® (alirocumab) is Food and Drug Administration (FDA)-approved as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic cardiovascular disease (ASCVD), who require additional lowering of low density lipoprotein cholesterol (LDL-C).[1] Praluent® is administered subcutaneously once every two weeks and is available as a pre-filled syringe and a pre-filled pen.[1]

The 2013 consensus guidelines from the American Heart Association /American College of Cardiology emphasize the use of statin therapy with intensity stratified by risk level.[2] This differed significantly from the previous gold standard guidelines from the 2004 National Cholesterol Education Program that emphasized the use LDL-C to monitor response to therapy.[4] Significant discussion exists in the provider community over the best approach to treatment. In November 2014, results of the IMPROVE-IT trial supported the use of LDL-C target goals. In this trial, patients who had been hospitalized for an acute coronary syndrome within the preceding ten days were randomized to simvastatin alone or in combination with ezetimibe (N=18,144). The combination treatment group achieved an average lower LDL-C (53.7 vs 69.5 mg/dL; P<0.001) and had a significantly lower

event rate at seven years (32.7 vs 34.7%; P=0.016). The investigators concluded that "lowering LDL-C to levels below previous targets provided additional benefit" reemphasizing the use of LDL-C target goals as a marker of cholesterol response.[14]

In July 2016, the American College of Cardiology released the Expert Consensus Decision Pathway on the Role of Non-Statin Therapies for LDL-Cholesterol Lowering in the Management of Atherosclerotic Cardiovascular Disease Risk. In general, the use of PCSK9 inhibitors is only recommended for consideration after addressing statin intolerance, intensifying lifestyle modifications, increasing to high-intensity statin if not already taking, evaluating for statin intolerance if unable to tolerate moderate-intensity statin, controlling other risk factors, and adding ezetimibe or a bile acid sequestrant to therapy. If ASCVD patients who are on maximally tolerated statin–ezetimibe or non-statin combination therapy in the setting of documented statin intolerance, achieve a less-than-anticipated response, it is reasonable to consider the net benefit of a PCSK9 inhibitor to achieve further LDL-C reduction. Patient preference should be considered in the discussion to initiate PCSK9 inhibitor therapy, including considerations of the patient's perception of net benefit, convenience/burden of additional therapy, cost, quality of life, and the potential to jeopardize adherence to other evidence-based therapies.[3] Although alirocumab has demonstrated a benefit in reducing various measures of cholesterol, the extent of benefit on cardiovascular morbidity and mortality has not been determined. In addition, the agent was only approved as adjunctive therapy to maximally-dosed statin therapy, not in statin intolerant patients.[1]

The FDA-approval of alirocumab is based on data from twelve phase III ODYSSEY trials (>5,000 patients). These trials include patients with HeFH, those with coronary heart disease (CHD) and those at risk for cardiovascular events (CVE).[1,7-13] Across the clinical trial program, alirocumab was associated with an approximate 40 to 60% decrease in LDL-C from baseline. In addition, other lipid measures generally decreased at higher levels than with placebo. Most studies evaluated a protocol in which patients started at 75 mg every two weeks and were increased to 150 mg if LDL was above 70 mg/dL at week 12. In several studies, the majority of patients were able to reach goal LDL-C levels by week 12 without requiring dose titration. For example, in ODYSSEY COMBO I, 83.2% of evaluable alirocumab-treated patients remained on the 75 mg dose throughout the study. ODYSSEY CHOICE I also evaluated alirocumab at a dose of 300 mg every four weeks; however, the agent did not receive approval for use at this dose.[1,7-13] In a post-hoc analysis of one key study, ODYSSEY LONG-TERM, investigators observed a decreased risk of cardiovascular events compared to placebo (1.7 vs 3.3%; hazard ratio, 0.52; 95% confidence interval, 0.31 to 0.90; P=0.02).[10]

At this time, there is insufficient data to conclude that alirocumab is safer or more efficacious than other brand or generic products within its class and that it offers a significant clinical advantage over other alternatives in general use. 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 alirocumab 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.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
New Drug Review: Epclusa®
AHFS Class 081840
November 9, 2016

I. Overview

Epclusa® (sofosbuvir-velpatasvir) is a once-daily combination product Food and Drug Administration (FDA)-approved for 12-week treatment of chronic hepatitis C virus (HCV) genotype 1, 2, 3, 4, 5, or 6 infection in adults with or without cirrhosis. The addition of ribavirin is recommended in patients with decompensated cirrhosis. It is the first combination product approved to treat all six major HCV genotypes.[1-4] Epclusa® contains sofosbuvir, an HCV nucleotide analog NS5B polymerase inhibitor, and velpatasvir, an HCV NS5A inhibitor. Both drugs interfere with the enzymes required for viral replication. The FDA has previously granted Epclusa® priority review and breakthrough therapy designation due to its potential to offer major advances in treatment over existing options.[4]

In July 2016, the American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) consensus guidelines were updated to recommend sofosbuvir-velpatasvir treatment for 12 weeks for genotypes one through six in patients without cirrhosis or with compensated cirrhosis. Sofosbuvir-velpatasvir is also recommended in other populations, including retreatment of patients after failed therapy (with peginterferon alfa and ribavirin, HCV protease inhibitor plus peginterferon alfa and ribavirin, and sofosbuvir and ribavirin) and patients with decompensated cirrhosis when used in combination with ribavirin.[5]

The sofosbuvir-velpatasvir products 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.

Table 1. Sofosbuvir-Velpatasvir Products Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Sofosbuvir and Velpatasvir	tablet	Epclusa®	none

PDL=Preferred Drug List

II. Evidence-Based Medicine and Current Treatment Guidelines

Current treatment guidelines that incorporate the use of sofosbuvir-velpatasvir are summarized in Table 2.

Table 2. Treatment Guidelines Using Sofosbuvir-Velpatasvir

Clinical Guideline	Recommendation(s)
American Association for the Study of Liver Diseases and Infectious Diseases Society of America: **Recommendations for testing, managing, and treating hepatitis C (2016)**[5]	Goal of treatment • The goal of treatment of hepatitis C virus (HCV)-infected persons is to reduce all-cause mortality and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma, by the achievement of virologic cure as evidenced by a sustained virologic response (SVR). When and in whom to initiate treatment • Treatment is recommended for all patients with chronic HCV infection, except those with short life expectancies that cannot be remediated by treating HCV, by transplantation, or by other directed therapy. Patients with short life expectancies owing to liver disease should be managed in consultation with an expert. • An evaluation of advanced fibrosis using liver biopsy, imaging, and/or noninvasive markers is recommended. • There are no data to support pretreatment screening for illicit drug or alcohol use in identifying a population more likely to successfully complete HCV

Clinical Guideline	Recommendation(s)

	therapy. These requirements should be abandoned, because they create barriers to treatment, add unnecessary cost and effort, and potentially exclude populations that are likely to obtain substantial benefit from therapy.
	• Strong and accumulating evidence argue against deferral because of decreased all-cause morbidity and mortality, prevention of onward transmission, and quality-of-life improvements for patients treated regardless of baseline fibrosis. Deferral practices based on fibrosis stage alone are inadequate and shortsighted. Ongoing assessment of liver disease is recommended for persons in whom therapy is deferred.
	• Recommended and alternative regimens below are generally listed in groups by level of evidence, then alphabetically.
	
	<u>Initial treatment of HCV infection (treatment-naïve)</u>
	• <u>Genotype 1a (no cirrhosis)</u>
	  o Elbasvir/grazoprevir for 12 weeks (baseline NS5A resistance-associated variants [RAVs] absent)
	  o Ledipasvir/sofosbuvir for 12 weeks
	  o Paritaprevir/ritonavir/ombitasvir plus dasabuvir and ribavirin for 12 weeks
	  o Sofosbuvir plus simeprevir for 12 weeks
	  o Sofosbuvir/velpatasvir for 12 weeks
	  o Daclatasvir plus sofosbuvir for 12 weeks
	  o Alternative: elbasvir/grazoprevir and ribavirin 16 weeks (baseline NS5A RAVs present)
	• <u>Genotype 1a (compensated cirrhosis)</u>
	  o Elbasvir/grazoprevir for 12 weeks (baseline NS5A RAVs absent)
	  o Ledipasvir/sofosbuvir for 12 weeks
	  o Sofosbuvir/velpatasvir for 12 weeks
	  o Alternative: paritaprevir/ritonavir/ombitasvir plus dasabuvir and ribavirin for 24 weeks
	  o Alternative: sofosbuvir plus simeprevir with or without ribavirin for 24 weeks (Q80K polymorphism not detected)
	  o Alternative: daclatasvir plus sofosbuvir with or without ribavirin for 24 weeks
	  o Alternative: elbasvir/grazoprevir and ribavirin 16 weeks (baseline NS5A RAVs present)
	• <u>Genotype 1b (no cirrhosis)</u>
	  o Elbasvir/grazoprevir for 12 weeks
	  o Ledipasvir/sofosbuvir for 12 weeks
	  o Paritaprevir/ritonavir/ombitasvir plus dasabuvir for 12 weeks
	  o Sofosbuvir plus simeprevir for 12 weeks
	  o Sofosbuvir/velpatasvir for 12 weeks
	  o Daclatasvir plus sofosbuvir for 12 weeks
	• <u>Genotype 1b (compensated cirrhosis)</u>
	  o Elbasvir/grazoprevir for 12 weeks
	  o Ledipasvir/sofosbuvir for 12 weeks
	  o Paritaprevir/ritonavir/ombitasvir plus dasabuvir for 12 weeks
	  o Sofosbuvir/velpatasvir for 12 weeks
	  o Alternative: sofosbuvir plus simeprevir with or without ribavirin for 24 weeks
	  o Alternative: daclatasvir plus sofosbuvir with or without ribavirin for 24 weeks
	• Shortening treatment with ledipasvir/sofosbuvir to less than 12 weeks for patients without cirrhosis should be done with caution and performed at the discretion of the practitioner.
	• <u>Genotype 2 (no cirrhosis)</u>

Clinical Guideline	Recommendation(s)
	o Sofosbuvir/velpatasvir for 12 weeks o Alternative: Daclatasvir plus sofosbuvir for 12 weeks • Genotype 2 (compensated cirrhosis) o Sofosbuvir/velpatasvir for 12 weeks o Alternative: Daclatasvir plus sofosbuvir for 16 to 24 weeks • Genotype 3 (no cirrhosis) o Daclatasvir plus sofosbuvir for 12 weeks Sofosbuvir/velpatasvir for 12 weeks • Genotype 3 (compensated cirrhosis) o Sofosbuvir/velpatasvir for 12 weeks • Daclatasvir plus sofosbuvir with or without ribavirin for 24 weeks Genotype 4 o Paritaprevir/ritonavir/ombitasvir and ribavirin for 12 weeks o Sofosbuvir/velpatasvir for 12 weeks o Elbasvir/grazoprevir for 12 weeks o Ledipasvir/sofosbuvir for 12 weeks • Genotype 5 or 6 o Sofosbuvir/velpatasvir for 12 weeks o Ledipasvir/sofosbuvir for 12 weeks Retreatment after failed therapy (peginterferon alfa and ribavirin) • Genotype 1a (no cirrhosis) o Elbasvir/grazoprevir for 12 weeks (baseline NS5A RAVs absent) o Ledipasvir/sofosbuvir for 12 weeks o Paritaprevir/ritonavir/ombitasvir plus dasabuvir and ribavirin for 12 weeks o Sofosbuvir plus simeprevir for 12 weeks o Sofosbuvir/velpatasvir for 12 weeks o Daclatasvir plus sofosbuvir for 12 weeks o Alternative: elbasvir/grazoprevir and ribavirin 16 weeks (baseline NS5A RAVs present) • Genotype 1a (compensated cirrhosis) o Elbasvir/grazoprevir for 12 weeks (baseline NS5A RAVs absent) o Ledipasvir/sofosbuvir and ribavirin for 12 weeks o Sofosbuvir/velpatasvir for 12 weeks o Alternative: paritaprevir/ritonavir/ombitasvir plus dasabuvir and ribavirin for 24 weeks o Alternative: ledipasvir/sofosbuvir for 24 weeks o Alternative: elbasvir/grazoprevir and ribavirin 16 weeks (baseline NS5A RAVs present) o Alternative: daclatasvir plus sofosbuvir with or without ribavirin for 24 weeks. o Alternative: sofosbuvir plus simeprevir with or without ribavirin for 24 weeks (Q80K polymorphism not detected) • Genotype 1b (no cirrhosis) o Elbasvir/grazoprevir for 12 weeks o Ledipasvir/sofosbuvir for 12 weeks o Paritaprevir/ritonavir/ombitasvir plus dasabuvir for 12 weeks o Sofosbuvir plus simeprevir for 12 weeks o Sofosbuvir/velpatasvir for 12 weeksDaclatasvir plus sofosbuvir for 12 weeks • Genotype 1b (compensated cirrhosis) o Elbasvir/grazoprevir for 12 weeks o Ledipasvir/sofosbuvir and ribavirin for 12 weeks o Paritaprevir/ritonavir/ombitasvir plus dasabuvir for 12 weeks o Sofosbuvir/velpatasvir for 12 weeks o Alternative: Ledipasvir/sofosbuvir for 24 weeks

Clinical Guideline	Recommendation(s)
	o Alternative: sofosbuvir plus simeprevir with or without ribavirin for 24 weeks o Alternative: daclatasvir plus sofosbuvir with or without ribavirin for 24 weeks. • Genotype 2 o Sofosbuvir/velpatasvir for 12 weeks o Alternative: daclatasvir plus sofosbuvir for 12 weeks (no cirrhosis) or 16 to 24 weeks (compensated cirrhosis) • Genotype 3 o Daclatasvir plus sofosbuvir for 12 weeks (no cirrhosis); or with ribavirin for 24 weeks (compensated cirrhosis) o Sofosbuvir/velpatasvir for 12 weeks (or cirrhosis); or with ribavirin for 12 weeks (compensated cirrhosis) • Genotype 4 o Paritaprevir/ritonavir/ombitasvir and ribavirin for 12 weeks o Sofosbuvir/velpatasvir for 12 weeks o Elbasvir/grazoprevir for 12 weeks (virologic relapse after prior peginterferon alfa and ribavirin) or 16 weeks with ribavirin (failure to suppress or breakthrough on prior peginterferon alfa and ribavirin) o Ledipasvir/sofosbuvir for 12 weeks (no cirrhosis) or 12 weeks with ribavirin (compensated cirrhosis) • Alternative: Ledipasvir/sofosbuvir for 24 weeks (compensated cirrhosis)Genotype 5 or 6 o Sofosbuvir/velpatasvir for 12 weeks o Ledipasvir/sofosbuvir for 12 weeks • Mixed Genotypes o Treatment data for mixed genotypes with direct-acting antivirals are sparse, and awaiting availability of a pangenotypic regimen may be considered. o When treatment is necessary, the choice of antiviral combination and duration of treatment should maximize efficacy against each genotype represented in the assay. Retreatment after failed therapy (sofosbuvir and ribavirin with or without peginterferon alfa) • Genotype 1 o Ledipasvir/sofosbuvir and ribavirin for 12 weeks (no cirrhosis) or 24 weeks (compensated cirrhosis) Retreatment after failed therapy (HCV protease inhibitor plus peginterferon alfa and ribavirin) • Genotype 1 (no cirrhosis) o Ledipasvir/sofosbuvir for 12 weeks o Sofosbuvir/velpatasvir for 12 weeks o Daclatasvir plus sofosbuvir for 12 weeks o Elbasvir/grazoprevir and ribavirin for 12 weeks (baseline NS5A RAVs absent) or 16 weeks (for genotype 1a with baseline NS5A RAVs present) • Genotype 1 (compensated cirrhosis) o Ledipasvir/sofosbuvir and ribavirin for 12 weeks o Ledipasvir/sofosbuvir for 24 weeks o Sofosbuvir/velpatasvir for 12 weeks o Daclatasvir plus sofosbuvir with or without ribavirin for 24 weeks o Elbasvir/grazoprevir and ribavirin for 12 weeks (baseline NS5A RAVs absent) or 16 weeks (for genotype 1a with baseline NS5A RAVs present) Retreatment after failed therapy (sofosbuvir plus simeprevir or HCV NS5A

Clinical Guideline	Recommendation(s)

	inhibitor)
	Genotype 1
	• Deferral of treatment is recommended for patients who do not have cirrhosis, pending availability of data
	• Testing for RAVs that confer decreased susceptibility to NS3 protease inhibitors and to NS5A inhibitors is recommended who have compensated cirrhosis or have reasons for urgent retreatment. Specific drugs should be tailored to the results of this testing.
	• When using nucleotide-based (e.g., sofosbuvir) dual direct-acing antiviral therapy treatment duration of 24 weeks is recommended, with ribavirin, unless contraindicated.
	• If available, nucleotide-based (e.g., sofosbuvir) triple or quadruple direct-acing antiviral regimens may be considered for 12 to 24 weeks with ribavirin, unless contraindicated.
	
