



Department of Vermont Health Access

Therapeutic Class Review Second Generation Cephalosporins

Overview/Summary

The cephalosporin family of antibiotics is part of a larger group known as β -lactam antibiotics. Agents within this group share the structural feature of a β -lactam ring. The β -lactam antibiotics are generally considered bactericidal and work by inactivating enzymes involved with bacterial cell wall synthesis.¹ Cephalosporins cover a wide range of organisms and are frequently used antibacterial agents due to their spectrum of activity and ease of administration.²

Cephalosporins are grouped into generations, based on their spectrum of activity. The first generation cephalosporins are active against gram-positive aerobes but are inactive against penicillin-resistant pneumococci. They typically have poor activity against gram-negative organisms, though some strains of *Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis* and *Shigella* may be susceptible. Second generation cephalosporins have greater activity against *Haemophilus influenza* compared to the first generation cephalosporins and have enhanced activity against gram-negative bacteria in vitro. Third generation cephalosporins are active against streptococci, *H influenza* and *Moraxella catarrhalis* and are more active against gram-negative bacilli compared to first or second generation cephalosporins.^{2,3} However, they are not as active against susceptible strains of staphylococci as compared to first generation cephalosporins. Fourth generation cephalosporins have enhanced activity against gram-negative bacteria compared to the first and second generation cephalosporins and have activity in vitro against gram-negative bacteria that are typically resistant to the third generation cephalosporins, including *Pseudomonas aeruginosa* and Enterobacteriaceae. Additionally, they may be more active against gram-positive bacteria compared to some third generation cephalosporins. The only fourth generation cephalosporin is cefepime, which is only available parenterally. As a family, cephalosporins have poor activity against enterococci, Listeria and oxacillin-resistant staphylococci (also known as MRSA).^{2,3}

Collectively, the cephalosporins are able to reach therapeutic levels in urine and in pleural, pericardial, peritoneal and synovial fluid. With the exception of cefuroxime, the first and second generation cephalosporins are not able to effectively penetrate the cerebrospinal fluid and therefore should not be used to treat central nervous system infections. Conversely, the third generation cephalosporins do effectively penetrate the cerebrospinal fluid.²

This review will focus on the oral second generation cephalosporins. Each agent is available generically in at least one dosage form or strength.

Medications

Table 1. Medications Included Within Class Review

Generic Name (Trade name)	Medication Class	Generic Availability
Cefaclor*	Second generation cephalosporin	✓
Cefprozil*	Second generation cephalosporin	✓
Cefuroxime (Ceftin ^{®*})	Second generation cephalosporin	✓

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

The second generation cephalosporins have been shown to be active against the strains of microorganisms indicated in Table 2. This activity has been demonstrated in clinical infections and is represented by the Food and Drug Administration-approved indications for the second generation

cephalosporins that are noted in Table 3. 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 Second Generation Cephalosporins⁴⁻⁹

Bacteria	Cefaclor	Cefaclor Extended-Release	Cefprozil	Cefuroxime
Gram-Positive Aerobes				
<i>Staphylococcus</i> spp.	✓			
<i>Staphylococcus aureus</i>	✓	✓*	✓ †	✓ †
<i>Streptococcus pneumoniae</i>	✓	✓	✓	✓
<i>Streptococcus pyogenes</i>	✓	✓	✓	✓
Gram-Negative Aerobes				
<i>Escherichia coli</i>	✓			✓
<i>Haemophilus influenzae</i>	✓ ‡	✓ §	✓	✓ ¶
<i>Haemophilus parainfluenzae</i>				✓ §
<i>Klebsiella</i> spp.	✓			✓
<i>Moraxella (Branhamella) catarrhalis</i>		✓	✓	✓
<i>Neisseria gonorrhoeae</i>				✓
<i>Proteus mirabilis</i>	✓			
Spirochetes				
<i>Borrelia burgdorferi</i>				✓

*Methicillin-susceptible.

†Including penicillinase-producing strains.

‡β-lactamase negative ampicillin-resistant strains should be considered resistant to cefaclor.

§ Non-β-lactamase producing strains only.

|| Including β-lactamase producing strains.

¶ Non-β-lactamase producing strains only in patients with acute bacterial maxillary sinusitis and acute bacterial exacerbations of chronic bronchitis and secondary bacterial infections of acute bronchitis. Cefuroxime can be used for β-lactamase producing strains of *Haemophilus influenzae* for the treatment of acute bacterial otitis media.

Indications

Table 3. Food and Drug Administration (FDA) Approved Indications⁴⁻⁹

Indication	Cefaclor	Cefaclor Extended-Release	Cefprozil	Cefuroxime
Dermatologic				
Skin and skin structure infections	✓	✓	✓	✓
Genitourinary				
Gonorrhea, uncomplicated				✓
Urinary tract infections	✓			✓
Respiratory				
Acute bacterial exacerbations of chronic bronchitis		✓	✓	✓
Acute sinusitis			✓	✓
Otitis media	✓		✓	✓
Pharyngitis and/or tonsillitis	✓	✓	✓	✓
Respiratory tract infections, lower	✓			
Secondary bacterial infections of acute bronchitis		✓	✓	✓
Other				
Lyme disease, early				✓

Pharmacokinetics

Table 4. Pharmacokinetics^{4-9,10,11}

Generic Name	Time to Peak Blood Levels (hours)	Protein Binding (%)	Renal Excretion (%)	Serum Half-Life (hours)
Cefaclor	0.5 to 1.5	25	65 to 85	0.6 to 0.9
Cefaclor extended-release	1.5 to 2.5	25	65 to 85	1
Cefprozil	1.5	36	60	1.3
Cefuroxime	2.2 to 3.6	50	50	1.2 to 1.9

Clinical Trials

Overall, the second generation cephalosporins have demonstrated efficacy for their respective indications. Comparisons with the second generation as well as other generation cephalosporins have failed to consistently demonstrate the "superiority" of one agent over another.¹²⁻⁴⁴ One study summarized by Ball found significantly better clinical efficacy rates with cefprozil compared to cefuroxime for the treatment of lower respiratory tract infections.¹⁹ Gooch et al compared cefuroxime, cefadroxil and cephalexin in patients with mild to moderate skin and skin structure infections and found no significant difference between cefuroxime and cefadroxil in clinical or bacteriological outcomes, though a significant difference in favor of cefuroxime was observed when compared to cephalexin.³⁹ Two studies compared cefaclor to cefaclor extended-release in the treatment of pneumonia and pharyngitis/tonsillitis. Derriennic and colleagues found similar clinical and bacteriologic response rates between agents in the treatment of pharyngitis/tonsillitis, and Casali and colleagues reported no significant differences between agents in favorable clinical response and pathogen eradication in patients with pneumonia.^{24,29}

Table 5. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Acute Bacterial Exacerbations of Chronic Bronchitis and Secondary Bacterial Infections of Acute Bronchitis				
Phillips et al ¹² Cefaclor 250 mg TID vs cefpodoxime 200 mg BID	DB, MC, RCT Patients with signs and symptoms of acute bacterial exacerbation of COPD	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; no <i>P</i> value reported) or in clinical response at three to seven days post-treatment (99 vs 92%, respectively; <i>P</i> value not reported). Secondary: More bacterial isolates were susceptible to cefpodoxime compared to cefaclor (91 vs 84%, respectively; <i>P</i> <0.001). Secondary: There were no statistically significant differences between cefpodoxime and cefaclor in adverse events (11 vs 12%, respectively; <i>P</i> value not reported).
Chirurgi et al ¹³ Cefaclor 250 mg every 8 hours vs ceftibuten 400 mg once daily	PRO, RCT Patients with acute bronchitis, not pneumonia	N=45 Unspecified (from 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 (<i>P</i> value not reported). Bacteriologic efficacy was reported as 87.5 and 80.0% of patients treated with ceftibuten and cefaclor, respectively (<i>P</i> value not reported). Secondary: The rates of adverse events were reported as 7.9 and 5.6% in patients treated with ceftibuten and cefaclor, respectively (<i>P</i> value not reported).
Fogarty et al ¹⁴ Cefprozil 500 mg BID (for 10 days) vs cefdinir 300 m BID (for 5 days)	DB, MC, PRO, RCT Patients with acute exacerbations of chronic bronchitis	N=281 5 to 10 days	Primary: Clinical evaluations, microbiologic evaluations Secondary: Adverse events	Primary: Seven to eleven days after the patient had stopped therapy, clinical cure rates were reported as 80 and 72% for patients treated with cefdinir and cefprozil, respectively (<i>P</i> value not reported). Secondary: Seven to eleven days after the patient had stopped therapy, microbiological eradication rates were reported as 81 and 84% for patients treated with cefdinir and cefprozil, respectively (<i>P</i> value not reported). Secondary: Patients treated with cefdinir experienced more cases of mild diarrhea than patients treated with cefprozil (17 vs 6%, respectively; <i>P</i> <0.01).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Alvarez-Sala et al ¹⁵ Cefuroxime 250 mg BID (for 10 days) vs cefditoren 200 mg BID (for 5 days)	DB, DD, PG, RCT Patients 18 years of age and older 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 (<i>P</i> =NS). On day 30, clinical success rate was reported as 81.0% and 85.5% for patients treated with cefditoren and cefuroxime, respectively (<i>P</i> =NS). On day 11, bacteriological response was reported as 72.8 and 67.0% for patients treated with cefditoren and cefuroxime, respectively (<i>P</i> =NS). Secondary: Drug-related adverse events were reported in 7.7 and 11.4% of patients treated with cefditoren and cefuroxime, respectively (<i>P</i> value not reported).
Zuck et al ¹⁶ Cefuroxime 250 mg PO BID vs cefixime 200 mg 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 (<i>P</i> =NS); microbiological eradication occurred more quickly in patients treated with cefuroxime compared to patients treated with cefixime (<i>P</i> =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.
Van Herwaarden et al ¹⁷ Cefdinir 600 mg once daily vs cefdinir 300 mg BID vs cefuroxime 250 mg BID	DB, MC, PG, RCT Patients 13 years of age and older with a history of chronic bronchitis and a current diagnosis of an acute exacerbation of chronic	N=1,045 Up to 35 days post-treatment	Primary: Clinical response rate, microbiological eradication Secondary: Appearance of new pathogens during or after treatment	Primary: The clinical response rates for the cefdinir once daily, cefdinir BID and cefuroxime groups were 81, 74 and 80%, respectively. No significant difference between groups was observed in clinical response rates (<i>P</i> values not reported). Microbiological cure rates at test-of-cure assessment (seven to 14 days post-treatment) were 90% in the cefdinir once daily group, 85% in the cefdinir BID group, and 88% in the cefuroxime group. The cefdinir once daily and BID groups were comparable to the cefuroxime group in microbiological cure rates at test-of-cure assessment but the cefdinir once daily group was slightly more effective than the BID group (<i>P</i> values not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	bronchitis			<p>At the long-term follow-up assessment (21 to 35 days post-treatment), the microbiological eradication rates were 95% for cefdinir once daily, 99% for cefdinir BID and 99% for cefuroxime (<i>P</i> values not reported).</p> <p>The corresponding values for clinical response rates were 93, 95 and 93%, respectively (<i>P</i> values not reported).</p> <p>Secondary: Thirty-two patients in the cefdinir once daily group, 45 patients in the cefdinir BID group and 39 patients in the cefuroxime group developed a respiratory tract superinfection during the study (<i>P</i> values not reported).</p> <p>Eleven patients were reinfected with pathogens not present at baseline after the test-of-cure assessment (three patients in the cefdinir once daily group, six patients in the cefdinir BID group and two patients in the cefuroxime group; <i>P</i> values not reported).</p>
<p>Henry et al¹⁸</p> <p>Cefuroxime 250 mg BID (for 5 days) and placebo BID (for 5 days)</p> <p>vs</p> <p>cefuroxime 250 mg BID (for 10 days)</p> <p>vs</p> <p>amoxicillin/clavulanate 500 mg TID (for 10 days)</p>	<p>DB, MC, RCT</p> <p>Patients with secondary bacterial infections of acute bronchitis</p>	<p>N=423</p> <p>5 to 10 days</p>	<p>Primary: Clinical efficacy, bacteriologic efficacy</p> <p>Secondary: Adverse events</p>	<p>Primary: Clinical success was reported as 82, 86, and 83% in patients treated with cefuroxime (five days), cefuroxime (10 days), and amoxicillin/clavulanate, respectively. Microbiologic eradication was reported as 87, 91, and 86% in patients treated with cefuroxime (five days), cefuroxime (10 days), and amoxicillin/clavulanate, respectively (<i>P</i> value not reported).</p> <p>Secondary: Patients treated with amoxicillin/clavulanate reported a higher incidence of drug-related adverse events compared to patients treated with cefuroxime (<i>P</i>=0.001). A greater incidence of diarrhea and nausea was reported for patients treated with amoxicillin/clavulanate compared to patients treated with cefuroxime (five days) and cefuroxime (10 days); 37 vs 19, vs 15%, respectively; <i>P</i><0.001.</p>
<p>Ball¹⁹</p> <p>Cefaclor 500 mg every 8 hours</p>	<p>MA (3 MC, PRO)</p> <p>Patients 18</p>	<p>N=1,352</p> <p>5 to 10 days</p>	<p>Primary: Clinical efficacy, bacteriological efficacy</p>	<p>Primary: In study A, clinical efficacy in acute bronchitis was reported as 88% for patients treated with either cefprozil or cefaclor; bacteriological eradication was reported as 86 and 82%, respectively (<i>P</i> values not reported). Clinical efficacy in acute</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>vs</p> <p>cefprozil 500 mg every 12 hours</p> <p>vs</p> <p>cefuroxime 500 mg every 12 hours</p> <p>vs</p> <p>amoxicillin/clavulanate 500 mg every 8 hours</p> <p>In study A, participants received either cefprozil or cefaclor.</p> <p>In study B, participants received either cefprozil or cefuroxime.</p> <p>Study C participants received either cefprozil or amoxicillin/clavulanate.</p>	<p>years of age and older with acute mild-to-moderate respiratory tract infections, including acute bronchitis, acute exacerbations of chronic bronchitis, and bacterial pneumonia</p>		<p>Secondary: Adverse effects</p>	<p>exacerbation of chronic bronchitis was reported as 80 and 62% in patients treated with cefprozil and cefaclor, respectively ($P=0.067$); bacteriological eradication was reported as 62 and 74%, respectively (P value not reported). Clinical efficacy in pneumonia was reported as 82 and 79% in patients treated with cefprozil and cefaclor, respectively; bacteriological eradication was reported as 82 and 71%, respectively (P values not reported).</p> <p>In study B, clinical efficacy was reported as 95 and 84% for patients treated every 12 hours with cefprozil and cefuroxime, respectively ($P=0.03$); bacteriologic eradication was reported as 100 and 75%, respectively (P values not reported).</p> <p>In study C, clinical and bacteriological efficacy was similar between cefprozil and amoxicillin/clavulanate both given every eight hours; $P=NS$.</p> <p>Secondary: All treatment regimens were well-tolerated. In study C, diarrhea was reported more frequently in patients treated with amoxicillin/clavulanate compared to patients treated with cefprozil (19 vs 7%, respectively).</p>
Female Pelvic and Genital Tract Infections				
<p>French et al⁴⁵</p> <p>Clindamycin plus an aminoglycoside</p> <p>vs</p>	<p>MA</p> <p>Women with postpartum endometritis, after cesarean section or</p>	<p>N=1,902</p> <p>Precise duration of therapy not specified</p>	<p>Primary: Treatment failure</p> <p>Secondary: Not reported</p>	<p>Primary: Nineteen studies comparing clindamycin plus an aminoglycoside (usually gentamicin) with an alternative regimen demonstrated more treatment failures with the other regimen (RR, 1.44; 95% CI, 1.15 to 1.8).</p> <p>The overall failure rate of clindamycin plus gentamicin was 11.4% (106/928).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
various alternative antibacterial regimens	vaginal birth			<p>The incidence of diarrhea was more common with the clindamycin regimens, though not at a statistically significant level (95% CI, 0.35 to 1.25).</p> <p>Seven studies (N=741) compared a second or third generation cephalosporin with another regimen (usually clindamycin plus gentamicin) and demonstrated no difference in treatment failures between groups (RR, 1.39; 95% CI, 0.90 to 2.15). The incidence of diarrhea was less frequent with the cephalosporin group.</p> <p>Four trials (N=603) compared aztreonam plus clindamycin with other regimens (i.e., clindamycin plus gentamicin or trospectomycin*) and did not reveal evidence of a difference between groups.</p> <p>One trial (N=97) investigated the difference between ciprofloxacin and clindamycin plus gentamicin and demonstrated more treatment failures in the ciprofloxacin group, though not at a statistically significant level (RR, 1.96; 95% CI, 0.20 to 4.21).</p> <p>Secondary: Not reported</p>
Gonorrhea				
<p>Reichman et al⁴⁶</p> <p>Cefuroxime 1 g as a single dose</p> <p>vs</p> <p>cefuroxime 1 g as a single dose plus probenecid 1g</p> <p>vs</p> <p>amoxicillin 3 g as a single dose plus probenecid 1 g</p>	<p>DB, RCT</p> <p>Patients 18 years of age and older with urethral gram stain showing polymorpho-nuclear leukocytes with typical intracellular gram-negative diplococci (men) or documented</p>	<p>N=184</p> <p>7 days post-treatment</p>	<p>Primary: Cure rates</p> <p>Secondary: Adverse effects</p>	<p>Primary: No significant differences were observed between groups in cure rates.</p> <p>Secondary: Nausea was significantly more common in regimens which included probenecid compared to cefuroxime treatment alone ($P<0.05$).</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	gonorrhea (women)			