	Retreatment after failed therapy (sofosbuvir and ribavirin)
	• Genotype 2
	  o Daclatasvir plus sofosbuvir with or without ribavirin for 24 weeks (peginterferon alfa or ribavirin ineligible)
	  o Sofosbuvir/velpatasvir for 12 weeks and ribavirin for 12 weeks
	• Genotype 3
	  o Daclatasvir plus sofosbuvir and ribavirin for 24 weeks Sofosbuvir/velpatasvir and ribavirin for 12 weeks
	
	Recommendations for discontinuation of treatment due to lack of efficacy
	  o If HCV viral load is detectable at week four, repeat quantitative HCV viral load after two additional weeks of treatment (treatment week six).
	  ▪ If quantitative HCV viral load has increased by greater than 10-fold (>1 $\log_{10}$ IU/mL) on repeat testing at week six (or thereafter), discontinue HCV treatment.
	  o The significance of a positive HCV RNA test result at week four that remains positive, but lower, at week six or week eight is unknown.
	  ▪ No recommendation to stop therapy or extend therapy can be provided at this time.
	
	Special populations – human immunodeficiency virus (HIV)/HCV coinfection
	• HIV/HCV-coinfected persons should be treated and re-treated the same as persons without HIV infection, after recognizing and managing interactions with antiretroviral medications.
	• Daclatasvir and sofosbuvir, with or without ribavirin is recommended when antiretroviral regimen changes cannot be made to accommodate alternative HCV direct-acting antivirals
	
	Special populations – decompensated cirrhosis
	• Patients with decompensated cirrhosis (Child Turcotte Pugh [CTP] class B or C) should be referred to a medical practitioner with expertise in that condition (ideally in a liver transplant center).
	• Genotype 1 or 4 (patients who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma)
	  o Ledipasvir/sofosbuvir and ribavirin for 12 weeks
	  o Sofosbuvir/velpatasvir and ribavirin for 12 weeks
	  o Daclatasvir plus sofosbuvir and ribavirin for 12 weeks
	  o Alternative (ribavirin intolerant or ineligible): sofosbuvir/velpatasvir for 24 weeks
	  o Alternative (ribavirin intolerant or ineligible): daclatasvir plus sofosbuvir for 24 weeks

Clinical Guideline	Recommendation(s)
	o Alternative (ribavirin intolerant or ineligible): ledipasvir/sofosbuvir for 24 weeks o Alternative (prior failure with a sofosbuvir-based regimen): ledipasvir/sofosbuvir and ribavirin for 24 weeks o Alternative (prior failure with a sofosbuvir-based regimen): sofosbuvir/velpatasvir and ribavirin for 24 weeks • Genotype 2 or 3 (patients who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma) o Sofosbuvir/velpatasvir and ribavirin for 12 weeks o Daclatasvir plus sofosbuvir and ribavirin for 12 weeks Special populations – recurrent HCV infection post-liver transplantation • Genotype 1 or 4 infection in the allograft (including compensated cirrhosis), treatment-naïve or treatment-experienced o Ledipasvir/sofosbuvir with ribavirin for 12 weeks (including decompensated cirrhosis) o Daclatasvir plus sofosbuvir and ribavirin for 12 weeks o Alternative (ribavirin intolerant or ineligible): ledipasvir/sofosbuvir for 24 weeks (treatment-naïve only) o Alternative (ribavirin intolerant or ineligible): daclatasvir plus sofosbuvir for 24 weeks o Alternative (genotype 1 only): sofosbuvir plus simeprevir with or without ribavirin for 12 weeks o Alternative (genotype 1, Metavir fibrosis stage F0-F2): paritaprevir/ritonavir/ombitasvir plus dasabuvir and ribavirin for 24 weeks • Genotype 2 infection in the allograft (including compensated cirrhosis), treatment-naïve or treatment-experienced o Daclatasvir plus sofosbuvir and ribavirin for 12 weeks o Sofosbuvir and ribavirin for 24 weeks o Alternative (ribavirin intolerant or ineligible): daclatasvir plus sofosbuvir for 24 weeks • Genotype 2 infection in the allograft, liver transplant recipients (with decompensated cirrhosis), treatment-naïve or treatment-experienced o Sofosbuvir and ribavirin for 24 weeks • Genotype 3 infection in the allograft (including compensated cirrhosis), treatment-naïve or treatment-experienced o Daclatasvir plus sofosbuvir and ribavirin for 12 weeks o Alternative (ribavirin ineligible): daclatasvir plus sofosbuvir for 24 weeks Special populations – renal impairment • Mild to moderate renal impairment (CrCl >30 mL/min) o Daclatasvir: no dosage adjustment is required o Ledipasvir/sofosbuvir: no dosage adjustment is required o Sofosbuvir/velpatasvir: no dosage adjustment is required o Paritaprevir/ritonavir/ombitasvir with and without dasabuvir: no dosage adjustment is required o Simeprevir: no dosage adjustment is required o Sofosbuvir: no dosage adjustment is required • Severe renal impairment (CrCl<30 mL/min or end-stage renal disease) with high urgency to treat and kidney transplant is not an immediate option o HCV genotype 1a, 1b or 4 infection: elbasvir/grazoprevir for 12 weeks o HCV genotype 1b infection: paritaprevir/ritonavir/ombitasvir plus dasabuvir for 12 weeks o HCV genotype 2, 3, 5, or 6 infection: peginterferon alfa and ribavirin o Alternative (HCV genotype 1a infection): daily

Clinical Guideline	Recommendation(s)

	paritaprevir/ritonavir/ombitasvir plus dasabuvir (and ribavirin if hemoglobin >10 g/dL at a dose of 200 mg trice weekly to daily)
	
	Management of acute HCV infection
	• HCV antibody and HCV RNA testing are recommended when acute HCV infection is suspected due to exposure, clinical presentation, or elevated aminotransferase levels
	• Preexposure or postexposure prophylaxis with antiviral therapy is NOT recommended.
	• Medical management and monitoring
	  o Regular laboratory monitoring is recommended in the setting of acute HCV infection. Monitoring HCV RNA (every four to eight weeks) for six to 12 months is recommended to determine spontaneous clearance of HCV infection versus persistence of infection.
	  o Counseling is recommended for patients with acute HCV infection to avoid hepatotoxic insults including hepatotoxic drugs and alcohol consumption, and to reduce the risk of HCV transmission to others.
	  o Referral to an addiction medicine specialist is recommended for patients with acute HCV infection related to substance use.
	• Treatment for patients with acute HCV infection
	  o If treatment is delayed, monitoring for spontaneous clearance is recommended for a minimum of six months.
	  o If treatment is to begin during the acute infection period, monitor HCV RNA for at least 12 to 16 weeks before starting treatment to allow for spontaneous clearance.
	  o Treatment with the same standard regimens is recommended for chronic and acute HCV infection.

Department of Veterans Affairs National Hepatitis C Resource Center Program and the Office of Public Health: **HCV Infection: Treatment Considerations (2016)**[6]	Goal of treatment • The goal of hepatitis C antiviral treatment is to achieve a sustained virological response (SVR), defined as undetectable HCV RNA in the blood 12 or more weeks after completing antiviral treatment. Principles for patient selection for HCV treatment • All patients with chronic HCV who do not have medical contraindications are potential candidates for antiviral treatment. • 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 (HCC) awaiting liver transplant, post-transplant recipients with cirrhosis, and patients with serious extra-hepatic manifestations of HCV, and women of childbearing potential who desire to conceive a child in the next 12 months. • Patients with mild liver disease (METAVIR F0-2) have less urgency for treatment in the short term, but should be informed of new treatments and their potential to cure HCV. • Patients with severe mental health conditions who are engaged in treatment or those with ongoing substance use including drinking alcohol, using illicit drugs, including marijuana, or participating in opioid replacement programs should not be excluded from HCV treatment. • Treatment is not indicated in patients with limited life expectancy of less than 12 months unless there is reason to anticipate that duration or quality of life can be improved by eradication of HCV. • Factors that may complicate adherence, such as active substance abuse, depression, neurocognitive disorders, and lack of social support, should be

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	addressed before initiating medications.
	
	Treatment of HCV genotype 1 in treatment-naïve patients without cirrhosis
	• Ledipasvir/sofosbuvir for eight weeks if baseline HCV RNA <6 million IU/mL; 12 weeks if HIV/HCV co-infected or HCV RNA ≥6 million IU/mL.
	
	Treatment of HCV genotype 1 in treatment-naïve or -experienced (prior peginterferon alfa and ribavirin) patients without or with cirrhosis (CTP A)
	• Elbasvir/grazoprevir.
	  o Genotype 1a without baseline NS5A RAVs: 12 weeks.
	  o Genotype 1a with baseline NS5A RAVs: 16 weeks with ribavirin.
	  o Genotype 1b: 12 weeks.
	• Ledipasvir/sofosbuvir for 12 weeks (with ribavirin if treatment-experienced with cirrhosis).
	• Paritaprevir/ritonavir/ombitasvir plus dasabuvir and ribavirin; may consider 24 weeks in cirrhotics or prior null responders; genotype 1b: ribavirin not required.
	
	Treatment of HCV genotype 1 in treatment-experienced (prior NS3/4A inhibitor plus peginterferon alfa and ribavirin, or prior sofosbuvir and ribavirin with or without peginterferon alfa) patients without or with cirrhosis (CTP A)
	• Elbasvir/grazoprevir and ribavirin.
	  o Genotype 1a without baseline NS5A RAVs: 12 weeks.
	  o Genotype 1a with baseline NS5A RAVs: 16 weeks.
	  o Genotype 1b: 12 weeks.
	• Ledipasvir/sofosbuvir and ribavirin.
	
	Treatment of HCV genotype 1 in treatment-naïve or -experienced (prior peginterferon alfa and ribavirin, prior NS3/4A inhibitor plus peginterferon alfa and ribavirin, or prior sofosbuvir and ribavirin with or without peginterferon alfa) patients with decompensated cirrhosis (CTP B or C)
	• Ledipasvir/sofosbuvir and ribavirin (600 mg, increased monthly by 200 mg/day every two weeks as tolerated).
	
	Treatment of HCV genotype 1 in treatment-experienced (prior NS5A-containing regimen) patients with or without cirrhosis
	• Test for RAVs to NS5A prior to re-treatment and consult with an expert.
	
	Treatment of HCV genotype 2 in treatment-naïve patients without cirrhosis
	• Sofosbuvir and ribavirin for 12 weeks.
	• Alternative (if ribavirin intolerant or contraindicated): ledipasvir/sofosbuvir for 12 weeks.
	• Alternative: daclatasvir plus sofosbuvir for 12 weeks.
	
	Treatment of HCV genotype 2 in treatment-naïve patients with cirrhosis (CTP A)
	• Sofosbuvir and ribavirin for 16 weeks.
	
	Treatment of HCV genotype 2 in treatment-experienced (prior peginterferon and ribavirin only) patients with or without cirrhosis (CTP A)
	• Sofosbuvir and ribavirin for 16 weeks.
	• Alternative (no cirrhosis): daclatasvir plus sofosbuvir for 12 weeks.
	• Alternative (no cirrhosis): Ledipasvir/sofosbuvir for 12 weeks.
	
	Treatment of HCV genotype 3 in treatment-naïve patients without cirrhosis
	• Ledipasvir/sofosbuvir and ribavirin for 12 weeks.
	• Alternative: daclatasvir plus sofosbuvir for 12 weeks.

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	• Alternative: sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks.
	• Alternative: sofosbuvir and ribavirin for 24 weeks.
	
	Treatment of HCV genotype 3 in treatment-naïve patients with cirrhosis
	• Daclatasvir plus sofosbuvir and ribavirin for 12 weeks (CTP A) or 12 to 24 weeks (CTP B or C).
	• Alternative: sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks (CTP A).
	
	Treatment of HCV genotype 3 in treatment-experienced patients (prior peginterferon and ribavirin only) without cirrhosis
	• Ledipasvir/sofosbuvir and ribavirin for 12 weeks.
	• Alternative: daclatasvir plus sofosbuvir for 12 weeks
	• Alternative: sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks.
	• Sofosbuvir and ribavirin for 24 weeks.
	
	Treatment of HCV genotype 3 in treatment-experienced patients (prior peginterferon and ribavirin only) with cirrhosis
	• Daclatasvir plus sofosbuvir and ribavirin for 12 weeks (CTP A) or 12 to 24 weeks (CTP B or C).
	• Daclatasvir plus sofosbuvir for 24 weeks (if ribavirin ineligible).
	
	Treatment of HCV genotype 4 in treatment-naïve and treatment-experienced patients with or without cirrhosis (CTP A)
	• Elbasvir/grazoprevir for 12 weeks.
	• Ledipasvir/sofosbuvir for 12 weeks.
	• Paritaprevir/ritonavir/ombitasvir and ribavirin for 12 weeks.
	
	Stopping rules based on lack of virologic response
	• Patients should have an HCV RNA level assessed at week 4 of treatment.
	• If the HCV RNA is quantifiable at week 4 or at any time point thereafter, reassess HCV RNA in two weeks. If the repeated HCV RNA increases (i.e., >1 $\log_{10}$ IU/mL from nadir), discontinuation of all treatment should be strongly considered.
	• HCV RNA levels should be assessed at 12 weeks after completion of treatment to determine whether SVR was achieved.
	
	Use in HIV/HCV-coinfection
	• HIV/HCV-coinfected patients receive the same HCV antiviral regimen as HCV-monoinfected patients, provided the patient is receiving appropriate HIV care and drug-drug interactions are addressed appropriately.
	
	Treatment in pre-liver transplant
	• Genotype 1, including patients with CTP A, B, or C, as well as HCC
	  o Ledipasvir/sofosbuvir and ribavirin for 12 weeks
	• Genotype 2, including patients with HCC
	  o Sofosbuvir and ribavirin for 24 to 48 weeks; the addition of peginterferon alfa may be considered
	• Genotype 3 or 4
	  o Consult with a transplant center prior to starting treatment. In general, the preferred treatment is the same treatment as is recommended for treatment-naïve or treatment-experienced (as appropriate) patients.
	
	Treatment in post-liver or other solid organ transplant
	• Genotype 1

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	o Ledipasvir/sofosbuvir and ribavirin for 12 weeks. o If ribavirin intolerant: ledipasvir/sofosbuvir for 24 weeks. • Genotype 2 o Sofosbuvir and ribavirin for 24 weeks; the addition of peginterferon alfa may be considered • Genotype 3 o The decision to treat, regimen selection, and management of treatment should be coordinated with the transplant center and/or by specialists with extensive experience in the treatment of pre- or post-transplant patients. • Genotype 4 o Ledipasvir/sofosbuvir and ribavirin for 12 weeks o If ribavirin intolerant: ledipasvir/sofosbuvir for 24 weeks.
European Association for the Study of the Liver: **Treatment of Hepatitis (2015)**[7]	Goals and endpoints of HCV therapy • The goal of therapy is to cure HCV infection, to prevent hepatic cirrhosis, decompensation of cirrhosis, hepatocellular carcinoma, severe extra-hepatic manifestations, 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 or decompensated chronic liver disease due to HCV should be considered for therapy. • Treatment should be prioritized for patients with significant fibrosis or cirrhosis (F3 to F4). • Patients with decompensated cirrhosis (Child Pugh B or C) should be urgently treated with an interferon-free regimen. • Treatment should be prioritized regardless of the fibrosis stage for individuals at risk of transmitting HCV, including active injection drug users, men who have sex with men with high-risk sexual practices, women of childbearing age who wish to get pregnant, hemodialysis patients, and incarcerated individuals • 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. • Treatment is not recommended in patients with limited life expectancy due to non-liver related comorbidities 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. • Interferon-free regimens are the best options when available in all HCV-monoinfected and in HIV-coinfected patients because of their virological efficacy, ease of use and tolerability. • 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. • The combination of sofosbuvir and ledipasvir can be used with all antiretrovirals. However, this regimen should not be used with the combination

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	of tenofovir/emtricitabine with atazanavir/ritonavir, darunavir/ritonavir, lopinavir/ritonavir or elvitegravir/ cobicistat when possible, or used with caution with frequent renal monitoring.
	• The combination of ombitasvir/paritaprevir/ritonavir and dasabuvir should not be used with efavirenz, etravirine or nevirapine, and rilpivirine should be used cautiously with repeat electrocardiogram monitoring. Atazanavir and darunavir should be taken without ritonavir and other protease inhibitors are contraindicated with this combination. Elvitegravir/cobicistat should not be used with this regimen because of the additional boosting effect.
	