Thorpe et al ⁴⁷ Cefuroxime 1 g as a single dose vs ciprofloxacin 500 mg as a single dose	MC, RCT, SB Patients 18 to 65 years of age with gonorrhea or sexual contacts of individuals with known gonorrhea	N=832 8 days post-treatment	Primary: Bacteriological eradication Secondary: Not reported	Primary: Eradication was observed in the cervix of 97% of cefuroxime and 99% of ciprofloxacin female patients ($P=0.213$). Eradication was observed in the urethra of 93% of cefuroxime and 100% of ciprofloxacin male patients ($P<0.001$). No significant differences were observed between groups in eradication rates in females with rectal infections (97% of cefuroxime patients and 100% of ciprofloxacin patients; $P=1.00$). In a small number of patients, cefuroxime was less effective in eradicating pharyngeal infections in men ($P=0.013$). No significant differences were observed between groups in eradication of penicillinase-producing <i>N gonorrhoeae</i> in men or women ($P\geq 0.418$). Secondary: Not reported
Baddour et al ⁴⁸ Cefuroxime 1 g as a single dose vs amoxicillin 3 g plus probenecid 1 g as a single dose	RCT Female sexual contacts of partners with culture-proven gonorrhea	N=466 7 days post-treatment	Primary: Cure rates Secondary: Not reported	Primary: No significant differences were observed in cure rates between groups for cervical, urethral, rectal or pharyngeal infections ($P>0.05$). Secondary: Not reported
Lyme Disease				
Luger et al ⁴⁹ Cefuroxime 500 mg BID	MC, RCT, SB Patients 12 years of age	N=232 12 months post-treatment	Primary: Clinical response at one month post-treatment, clinical	Primary: Satisfactory clinical response was observed in 90% of cefuroxime patients and 95% of doxycycline patients at one month post-treatment (difference, -5%; 95% CI, -12 to 3).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs doxycycline 100 mg TID	and older weighing at least 45 kg with early Lyme disease		signs and symptoms Secondary: Adverse effects	No significant differences were observed between groups in the number and severity of signs and symptoms. Of patients with satisfactory clinical response at one month post-treatment, 95% of cefuroxime patients and 100% of doxycycline patients had a satisfactory clinical outcomes at 12 months post-treatment (difference, -5%; 95% CI, -10 to 4). Secondary: Significantly more patients in the doxycycline group reported one or more adverse events ($P=0.041$). Adverse effects related to the skin were significantly more common in the doxycycline group compared to the cefuroxime group ($P=0.009$). Significantly more patients in the cefuroxime group reported diarrhea compared to those in the doxycycline group ($P=0.03$).
Eppes et al ⁵⁰ Cefuroxime 20 to 30 mg/kg/day divided every 12 hours vs amoxicillin 50 mg/kg/day divided every 8 hours	NB, RCT Patients 3 months to 12 years of age with early Lyme disease	N=43 12 months post-treatment	Primary: Clinical response Secondary: Not reported	Primary: Total resolution of erythema migrans was observed in 92% of low dose cefuroxime patients, 87% of high dose cefuroxime patients and 67% of amoxicillin patients at the completion of treatment. Resolution of constitutional symptoms occurred in 69% of low dose cefuroxime patients, 87% of high dose cefuroxime patients and 100% of amoxicillin patients. The study was not powered to detect differences between groups. Secondary: Not reported
Otitis Media				
Piippo et al ²⁰ Cefaclor 40 mg/kg/day divided BID	DB, PG, RCT Pediatric patients aged 6 months to 12	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 ($P=0.12$).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs cefixime 8 mg/kg/day divided BID	years with acute otitis media			Secondary: Adverse events were reported in 17.9 and 10.6% of patients treated with cefixime and cefaclor, respectively (<i>P</i> value not reported).
MacLoughlin et al ²¹ Cefaclor suspension 40 mg/kg/day divided TID vs cefpodoxime suspension 10 mg/kg/day divided BID	MC, OL, RCT Pediatric patients aged 1 month to 11 years 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 (<i>P</i> >0.05); at study day 30, clinical recurrence was reported as 99 and 94%, respectively (<i>P</i> >0.05). Secondary: Patients were able to tolerate both cefpodoxime and cefaclor (99 vs 94%, respectively; <i>P</i> >0.05).
Blumer et al ²² Cefaclor 40 mg/kg/day in 3 divided doses (maximum 1 g/day) vs ceftibuten 9 mg/kg/day for 1 dose (maximum 400 mg/day)	MC, RCT, SB Pediatric patients aged 3 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 (<i>P</i> =NS). At two to four weeks post-treatment, clinical cure was reported in 88 and 82% of patients treated with ceftibuten and cefaclor, respectively (<i>P</i> =NS). Secondary: Mild to moderate drug-related adverse events were reported in 8 and 14% of patients treated with ceftibuten and cefaclor, respectively (<i>P</i> values not reported).
Block et al ²³ Cefprozil 30 mg/kg/day divided BID (for 10 days) vs cefdinir 14 mg/kg/day divided BID (for 5 days)	DB, MC, PRO Pediatric patients aged 6 months to 12 years 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 (<i>P</i> =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; <i>P</i> =0.116).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Pharyngitis/Tonsillitis				
Derriennic et al ²⁴ (abstract) Cefaclor advanced formulation 375 mg BID vs cefaclor 250 mg TID	MA (2 DB, DD, MC, RCTs) Patients with group A β -hemolytic streptococcal pharyngitis/ tonsillitis	N=1,138 3 weeks post-treatment	Primary: Clinical response, bacteriological response Secondary: Not reported	Primary: Clinical success was observed in 96.7% of cefaclor advanced formulation patients and 98.1% of cefaclor patients (<i>P</i> value not reported). Bacteriological cure was observed in 93.6% of cefaclor advanced formulation patients and 94.1% of cefaclor patients (<i>P</i> value not reported). Secondary: Not reported
Randolph et al ²⁵ Cefadroxil 30 mg/kg once daily vs cefaclor 20 mg/kg TID	PRO, RCT Patients 3 to 21 years of age with clinical signs and symptoms of acute group A β -hemolytic streptococcal pharyngitis	N=250 10 days	Primary: Clinical evaluation, microbiologic evaluations Secondary: Adverse event	Primary: On day 14 (<i>P</i> =0.020) and days 21 to 28 (<i>P</i> =0.043), a greater number of patients treated with cefadroxil had good therapeutic response to therapy 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; no <i>P</i> value reported). Secondary: No significant drug-related adverse event reported.
Aujard et al ⁵¹ Cefuroxime suspension 20 mg/kg/day divided BID (maximum 500 mg/day; for 4 days) vs penicillin suspension 45 mg/kg/day divided TID (for 10 days)	MC, PRO, RCT Pediatric patients aged 2 to 15 years with group A β -hemolytic streptococcal pharyngitis	N=200 4 to 10 days	Primary: Clinical cure, microbiological cure Secondary: Adverse events	Primary: At two to four days post-treatment, clinical cure rates were reported as 94.8 and 96.1% of patients treated with cefuroxime and penicillin, respectively (<i>P</i> =NS). At two to four days post-treatment, microbiological eradication was reported as 87.6 and 87.4% in patients treated with cefuroxime and penicillin, respectively (<i>P</i> =NS); at 28 to 33 days post-treatment, microbiological eradication was reported as 94.4 and 91.9%, respectively (<i>P</i> =NS). Clinical success in terms of resolution of sore throat and dysphagia occurred more rapidly in patients treated with cefuroxime compared to penicillin (<i>P</i> =0.024 and <i>P</i> =0.027, respectively). Secondary: Both treatments were well tolerated. Drug-related adverse events were reported in 2.1 and 2.7% of patients treated with cefuroxime and penicillin, respectively (<i>P</i> =NS).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>McCarty²⁶</p> <p>Cefaclor 20 mg/kg/day divided TID (maximum, 750 mg/day)</p> <p>vs</p> <p>cefprozil 20 mg/kg/day once daily (maximum, 500 mg/day)</p> <p>vs</p> <p>cefprozil 15 mg/kg/day divided BID (maximum, 500 mg/day)</p> <p>vs</p> <p>erythromycin 30 mg/kg/day divided QID (maximum, 1,600 mg/day)</p> <p>vs</p> <p>penicillin 46 mg/kg/day divided TID (maximum, 780 mg/day)</p> <p>In study A, participants received either cefprozil once daily or penicillin.</p>	<p>MA (4 MC, RCTs)</p> <p>Patients 2 years of age and older with mild to moderate group A β-hemolytic streptococcal tonsillitis and pharyngitis</p>	<p>N=1,186</p> <p>10 days</p>	<p>Primary: Clinical efficacy, bacteriologic efficacy</p> <p>Secondary: Adverse events</p>	<p>Primary: In study A, clinical efficacy was reported as 89 and 74% in patients treated with cefprozil and penicillin, respectively; bacteriologic eradication was reported as 89 and 67%, respectively (<i>P</i> value not reported).</p> <p>In study B, clinical efficacy was reported as 93 and 90% in patients treated with cefprozil and cefaclor, respectively; bacteriologic eradication was reported as 95 and 94%, respectively (<i>P</i> value not reported).</p> <p>In study C, clinical efficacy was reported as 94 and 88% in patients treated with cefprozil and penicillin, respectively (<i>P</i> value not reported).</p> <p>In study D, clinical and bacteriologic efficacy was reported as 95% for both treatment groups (i.e., cefprozil and erythromycin; <i>P</i> values not reported).</p> <p>Secondary: There was no statistically significant difference in patients treated with any of the treatments in regards to adverse events. Adverse events were mostly gastrointestinal.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>In study B, participants received either cefprozil once daily or cefaclor.</p> <p>In study C, participants received either cefprozil BID or penicillin.</p> <p>In study D, participants received either cefprozil once daily or erythromycin.</p>				
<p>Esposito et al⁵²</p> <p>Erythromycin ethylsuccinate 15 mg/kg TID for 10 days</p> <p>vs</p> <p>cefaclor 25 mg/kg BID for 10 days</p> <p>vs</p> <p>amoxicillin/clavulanate 15 mg/kg TID for 10 days</p>	<p>RCT</p> <p>Patients 2 to 12 years of age with signs and symptoms of acute pharyngotonsillitis</p>	<p>N=245</p> <p>30 days</p>	<p>Primary: Clinical outcomes, bacteriologic outcomes</p> <p>Secondary: Not reported</p>	<p>Primary: On day 10, clinical cure and microbiologic eradication was observed in 91.9% of patients in the cefaclor group, 90.5% of patients in the amoxicillin/clavulanate group, and 76.8% of patients in the erythromycin group.</p> <p>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.</p> <p>The clinical and bacteriologic cure rates were significantly higher in the cefaclor and amoxicillin/clavulanate groups compared to the erythromycin group ($P<0.05$).</p> <p>Secondary: Not reported</p>
Pneumonia/Lower Respiratory Tract Infections				
<p>Ball²⁷</p> <p>Cefaclor 500 mg TID</p> <p>vs</p> <p>cefprozil 500 mg BID to</p>	<p>Series of 4 MC, RCT trials</p> <p>Patients 18 years of age and older with mild to</p>	<p>N=1,352</p> <p>10 days of therapy</p>	<p>Primary: Clinical response, bacteriologic response</p> <p>Secondary: Not reported</p>	<p>Primary: For acute bronchitis: clinical response was observed in 88% of cefprozil patients and 88% of cefaclor patients. Successful bacteriologic eradication occurred in 86 and 82% of patients respectively (P values not reported).</p> <p>For acute exacerbations of chronic bronchitis: clinical response was observed in 80% of cefprozil patients and 62% of cefaclor patients ($P=0.067$). Successful</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
TID vs cefuroxime 500 mg BID vs amoxicillin/clavulanate 500 mg TID	moderate respiratory tract infections			bacteriologic eradication occurred in 62 and 74% of patients respectively (<i>P</i> values not reported). For pneumonia: clinical response was observed in 82% of cefprozil patients and 79% of cefaclor patients. Successful bacteriologic eradication occurred in 82 and 71% of patients respectively (<i>P</i> values not reported). In the comparison of cefprozil to cefuroxime, clinical response was observed in 95% of cefprozil patients and 84% of cefuroxime patients. Successful bacteriologic eradication occurred in 100 and 75% of patients respectively (<i>P</i> =0.03). In the comparison of cefprozil to amoxicillin/clavulanate, no significant differences between clinical or bacteriological responses were observed. Secondary: Not reported
Schleupner et al ²⁸ Cefuroxime 250 mg BID vs cefuroxime 500 mg BID vs cefaclor 500 mg TID	RCT Patients 12 years of age and older with evidence of a lower respiratory tract infection	N=69 10 days	Primary: Clinical response, bacteriological response Secondary: Not reported	Primary: No significant difference was observed between groups in clinically cured and improved patients (<i>P</i> value not reported). Bacteriologic cure rates were 80% for cefuroxime 250 mg, 93% for cefuroxime 500 mg and 60% for cefaclor patients, respectively (<i>P</i> values not reported). Secondary: Not reported
Casali et al ²⁹ (abstract) Cefaclor advanced formulation 750 mg BID vs	DB, DD, MC, PG, RCT Patients with lobar pneumonia or broncho-pneumonia	N=266 10 to 14 days of treatment	Primary: Clinical response, bacteriological response Secondary: Not reported	Primary: No significant differences were observed between groups in favorable clinical response (92.5% for cefaclor advanced formulation and 95.6% for cefaclor). No significant differences were observed between groups in proven or presumed pathogen elimination (87.5% for cefaclor advanced formulation and 86.7% for cefaclor).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
cefaclor 500 mg TID				Secondary: Not reported
Zeluff et al ³⁰ Cefadroxil 1 g every 12 hours vs cefaclor 500 mg every 8 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 (no <i>P</i> values were reported). Microbiologic cure was reported in 98 and 96% of patients treated with cefadroxil and cefaclor, respectively (no <i>P</i> values were reported). 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 ³¹ Cefaclor 500 mg TID vs cefdinir 300 mg BID	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 (<i>P</i> =NS). Secondary: Patients treated with cefdinir reported a higher incidence of diarrhea compared to patients treated with cefaclor (13.7 vs 5.3%, respectively; <i>P</i> <0.001).
Skin and Soft Tissue Infections				
Parish et al ³² (abstract) Cefaclor 250 mg TID (or 20 mg/kg/day in 3 divided doses) vs cefprozil 500 mg once daily (or 20 mg/kg/day)	MC, RCT Patients 2 to 99 years of age with skin or skin structure infections	N=422 5 to 10 days of treatment	Primary: Clinical response, pathogen eradication Secondary: Not reported	Primary: Satisfactory clinical response was observed in 92% of patients in the cefaclor group and 93% of patients in the cefprozil group (<i>P</i> value not reported). Pathogens were eradicated in 89% of patients in the cefaclor group and 91% of patients in the cefprozil group (<i>P</i> value not reported). Secondary: Not reported
Faingezicgt et al ³³ Cefaclor 20 mg/kg/day divided TID	PRO, RCT Patients 2 to 12 years of age	N=89 10 days of treatment	Primary: Clinical response Secondary:	Primary: No significant differences were observed between groups in time to clinical cure (average 4.2 days for cefprozil and 4.3 days for cefaclor; <i>P</i> =0.70).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs cefprozil 20 mg/kg/day given once daily	with mild to moderate skin and soft tissue infections		Not reported	No therapeutic failures or relapses were observed in either group. Secondary: Not reported
Parish et al ³⁴ Cefuroxime 250 mg BID vs cefuroxime 500 mg BID vs cefaclor 250 mg TID	MC, OL, RCT Patients 10 to 84 years of age with primary or secondarily infected dermatoses	N=125 3 days post-treatment	Primary: Clinical response, bacteriological response Secondary: Not reported	Primary: No significant differences were observed between groups in rates of clinical cure, improvement or failure (<i>P</i> value not reported). No significant differences were observed between groups in rates of bacteriological eradication (<i>P</i> value not reported). Secondary: Not reported
Ballantyne et al ³⁵ Cefadroxil 1,000 mg once daily vs cefaclor 250 mg TID	OL, RCT Black patients 6 to 80 years of age with skin and soft-tissue infections	N=200 10 days	Primary: Clinical/ 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; <i>P</i> =0.41). However, 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; no <i>P</i> value reported). Secondary: Not reported
Stevens et al ³⁶ Cefaclor 500 mg TID vs cefpodoxime 400 mg BID vs	DB, MC, PC, RCT Patients 12 years of age and older with acute single-site skin or skin-structure infections	N=371 7 to 10 days	Primary: Clinical efficacy and safety Secondary; Not reported	Primary: High pathogen eradication rates were observed for patients treated with either cefaclor or cefpodoxime (98 vs 99%, respectively; <i>P</i> value not reported). Patients with infected wounds responded better to cefpodoxime compared to cefaclor (100 vs 83%, respectively; <i>P</i> value not reported). Patients treated with cefaclor reported a higher failure rate compared to patients treated with cefpodoxime (4 vs 1%, respectively; <i>P</i> =NS). Both active drug regimens were well tolerated. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>placebo BID to TID</p>				
<p>Jacobs et al³⁷</p> <p>Cefuroxime 30 mg/kg/day divided every 12 hours</p> <p>vs</p> <p>cefadroxil 30 mg/kg/day divided every 12 hours</p>	<p>Investigator-blinded, MC, RCT</p> <p>Patients 3 months to 12 years of age with skin or skin structure infections</p>	<p>N=238</p> <p>Up to 20 days post-treatment</p>	<p>Primary: Clinical response, bacteriological response</p> <p>Secondary: Not reported</p>	<p>Primary: Satisfactory clinical response was observed in 97.8 and 90.3% of cefuroxime and cefadroxil patients, respectively ($P=0.009$). When all patients were included in an ITT analysis, the difference between cefuroxime and cefadroxil was no longer significant (81.5 and 78.6%, respectively; $P=0.50$)</p> <p>Satisfactory bacteriological response was observed in 97.1 and 94.3% of cefuroxime and cefadroxil patients, respectively ($P=0.242$). When all patients were included in an ITT analysis, satisfactory responses occurred in 70.9 and 68.4%, respectively ($P=0.625$).</p> <p>Secondary: Not reported</p>
<p>Bucko et al³⁸</p> <p>Cefadroxil 500 mg BID</p> <p>vs</p> <p>cefditoren 200 mg BID</p> <p>vs</p> <p>cefditoren 400 mg BID</p> <p>vs</p> <p>cefuroxime 250 mg BID</p> <p>In study A, participants received cefditoren 200 mg or cefuroxime; in study B, participants received cefditoren 400</p>	<p>MA (2 DB, MC, PG)</p> <p>Patients with uncomplicated skin and skin structure infections</p>	<p>N=1,685</p> <p>10 days</p>	<p>Primary: Clinical evaluation, microbiologic evaluation</p> <p>Secondary: Adverse events</p>	<p>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 (no P values reported).</p> <p>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 one ($P=0.043$). At seven to 14 days after treatment completion, eradication rates were higher for cefditoren 400 mg compared to patients treated with cefadroxil in study two ($P=0.018$).</p> <p>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.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg or cefadroxil.				
Gooch et al ³⁹ Cefadroxil 500 mg BID vs cephalexin 500 mg BID vs cefuroxime 250 mg 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).
Montero ⁵³ Azithromycin 10 mg/kg once daily for 3 days vs cefaclor 20 mg/kg/day in 3 divided doses for 10 days	MC, OL, RCT Patients 6 months to 12 years of age with skin and/or soft tissue infections	N=200 10 days	Primary: Clinical response, bacteriologic response Secondary: Not reported	Primary: The clinical efficacy was comparable between treatment groups (94% in the azithromycin group and 95% in the cefaclor group; P values not reported). In the azithromycin group, 95% of pathogens were eradicated and 99% of pathogens were eradicated in the cefaclor group (P value not reported). Secondary: Not reported
Sinusitis				
Gehanno et al ⁴⁰ Cefaclor 500 mg TID vs cefpodoxime 200 mg 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% of 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; P value not reported.
Adelglass et al ⁵⁴	MC, OL, RCT	N=219	Primary: Satisfactory clinical	Primary; At day 10, satisfactory clinical response was reported in 84.5 and 89.9% of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Cefprozil 500 mg BID vs amoxicillin/clavulanate 500/125 mg TID	Patients 13 years of age and older with severe acute bacterial sinusitis	10 days	response Secondary: Adverse events	patients taking cefprozil and amoxicillin/clavulanate, respectively ($P=NS$). Two weeks post treatment, satisfactory clinical responses were reported as 80.8 and 81.0% of patients taking cefprozil and amoxicillin/clavulanate, respectively ($P=NS$). Relapse was reported in 3.1 and 8.6% of patients taking cefprozil and amoxicillin/clavulanate, respectively ($P=NS$). Secondary: More patients taking amoxicillin/clavulanate reported adverse events compared to patients taking cefprozil ($P<0.001$); adverse events included diarrhea ($P<0.001$), nausea ($P<0.042$), and rash ($P<0.035$).
Camacho et al ⁵⁵ Cefuroxime 250 mg BID vs amoxicillin/clavulanate 500 mg TID	DB, MC, PG, RCT Patients 18 years of age and older with acute bacterial maxillary sinusitis with a duration <30 days	N=239 10 days	Primary: Clinical efficacy, bacteriologic efficacy Secondary: Adverse events	Primary: Clinical efficacy was reported as 85 and 82% of patients treated with cefuroxime or amoxicillin/clavulanate, respectively ($P=0.446$). Bacteriologic efficacy was reported as 84 and 87% of patients treated with cefuroxime and amoxicillin/clavulanate, respectively ($P=0.567$). Secondary: Drug-related adverse events were reported as 3 and 13% of patients treated with cefuroxime and amoxicillin/clavulanate, respectively ($P=0.001$), particularly for diarrhea (1 vs 3%, respectively; $P=0.001$).
Surgical Prophylaxis				
Song et al ⁵⁶ Cefuroxime plus metronidazole vs gentamicin plus metronidazole vs first generation or second generation	MA MA of 147 relevant RCTs published between 1984 and 1995	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,