	<u>Treatment options for HCV genotype 1 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 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 4, 12 or 24.
	• Ledipasvir/sofosbuvir without ribavirin for 12 weeks (no cirrhosis) or with ribavirin for 12 weeks (compensated cirrhosis)
	• Ledipasvir/sofosbuvir for eight weeks may be considered in treatment-naïve patients without cirrhosis and baseline HCV RNA <6 million. This should be done with caution especially in in patients with F3.
	• Ledipasvir/sofosbuvir and ribavirin for 24 weeks in treatment-experienced patients with compensated cirrhosis and negative predictors of response, such as a platelet count <75,000/µL.
	• Ombitasvir/paritaprevir/ritonavir and dasabuvir without ribavirin for 12 weeks (HCV genotype 1b without cirrhosis) or with ribavirin for 12 weeks (HCV genotype 1b with cirrhosis or HCV genotype 1a without cirrhosis)
	• Ombitasvir/paritaprevir/ritonavir and dasabuvir with ribavirin for 24 weeks (HCV genotype 1a with cirrhosis)
	• Sofosbuvir and simeprevir without ribavirin for 12 weeks (patients without cirrhosis) or with ribavirin for 12 weeks (cirrhotics)
	• Sofosbuvir and simeprevir for 24 weeks (patients with cirrhosis and contraindication to ribavirin)
	• Daclatasvir and sofosbuvir without ribavirin for 12 weeks (no cirrhosis) or with ribavirin for 12 weeks (cirrhosis)
	• Daclatasvir and sofosbuvir for 24 weeks (patients with cirrhosis and contraindication to ribavirin)
	
	<u>Treatment options for HCV genotype 2 infection</u>
	• Sofosbuvir and 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.
	• Daclatasvir and sofosbuvir 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 (including patients who failed prior treatment with sofosbuvir and ribavirin)
	• Sofosbuvir and ribavirin for 24 weeks
	  o Suboptimal in treatment-experienced cirrhotics or those who failed prior treatment with sofosbuvir and ribavirin
	• Daclatasvir and sofosbuvir without ribavirin for 12 weeks (no cirrhosis) or with

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	ribavirin 24 weeks (cirrhosis, pending data with 12 weeks of therapy). 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 4, 12 or 24. • Ledipasvir/sofosbuvir without ribavirin for 12 weeks (no cirrhosis) or with ribavirin for 12 weeks (cirrhosis) • Ledipasvir/sofosbuvir for 24 weeks (patients with cirrhosis and contraindication to ribavirin) • Ledipasvir/sofosbuvir with ribavirin for 24 weeks is an option in treatment-experienced cirrhotics and negative predictors of response, such as a platelet count <75,000/µL. • Ombitasvir/paritaprevir/ritonavir and ribavirin for 12 weeks (no cirrhosis) or for 24 weeks (cirrhosis) • Sofosbuvir and simeprevir without ribavirin for 12 weeks (patients without cirrhosis) or with ribavirin for 12 weeks (cirrhotics) • Sofosbuvir and simeprevir for 24 weeks (patients with cirrhosis and contraindication to ribavirin) • Daclatasvir and sofosbuvir without ribavirin for 12 weeks (no cirrhosis) or with ribavirin for 12 weeks (cirrhosis). • Daclatasvir and sofosbuvir for 24 weeks (patients with cirrhosis and contraindication to ribavirin) Treatment options for HCV genotype 5 or 6 infection • Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Ledipasvir/sofosbuvir without ribavirin for 12 weeks (no cirrhosis) or with ribavirin for 12 weeks (compensated cirrhosis) • Ledipasvir/sofosbuvir for 24 weeks (cirrhotic patients with contraindication or intolerance to ribavirin) • Ledipasvir/sofosbuvir and ribavirin for 24 weeks (treatment-experienced cirrhotics with negative predictors of response, such as a platelet count <75,000/µL). • Daclatasvir and sofosbuvir without ribavirin for 12 weeks (no cirrhosis) or with ribavirin for 12 weeks (cirrhosis). • Daclatasvir and sofosbuvir for 24 weeks (patients with cirrhosis and contraindication to ribavirin) 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 4, 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 an interferon-free regimen, HCV RNA should be measured at baseline, week 2 (assessment of adherence), week 4, week 12 or 24

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	(end of treatment in patients treated 12 or 24 weeks, respectively), 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 4, 12 or 24; an immediate switch to another interferon-containing direct-acting antiviral-containing or an interferon-free regimen without a protease inhibitor should be considered • 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 4 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 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 • HCV genotype 1 patients who failed telaprevir or boceprevir plus peginterferon alfa and ribavirin should be retreated with ledipasvir/sofosbuvir, or daclatasvir and sofosbuvir, with ribavirin for 12 weeks. • Recommendations for retreatment after failure of second-wave direct-acting antiviral-based anti-HCV regimens are based on indirect evidence and subject to change when more data become available. • Patients who failed on a second-wave direct-acting-antiviral-containing regimen, with or without peginterferon alfa or ribavirin, should be retreated with an interferon-free regimen for 12 weeks with ribavirin; extending therapy to 24 weeks with ribavirin may be considered, especially in patients with liver fibrosis stage F3 or F4. • Patients who failed on sofosbuvir alone or sofosbuvir and ribavirin or sofosbuvir plus peginterferon alfa and ribavirin can be retreated with a combination of sofosbuvir plus simeprevir (genotype 1 or 4), sofosbuvir plus daclatasvir (all genotypes) or ledipasvir/sofosbuvir (genotypes 1, 4, 5 or 6), or with ombitasvir/paritaprevir/ritonavir and dasabuvir (genotype 1), or with ombitasvir/paritaprevir/ritonavir (genotype 4). • Patients infected with genotype 1 or 4 who failed on a regimen combining peginterferon alfa, ribavirin and simeprevir should be retreated with daclatasvir plus sofosbuvir or ledipasvir/sofosbuvir. • Patients who failed on a regimen combining peginterferon alfa, ribavirin and

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	daclatasvir should be retreated with a combination of sofosbuvir and simeprevir (genotype 1 or 4). Patients infected with other genotypes should be retreated with daclatasvir plus sofosbuvir (genotypes 2, 3, 5 and 6) or ledipasvir/sofosbuvir (genotypes 5 and 6). • Patients infected with genotype 1 or 4 who failed on a regimen containing sofosbuvir and simeprevir should be retreated with daclatasvir plus sofosbuvir of ledipasvir/sofosbuvir. • Patients who failed on a regimen containing daclatasvir and sofosbuvir or ledipasvir/sofosbuvir should be retreated with a combination of sofosbuvir and simeprevir (genotype 1 and 4); patients infected with other genotypes should be retreated with the combination of daclatasvir and sofosbuvir (genotypes 2, 3, 5 and 6) or with the combination of ledipasvir/sofosbuvir (genotypes 5 and 6) for 24 weeks. • Patients infected with genotype 1 who failed ombitasvir/paritaprevir/ritonavir and dasabuvir should be retreated with a sofosbuvir-based regimen (e.g., sofosbuvir and simeprevir, daclatasvir plus sofosbuvir and ledipasvir/sofosbuvir. • Patients infected with genotype 4 who failed ombitasvir/paritaprevir/ritonavir should be retreated with a sofosbuvir-based regimen (e.g., sofosbuvir and simeprevir, daclatasvir plus sofosbuvir and ledipasvir/sofosbuvir). • Alternatively, patients without an urgent need for treatment can wait until more data and/or alternative therapeutic options become available. • The efficacy and safety of a triple combination regimen including sofosbuvir, an NS3 protease inhibitor and an NS5A protease inhibitor in patients who failed on a direct-acting antiviral-containing regimen is unknown. • The utility of HCV resistance testing prior to retreatment in patients who failed on any of the direct-acting antiviral-containing treatment regimens is unknown. <u>Treatment of patients with severe liver disease</u> • Patients with decompensated cirrhosis (CTP B and C) not on the waiting list for liver transplantation and without concomitant comorbidities that could impact their survival can be treated with the combination of sofosbuvir and ribavirin for 16 to 20 weeks (genotype 2), ledipasvir/sofosbuvir (genotypes 1, 4, 5 and 6), or daclatasvir plus sofosbuvir (all genotypes), with ribavirin, for 12 weeks. • Patients with decompensated cirrhosis with contraindication or intolerance to ribavirin should receive ledipasvir/sofosbuvir (genotypes 1, 4, 5 or 6), or daclatasvir plus sofosbuvir (all genotypes) for 24 weeks. <u>Patients with an indication for liver transplantation</u> • In patients awaiting liver transplantation, antiviral therapy is indicated, because it prevents graft infection. • Treatment should be initiated as soon as possible in order to complete a full treatment course before transplantation. • Patients awaiting liver transplantation should be treated with an interferon-free regimen, in principle for 12 or 24 weeks, practically up to transplantation, with ribavirin. • Patients with conserved liver function (CTP A) in whom the indication for transplantation is hepatocellular carcinoma can be treated with the combination of sofosbuvir and ribavirin for 16 to 20 weeks (genotype 2), with ledipasvir/sofosbuvir and ribavirin for 12 weeks (genotypes 1, 4, 5 or 6), with ombitasvir/paritaprevir/ritonavir and dasabuvir with ribavirin for 12 weeks (genotype 1b) or 24 weeks (genotype 1a), with ombitasvir/paritaprevir/ritonavir with ribavirin for 12 weeks (genotype 4), with sofosbuvir plus simeprevir with ribavirin for 12 weeks (genotypes 1 and 4), or with daclatasvir plus sofosbuvir with ribavirin for 12 weeks (all genotypes). • Treatment with sofosbuvir plus interferon alfa and ribavirin for 12 weeks is

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	acceptable in patients with compensated (CTP A) cirrhosis awaiting liver transplantation if interferon-free options are not available. • Patients with decompensated cirrhosis (CTP B or C) awaiting liver transplantation can be treated with the combination of sofosbuvir and ribavirin for 16 to 20 weeks (genotype 2), with ledipasvir/sofosbuvir with ribavirin for 12 weeks (genotypes 1, 4, 5 or 6), or with daclatasvir plus sofosbuvir with ribavirin for 12 weeks (all genotypes); however, data are limited in patients with CTP C cirrhosis >12 points or with a MELD score >20. • The optimal timing of treatment (before transplantation or post-transplantation) to maximize survival is still debatable and requires individual assessment. Post-liver transplantation recurrence • Patients with post-transplant recurrence of HCV infection should be considered for therapy. • Patients with post-transplant recurrence of HCV should be treated with an interferon-free regimen, for 12 or 24 weeks with ribavirin. • Patients without cirrhosis or with compensated (ChildPugh A) cirrhosis post-transplant can be treated with the combination of sofosbuvir and ribavirin for 12 weeks (genotype 2), with ledipasvir/sofosbuvir with ribavirin for 12 weeks (genotypes 1, 4, 5 or 6), or with daclatasvir/sofosbuvir with ribavirin for 12 weeks (all genotypes), without the need for immunosuppressant drug dose adjustments. • Patients without cirrhosis or with compensated (ChildPugh A) cirrhosis post-transplant can be treated with ombitasvir/paritaprevir/ritonavir and dasabuvir with ribavirin for 12 weeks (genotype 1b) or 24 weeks (genotype 1a with cirrhosis), with ombitasvir/paritaprevir/ritonavir for 12 or 24 weeks with ribavirin (genotype 4 without or with cirrhosis, respectively), or with sofosbuvir and simeprevir with ribavirin for 12 weeks (genotypes 1 and 4), with the need for immunosuppressant drug dose adjustments or, in the case of the sofosbuvir and simeprevir combination, the need to avoid cyclosporine A. • Patients with decompensated (CTP B or C) cirrhosis can be treated with the combination of sofosbuvir and ribavirin for 12 weeks (genotype 2), with ledipasvir/sofosbuvir with ribavirin for 12 weeks (genotypes 1, 4, 5 or 6), or with daclatasvir plus sofosbuvir with ribavirin for 12 weeks (all genotypes). In these patients, ribavirin can be started at the dose of 600 mg daily and the dose subsequently adjusted depending on tolerance. • No dose adjustment is required for tacrolimus or cyclosporine with sofosbuvir and ribavirin, ledipasvir/sofosbuvir or daclatasvir plus sofosbuvir. • Because of significantly increased plasma concentrations of simeprevir, the concomitant use of simeprevir and cyclosporine A is not recommended in liver transplant recipients; no simeprevir dose changes are required with tacrolimus and sirolimus, but regular monitoring of their blood concentrations should be performed. • When using the combination of ombitasvir/paritaprevir/ritonavir and dasabuvir, the tacrolimus and cyclosporine A doses must be adjusted; prednisone use at doses ≤5 mg/ day is permitted, but the use of mTOR inhibitors is not recommended. 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. Immune complex-mediated manifestations of chronic hepatitis C

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	• Treatment of HCV-associated lymphoma should utilize new interferon-free regimens as appropriate, but the effect of an SVR on the overall prognosis is not yet known. The effect of new antiviral therapies together with B cell depletion requires further study. An interdisciplinary approach with close monitoring of liver function is required. • Appropriate antiviral therapy should be considered for the treatment of mixed cryoglobulinemia and renal disease associated with chronic HCV infection. The role of rituximab in HCV-related renal disease requires evaluation. The more rapid inhibition of HCV replication and high SVR rates will need correlation with the response of the renal injury and the cryoglobulinemia. Careful monitoring for adverse events is mandatory. <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, if possible ribavirin-free regimen, for 12 weeks in patients without cirrhosis, for 24 weeks in patients with cirrhosis • Simeprevir, daclatasvir, and ombitasvir/paritaprevir/ritonavir and dasabuvir are cleared by hepatic metabolism and can be used in patients with severe renal disease • Sofosbuvir should not be administered to patients with an eGFR <30 ml/min/1.73 m^2 or with end-stage renal disease until more data is available • The need for dose adjustments for the approved HCV direct-acting antivirals in patients on dialysis is unknown. No safety dosing and efficacy data is available in this population. These drugs should thus be used with extreme caution in patients with severe renal disease, and only in extreme life-threatening situations for patients on dialysis. <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 for 12 weeks in patients without cirrhosis, for 24 weeks in patients with compensated (CTP A) cirrhosis, following the above recommendations, should be given to potential transplant recipients before listing for renal transplantation; however, no safety and efficacy data is available in this population, and the need for dose adjustments for the new direct-acting antivirals is unknown. • These drugs should thus be used with extreme caution and sofosbuvir should not be administered to patients with an eGFR <30 ml/min/1.73 m^2 or with end-stage renal disease until more data is available. • In non-hepatic solid organ transplant recipients, patients with an indication for anti-HCV therapy should receive an interferon-free regimen, following the above recommendations on treatment regimen and management of drug-drug interactions with cyclosporine and tacrolimus when appropriate. <u>Treatment of acute hepatitis C</u> • Peginterferon alfa monotherapy for 12 weeks can be used in patients with acute hepatitis C, who will achieve SVR in as many as 90% of cases. • Peginterferon alfa and 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.

III. Indications

The Food and Drug Administration (FDA)-approved indications for sofosbuvir-velpatasvir 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 Sofosbuvir-Velpatasvir[1]

Indication	Sofosbuvir-Velpatasvir
Treatment of adult patients with chronic HCV genotype 1, 2, 3, 4, 5 or 6 infection	✔

IV. Pharmacokinetics

The pharmacokinetic parameters of sofosbuvir-velpatasvir are listed in Table 4.

Table 4. Pharmacokinetic Parameters of Sofosbuvir-Velpatasvir[2]

Generic Name	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Sofosbuvir	Not reported	61 to 65	Liver	Renal (78) Feces (14)	0.5
Velpatasvir	Not reported	>99.5	Liver	Renal (0.4) Feces (94)	15

V. Drug Interactions

Significant drug interactions with sofosbuvir-velpatasvir are listed in Table 5.