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
cephalosporin vs third generation cephalosporin vs other antibiotic agents as mono or combination therapy				1.07; 95% CI, 0.54 to 2.12). Secondary: Not reported
Urinary Tract Infections				
Leigh et al ⁴¹ Cefaclor 250 mg TID vs cefdinir 100 mg BID	DB, MC, PG, RCT Patients 13 years of age and older 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 treatment with cefdinir (6.7 vs 3.7%, respectively; $P<0.003$). Isolates of <i>E coli</i> were more resistant to treatment with cefaclor compared to treatment with 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%, 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 ⁴² Cefaclor 250 mg TID vs cefprozil 500 mg once daily	OL, RCT Patients 18 years of age and older with acute, uncomplicated urinary tract infections	N=98 10 days	Primary: Clinical efficacy, bacteriologic efficacy Secondary: Adverse events	Primary: Clinical efficacy was reported as 87 and 78% of patients treated with cefprozil and cefaclor, respectively ($P=NS$). Bacteriologic eradication was reported as 80 and 82% of 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 was not statistically significant ($P=0.08$ and $P=0.07$, respectively).
Iravani ⁴³	RCT	N=108	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Cefaclor 250 mg TID vs cefprozil 500 mg once daily	Female patients 18 years of age and older with symptoms of acute urinary tract infections	10 days 5 to 9 days post-therapy	Clinical response, bacteriological response Secondary: Not reported	Clinical cure rates were 94% in both the cefaclor and cefprozil groups (<i>P</i> value not significant). Bacteriological cure rates were 94% in the cefaclor group and 93% in the cefprozil group (<i>P</i> value not significant). Secondary: Not reported
Cooper et al ⁴⁴ Cefuroxime 125 mg BID vs cephradine* 500 mg BID	PRO, RCT Patients 17 years of age and older with dysuria or frequency and diagnosed urinary tract infections	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 (<i>P</i> <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 (<i>P</i> >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; <i>P</i> <0.05).

*Agent not available in the United States.

Drug regimen abbreviations: BID=twice daily, QID=four times daily, TID=three times daily

Study abbreviations: CI=confidence interval, DB=double blind, DD=double-dummy, ITT=intent-to-treat analysis, MA=meta-analysis, MC=multi-center, NB=non-blinded, NS=non-significant, OL=open label, PC=placebo controlled, PG=parallel group, PRO=prospective, SB=single blinded, RCT=randomized controlled trial

Miscellaneous abbreviations: COPD=chronic obstructive pulmonary disease

Special Populations**Table 6. Special Populations**⁴⁻⁹

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Cefaclor	No dosage adjustment required in the elderly. Safety and efficacy have not been established in children <1 month of age.	No dosage adjustment required.	No dosage adjustment required.	B	Yes
Cefaclor extended-release	No dosage adjustment required in the elderly. Safety and efficacy have not been established in children <16 years of age.	Hemodialysis shortens half-life by 25 to 30%. Excretion pathways in patients with markedly impaired renal function have not been established.	No dosage adjustment required.	B	Yes
Cefprozil	No dosage adjustment required in the elderly. Safety and efficacy in children <6 months of age have not been established.	Administer 50% of the standard dose in patients with creatinine clearance 0 to 29 mL/minute; administer after the completion of hemodialysis.	No dosage adjustment required.	B	Yes
Cefuroxime	No dosage adjustment required in the elderly. Approved for use in children three months to 12 years of age for acute bacterial maxillary sinusitis.	Safety and efficacy have not been established in patients with renal failure.	No dosage adjustment required.	B	Yes

Adverse Drug Events**Table 7. Adverse Drug Events (%)**⁴⁻⁹

Adverse Event	Cefaclor	Cefaclor Extended-Release	Cefprozil	Cefuroxime
Cardiovascular				
Chest pain	-	>0.1<1.0	-	>0.1<1.0
Congestive heart failure	-	>0.1<1.0	-	-
Hypotension	✓	✓	-	-
Palpitation	-	>0.1<1.0	-	-
Syncope	✓	✓	-	-
Tachycardia	-	-	-	>0.1<1.0

Adverse Event	Cefaclor	Cefaclor Extended-Release	Cefprozil	Cefuroxime
Vasodilation	✓	✓	-	-
Central Nervous System				
Agitation	✓	-	-	-
Anxiety	-	>0.1<1.0	-	-
Asthenia	✓	-	-	-
Confusion	✓	✓	<1	-
Dizziness	✓	>0.1<1.0	1	>0.1<1.0
Fever	✓	>0.1<1.0	✓	>0.1<1.0
Hallucinations	✓	-	-	-
Headache	-	4.9	<1	>0.1<1.0
Hyperactivity	✓	✓	<1	>0.1<1.0
Hypertonia	✓	✓	-	-
Insomnia	✓	>0.1<1.0	<1	-
Irritable behavior	-	-	-	>0.1<1.0
Nervousness	✓	>0.1<1.0	<1	-
Paresthesias	✓	✓	-	-
Seizures	✓	-	✓	✓
Sleepiness	-	-	-	>0.1<1.0
Somnolence	✓	>0.1<1.0	<1	>0.1<1.0
Tremor	-	>0.1<1.0	-	-
Vertigo	-	✓	-	-
Dermatological				
Diaper rash	-	-	1.5	3.4
Erythema	-	-	-	>0.1<1.0
Erythema multiforme	✓	✓	✓	✓
Hives	-	-	-	>0.1<1.0
Maculopapular rash	-	>0.1<1.0	-	-
Pruritis	✓	1.4	-	>0.1<1.0
Rash	✓	>0.1<1.0	0.9	>0.1<1.0
Stevens-Johnson syndrome	✓	✓	✓	✓
Toxic epidermal necrolysis	✓	✓	✓	✓
Urticaria	✓	>0.1<1.0	0.1	✓
Gastrointestinal				
Abdominal cramps	-	-	-	>0.1<1.0
Abdominal pain	✓	1.6	1	>0.1<1.0
Colitis	-	-	✓	-
Constipation	-	>0.1<1.0	-	-
Diarrhea	✓	3.8	2.9	3.7 to 8.6
Dislike taste	-	-	-	5
Dyspepsia	-	>0.1<1.0	-	>0.1<1.0
Flatulence	-	>0.1<1.0	-	>0.1<1.0
Gastritis	-	>0.1<1.0	-	-
Gastrointestinal infection	-	-	-	>0.1<1.0
Indigestion	-	-	-	>0.1<1.0
Mouth ulcers	-	-	-	>0.1<1.0
Nausea/vomiting	✓	3.4	1.0 to 3.5	2.6 to 6.8
Pseudomembranous colitis	✓	-	✓	✓
Genitourinary				
Dysmenorrhea	-	>0.1<1.0	-	-
Dysuria	-	>0.1<1.0	-	>0.1<1.0
Genital moniliasis	✓	2.2	-	>0.1<1.0

Adverse Event	Cefaclor	Cefaclor Extended-Release	Cefprozil	Cefuroxime
Genital pruritus	✓	✓	1.6	>0.1<1.0
Menstrual disorder	-	>0.1<1.0	-	-
Nocturia	-	>0.1<1.0	-	-
Urethral bleeding and pain	-	-	-	>0.1<1.0
Urinary tract infection	-	-	-	>0.1<1.0
Vaginal discharge	-	-	-	>0.1<1.0
Vaginal irritation	-	-	-	>0.1<1.0
Vaginitis	✓	2.4	1.6	>0.1<1.0
Vulvar itch	-	-	-	>0.1<1.0
Hematological				
Agranulocytosis	✓	-	✓	✓
Aplastic anemia	✓	-	✓	✓
Eosinophilia	✓	✓	2.3	1.1
Hemolytic anemia	✓	✓	✓	✓
Hemorrhage	✓	-	✓	✓
Leukopenia	✓	✓	0.2	✓
Leukorrhea	-	>0.1<1.0	-	-
Lymphocytosis	✓	-	-	-
Neutropenia	✓	✓	✓	✓
Pancytopenia	✓	-	✓	✓
Positive Coomb's test	✓	✓	✓	>0.1<1.0
Prothrombin time increased	✓	-	✓	✓
Thrombocytopenia	✓	✓	✓	✓
Hepatic				
Cholestatic jaundice	✓	-	✓	✓
Cholestasis	-	✓	-	✓
Elevated liver enzymes	✓	✓	<0.1 to 2.0	1 to 2
Hepatic dysfunction	-	✓	-	✓
Hepatitis, transient	✓	-	-	-
Musculoskeletal				
Arthritis	✓	✓	-	-
Arthralgia	✓	>0.1<1.0	-	>0.1<1.0
Back pain	-	1	-	-
Joint swelling	-	-	-	>0.1<1.0
Muscle cramps	-	-	-	>0.1<1.0
Muscle spasm, neck	-	-	-	>0.1<1.0
Muscle stiffness	-	-	-	>0.1<1.0
Myalgia	-	>0.1<1.0	-	-
Neck pain	-	>0.1<1.0	-	-
Renal				
BUN increased	✓	-	0.1	✓
Creatinine increased	✓	-	0.1	✓
Interstitial nephritis, reversible	✓	✓	-	-
Kidney pain	-	-	-	>0.1<1.0
Renal insufficiency	✓	-	✓	✓
Toxic nephropathy	✓	-	✓	✓
Respiratory				
Asthma	-	>0.1<1.0	-	-
Bronchitis	-	>0.1<1.0	-	-
Cough	-	1.5	-	>0.1<1.0

Adverse Event	Cefaclor	Cefaclor Extended-Release	Cefprozil	Cefuroxime
Dyspnea	✓	-	-	-
Lung disorder	-	>0.1<1.0	-	-
Pharyngitis	-	1.4	-	-
Respiratory disorder	-	>0.1<1.0	-	-
Rhinitis	-	3.9	-	-
Shortness of breath	-	-	-	>0.1<1.0
Sinusitis	-	-	-	>0.1<1.0
Upper respiratory infection	-	-	-	>0.1<1.0
Miscellaneous				
Accidental injury	-	>0.1<1.0	-	-
Anaphylaxis	✓	✓	✓	✓
Angioedema	✓	✓	✓	✓
Anorexia	-	>0.1<1.0	-	>0.1<1.0
Candidiasis	-	-	-	>0.1<1.0
Chills	-	>0.1<1.0	-	>0.1<1.0
Conjunctivitis	-	>0.1<1.0	-	-
Ear pain	-	>0.1<1.0	-	-
Edema	✓	>0.1<1.0	-	-
Flu syndrome	-	>0.1<1.0	-	-
Infection	-	>0.1<1.0	-	-
Lockjaw-type reaction	-	-	-	>0.1<1.0
Malaise	-	>0.1<1.0	-	-
Otitis media	-	>0.1<1.0	-	-
Peripheral edema	-	>0.1<1.0	-	-
Ptyalism	-	-	-	>0.1<1.0
Serum sickness-like reaction	✓	✓	✓	✓
Superinfection	✓	-	1.5	-
Surgical procedure	-	>0.1<1.0	-	-
Sweating	-	>0.1<1.0	-	-
Swollen tongue	-	-	-	>0.1<1.0
Thirst	-	-	-	>0.1<1.0
Viral illness	-	-	-	>0.1<1.0

✓ Percent not specified.

- Event not reported.