Table 5. Drug Interactions (Not All Inclusive)[1]

Concomitant Drug Class: Drug Name	Effect on Concentration	Recommendations
Antacids (e.g., aluminum and magnesium hydroxide)	↓ velpatasvir	It is recommended to separate antacid and Epclusa® (sofosbuvir-velpatasvir) administration by four hours.
H_2-receptor antagonists (e.g., famotidine)	↓ velpatasvir	H_2-receptor antagonists may be administered simultaneously with or 12 hours apart from Epclusa® (sofosbuvir-velpatasvir) at a dose that does not exceed doses comparable to famotidine 40 mg twice daily.
PPIs (e.g., omeprazole)	↓ velpatasvir	Coadministration of omeprazole or other PPIs is not recommended. If coadministration is medical necessary, administer Epclusa® (sofosbuvir-velpatasvir) with food four hours before omeprazole 20 mg. Use with other PPIs has not been studied.
Antiarrhythmics: amiodarone	Unknown	Coadministration with of amiodarone may result in serious symptomatic bradycardia. Coadministration is not recommended; if coadministration is required, cardiac monitoring is recommended.
Antiarrhythmics: digoxin	↑ digoxin	Coadministration with digoxin may increase the concentration of digoxin. Monitor therapeutic concentration of digoxin during coadministration.
Anticancers: topotecan	↑ topotecan	Coadministration is not recommended.
Anticonvulsants:	↓ sofosbuvir	Coadministration is not recommended.

Concomitant Drug Class: Drug Name	Effect on Concentration	Recommendations
carbamazepine, phenytoin, phenobarbital, oxcarbazepine	↓ velpatasvir	
Antimycobacterial: rifabutin, rifampin, rifapentine	↓ sofosbuvir ↓ velpatasvir	Coadministration is not recommended.
Efavirenz	↓ velpatasvir	Coadministration with efavirenz-containing regimens is not recommended.
Regimens containing tenofovir disoproxil fumarate	↑ tenofovir	Monitor for tenofovir-associated adverse reactions (e.g., renal function) during concomitant administration.
Tipranavir/ritonavir	↓ sofosbuvir ↓ velpatasvir	Coadministration is not recommended.
Herbal Supplements: St. John's wort	↓ sofosbuvir ↓ velpatasvir	Coadministration is not recommended.
rosuvastatin	↑ rosuvastatin	Coadministration may significantly increase the concentration of rosuvastatin, increasing the risk of myopathy, including rhabdomyolysis. The dose of rosuvastatin should not exceed 10 mg.
atorvastatin	↑ atorvastatin	Coadministration is expected to increase atorvastatin concentrations, increasing the risk of myopathy, including rhabdomyolysis. Monitor for these adverse reactions.

PPIs=proton pump inhibitors

VI. Adverse Drug Events

The safety of Epclusa® (sofosbuvir-velpatasvir) was based on four phase III clinical trials in over 1,000 patients with HCV infection, including decompensated liver disease. In patients receiving the 12-week regimen without ribavirin (ASTRAL-1, ASTRAL-2, and ASTRAL-3), the most commonly reported adverse reactions (≥10%) were fatigue and headache. In ASTRAL-1 study, asthenia was the only side effect that occurred at a greater frequency with Epclusa® (sofosbuvir-velpatasvir) treatment as compared to placebo (5 vs 3%). Only 0.2% for patients discontinued treatment due to adverse events.[1] In the ASTRAL-4 study of patients with decompensated cirrhosis (Child Pugh Class B), the most common adverse reactions (≥10%) in patients receiving Epclusa® (sofosbuvir-velpatasvir) plus ribavirin for 12 weeks were fatigue (32%), anemia (26%), nausea (15%), headache (11%), insomnia (11%), and diarrhea (10%). Nearly all adverse reactions (98%) were of mild to moderate in severity.[1]

VII. Dosing and Administration

The usual dosing regimens for sofosbuvir-velpatasvir are listed in Table 6.

Table 6. Usual Dosing Regimens for Sofosbuvir-Velpatasvir[1]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Sofosbuvir-Velpatasvir	Chronic HCV infection in patients without cirrhosis and patients with compensated cirrhosis (Child-Pugh A) Tablet: one tablet once daily for 12 weeks Chronic HCV infection in patients with decompensated cirrhosis (Child-Pugh B and C) Tablet: one tablet once daily daily plus ribavirin for 12 weeks	Safety and efficacy in children have not been established	Tablet: 400-100 mg

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of sofosbuvir-velpatasvir are summarized in Table 7.

Table 7. Comparative Clinical Trials with Sofosbuvir-Velpatasvir

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Treatment-naïve or treatment-experienced cirrhotic and noncirrhotic patients with HCV genotype 1, 2, 4, 5 or 6 infection				
Feld et al.[8] (2015) ASTRAL-1 Sofosbuvir 400 mg/ velpatasvir 100 mg once daily for 12 weeks vs placebo	DB, MC, PC, R[†] Patients >18 years of age with chronic HCV genotype 1, 2, 4, 5, or 6.	N=706 12 weeks	Primary: SVR12[‡] Secondary: Not reported	Primary: Overall, SVR12 rate in the sofosbuvir/velpatasvir group of 99% (618/624; 95% CI, 98 to >99) was higher than the prespecified benchmark rate of 85% (P<0.001). None of the 116 patients in the placebo group achieved SVR12. In the sofosbuvir/velpatasvir group, SVR12 rates were 98% (206/210; 95% CI, 95 to >99) in patients with genotype 1a infection, 99% (117/118; 95% CI, 95 to 100) with genotype 1b, 100% (104/104; 95% CI, 97 to 100) with genotype 2, 100% (116/116; 95% CI, 97 to 100) with genotype 4, 97% (34/35; 95% CI, 85 to >99) with genotype 5, and 100% (41/41; 95% CI, 91 to 100) with genotype 6. Of 121 patients in the sofosbuvir/velpatasvir group with any genotype who had cirrhosis, 120 (99%; 95% CI, 95 to >99) achieved SVR12. Of 201 treatment-experienced patients in the sofosbuvir/ velpatasvir group, 200 (>99%) achieved SVR12; all 56 patients who previously failed a regimen containing an HCV protease inhibitor, peginterferon alfa, and ribavirin achieved SVR12. Secondary: Not reported
Patients with HCV genotype 2 and 3 infection				
Foster et al.[9] (2015) ASTRAL-2 and ASTRAL-3 Sofosbuvir 400 mg/ velpatasvir 100 mg once daily for 12 weeks	AC, MC, OL, R Patients >18 years of age with chronic HCV genotype 2 (ASTRAL-2) or HCV genotype 3	N=266 (ASTRAL-2) N=552 (ASTRAL-3) 12 to 24	Primary: SVR12[‡] Secondary: Not reported	Primary: **ASTRAL-2** Among patients with HCV genotype 2, the overall SVR12 rate in the 12-week sofosbuvir/velpatasvir group was 99% (133/134; 95% CI, 96 to 100) as compared to 94% (124/132; 95% CI, 88 to 97) in the 12-week sofosbuvir/ribavirin (difference, 5.2; 95% CI, 0.2 to 10.3; P=0.02).

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
vs sofosbuvir 400 mg for 12 weeks (HCV genotype 2) or 24 weeks (HCV genotype 3) and ribavirin (1,000 mg/day if weight <75 kg or 1,200 mg/day if weight ≥75 kg) twice daily for 12 weeks (HCV genotype 2) or 24 weeks (HCV genotype 3)	(ASTRAL-3)	weeks		**ASTRAL-3** Among patients with HCV genotype 3, the overall SVR12 rate in the 12-week sofosbuvir/velpatasvir group was 95% (264/277; 95% CI, 92 to 98) as compared to 80% (221/275; 95% CI, 75 to 85) in the 24-week sofosbuvir/ribavirin group (difference, 14.8; 95% CI, 9.6 to 20.0; P<0.001). In the 12-week sofosbuvir/velpatasvir group and 24-week sofosbuvir/ribavirin group, respectively, the SVR12 rates were 98% (160/163) and 90% (141/156) in treatment-naïve patients without cirrhosis, 93% (40/43) and 73% (33/45) in treatment-naïve patients with cirrhosis, 91% (31/34) and 71% (22/31) in treatment-experienced patients without cirrhosis, and 89% (33/37) and 58% (22/38) in treatment-experienced patients with cirrhosis. In the 12-week sofosbuvir/velpatasvir group, SVR12 rates were higher (97%; 225/231) in patients without baseline NS5A RAVs as compared to those with baseline NS5A RAVs (88%; 38/43). The absence of Y93H NS5A RAV at baseline was associated with higher SVR12 (97% [42/249] vs 84% [21/25]). Secondary: Not reported
Patients with HCV genotype 1, 2, 3, 4, or 6 infection and decompensated cirrhosis (CTP class B)				
Curry et al.[10] (2015) ASTRAL-4 Sofosbuvir 400 mg/ velpatasvir 100 mg once daily for 12 weeks vs sofosbuvir 400 mg/ velpatasvir 100 mg once daily	MC, OL, R Patients >18 years of age with chronic HCV infection of any genotype and decompensated cirrhosis classified as CTP class B (score of 7 to 9)	N=267 12 to 24 weeks	Primary: SVR12[‡] Secondary: Change from baseline in the CTP and MELD scores at 12 weeks after the end of treatment	Primary: Overall SVR12 rates were 83% (75/90; 95% CI, 74 to 90), 94% (82/87; 95% CI, 87 to 98), and 86% (77/90; 95% CI, 77 to 92) among patients who received sofosbuvir/velpatasvir for 12 weeks, sofosbuvir/velpatasvir and ribavirin, and sofosbuvir/velpatasvir for 24 weeks, respectively. All three treatment groups met the prespecified primary efficacy end point of SVR rates exceeding assumed spontaneous rate of HCV clearance of 1% at 12 weeks after treatment (P<0.001 for all three comparisons). Among patients with HCV genotype 1, SVR12 rate was 88% (60/68) for those who received sofosbuvir/velpatasvir for 12 weeks, 96%

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
for 12 weeks and ribavirin (1,000 mg/day if weight <75 kg or 1,200 mg/day if weight ≥75 kg) twice daily for 12 weeks vs sofosbuvir 400 mg/ velpatasvir 100 mg once daily for 24 weeks				(65/68) for those who received sofosbuvir/velpatasvir and ribavirin, and 92% (65/71) for those who received sofosbuvir/velpatasvir for 24 weeks. Among patients with HCV genotype 3, SVR12 rate was 85% (11/13) for those who received sofosbuvir/velpatasvir and ribavirin as compared with 50% (7/14) and 50% (6/12) for those who received sofosbuvir/velpatasvir alone for 12 weeks and 24 weeks, respectively. All patients with HCV genotype 2, 4, or 6 achieved SVR12 except for one patient with HCV genotype 2 who died of liver failure after completing 28 days of 24-week sofosbuvir/velpatasvir treatment. Secondary: Of the 250 patients with CTP and MELD scores available at post-treatment week 12, 117 (47%) had an improvement in the CTP score over baseline, 106 (42%) had no change in the CTP score, and 27 (11%) had a worsening in the CTP score. Of the 223 patients with a baseline MELD score of less than 15 for whom MELD data were available at post-treatment week 12, 114 (51%) had an improved MELD score, 49 (22%) had no change in the MELD score, and 60 (27%) had a worsening in the MELD score. Of the 27 patients with a baseline MELD score of 15 or more, 22 (81%) had an improved MELD score, three (11%) had no change in the MELD score, and two (7%) had a worsening in the MELD score.

[†]All patients were randomized with the exception of those with HCV genotype 5 who were assigned to the sofosbuvir/velpatasvir group due to low prevalence of HCV genotype 5 in the study regions.
[‡]SVR was defined as HCV RNA level of less than 15 IU/mL at 12 weeks after the end of treatment in all patients who received at least one dose of sofosbuvir/velpatasvir or placebo.
Study abbreviations: AC=active-controlled, CTP=Child-Turcotte-Pugh, DB=double-blind, HCV=hepatitis C virus, OL=open-label, MELD=Model for End-Stage Liver Disease, MC=multicenter, PC=placebo-controlled, R=randomized, RAV=resistance associated variants, SVR=sustained virologic response

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 Sofosbuvir-Velpatasvir

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Sofosbuvir and Velpatasvir	tablet	Epclusa®	$$$$$	N/A

N/A=Not available

X. Conclusions

Epclusa® (sofosbuvir-velpatasvir) is the first FDA-approved combination product indicated for all six major HCV genotypes. It offers a ribavirin and peginterferon alfa-free option for most patients with chronic HCV infection. It contains sofosbuvir, an HCV nucleotide analog NS5B polymerase inhibitor, and velpatasvir, an HCV NS5A inhibitor.[1]

In several phase III trials, treatment with sofosbuvir-velpatasvir resulted in high SVR12 rates of 94 to 100% in patients with HCV genotype 1 through 6, including those with HIV-coinfection and decompensated cirrhosis.[1,8-10] The American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) consensus guidelines were updated to recommend sofosbuvir-velpatasvir treatment for 12 weeks for genotypes one through six in patients without cirrhosis or with compensated cirrhosis. Sofosbuvir-velpatasvir is also recommended in other populations, including retreatment after failed therapy (with peginterferon alfa and ribavirin, HCV protease inhibitor plus peginterferon alfa and ribavirin, and sofosbuvir and ribavirin) and patients with decompensated cirrhosis when used in combination with ribavirin.[5]

At this time, there is insufficient data to conclude that sofosbuvir-velpatasvir is safer or more efficacious than other brand or generic products within its class and that it offers a significant clinical advantage over other alternatives in general use. 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 sofosbuvir-velpatasvir 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.

XII. References

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Alabama Medicaid Agency
Pharmacy and Therapeutics Committee Meeting
New Drug Review: Viekira XR®
AHFS Class 081840
November 9, 2016

I. Overview

Viekira XR® (ombitasvir-paritaprevir-ritonavir-dasabuvir) is a once-daily, four-drug, fixed-dose combination product Food and Drug Administration (FDA)-approved for treatment of chronic hepatitis C virus (HCV) genotype 1a and 1b infection in adults with or without cirrhosis. The approval of Viekira XR® is based on comparability of bioavailability for each of the components in Viekira XR® compared to that of the previously approved formulations in Viekira Pak®. Viekira XR® and Viekira Pak® share the same FDA-approved indications.[1-4] The direct-acting antiviral agents act via several different mechanisms of action and include inhibition of non-structural (NS) 3/4A protease, NS5B polymerase, and HCV NS5A.[1-6] Paritaprevir and dasabuvir exert their mechanisms of action by inhibiting NS3/4A protease and NS5B polymerase, respectively. Ombitasvir works similarly, specifically inhibiting HCV non-structural protein NS5A. Each of these agents prevents the replication of HCV host cells. Ritonavir, when used in Viekira® products, is a boosting agent that increases the peak and trough plasma drug concentrations of paritaprevir along with overall drug exposure; it has no direct effect on the hepatitis C virus. [1-4]

The American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) consensus guidelines do not currently provide recommendation on the place in therapy of Viekira XR®. In general, the recommendations are consistent with FDA labeling.[5]

The Viekira XR® ombitasvir-paritaprevir-ritonavir-dasabuvir products included in this review are listed in Table 1. This review encompasses all dosage forms and strengths. There are no generic products available.

Table 1. Ombitasvir-Paritaprevir-Ritonavir-Dasabuvir Products Included in this Review

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Current PDL Agent(s)
Ombitasvir, paritaprevir, ritonavir, and dasabuvir	extended release tablets	Viekira XR®	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 Study of Liver Diseases and Infectious Diseases Society of America: **Recommendations for testing, managing, and treating hepatitis C (2016)**[5]	Goal of treatment • The goal of treatment of hepatitis C virus (HCV)-infected persons is to reduce all-cause mortality and liver-related health adverse consequences, including end-stage liver disease and hepatocellular carcinoma, by the achievement of virologic cure as evidenced by a sustained virologic response (SVR). When and in whom to initiate treatment • Treatment is recommended for all patients with chronic HCV infection, except those with short life expectancies that cannot be remediated by treating HCV, by transplantation, or by other directed therapy. Patients with short life expectancies owing to liver disease should be managed in consultation with an expert. • An evaluation of advanced fibrosis using liver biopsy, imaging, and/or noninvasive markers is recommended.