Contraindications/Precautions

The second generation cephalosporins are contraindicated in patients with a known allergy to the cephalosporin group of antibiotics.⁴⁻⁹

Before therapy with a second generation cephalosporin is initiated, careful inquiry should be made to determine whether the patient has had previous hypersensitivity reactions to cephalosporins, penicillins or other drugs. If a second generation cephalosporin is to be given to penicillin-sensitive patients, caution should be exercised because cross-sensitivity among β -lactam antibiotics has been clearly documented and may occur in up to 10% of patients with a history of penicillin allergy. If an allergic reaction occurs, discontinue the drug. Serious acute hypersensitivity reactions may require treatment with epinephrine and other emergency measures including oxygen, intravenous fluids, intravenous antihistamines, corticosteroids, pressor amines, and airway management as clinically indicated.⁴⁻⁹

Clostridium difficile associated diarrhea (CDAD) has been reported with the use of almost all antibacterial agents, ranging in severity from mild diarrhea to fatal colitis. *C. difficile* produces toxins A and B which contribute to the development of CDAD. These strains may increase morbidity and mortality as these infections may be refractory to antimicrobial therapy and may require colectomy. CDAD should be

considered in all patients who present with diarrhea after antibiotic use. Careful medical history is required as CDAD may occur over two months after administration of antibiotics. If CDAD is suspected or confirmed, ongoing antibiotics not intended to treat CDAD may have to be discontinued. Appropriate management, including fluid and electrolyte management, protein supplementation, antibiotic therapy active against CDAD and surgery should be initiated as appropriate.⁴⁻⁹

Prolonged administration may result in an overgrowth of non-susceptible organisms.⁴⁻⁹

The second generation cephalosporins should not be prescribed in the absence of a confirmed or strongly suspected bacterial infection or prophylactic indication. This may lead to the development of drug-resistant bacteria.⁴⁻⁹

The second generation cephalosporins should be used with caution in patients with markedly impaired renal function. Careful monitoring and laboratory testing is recommended.⁴⁻⁹

The second generation cephalosporins should be used with caution in patients with a history of gastrointestinal disease and/or colitis.⁴⁻⁹

Cephalosporins may be associated with a fall in prothrombin activity. Renal or hepatic impairment, poor nutritional state, patients receiving a protracted course of antibiotic therapy and patients previously stabilized on anticoagulant therapy are at an increased risk. Prothrombin time should be monitored in patients at risk.⁴⁻⁹

Cephalosporins have been associated with positive direct Coomb's tests. It should be recognized that a positive Coomb's test may be due to the drug.⁴⁻⁹

Patients receiving cefaclor, cefprozil or cefuroxime may show false-positive reactions for glucose in the urine with tests that use Benedict's and Fehling's solutions and also with Clinitest[®] tablets.⁴⁻⁹

Drug Interactions

Table 8. Drug Interactions⁵⁷

Drug	Interaction	Mechanism
Cefuroxime	Aminoglycosides	Nephrotoxicity may be increased. Monitor aminoglycoside levels and renal function.

Dosage and Administration

Table 9. Dosing and Administration⁴⁻⁹

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Cefaclor	<p><u>Infections (skin and skin structure infections, urinary tract infections, pharyngitis and/or tonsillitis, and respiratory tract infections, lower):</u> 250 mg every 8 hours</p> <p><u>Severe infections (such as pneumonia) or those caused by less susceptible organisms:</u> 500 mg every 8 hours</p>	<p><u>Infections (skin and skin structure infections, urinary tract infections, pharyngitis and/or tonsillitis, and respiratory tract infections, lower):</u> 20 mg/kg/day in divided doses every 8 hours</p> <p><u>Serious infections, otitis media, or infections caused by less susceptible organisms:</u> 40 mg/kg/day in divided doses every 8 hours; maximum 1 g/day</p>	Capsule: 250 mg 500 mg

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
		Safety and efficacy have not been established in children <1 month of age.	
Cefaclor extended-release	<u>Acute bacterial exacerbations of chronic bronchitis and secondary bacterial infections of acute bronchitis:</u> 500 mg every 12 hours <u>Pharyngitis and/or tonsillitis:</u> 375 mg every 12 hours <u>Uncomplicated skin and skin structure infections:</u> 375 mg every 12 hours	Safety and efficacy have not been established in children <16 years of age.	Extended-release tablet: 500 mg*
Cefprozil	<u>Acute sinusitis:</u> 250 to 500 mg every 12 hours <u>Pharyngitis and/or tonsillitis:</u> 500 mg once daily <u>Secondary bacterial infection of acute bronchitis or acute bacterial exacerbation of chronic bronchitis:</u> 500 mg every 12 hours <u>Skin and skin structure infections:</u> 250 to 500 mg every 12 hours or 500 mg once daily	<u>Acute sinusitis in children six months to 12 years of age:</u> 7.5 to 15 mg/kg every 12 hours <u>Pharyngitis and/or tonsillitis in children two to 12 years of age:</u> 7.5 mg/kg every 12 hours <u>Skin and skin structure infections in children two to 12 years of age:</u> 20 mg/kg every 24 hours <u>Otitis media in children six months to 12 years of age:</u> 15 mg/kg every 12 hours	Powder for oral suspension: 125 mg/5 mL 250 mg/5 mL Tablet: 250 mg 500 mg
Cefuroxime†	<u>Acute bacterial exacerbations of chronic bronchitis, secondary bacterial infections of acute bronchitis and skin and skin structure infections:</u> Tablet: 250 to 500 mg twice daily <u>Acute sinusitis, pharyngitis and/or tonsillitis and uncomplicated urinary tract infections:</u> Tablet: 250 mg twice daily <u>Lyme disease, early:</u> Tablet: 500 mg twice daily <u>Gonorrhea, uncomplicated:</u> Tablet: 1,000 mg as a single dose	<u>Acute otitis media, acute sinusitis and impetigo in children three months to 12 years of age:</u> Powder for suspension: 30 mg/kg/day divided twice daily; maximum 500 mg <u>Pharyngitis and/or tonsillitis in children three months to 12 years of age:</u> Powder for suspension: 20 mg/kg/day divided twice daily; maximum 1,000 mg <u>Acute otitis media and acute sinusitis:</u> Tablet: 250 mg twice daily	Powder for oral suspension: 125 mg/5 mL 250 mg/5 mL Tablet: 250 mg 500 mg

*500 mg every 12 hours of cefaclor extended-release is clinically equivalent to 250 mg three times daily of cefaclor immediate-release capsules. 500 mg every 12 hours is not equivalent to 500 mg three times daily of other cefaclor formulations.

†Cefuroxime tablets and cefuroxime for oral suspension are not bioequivalent and are not substitutable on a mg-per-mg basis.

Clinical Guidelines

The clinical guidelines contained in Table 10 are summarized globally and are not limited to the role of the second generation cephalosporins. However, the summary of the Chronic Obstructive Pulmonary Disease (COPD) guidelines focuses only on the treatment of exacerbations which have a bacterial component. The global treatment strategy for COPD is not discussed in this summary.

Table 10. Clinical Guidelines

Clinical Guideline	Recommendations
<p>Infectious Diseases Society of America/ American Thoracic Society: Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults (2007)⁵⁸</p>	<p><u>General recommendations</u></p> <ul style="list-style-type: none"> • Selection of antimicrobial regimens for empirical therapy is based on prediction of the most likely pathogens(s) and knowledge of local susceptibility patterns. • Once the etiology of community acquired pneumonia has been identified via microbiological testing, antimicrobial therapy should be directed at that pathogen. <p><u>Empiric therapy - outpatient treatment</u></p> <ul style="list-style-type: none"> • For previously healthy patients with no risk factors for drug resistant <i>Streptococcus pneumoniae</i> infection, a macrolide (azithromycin, clarithromycin, or erythromycin) can be used. Doxycycline may also be an alternate option. • A respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin) is the treatment option in regions with a high rate of macrolide-resistant <i>S pneumoniae</i>, or for patients with comorbidities, such as chronic heart, lung, liver or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressive conditions or use of immunosuppressive drugs. Fluoroquinolones may also be used for patients who have used antimicrobials within the previous three months. Other preferred options for these patients would be the combination of a β-lactam (ceftriaxone, cefpodoxime, or cefuroxime) plus a macrolide or doxycycline, or amoxicillin/clavulanate. <p><u>Empiric therapy - inpatient, non-intensive care unit treatment</u></p> <ul style="list-style-type: none"> • A respiratory fluoroquinolone or a combination of a β-lactam plus a macrolide is recommended. • Preferred β-lactam agents include cefotaxime, ceftriaxone, and ampicillin; ertapenem may also be used for selected patients. • A respiratory fluoroquinolone should be used for penicillin allergic patients. <p><u>Empiric therapy - inpatient, intensive care unit treatment</u></p> <ul style="list-style-type: none"> • A β-lactam (cefotaxime, ceftriaxone, or ampicillin/sulbactam) plus either azithromycin or a respiratory fluoroquinolone. • For penicillin-allergic patients, a respiratory fluoroquinolone and aztreonam are recommended. • For <i>Pseudomonas</i> infection, use an antipseudomonal, antipseudomonal β-lactam (piperacillin/tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin. • The antipseudomonal, antipseudomonal β-lactams listed above can also be used with either an aminoglycoside and azithromycin, or an aminoglycoside and an antipseudomonal fluoroquinolone. • For penicillin-allergic patients, substitute aztreonam for the above β-lactam for <i>Pseudomonas</i> infection.