Clinical Guideline	Recommendation(s)

	• There are no data to support pretreatment screening for illicit drug or alcohol use in identifying a population more likely to successfully complete HCV therapy. These requirements should be abandoned, because they create barriers to treatment, add unnecessary cost and effort, and potentially exclude populations that are likely to obtain substantial benefit from therapy.
	• Strong and accumulating evidence argue against deferral because of decreased all-cause morbidity and mortality, prevention of onward transmission, and quality-of-life improvements for patients treated regardless of baseline fibrosis. Deferral practices based on fibrosis stage alone are inadequate and shortsighted. Ongoing assessment of liver disease is recommended for persons in whom therapy is deferred.
	• Recommended and alternative regimens below are generally listed in groups by level of evidence, then alphabetically.
	
	<u>Initial treatment of HCV infection (treatment-naïve)</u>
	• <u>Genotype 1a (no cirrhosis)</u>
	  o Elbasvir/grazoprevir for 12 weeks (baseline NS5A resistance-associated variants [RAVs] absent)
	  o Ledipasvir/sofosbuvir for 12 weeks
	  o Paritaprevir/ritonavir/ombitasvir plus dasabuvir and ribavirin for 12 weeks
	  o Sofosbuvir plus simeprevir for 12 weeks
	  o Sofosbuvir/velpatasvir for 12 weeks
	  o Daclatasvir plus sofosbuvir for 12 weeks
	  o Alternative: elbasvir/grazoprevir and ribavirin 16 weeks (baseline NS5A RAVs present)
	• <u>Genotype 1a (compensated cirrhosis)</u>
	  o Elbasvir/grazoprevir for 12 weeks (baseline NS5A RAVs absent)
	  o Ledipasvir/sofosbuvir for 12 weeks
	  o Sofosbuvir/velpatasvir for 12 weeks
	  o Alternative: paritaprevir/ritonavir/ombitasvir plus dasabuvir and ribavirin for 24 weeks
	  o Alternative: sofosbuvir plus simeprevir with or without ribavirin for 24 weeks (Q80K polymorphism not detected)
	  o Alternative: daclatasvir plus sofosbuvir with or without ribavirin for 24 weeks
	  o Alternative: elbasvir/grazoprevir and ribavirin 16 weeks (baseline NS5A RAVs present)
	• <u>Genotype 1b (no cirrhosis)</u>
	  o Elbasvir/grazoprevir for 12 weeks
	  o Ledipasvir/sofosbuvir for 12 weeks
	  o Paritaprevir/ritonavir/ombitasvir plus dasabuvir for 12 weeks
	  o Sofosbuvir plus simeprevir for 12 weeks
	  o Sofosbuvir/velpatasvir for 12 weeks
	  o Daclatasvir plus sofosbuvir for 12 weeks
	• <u>Genotype 1b (compensated cirrhosis)</u>
	  o Elbasvir/grazoprevir for 12 weeks
	  o Ledipasvir/sofosbuvir for 12 weeks
	  o Paritaprevir/ritonavir/ombitasvir plus dasabuvir for 12 weeks
	  o Sofosbuvir/velpatasvir for 12 weeks
	  o Alternative: sofosbuvir plus simeprevir with or without ribavirin for 24 weeks
	  o Alternative: daclatasvir plus sofosbuvir with or without ribavirin for 24 weeks
	• Shortening treatment with ledipasvir/sofosbuvir to less than 12 weeks for patients without cirrhosis should be done with caution and performed at the

Clinical Guideline	Recommendation(s)
	discretion of the practitioner. • Genotype 2 (no cirrhosis) o Sofosbuvir/velpatasvir for 12 weeks o Alternative: Daclatasvir plus sofosbuvir for 12 weeks • Genotype 2 (compensated cirrhosis) o Sofosbuvir/velpatasvir for 12 weeks o Alternative: Daclatasvir plus sofosbuvir for 16 to 24 weeks • Genotype 3 (no cirrhosis) o Daclatasvir plus sofosbuvir for 12 weeks Sofosbuvir/velpatasvir for 12 weeks • Genotype 3 (compensated cirrhosis) o Sofosbuvir/velpatasvir for 12 weeks • Daclatasvir plus sofosbuvir with or without ribavirin for 24 weeks Genotype 4 o Paritaprevir/ritonavir/ombitasvir and ribavirin for 12 weeks o Sofosbuvir/velpatasvir for 12 weeks o Elbasvir/grazoprevir for 12 weeks o Ledipasvir/sofosbuvir for 12 weeks • Genotype 5 or 6 o Sofosbuvir/velpatasvir for 12 weeks o Ledipasvir/sofosbuvir for 12 weeks Retreatment after failed therapy (peginterferon alfa and ribavirin) • Genotype 1a (no cirrhosis) o Elbasvir/grazoprevir for 12 weeks (baseline NS5A RAVs absent) o Ledipasvir/sofosbuvir for 12 weeks o Paritaprevir/ritonavir/ombitasvir plus dasabuvir and ribavirin for 12 weeks o Sofosbuvir plus simeprevir for 12 weeks o Sofosbuvir/velpatasvir for 12 weeks o Daclatasvir plus sofosbuvir for 12 weeks o Alternative: elbasvir/grazoprevir and ribavirin 16 weeks (baseline NS5A RAVs present) • Genotype 1a (compensated cirrhosis) o Elbasvir/grazoprevir for 12 weeks (baseline NS5A RAVs absent) o Ledipasvir/sofosbuvir and ribavirin for 12 weeks o Sofosbuvir/velpatasvir for 12 weeks o Alternative: paritaprevir/ritonavir/ombitasvir plus dasabuvir and ribavirin for 24 weeks o Alternative: ledipasvir/sofosbuvir for 24 weeks o Alternative: elbasvir/grazoprevir and ribavirin 16 weeks (baseline NS5A RAVs present) o Alternative: daclatasvir plus sofosbuvir with or without ribavirin for 24 weeks. o Alternative: sofosbuvir plus simeprevir with or without ribavirin for 24 weeks (Q80K polymorphism not detected) • Genotype 1b (no cirrhosis) o Elbasvir/grazoprevir for 12 weeks o Ledipasvir/sofosbuvir for 12 weeks o Paritaprevir/ritonavir/ombitasvir plus dasabuvir for 12 weeks o Sofosbuvir plus simeprevir for 12 weeks o Sofosbuvir/velpatasvir for 12 weeks o Daclatasvir plus sofosbuvir for 12 weeks • Genotype 1b (compensated cirrhosis) o Elbasvir/grazoprevir for 12 weeks o Ledipasvir/sofosbuvir and ribavirin for 12 weeks o Paritaprevir/ritonavir/ombitasvir plus dasabuvir for 12 weeks

Clinical Guideline	Recommendation(s)
	o Sofosbuvir/velpatasvir for 12 weeks o Alternative: Ledipasvir/sofosbuvir for 24 weeks o Alternative: sofosbuvir plus simeprevir with or without ribavirin for 24 weeks o Alternative: daclatasvir plus sofosbuvir with or without ribavirin for 24 weeks. • Genotype 2 o Sofosbuvir/velpatasvir for 12 weeks o Alternative: daclatasvir plus sofosbuvir for 12 weeks (no cirrhosis) or 16 to 24 weeks (compensated cirrhosis) • Genotype 3 o Daclatasvir plus sofosbuvir for 12 weeks (no cirrhosis); or with ribavirin for 24 weeks (compensated cirrhosis) o Sofosbuvir/velpatasvir for 12 weeks (or cirrhosis); or with ribavirin for 12 weeks (compensated cirrhosis) • Genotype 4 o Paritaprevir/ritonavir/ombitasvir and ribavirin for 12 weeks o Sofosbuvir/velpatasvir for 12 weeks o Elbasvir/grazoprevir for 12 weeks (virologic relapse after prior peginterferon alfa and ribavirin) or 16 weeks with ribavirin (failure to suppress or breakthrough on prior peginterferon alfa and ribavirin) o Ledipasvir/sofosbuvir for 12 weeks (no cirrhosis) or 12 weeks with ribavirin (compensated cirrhosis) • Alternative: Ledipasvir/sofosbuvir for 24 weeks (compensated cirrhosis) Genotype 5 or 6 o Sofosbuvir/velpatasvir for 12 weeks o Ledipasvir/sofosbuvir for 12 weeks • Mixed Genotypes o Treatment data for mixed genotypes with direct-acting antivirals are sparse, and awaiting availability of a pangenotypic regimen may be considered. o When treatment is necessary, the choice of antiviral combination and duration of treatment should maximize efficacy against each genotype represented in the assay. Retreatment after failed therapy (sofosbuvir and ribavirin with or without peginterferon alfa) • Genotype 1 o Ledipasvir/sofosbuvir and ribavirin for 12 weeks (no cirrhosis) or 24 weeks (compensated cirrhosis) Retreatment after failed therapy (HCV protease inhibitor plus peginterferon alfa and ribavirin) • Genotype 1 (no cirrhosis) o Ledipasvir/sofosbuvir for 12 weeks o Sofosbuvir/velpatasvir for 12 weeks o Daclatasvir plus sofosbuvir for 12 weeks o Elbasvir/grazoprevir and ribavirin for 12 weeks (baseline NS5A RAVs absent) or 16 weeks (for genotype 1a with baseline NS5A RAVs present) • Genotype 1 (compensated cirrhosis) o Ledipasvir/sofosbuvir and ribavirin for 12 weeks o Ledipasvir/sofosbuvir for 24 weeks o Sofosbuvir/velpatasvir for 12 weeks o Daclatasvir plus sofosbuvir with or without ribavirin for 24 weeks o Elbasvir/grazoprevir and ribavirin for 12 weeks (baseline NS5A RAVs absent) or 16 weeks (for genotype 1a with baseline NS5A RAVs present)

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	Retreatment after failed therapy (sofosbuvir plus simeprevir or HCV NS5A inhibitor)
	Genotype 1
	• Deferral of treatment is recommended for patients who do not have cirrhosis, pending availability of data
	• Testing for RAVs that confer decreased susceptibility to NS3 protease inhibitors and to NS5A inhibitors is recommended who have compensated cirrhosis or have reasons for urgent retreatment. Specific drugs should be tailored to the results of this testing.
	• When using nucleotide-based (e.g., sofosbuvir) dual direct-acing antiviral therapy treatment duration of 24 weeks is recommended, with ribavirin, unless contraindicated.
	• If available, nucleotide-based (e.g., sofosbuvir) triple or quadruple direct-acing antiviral regimens may be considered for 12 to 24 weeks with ribavirin, unless contraindicated.
	
	Retreatment after failed therapy (sofosbuvir and ribavirin)
	• Genotype 2
	  o Daclatasvir plus sofosbuvir with or without ribavirin for 24 weeks (peginterferon alfa or ribavirin ineligible)
	  o Sofosbuvir/velpatasvir for 12 weeks and ribavirin for 12 weeks
	• Genotype 3
	  o Daclatasvir plus sofosbuvir and ribavirin for 24 weeks Sofosbuvir/velpatasvir and ribavirin for 12 weeks
	
	Recommendations for discontinuation of treatment due to lack of efficacy
	  o If HCV viral load is detectable at week four, repeat quantitative HCV viral load after two additional weeks of treatment (treatment week six).
	  ▪ If quantitative HCV viral load has increased by greater than 10-fold (>1 $\log_{10}$ IU/mL) on repeat testing at week six (or thereafter), discontinue HCV treatment.
	  o The significance of a positive HCV RNA test result at week four that remains positive, but lower, at week six or week eight is unknown.
	  ▪ No recommendation to stop therapy or extend therapy can be provided at this time.
	
	Special populations – human immunodeficiency virus (HIV)/HCV coinfection
	• HIV/HCV-coinfected persons should be treated and re-treated the same as persons without HIV infection, after recognizing and managing interactions with antiretroviral medications.
	• Daclatasvir and sofosbuvir, with or without ribavirin is recommended when antiretroviral regimen changes cannot be made to accommodate alternative HCV direct-acting antivirals
	
	Special populations – decompensated cirrhosis
	• Patients with decompensated cirrhosis (Child Turcotte Pugh [CTP] class B or C) should be referred to a medical practitioner with expertise in that condition (ideally in a liver transplant center).
	• Genotype 1 or 4 (patients who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma)
	  o Ledipasvir/sofosbuvir and ribavirin for 12 weeks
	  o Sofosbuvir/velpatasvir and ribavirin for 12 weeks
	  o Daclatasvir plus sofosbuvir and ribavirin for 12 weeks
	  o Alternative (ribavirin intolerant or ineligible): sofosbuvir/velpatasvir for 24 weeks

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	o Alternative (ribavirin intolerant or ineligible): daclatasvir plus sofosbuvir for 24 weeks o Alternative (ribavirin intolerant or ineligible): ledipasvir/sofosbuvir for 24 weeks o Alternative (prior failure with a sofosbuvir-based regimen): ledipasvir/sofosbuvir and ribavirin for 24 weeks o Alternative (prior failure with a sofosbuvir-based regimen): sofosbuvir/velpatasvir and ribavirin for 24 weeks • Genotype 2 or 3 (patients who may or may not be candidates for liver transplantation, including those with hepatocellular carcinoma) o Sofosbuvir/velpatasvir and ribavirin for 12 weeks o Daclatasvir plus sofosbuvir and ribavirin for 12 weeks Special populations – recurrent HCV infection post-liver transplantation • Genotype 1 or 4 infection in the allograft (including compensated cirrhosis), treatment-naïve or treatment-experienced o Ledipasvir/sofosbuvir with ribavirin for 12 weeks (including decompensated cirrhosis) o Daclatasvir plus sofosbuvir and ribavirin for 12 weeks o Alternative (ribavirin intolerant or ineligible): ledipasvir/sofosbuvir for 24 weeks (treatment-naïve only) o Alternative (ribavirin intolerant or ineligible): daclatasvir plus sofosbuvir for 24 weeks o Alternative (genotype 1 only): sofosbuvir plus simeprevir with or without ribavirin for 12 weeks o Alternative (genotype 1, Metavir fibrosis stage F0-F2): paritaprevir/ritonavir/ombitasvir plus dasabuvir and ribavirin for 24 weeks • Genotype 2 infection in the allograft (including compensated cirrhosis), treatment-naïve or treatment-experienced o Daclatasvir plus sofosbuvir and ribavirin for 12 weeks o Sofosbuvir and ribavirin for 24 weeks o Alternative (ribavirin intolerant or ineligible): daclatasvir plus sofosbuvir for 24 weeks • Genotype 2 infection in the allograft, liver transplant recipients (with decompensated cirrhosis), treatment-naïve or treatment-experienced o Sofosbuvir and ribavirin for 24 weeks • Genotype 3 infection in the allograft (including compensated cirrhosis), treatment-naïve or treatment-experienced o Daclatasvir plus sofosbuvir and ribavirin for 12 weeks o Alternative (ribavirin ineligible): daclatasvir plus sofosbuvir for 24 weeks Special populations – renal impairment • Mild to moderate renal impairment (CrCl >30 mL/min) o Daclatasvir: no dosage adjustment is required o Ledipasvir/sofosbuvir: no dosage adjustment is required o Sofosbuvir/velpatasvir: no dosage adjustment is required o Paritaprevir/ritonavir/ombitasvir with and without dasabuvir: no dosage adjustment is required o Simeprevir: no dosage adjustment is required o Sofosbuvir: no dosage adjustment is required • Severe renal impairment (CrCl<30 mL/min or end-stage renal disease) with high urgency to treat and kidney transplant is not an immediate option o HCV genotype 1a, 1b or 4 infection: elbasvir/grazoprevir for 12 weeks o HCV genotype 1b infection: paritaprevir/ritonavir/ombitasvir plus dasabuvir for 12 weeks

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	○ HCV genotype 2, 3, 5, or 6 infection: peginterferon alfa and ribavirin ○ Alternative (HCV genotype 1a infection): daily paritaprevir/ritonavir/ombitasvir plus dasabuvir (and ribavirin if hemoglobin >10 g/dL at a dose of 200 mg trice weekly to daily) Management of acute HCV infection • HCV antibody and HCV RNA testing are recommended when acute HCV infection is suspected due to exposure, clinical presentation, or elevated aminotransferase levels • Preexposure or postexposure prophylaxis with antiviral therapy is NOT recommended. • Medical management and monitoring ○ Regular laboratory monitoring is recommended in the setting of acute HCV infection. Monitoring HCV RNA (every four to eight weeks) for six to 12 months is recommended to determine spontaneous clearance of HCV infection versus persistence of infection. ○ Counseling is recommended for patients with acute HCV infection to avoid hepatotoxic insults including hepatotoxic drugs and alcohol consumption, and to reduce the risk of HCV transmission to others. ○ Referral to an addiction medicine specialist is recommended for patients with acute HCV infection related to substance use. • Treatment for patients with acute HCV infection ○ If treatment is delayed, monitoring for spontaneous clearance is recommended for a minimum of six months. ○ If treatment is to begin during the acute infection period, monitor HCV RNA for at least 12 to 16 weeks before starting treatment to allow for spontaneous clearance. ○ Treatment with the same standard regimens is recommended for chronic and acute HCV infection.
Department of Veterans Affairs National Hepatitis C Resource Center Program and the Office of Public Health: **HCV Infection: Treatment Considerations (2016)**[6]	Goal of treatment • The goal of hepatitis C antiviral treatment is to achieve a sustained virological response (SVR), defined as undetectable HCV RNA in the blood 12 or more weeks after completing antiviral treatment. Principles for patient selection for HCV treatment • All patients with chronic HCV who do not have medical contraindications are potential candidates for antiviral treatment. • 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 (HCC) awaiting liver transplant, post-transplant recipients with cirrhosis, and patients with serious extra-hepatic manifestations of HCV, and women of childbearing potential who desire to conceive a child in the next 12 months. • Patients with mild liver disease (METAVIR F0-2) have less urgency for treatment in the short term, but should be informed of new treatments and their potential to cure HCV. • Patients with severe mental health conditions who are engaged in treatment or those with ongoing substance use including drinking alcohol, using illicit drugs, including marijuana, or participating in opioid replacement programs should not be excluded from HCV treatment. • Treatment is not indicated in patients with limited life expectancy of less than 12 months unless there is reason to anticipate that duration or quality of life can be improved by eradication of HCV.

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	• Factors that may complicate adherence, such as active substance abuse, depression, neurocognitive disorders, and lack of social support, should be addressed before initiating medications.
	
	Treatment of HCV genotype 1 in treatment-naïve patients without cirrhosis
	• Ledipasvir/sofosbuvir for eight weeks if baseline HCV RNA <6 million IU/mL; 12 weeks if HIV/HCV co-infected or HCV RNA ≥6 million IU/mL.
	
	Treatment of HCV genotype 1 in treatment-naïve or -experienced (prior peginterferon alfa and ribavirin) patients without or with cirrhosis (CTP A)
	• Elbasvir/grazoprevir.
	  o Genotype 1a without baseline NS5A RAVs: 12 weeks.
	  o Genotype 1a with baseline NS5A RAVs: 16 weeks with ribavirin.
	  o Genotype 1b: 12 weeks.
	• Ledipasvir/sofosbuvir for 12 weeks (with ribavirin if treatment-experienced with cirrhosis).
	• Paritaprevir/ritonavir/ombitasvir plus dasabuvir and ribavirin; may consider 24 weeks in cirrhotics or prior null responders; genotype 1b: ribavirin not required.
	
	Treatment of HCV genotype 1 in treatment-experienced (prior NS3/4A inhibitor plus peginterferon alfa and ribavirin, or prior sofosbuvir and ribavirin with or without peginterferon alfa) patients without or with cirrhosis (CTP A)
	• Elbasvir/grazoprevir and ribavirin.
	  o Genotype 1a without baseline NS5A RAVs: 12 weeks.
	  o Genotype 1a with baseline NS5A RAVs: 16 weeks.
	  o Genotype 1b: 12 weeks.
	• Ledipasvir/sofosbuvir and ribavirin.
	
	Treatment of HCV genotype 1 in treatment-naïve or -experienced (prior peginterferon alfa and ribavirin, prior NS3/4A inhibitor plus peginterferon alfa and ribavirin, or prior sofosbuvir and ribavirin with or without peginterferon alfa) patients with decompensated cirrhosis (CTP B or C)
	• Ledipasvir/sofosbuvir and ribavirin (600 mg, increased monthly by 200 mg/day every two weeks as tolerated).
	
	Treatment of HCV genotype 1 in treatment-experienced (prior NS5A-containing regimen) patients with or without cirrhosis
	• Test for RAVs to NS5A prior to re-treatment and consult with an expert.
	
	Treatment of HCV genotype 2 in treatment-naïve patients without cirrhosis
	• Sofosbuvir and ribavirin for 12 weeks.
	• Alternative (if ribavirin intolerant or contraindicated): ledipasvir/sofosbuvir for 12 weeks.
	• Alternative: daclatasvir plus sofosbuvir for 12 weeks.
	
	Treatment of HCV genotype 2 in treatment-naïve patients with cirrhosis (CTP A)
	• Sofosbuvir and ribavirin for 16 weeks.
	
	Treatment of HCV genotype 2 in treatment-experienced (prior peginterferon and ribavirin only) patients with or without cirrhosis (CTP A)
	• Sofosbuvir and ribavirin for 16 weeks.
	• Alternative (no cirrhosis): daclatasvir plus sofosbuvir for 12 weeks.
	• Alternative (no cirrhosis): Ledipasvir/sofosbuvir for 12 weeks.
	
	Treatment of HCV genotype 3 in treatment-naïve patients without cirrhosis

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	• Ledipasvir/sofosbuvir and ribavirin for 12 weeks.
	• Alternative: daclatasvir plus sofosbuvir for 12 weeks.
	• Alternative: sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks.
	• Alternative: sofosbuvir and ribavirin for 24 weeks.
	
	Treatment of HCV genotype 3 in treatment-naïve patients with cirrhosis
	• Daclatasvir plus sofosbuvir and ribavirin for 12 weeks (CTP A) or 12 to 24 weeks (CTP B or C).
	• Alternative: sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks (CTP A).
	
	Treatment of HCV genotype 3 in treatment-experienced patients (prior peginterferon and ribavirin only) without cirrhosis
	• Ledipasvir/sofosbuvir and ribavirin for 12 weeks.
	• Alternative: daclatasvir plus sofosbuvir for 12 weeks
	• Alternative: sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks.
	• Sofosbuvir and ribavirin for 24 weeks.
	
	Treatment of HCV genotype 3 in treatment-experienced patients (prior peginterferon and ribavirin only) with cirrhosis
	• Daclatasvir plus sofosbuvir and ribavirin for 12 weeks (CTP A) or 12 to 24 weeks (CTP B or C).
	• Daclatasvir plus sofosbuvir for 24 weeks (if ribavirin ineligible).
	
	Treatment of HCV genotype 4 in treatment-naïve and treatment-experienced patients with or without cirrhosis (CTP A)
	• Elbasvir/grazoprevir for 12 weeks.
	• Ledipasvir/sofosbuvir for 12 weeks.
	• Paritaprevir/ritonavir/ombitasvir and ribavirin for 12 weeks.
	
	Stopping rules based on lack of virologic response
	• Patients should have an HCV RNA level assessed at week 4 of treatment.
	• If the HCV RNA is quantifiable at week 4 or at any time point thereafter, reassess HCV RNA in two weeks. If the repeated HCV RNA increases (i.e., >1 $\log_{10}$ IU/mL from nadir), discontinuation of all treatment should be strongly considered.
	• HCV RNA levels should be assessed at 12 weeks after completion of treatment to determine whether SVR was achieved.
	
	Use in HIV/HCV-coinfection
	• HIV/HCV-coinfected patients receive the same HCV antiviral regimen as HCV-monoinfected patients, provided the patient is receiving appropriate HIV care and drug-drug interactions are addressed appropriately.
	
	Treatment in pre-liver transplant
	• Genotype 1, including patients with CTP A, B, or C, as well as HCC
	  o Ledipasvir/sofosbuvir and ribavirin for 12 weeks
	• Genotype 2, including patients with HCC
	  o Sofosbuvir and ribavirin for 24 to 48 weeks; the addition of peginterferon alfa may be considered
	• Genotype 3 or 4
	  o Consult with a transplant center prior to starting treatment. In general, the preferred treatment is the same treatment as is recommended for treatment-naïve or treatment-experienced (as appropriate) patients.

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	Treatment in post-liver or other solid organ transplant
	• Genotype 1
	  o Ledipasvir/sofosbuvir and ribavirin for 12 weeks.
	  o If ribavirin intolerant: ledipasvir/sofosbuvir for 24 weeks.
	• Genotype 2
	  o Sofosbuvir and ribavirin for 24 weeks; the addition of peginterferon alfa may be considered
	• Genotype 3
	  o The decision to treat, regimen selection, and management of treatment should be coordinated with the transplant center and/or by specialists with extensive experience in the treatment of pre- or post-transplant patients.
	• Genotype 4
	  o Ledipasvir/sofosbuvir and ribavirin for 12 weeks
	  o If ribavirin intolerant: ledipasvir/sofosbuvir for 24 weeks.

European Association for the Study of the Liver: **Treatment of Hepatitis (2015)**[7]	Goals and endpoints of HCV therapy • The goal of therapy is to cure HCV infection, to prevent hepatic cirrhosis, decompensation of cirrhosis, hepatocellular carcinoma, severe extra-hepatic manifestations, 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 or decompensated chronic liver disease due to HCV should be considered for therapy. • Treatment should be prioritized for patients with significant fibrosis or cirrhosis (F3 to F4). • Patients with decompensated cirrhosis (Child Pugh B or C) should be urgently treated with an interferon-free regimen. • Treatment should be prioritized regardless of the fibrosis stage for individuals at risk of transmitting HCV, including active injection drug users, men who have sex with men with high-risk sexual practices, women of childbearing age who wish to get pregnant, hemodialysis patients, and incarcerated individuals • 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. • Treatment is not recommended in patients with limited life expectancy due to non-liver related comorbidities 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. • Interferon-free regimens are the best options when available in all HCV-monoinfected and in HIV-coinfected patients because of their virological efficacy, ease of use and tolerability. • 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.

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	• The combination of sofosbuvir and ledipasvir can be used with all antiretrovirals. However, this regimen should not be used with the combination of tenofovir/emtricitabine with atazanavir/ritonavir, darunavir/ritonavir, lopinavir/ritonavir or elvitegravir/ cobicistat when possible, or used with caution with frequent renal monitoring.
	• The combination of ombitasvir/paritaprevir/ritonavir and dasabuvir should not be used with efavirenz, etravirine or nevirapine, and rilpivirine should be used cautiously with repeat electrocardiogram monitoring. Atazanavir and darunavir should be taken without ritonavir and other protease inhibitors are contraindicated with this combination. Elvitegravir/cobicistat should not be used with this regimen because of the additional boosting effect.
	
	<u>Treatment options for HCV genotype 1 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 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 4, 12 or 24.
	• Ledipasvir/sofosbuvir without ribavirin for 12 weeks (no cirrhosis) or with ribavirin for 12 weeks (compensated cirrhosis)
	• Ledipasvir/sofosbuvir for eight weeks may be considered in treatment-naïve patients without cirrhosis and baseline HCV RNA <6 million. This should be done with caution especially in in patients with F3.
	• Ledipasvir/sofosbuvir and ribavirin for 24 weeks in treatment-experienced patients with compensated cirrhosis and negative predictors of response, such as a platelet count <75,000/µL.
	• Ombitasvir/paritaprevir/ritonavir and dasabuvir without ribavirin for 12 weeks (HCV genotype 1b without cirrhosis) or with ribavirin for 12 weeks (HCV genotype 1b with cirrhosis or HCV genotype 1a without cirrhosis)
	• Ombitasvir/paritaprevir/ritonavir and dasabuvir with ribavirin for 24 weeks (HCV genotype 1a with cirrhosis)
	• Sofosbuvir and simeprevir without ribavirin for 12 weeks (patients without cirrhosis) or with ribavirin for 12 weeks (cirrhotics)
	• Sofosbuvir and simeprevir for 24 weeks (patients with cirrhosis and contraindication to ribavirin)
	• Daclatasvir and sofosbuvir without ribavirin for 12 weeks (no cirrhosis) or with ribavirin for 12 weeks (cirrhosis)
	• Daclatasvir and sofosbuvir for 24 weeks (patients with cirrhosis and contraindication to ribavirin)
	
	<u>Treatment options for HCV genotype 2 infection</u>
	• Sofosbuvir and 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.
	• Daclatasvir and sofosbuvir 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 (including patients who failed prior treatment with sofosbuvir and ribavirin)
	• Sofosbuvir and ribavirin for 24 weeks
	  o Suboptimal in treatment-experienced cirrhotics or those who failed

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	prior treatment with sofosbuvir and ribavirin • Daclatasvir and sofosbuvir without ribavirin for 12 weeks (no cirrhosis) or with ribavirin 24 weeks (cirrhosis, pending data with 12 weeks of therapy). 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 4, 12 or 24. • Ledipasvir/sofosbuvir without ribavirin for 12 weeks (no cirrhosis) or with ribavirin for 12 weeks (cirrhosis) • Ledipasvir/sofosbuvir for 24 weeks (patients with cirrhosis and contraindication to ribavirin) • Ledipasvir/sofosbuvir with ribavirin for 24 weeks is an option in treatment-experienced cirrhotics and negative predictors of response, such as a platelet count <75,000/µL. • Ombitasvir/paritaprevir/ritonavir and ribavirin for 12 weeks (no cirrhosis) or for 24 weeks (cirrhosis) • Sofosbuvir and simeprevir without ribavirin for 12 weeks (patients without cirrhosis) or with ribavirin for 12 weeks (cirrhotics) • Sofosbuvir and simeprevir for 24 weeks (patients with cirrhosis and contraindication to ribavirin) • Daclatasvir and sofosbuvir without ribavirin for 12 weeks (no cirrhosis) or with ribavirin for 12 weeks (cirrhosis). • Daclatasvir and sofosbuvir for 24 weeks (patients with cirrhosis and contraindication to ribavirin) Treatment options for HCV genotype 5 or 6 infection • Sofosbuvir plus peginterferon alfa and ribavirin for 12 weeks. • Ledipasvir/sofosbuvir without ribavirin for 12 weeks (no cirrhosis) or with ribavirin for 12 weeks (compensated cirrhosis) • Ledipasvir/sofosbuvir for 24 weeks (cirrhotic patients with contraindication or intolerance to ribavirin) • Ledipasvir/sofosbuvir and ribavirin for 24 weeks (treatment-experienced cirrhotics with negative predictors of response, such as a platelet count <75,000/µL). • Daclatasvir and sofosbuvir without ribavirin for 12 weeks (no cirrhosis) or with ribavirin for 12 weeks (cirrhosis). • Daclatasvir and sofosbuvir for 24 weeks (patients with cirrhosis and contraindication to ribavirin) 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 4, 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.

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	• In patients treated with an interferon-free regimen, HCV RNA should be measured at baseline, week 2 (assessment of adherence), week 4, week 12 or 24 (end of treatment in patients treated 12 or 24 weeks, respectively), 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 4, 12 or 24; an immediate switch to another interferon-containing direct-acting antiviral-containing or an interferon-free regimen without a protease inhibitor should be considered • 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 4 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 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 • HCV genotype 1 patients who failed telaprevir or boceprevir plus peginterferon alfa and ribavirin should be retreated with ledipasvir/sofosbuvir, or daclatasvir and sofosbuvir, with ribavirin for 12 weeks. • Recommendations for retreatment after failure of second-wave direct-acting antiviral-based anti-HCV regimens are based on indirect evidence and subject to change when more data become available. • Patients who failed on a second-wave direct-acting-antiviral-containing regimen, with or without peginterferon alfa or ribavirin, should be retreated with an interferon-free regimen for 12 weeks with ribavirin; extending therapy to 24 weeks with ribavirin may be considered, especially in patients with liver fibrosis stage F3 or F4. • Patients who failed on sofosbuvir alone or sofosbuvir and ribavirin or sofosbuvir plus peginterferon alfa and ribavirin can be retreated with a combination of sofosbuvir plus simeprevir (genotype 1 or 4), sofosbuvir plus daclatasvir (all genotypes) or ledipasvir/sofosbuvir (genotypes 1, 4, 5 or 6), or with ombitasvir/paritaprevir/ritonavir and dasabuvir (genotype 1), or with ombitasvir/paritaprevir/ritonavir (genotype 4). • Patients infected with genotype 1 or 4 who failed on a regimen combining peginterferon alfa, ribavirin and simeprevir should be retreated with daclatasvir

Clinical Guideline	Recommendation(s)
	plus sofosbuvir or ledipasvir/sofosbuvir. • Patients who failed on a regimen combining peginterferon alfa, ribavirin and daclatasvir should be retreated with a combination of sofosbuvir and simeprevir (genotype 1 or 4). Patients infected with other genotypes should be retreated with daclatasvir plus sofosbuvir (genotypes 2, 3, 5 and 6) or ledipasvir/sofosbuvir (genotypes 5 and 6). • Patients infected with genotype 1 or 4 who failed on a regimen containing sofosbuvir and simeprevir should be retreated with daclatasvir plus sofosbuvir of ledipasvir/sofosbuvir. • Patients who failed on a regimen containing daclatasvir and sofosbuvir or ledipasvir/sofosbuvir should be retreated with a combination of sofosbuvir and simeprevir (genotype 1 and 4); patients infected with other genotypes should be retreated with the combination of daclatasvir and sofosbuvir (genotypes 2, 3, 5 and 6) or with the combination of ledipasvir/sofosbuvir (genotypes 5 and 6) for 24 weeks. • Patients infected with genotype 1 who failed ombitasvir/paritaprevir/ritonavir and dasabuvir should be retreated with a sofosbuvir-based regimen (e.g., sofosbuvir and simeprevir, daclatasvir plus sofosbuvir and ledipasvir/sofosbuvir. • Patients infected with genotype 4 who failed ombitasvir/paritaprevir/ritonavir should be retreated with a sofosbuvir-based regimen (e.g., sofosbuvir and simeprevir, daclatasvir plus sofosbuvir and ledipasvir/sofosbuvir). • Alternatively, patients without an urgent need for treatment can wait until more data and/or alternative therapeutic options become available. • The efficacy and safety of a triple combination regimen including sofosbuvir, an NS3 protease inhibitor and an NS5A protease inhibitor in patients who failed on a direct-acting antiviral-containing regimen is unknown. • The utility of HCV resistance testing prior to retreatment in patients who failed on any of the direct-acting antiviral-containing treatment regimens is unknown. <u>Treatment of patients with severe liver disease</u> • Patients with decompensated cirrhosis (CTP B and C) not on the waiting list for liver transplantation and without concomitant comorbidities that could impact their survival can be treated with the combination of sofosbuvir and ribavirin for 16 to 20 weeks (genotype 2), ledipasvir/sofosbuvir (genotypes 1, 4, 5 and 6), or daclatasvir plus sofosbuvir (all genotypes), with ribavirin, for 12 weeks. • Patients with decompensated cirrhosis with contraindication or intolerance to ribavirin should receive ledipasvir/sofosbuvir (genotypes 1, 4, 5 or 6), or daclatasvir plus sofosbuvir (all genotypes) for 24 weeks. <u>Patients with an indication for liver transplantation</u> • In patients awaiting liver transplantation, antiviral therapy is indicated, because it prevents graft infection. • Treatment should be initiated as soon as possible in order to complete a full treatment course before transplantation. • Patients awaiting liver transplantation should be treated with an interferon-free regimen, in principle for 12 or 24 weeks, practically up to transplantation, with ribavirin. • Patients with conserved liver function (CTP A) in whom the indication for transplantation is hepatocellular carcinoma can be treated with the combination of sofosbuvir and ribavirin for 16 to 20 weeks (genotype 2), with ledipasvir/sofosbuvir and ribavirin for 12 weeks (genotypes 1, 4, 5 or 6), with ombitasvir/paritaprevir/ritonavir and dasabuvir with ribavirin for 12 weeks (genotype 1b) or 24 weeks (genotype 1a), with ombitasvir/paritaprevir/ritonavir with ribavirin for 12 weeks (genotype 4), with sofosbuvir plus simeprevir with ribavirin for 12 weeks (genotypes 1 and 4), or with daclatasvir plus sofosbuvir

Clinical Guideline	Recommendation(s)
	with ribavirin for 12 weeks (all genotypes). • Treatment with sofosbuvir plus interferon alfa and ribavirin for 12 weeks is acceptable in patients with compensated (CTP A) cirrhosis awaiting liver transplantation if interferon-free options are not available. • Patients with decompensated cirrhosis (CTP B or C) awaiting liver transplantation can be treated with the combination of sofosbuvir and ribavirin for 16 to 20 weeks (genotype 2), with ledipasvir/sofosbuvir with ribavirin for 12 weeks (genotypes 1, 4, 5 or 6), or with daclatasvir plus sofosbuvir with ribavirin for 12 weeks (all genotypes); however, data are limited in patients with CTP C cirrhosis >12 points or with a MELD score >20. • The optimal timing of treatment (before transplantation or post-transplantation) to maximize survival is still debatable and requires individual assessment. <u>Post-liver transplantation recurrence</u> • Patients with post-transplant recurrence of HCV infection should be considered for therapy. • Patients with post-transplant recurrence of HCV should be treated with an interferon-free regimen, for 12 or 24 weeks with ribavirin. • Patients without cirrhosis or with compensated (ChildPugh A) cirrhosis post-transplant can be treated with the combination of sofosbuvir and ribavirin for 12 weeks (genotype 2), with ledipasvir/sofosbuvir with ribavirin for 12 weeks (genotypes 1, 4, 5 or 6), or with daclatasvir/sofosbuvir with ribavirin for 12 weeks (all genotypes), without the need for immunosuppressant drug dose adjustments. • Patients without cirrhosis or with compensated (ChildPugh A) cirrhosis post-transplant can be treated with ombitasvir/paritaprevir/ritonavir and dasabuvir with ribavirin for 12 weeks (genotype 1b) or 24 weeks (genotype 1a with cirrhosis), with ombitasvir/paritaprevir/ritonavir for 12 or 24 weeks with ribavirin (genotype 4 without or with cirrhosis, respectively), or with sofosbuvir and simeprevir with ribavirin for 12 weeks (genotypes 1 and 4), with the need for immunosuppressant drug dose adjustments or, in the case of the sofosbuvir and simeprevir combination, the need to avoid cyclosporine A. • Patients with decompensated (CTP B or C) cirrhosis can be treated with the combination of sofosbuvir and ribavirin for 12 weeks (genotype 2), with ledipasvir/sofosbuvir with ribavirin for 12 weeks (genotypes 1, 4, 5 or 6), or with daclatasvir plus sofosbuvir with ribavirin for 12 weeks (all genotypes). In these patients, ribavirin can be started at the dose of 600 mg daily and the dose subsequently adjusted depending on tolerance. • No dose adjustment is required for tacrolimus or cyclosporine with sofosbuvir and ribavirin, ledipasvir/sofosbuvir or daclatasvir plus sofosbuvir. • Because of significantly increased plasma concentrations of simeprevir, the concomitant use of simeprevir and cyclosporine A is not recommended in liver transplant recipients; no simeprevir dose changes are required with tacrolimus and sirolimus, but regular monitoring of their blood concentrations should be performed. • When using the combination of ombitasvir/paritaprevir/ritonavir and dasabuvir, the tacrolimus and cyclosporine A doses must be adjusted; prednisone use at doses ≤5 mg/ day is permitted, but the use of mTOR inhibitors is not recommended. <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.

Clinical Guideline	Recommendation(s)
	Immune complex-mediated manifestations of chronic hepatitis C • Treatment of HCV-associated lymphoma should utilize new interferon-free regimens as appropriate, but the effect of an SVR on the overall prognosis is not yet known. The effect of new antiviral therapies together with B cell depletion requires further study. An interdisciplinary approach with close monitoring of liver function is required. • Appropriate antiviral therapy should be considered for the treatment of mixed cryoglobulinemia and renal disease associated with chronic HCV infection. The role of rituximab in HCV-related renal disease requires evaluation. The more rapid inhibition of HCV replication and high SVR rates will need correlation with the response of the renal injury and the cryoglobulinemia. Careful monitoring for adverse events is mandatory. 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, if possible ribavirin-free regimen, for 12 weeks in patients without cirrhosis, for 24 weeks in patients with cirrhosis • Simeprevir, daclatasvir, and ombitasvir/paritaprevir/ritonavir and dasabuvir are cleared by hepatic metabolism and can be used in patients with severe renal disease • Sofosbuvir should not be administered to patients with an eGFR <30 ml/min/1.73 m^2 or with end-stage renal disease until more data is available • The need for dose adjustments for the approved HCV direct-acting antivirals in patients on dialysis is unknown. No safety dosing and efficacy data is available in this population. These drugs should thus be used with extreme caution in patients with severe renal disease, and only in extreme life-threatening situations for patients on dialysis. 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 for 12 weeks in patients without cirrhosis, for 24 weeks in patients with compensated (CTP A) cirrhosis, following the above recommendations, should be given to potential transplant recipients before listing for renal transplantation; however, no safety and efficacy data is available in this population, and the need for dose adjustments for the new direct-acting antivirals is unknown. • These drugs should thus be used with extreme caution and sofosbuvir should not be administered to patients with an eGFR <30 ml/min/1.73 m^2 or with end-stage renal disease until more data is available. • In non-hepatic solid organ transplant recipients, patients with an indication for anti-HCV therapy should receive an interferon-free regimen, following the above recommendations on treatment regimen and management of drug-drug interactions with cyclosporine and tacrolimus when appropriate. Treatment of acute hepatitis C • Peginterferon alfa monotherapy for 12 weeks can be used in patients with acute hepatitis C, who will achieve SVR in as many as 90% of cases. • Peginterferon alfa and 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

Clinical Guideline	Recommendation(s)
	used in patients with acute hepatitis C and are expected to achieve high SVR rates.

III. Indications

The Food and Drug Administration (FDA)-approved indications for ombitasvir-paritaprevir-ritonavir-dasabuvir 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 Ombitasvir-Paritaprevir-Ritonavir-Dasabuvir[1]

Indication	Ombitasvir, paritaprevir, and ritonavir; dasabuvir
Treatment of adult patients with chronic hepatitis C genotype 1b infection without cirrhosis or with compensated cirrhosis	✔
Treatment of adult patients with chronic hepatitis C genotype 1a infection without cirrhosis or with compensated cirrhosis for use in combination with ribavirin	✔

IV. Pharmacokinetics

The pharmacokinetic parameters of ombitasvir-paritaprevir-ritonavir-dasabuvir are listed in Table 4.

Table 4. Pharmacokinetic Parameters of Ombitasvir-Paritaprevir-Ritonavir-Dasabuvir[2]

Generic Name(s)	Bioavailability (%)	Protein Binding (%)	Metabolism (%)	Excretion (%)	Half-Life (hours)
Ombitasvir, paritaprevir, and ritonavir; dasabuvir	OPR: Not reported D: 70	O: >99 P: 97 to 99 R: >99 D: >99	O: Amide hydrolysis P: Liver R: Liver D: Liver	O: Renal (2) Feces (90); P: Renal (9) Feces (88); R: Renal (11) Feces (86); D: Renal (2) Feces (94)	O: 21 to 25 P: 5.5 R: 4 D: 5.5 to 6

O=ombitasvir, P=paritaprevir, R=ritonavir, D=dasabuvir.

V. Drug Interactions

Significant drug interactions with the HCV antivirals are listed in Table 5.

Table 5. Drug Interactions - Ombitasvir-Paritaprevir-Ritonavir-Dasabuvir (Not All Inclusive)[1]

Generic Name	Interaction	Potential Result
Ombitasvir/paritaprevir/ritonavir/dasabuvir	Alfuzosin	Increased alfuzosin concentration, increased risk for hypotension; contraindicated
Ombitasvir/paritaprevir/ritonavir/dasabuvir	Anticonvulsants (carbamazepine, phenytoin, phenobarbital)	Decreased ombitasvir/paritaprevir/ritonavir/dasabuvir concentration; loss of therapeutic effect; contraindicated
Ombitasvir/paritaprevir/ritonavir/dasabuvir	Gemfibrozil	Increased concentration of dasabuvir (10x); increased risk of QT prolongation; contraindicated

Generic Name	Interaction	Potential Result
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Rifampin	Decreased ombitasvir/paritaprevir/ritonavir/dasabuvir concentration; loss of therapeutic effect; contraindicated
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Ergot derivatives (ergotamine, dihydroergotamine, ergonovine, methylergonovine)	Increased ergot derivative concentrations; acute ergot toxicity characterized by vasospasm and tissue ischemia; contraindicated.
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	St. John's Wort	Decreased ombitasvir/paritaprevir/ritonavir/dasabuvir concentration; loss of therapeutic effect; contraindicated
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Statins (lovastatin, simvastatin)	Increased concentrations of lovastatin and simvastatin; potential for myopathy; contraindicated
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Efavirenz	Coadministration was poorly tolerated and resulted in liver enzyme elevations.
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Sildenafil	Increased concentrations of sildenafil; potential for visual disturbances, hypotension, priapism and syncope; contraindicated
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Sedatives/hypnotics (triazolam midazolam [oral])	Coadministration may cause large increases in benzodiazepine concentration. The potential exists for serious and/or life threatening events such as sedation or respiratory depression; contraindicated
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Antiarrhythmics (amiodarone, bepridil, disopyramide, flecainide, lidocaine, mexiletine, propafenone, quinidine)	Decreased concentration of antiarrhythmics; caution is warranted and therapeutic concentration monitoring is recommended for antiarrhythmics when coadministered.
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Ketoconazole	Increased ketoconazole concentration; limit max daily dose of ketoconazole to 200 mg per day
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Voriconazole	Decreased voriconazole concentration; coadministration not recommended (benefit-to-risk justifies use)
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Amlodipine	Increased concentration of amlodipine; dose adjust
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Fluticasone	Increased fluticasone concentration; may alter cortisol levels; use an alternate corticosteroid
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Furosemide	Furosemide concentration increased, dose adjust
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Atazanavir/ritonavir, lopinavir/ritonavir	Increased concentrations of paritaprevir; only coadminister atazanavir without ritonavir and limit to 300 mg in the morning; do not coadminister lopinavir/ritonavir
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Darunavir/ritonavir	Decreased concentration of darunavir; coadministration is not recommended
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Rilpivirine	Increased concentration of rilpivirine; increased risk of QT interval prolongation
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Statins (rosuvastatin, pravastatin)	Increased concentrations of the statins; limit dose to 10 mg (rosuvastatin) and 40 mg (pravastatin)
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Cyclosporine	Increased concentration of cyclosporin; when coadministered, reduce cyclosporine dose to 1/5th of the current dose. Measure cyclosporine blood concentrations to determine subsequent dose modifications. Frequent assessment of renal function and cyclosporine-related side effects is recommended.
Ombitasvir/paritaprevir/ ritonavir/dasabuvir	Tacrolimus	Increased concentration of tacrolimus; when coadministered, reduce tacrolimus dose. Measure tacrolimus blood concentrations to determine subsequent

Generic Name	Interaction	Potential Result
		dose modifications. Frequent assessment of renal function and tacrolimus-related side effects is recommended.
Ombitasvir/paritaprevir/ritonavir/dasabuvir	Salmeterol	Increased concentration of salmeterol; increased risk of cardiovascular event; coadministration not recommended
Ombitasvir/paritaprevir/ritonavir/dasabuvir	Buprenorphine (±naloxone)	Increased concentration of buprenorphine; no dose adjustment required; monitor for adverse effects
Ombitasvir/paritaprevir/ritonavir/dasabuvir	Omeprazole	Decreased concentration of omeprazole; limit dose to 40 mg or less
Ombitasvir/paritaprevir/ritonavir/dasabuvir	Alprazolam	increased concentration of alprazolam; monitor for side effects; dose adjust based on clinical response

VI. Adverse Drug Events

The most common adverse drug events reported with ombitasvir-paritaprevir-ritonavir-dasabuvir are listed in Table 6.

Table 6. Adverse Drug Events (%) Reported with Ombitasvir-Paritaprevir-Ritonavir-Dasabuvir[1-3]

Adverse Events	Ombitasvir, paritaprevir, and ritonavir; dasabuvir
Central Nervous System	
Asthenia	4 to 14
Fatigue	34 to 50
Headache	16 to 44
Insomnia	5 to 26
Irritability	10
Dermatologic	
Pruritus	7 to 18
Rash	7 to 24
Gastrointestinal	
Nausea	8 to 22
Hematologic	
Decreased hemoglobin	<1 to 29
Musculoskeletal	
Muscle spasm	21
Weakness	4 to 14
Other	
Cough	11 to 32
Dyspnea	✔
Hyperbilirubinemia	2 to 15
Increased alanine aminotransferase	1
Scleral icterus	10

✔ Percent not specified
- Event not reported

VII. Dosing and Administration

The usual dosing regimens for ombitasvir-paritaprevir-ritonavir-dasabuvir are listed in Table 7.

Table 7. Usual Dosing Regimens for Ombitasvir-Paritaprevir-Ritonavir-Dasabuvir[1]

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
Ombitasvir-paritaprevir-ritonavir-dasabuvir	Treatment of chronic hepatitis C genotype 1a infection in adults: Extended release tablets: Three tablets	Safety and efficacy in children have not been established	Extended release tablets: 8.33-50-33.3-

Generic Name(s)	Usual Adult Dose	Usual Pediatric Dose	Availability
	once daily with a meal and with ribavirin for 12 weeks (without cirrhosis) or 24 weeks (compensated cirrhosis) Treatment of chronic hepatitis C genotype 1b infection in adults: Extended release tablets: Three tablets once daily with a meal for 12 weeks		200 mg tablet

VIII. Effectiveness

Clinical studies evaluating the safety and efficacy of ombitasvir-paritaprevir-ritonavir-dasabuvir are summarized in Table 8. The approval of Viekira XR® is based on comparability of bioavailability for each of the components in Viekira XR® compared to that of the previously approved formulations in Viekira Pak®. A clinical trial to evaluate the efficacy and safety of Viekira XR® was not required because the efficacy and safety of the components of Viekira XR® were established previously in six clinical trials enrolling 2,308 Chronic Hepatitis C patients with and without cirrhosis.[1-4]

Table 8. Comparative Clinical Trials with Ombitasvir-Paritaprevir-Ritonavir-Dasabuvir

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Treatment of Chronic Hepatitis C: Treatment-Naïve Patients				
Feld et al.[8] (2014) SAPPHIRE-I ABT-450 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg once daily for 12 weeks and dasabuvir 250 mg twice daily for 12 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 12 weeks (Group A) vs placebo for 12 weeks of double-blind period followed by active regimen as open-label therapy for 12 weeks (Group B) (ABT-450 is the experimental	DB, MC, PC, R Patients 18 to 70 years of age with chronic HCV genotype 1 infection, no cirrhosis, who had not previously received treatment for HCV infection, and HCV RNA > 10,000 IU/mL	N=631 12 weeks	Primary: SVR12 Secondary: Normalization of the alanine aminotransferase level, SVR12 by HCV subtype (1a or 1b), virologic failure during treatment, and posttreatment relapse	Primary: The SVR12 rate in group A (96.2%; 95% CI, 94.5 to 97.9) was statistically noninferior and superior to the calculated historical control rate of 78% (95% CI, 75 to 80) in treatment-naïve patients without cirrhosis who received telaprevir and PEG/RBV. Secondary: The SVR12 rate was 95.3% (95% CI, 93.0 to 97.6) among patients with HCV genotype 1a infection and 98.0% (95% CI, 95.8 to 100) among those with HCV genotype 1b infection. These rates were statistically superior to the historical control rates in the respective subgroups (72%; 95% CI, 68 to 75 in patients with HCV genotype 1a infection and 80%; 95% CI, 75 to 84 in those with HCV genotype 1b infection). The rate of normalization of the alanine aminotransferase level was 97.0% in group A as compared with 14.9% in group B (P<0.001). Virologic failure during treatment and relapse after treatment occurred in 0.2% and 1.5%, respectively, of the patients in group A.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
name for paritaprevir)				
Ferenci et al.[9] (2014) PEARL-III and PEARL-IV ABT-450 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg once daily for 12 weeks and dasabuvir 250 mg twice daily for 12 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 12 weeks vs ABT-450 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg once daily for 12 weeks and dasabuvir 250 mg twice daily for 12 weeks and placebo (ABT-450 is the experimental	DB, MC, R Patients 18 to 70 years of age with chronic HCV genotype 1b infection (PEARL-III) or HCV genotype 1a infection (PEARL-IV), no cirrhosis, who had not previously received treatment for HCV infection, and HCV RNA> 10,000 IU/mL	PEARL-III N=419 12 weeks PEARL-IV N=305 12 weeks	Primary: SVR12 Secondary: Superiority of the SVR12 rate at each group as compared with the historical rate with telaprevir plus PEG/RBV, noninferiority of the SVR12 rate in the groups that did and did not receive ribavirin, hemoglobin level below the lower limit of the normal range at the end of treatment, and the percentage of patients in each group with virologic failure during treatment or relapse after	Primary: In the genotype 1a study, the SVR12 rates were 97.0% (95% CI, 93.7 to 100) in patients who received the regimen with ribavirin and 90.2% (95% CI, 86.2 to 94.3) in patients who received the regimen without ribavirin. In the genotype 1b study, the SVR12 rates were 99.5% (95% CI, 98.6 to 100.0) in patients who received the regimen with ribavirin and 99.0% (95% CI, 97.7 to 100.0) in patients who received the regimen without ribavirin. Secondary: In the genotype 1a study, the SVR rates among patients who received ribavirin and those who did not were both noninferior and superior to the historical rate with telaprevir and PEG/RBV in treatment-naïve adults with HCV genotype 1a infection and no cirrhosis. The regimen without ribavirin did not meet the noninferiority criterion as compared with the regimen with ribavirin, because the lower boundary of the CI for the difference (-6.8%; 95% CI, -12.0 to -1.5) crossed the noninferiority margin of 10.5%. In addition, the upper boundary of the confidence interval did not cross zero, indicating a significant difference between groups. In the genotype 1b study, the SVR rates among patients who received ribavirin and those who did not were both noninferior and superior to the historical rate with telaprevir and PEG/RBV among previously untreated adults with HCV genotype 1b infection and no cirrhosis. In addition, the SVR rate among patients who did not receive ribavirin was noninferior to the rate among those who received ribavirin (difference, -0.5%; 95% CI, -2.1 to 1.1). Among the patients in the genotype 1a study who had a hemoglobin level within the normal range at baseline, 42.0% of patients who received the antiviral regimen with ribavirin and 3.9% of patients who received the ribavirin-free regimen had a hemoglobin level below the lower limit of the normal range at the end of treatment

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
name for paritaprevir)			treatment	(P<0.001). Similarly, in the genotype 1b study, 51.2% of patients who received ribavirin had a low hemoglobin level at the end of treatment, as compared with 3.4% of patients who did not receive ribavirin (P<0.001). Among patients with genotype 1a infection, the rate of virologic failure was higher in the ribavirin-free group than in the group receiving ribavirin (7.8 vs 2.0%). Of patients with genotype 1b infection, none had virologic failure in the ribavirin-free group and one had virologic failure (0.48%) in the group receiving ribavirin.
Poordad et al.[10] (2014) TURQUOISE-II ABT-450 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg once daily for 12 weeks and dasabuvir 250 mg twice daily for 12 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 12 weeks vs ABT-450 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg once daily for 24 weeks and	MC, OL, R Patients 18 to 70 years of age with chronic HCV genotype 1 infection, treatment-naïve or previously treated with PEG/RBV, documented cirrhosis by means of liver biopsy, Child–Pugh class A score <7, no current or past clinical evidence of Child–Pugh class B or C, HCV RNA >10,000 IU/mL, platelets ≥60,000/mm^3,	N=380 12 to 24 weeks	Primary: SVR12 compared to historical control Secondary: SVR12 with 12- vs 24-week treatment, virologic failure during treatment or relapse after treatment	Primary: The SVR12 rates were 91.8% (97.5% CI, 87.6 to 96.1) in the 12-week group and 95.9% (97.5% CI, 92.6 to 99.3) in the 24-week group. These rates were statistically noninferior and superior to the historical control rate with telaprevir and PEG/RBV among patients with HCV genotype 1 infection and cirrhosis (47%; 95% CI, 41 to 54). Secondary: The difference in the SVR12 rates between the 12- and 24-week treatment groups was not significant (P=0.09). The SVR rates with 12- vs 24-week treatment were 88.6 vs 94.2% in genotype 1a patients; 98.5 vs 100% in genotype 1b patients; 94.2 vs 94.6% in treatment-naïve patients; 96.6 vs 100% in relapsers with prior PEG/RBV; 94.4 vs 100% in prior partial responders to PEG/RBV; and 86.7 vs 95.2% in prior null responders to PEG/RBV. Among patients with HCV genotype 1a infection and a prior null response to PEG/RBV, SVR was achieved in 92.9% (95% CI, 85.1 to 100) in the 24-week group as compared to 80.0% (95% CI, 68.9 to 91.1) in the 12-week group. Virologic failure during treatment or relapse after treatment occurred in 6.2% and 2.3% of patients in the 12-week and 24-week groups, respectively. Virologic failure during treatment occurred 0.5% (95% CI, 0 to 1.4) and 1.7% (95% CI, 0 to 3.7) of patients in the 12-week

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
dasabuvir 250 mg twice daily for 24 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 24 weeks (ABT-450 is the experimental name for paritaprevir)	serum albumin ≥2.8 g/dL, total bilirubin <3 mg/dL, INR≤2.3, and serum alpha-fetoprotein ≤100 ng/mL			and 24-week groups, respectively. Significantly more patients in the 12-week group than in the 24-week group had a relapse: 5.9% (95% CI, 2.7 to 9.2) vs 0.6% (95% CI, 0 to 1.8).
Treatment of chronic hepatitis C: Treatment-experienced patients				
Zeuzem et al.[11] (2014) SAPPHIRE-II ABT-450 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg once daily for 12 weeks and dasabuvir 250 mg twice daily for 12 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 12 weeks vs placebo	DB, MC, PC, R Patients 18 to 70 years of age with chronic HCV genotype 1 infection without cirrhosis, relapsers or nonresponders with prior PEG/RBV treatment, and HCV RNA >10,000 IU/mL	N=394 12 weeks	Primary: SVR12 compared to historical control Secondary: Normalization of the alanine aminotransferase level, SVR by HCV genotype (1a or 1b), virologic failure during treatment, and post-treatment relapse	Primary: Treatment with the active-regimen lead to a SVR12 of 96.3% (95% CI, 94.2 to 98.4) which was noninferior and superior to the historical control SVR rate of 65% (95% CI, 60 to 70) among previously treated patients with HCV genotype 1 infection and no cirrhosis who had received retreatment with telaprevir and PEG/RBV (P value not reported). Secondary: The rate of normalization of the alanine aminotransferase level was significantly higher in the active-regimen group than in the placebo group (96.9 vs 12.8%, P<0.001). The SVR rates were similar between patients with HCV genotype 1a infection (96.0%; 95% CI, 93.0 to 98.9) and those with HCV genotype 1b infection (96.7%; 95% CI, 93.6 to 99.9). The HCV genotype (1a or 1b) could not be determined for one patient, who had a SVR12. No patient had virologic failure during treatment. Of the 293 patients who completed therapy, 2.4% had a post-treatment viral relapse.

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
(ABT-450 is the experimental name for paritaprevir)				
Andreone et al.[12] (2014) PEARL-II ABT-450 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg once daily for 12 weeks and dasabuvir 250 mg twice daily for 12 weeks and ribavirin 1,000 mg (weight <75 kg) or 1,200 mg/day (weight ≥75 kg) in two divided doses for 12 weeks vs ABT-450 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg once daily for 12 weeks and dasabuvir 250 mg twice daily for 12 weeks (ABT-450 is the experimental name for paritaprevir)	MC, OL, R Patients 18 to 70 years of age with chronic HCV genotype 1b infection for at least six months, and HCV RNA >10,000 IU/mL, no cirrhosis, and prior failure of therapy with PEG/RBV	N=179 12 weeks	Primary: SVR12 compared to historical control Secondary: Proportion of patients with decreased hemoglobin level to less than the lower limit of normal at the end of treatment, superiority of both groups to historical SVR rate, noninferiority of both treatment groups, virologic failure during treatment, and post-treatment relapse	Primary: The SVR12 rate was 96.6% (95% CI, 92.8 to 100) in the group receiving ribavirin and 100% (95% CI, 95.9 to 100) in the group not being treated with ribavirin. These rates were statistically noninferior to the historical SVR rate for telaprevir and PEG/RBV in comparable treatment-experienced patients. Secondary: Hemoglobin levels less than the lower limit of normal at the end of treatment were more common in patients receiving ribavirin compared to those that did not (42.0 vs 5.5%, respectively; P<0.001), although clinically significant grade 2 hemoglobin level declines to <10 g/dL at the end of treatment occurred in only two patients (1.1%), both in the group receiving ribavirin. The SVR12 rates in the group receiving ribavirin (96.6%) and in the group not being treated with ribavirin (100%) were statistically superior to the historical SVR rate for telaprevir and PEG/RBV in comparable treatment-experienced patients. The SVR12 rates in the group not receiving ribavirin were noninferior to those in the group receiving ribavirin (difference, 3.4%; 95% CI, -0.4 to 7.2) No patients from either treatment group experienced on-treatment virologic failure or post-treatment relapse. Of the three patients in the group receiving ribavirin who did not achieve SVR12, there were two patients (2.3%) who discontinued study drug.
Treatment of chronic hepatitis C: Treatment-naïve and experienced patients				

Study and Drug Regimen	Study Design and Demographics	Study Size and Study Duration	End Points	Results
Kwo et al.[13] (2014) CORAL-I ABT-450 150 mg/ ritonavir 100 mg/ ombitasvir 25 mg once daily for 24 weeks and dasabuvir 250 mg twice daily for 24 weeks and ribavirin (dosing at investigator's discretion) for 24 weeks A stable tacrolimus- or cyclosporine-based immunosuppressive regimen was required, and glucocorticoids were allowed at a dose of ≤5 mg/day. (ABT-450 is the experimental name for paritaprevir)	MC, OL Patients 18 to 70 years of age with chronic HCV genotype 1 infection, HCV RNA >10,000 IU/mL who received a liver transplant ≥12 months before screening because of chronic HCV infection, and Metavir score≤F2 on liver biopsy performed ≤6 months before screening	N=34 24 weeks	Primary: SVR12 Secondary: SVR24, virologic failure during treatment, and post-treatment relapse	Primary: The SVR12 rate was 97% (95% CI, 85 to 100). All five patients infected with genotype 1b (100%) and 28 of 29 patients infected with genotype 1a (97%) had a SVR. Secondary: The SVR24 rate was 97% (95% CI, 85 to 100). All the patients also had HCV RNA <25 IU/mL at the end of treatment. One patient did not have a SVR owing to a relapse on post-treatment day three. No relapses occurred after post-treatment week 12.

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
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 Ombitasvir-Paritaprevir-Ritonavir-Dasabuvir

Generic Name(s)	Formulation(s)	Example Brand Name(s)	Brand Cost	Generic Cost
Ombitasvir, paritaprevir, ritonavir, and dasabuvir	extended release tablets	Viekira XR®	$$$$$	N/A

N/A=Not available

X. Conclusions

Viekira XR® (ombitasvir-paritaprevir-ritonavir-dasabuvir) is a once-daily, four-drug, fixed-dose combination product Food and Drug Administration (FDA)-approved for treatment of chronic hepatitis C virus (HCV) genotype 1a and 1b infection in adults with or without cirrhosis. The approval of Viekira XR® is based on comparability of bioavailability for each of the components in Viekira XR® compared to that of the previously approved formulations in Viekira Pak®. Viekira XR® and Viekira Pak® share the same FDA-approved indications.[1-4]

The FDA approval of Viekira Pak® (ombitasvir-paritaprevir-ritonavir and dasabuvir) was based on the results of six randomized, multicenter, clinical trials (N=2,308) in HCV patients with genotype 1, including one trial exclusively in patients with cirrhosis and mild hepatic impairment (Child-Pugh A). These included the SAPPHIRE-I (double-blind), SAPPHIRE-II (double-blind), PEARL-II (open-label), PEARL-III (open-label), PEARL-IV (double-blind), and TURQUIOSE-II (open-label).[1] Viekira Pak® with ribavirin was also evaluated in

liver transplant recipients in CORAL-I and human immunodeficiency virus (HIV) coinfection in TURQUIOSE-I. Sustained virologic response (SVR), the primary endpoint, was defined as HCV RNA below the lower limit of quantification at 12 weeks after the end of treatment.[1,13] These trials resulted in SVR rates ranging from 91.8 to 100%.[8-13] The American Association for the Study of Liver Diseases (AASLD) and the Infectious Diseases Society of America (IDSA) consensus guidelines do not currently provide recommendation on the place in therapy of Viekira XR®. In general, the recommendations are consistent with FDA labeling.[5]

At this time, there is insufficient data to conclude that ombitasvir-paritaprevir-ritonavir-dasabuvir is safer or more efficacious than other brand or generic products within its class and that it offers a significant clinical advantage over other alternatives in general use. 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 ombitasvir-paritaprevir-ritonavir-dasabuvir 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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