Clinical Guideline	Recommendations
	<p><u>Pathogen-directed therapy</u></p> <ul style="list-style-type: none"> • <i>S pneumonia</i> (penicillin non-resistant)- penicillin G or amoxicillin preferred; alternative agents include macrolides, cephalosporins (oral cefpodoxime, cefprozil, cefuroxime, cefdinir, cefditoren or parenteral cefuroxime, ceftriaxone or cefotaxime), clindamycin, doxycycline or a respiratory fluoroquinolone. • <i>S pneumonia</i> (penicillin resistant)- agents chosen based on susceptibility; alternative agents include vancomycin, linezolid and high-dose amoxicillin (3 g/day). • <i>Haemophilus influenza</i> (non-β-lactamase producing)- amoxicillin preferred; alternative agents include fluoroquinolone, doxycycline, azithromycin, clarithromycin. • <i>H influenza</i> (β-lactamase producing)- second- or third-generation cephalosporin or amoxicillin/clavulanate preferred; alternative agents include fluoroquinolone, doxycycline, azithromycin, clarithromycin. • <i>Mycoplasma pneumonia/Chlamydia pneumonia</i>- macrolide, tetracycline preferred; alternative agent is fluoroquinolone. • <i>Legionella</i> species- fluoroquinolone, azithromycin preferred; alternative agent is doxycycline. • <i>Chlamydia psittaci</i>- tetracycline preferred; alternative agent is a macrolide. • <i>Coxiella burnetii</i>- tetracycline preferred; alternative agent is a macrolide. • <i>Francisella tularensis</i>- doxycycline preferred; alternative agents include gentamicin or streptomycin. • <i>Yersinia pestis</i>- streptomycin, gentamicin recommended; alternative agents include doxycycline or fluoroquinolone. • <i>Bacillus anthracis</i> (inhalation)- ciprofloxacin, levofloxacin, doxycycline preferred (usually with a second agent); alternative agents include other fluoroquinolones, rifampin, clindamycin, chloramphenicol, or a β-lactam if susceptible. • <i>Enterobacteriaceae</i>- third generation cephalosporin, carbapenem; alternative agents include a β-lactam/β-lactamase inhibitor or a fluoroquinolone. • <i>Pseudomonas aeruginosa</i>- antipseudomonal β-lactam plus ciprofloxacin or levofloxacin or aminoglycoside preferred; alternative agents include aminoglycoside plus ciprofloxacin or levofloxacin. • <i>Burkholderia pseudomallei</i>- carbapenem, ceftazidime preferred; alternative agents include fluoroquinolone or sulfamethoxazole/trimethoprim (SMX/TMP). • <i>Acinetobacter</i> species- carbapenem preferred; alternative agents include cephalosporin and aminoglycoside, ampicillin/sulbactam, colistin. • <i>Staphylococcus aureus</i> (methicillin susceptible)- antistaphylococcal penicillin preferred; alternative agents include cefazolin and clindamycin. • <i>S aureus</i> (methicillin resistant)- vancomycin or linezolid preferred; alternative agent is SMX/TMP. • <i>Bordetella pertussis</i>- macrolide preferred; alternative agent is SMX/TMP. • Anaerobe (aspiration)- β-lactam/β-lactamase inhibitor or clindamycin preferred; alternative agent is carbapenem.

Clinical Guideline	Recommendations
	<ul style="list-style-type: none"> • Influenza virus- oseltamivir or zanamivir preferred. • <i>Mycobacterium tuberculosis</i>- isoniazid plus rifampin plus ethambutol plus pyrazinamide preferred. • <i>Coccidioides</i> species- no therapy generally recommended in normal host for uncomplicated infection; if therapy desired, itraconazole or fluconazole preferred; alternative agent is amphotericin B. • <i>Histoplasmosis</i>- itraconazole preferred; alternative agent is amphotericin B. • <i>Blastomycosis</i>- itraconazole preferred; alternative agent is amphotericin B. • Suspected H1N1 pandemic influenza should be treated with oseltamivir and antibacterial agents targeting <i>S pneumonia</i> and <i>S aureus</i>.
<p>American College of Chest Physicians: Management of Community-Acquired Pneumonia in the Home: An American College of Chest Physicians Clinical Position Statement (2005)⁵⁹</p>	<ul style="list-style-type: none"> • The oral route for medications is recommended if the patient can tolerate it, and if the availability and activity of the agents are adequate. • Severity of illness, patient age, comorbidities, concomitant medications, and ease of administration are all factors that can impact the empiric treatment decision. • The use of a macrolide, doxycycline, or fluoroquinolone antibacterial agent is recommended by both the Infectious Disease Society of America and the American Thoracic Society consensus guidelines as appropriate empiric outpatient treatment for low-risk patients. • Amoxicillin/clavulanate and some second generation cephalosporins (cefuroxime, cefpodoxime, or cefprozil) are alternatives for low-risk patients. • A patient who is at high risk either because of complicated comorbidities or extensive prior antibiotic use may be a candidate for treatment with a β-lactam/macrolide combination or an antipneumococcal fluoroquinolone. • Double therapy with either a β-lactam/macrolide combination or a β-lactam/antipneumococcal fluoroquinolone should be considered in patients who would normally be considered for intensive care unit admission but have chosen to remain in the home.
<p>Infectious Diseases Society of America/ American Thoracic Society: Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia (2004)⁶⁰</p>	<ul style="list-style-type: none"> • Empiric therapy for hospital-acquired pneumonia, ventilator-associated pneumonia and healthcare-associated pneumonia should include agents from a different class than the patient has recently received. • Judicious use of combination therapy in hospital-acquired pneumonia for a specific pathogen is recommended with consideration of short-duration (five days) aminoglycoside therapy when used in combination with β-lactam to treat <i>P aeruginosa</i> pneumonia. • De-escalation of antibiotics should be considered once results are available of lower respiratory tract cultures and patient's clinical response. • For patients with uncomplicated hospital-acquired pneumonia, ventilator-associated pneumonia or healthcare-associated pneumonia who have received initially appropriate therapy and have had a good clinical response with no evidence of infection with nonfermenting gram-negative bacilli, a shorter duration of antibiotic therapy (seven to eight days) is recommended. • The following initial empiric therapy is recommended for hospital-

Clinical Guideline	Recommendations
	<p>acquired pneumonia or ventilator-associated pneumonia in patients with early onset of disease, no known risk factors for multidrug-resistant pathogens and any disease severity: ceftriaxone, levofloxacin, moxifloxacin, ciprofloxacin, ampicillin/sulbactam or ertapenem.</p> <ul style="list-style-type: none"> The following initial empiric therapy is recommended for hospital-acquired pneumonia, ventilator-associated pneumonia or healthcare-associated pneumonia in patients with late onset of disease or known risk factors for multidrug-resistant pathogens and all disease severity: 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.
<p>American Academy of Pediatrics and American Academy of Family Physicians, Subcommittee on Management of Acute Otitis Media: Diagnosis and Management of Acute Otitis Media (2004)⁶¹</p>	<ul style="list-style-type: none"> Treatment of existing pain, generally with acetaminophen or ibuprofen, is recommended regardless of initiation of antibacterial treatment. Amoxicillin (80 to 90 mg/kg/day) is considered first-line therapy for the treatment of acute otitis media in most children, when the decision is made to treat with an antibacterial agent. This is in part due to amoxicillin's effectiveness when used in sufficient doses against susceptible organisms; other factors include its safety, acceptable taste, and narrow microbiologic spectrum. Approximately 80% of patients with acute otitis media will respond to treatment with high-dose amoxicillin. Patients with a fever $\geq 102^{\circ}\text{F}$ or moderate-to-severe pain (severe illness) and/or who require additional coverage for <i>H influenzae</i> and <i>Moraxella catarrhalis</i> should be treated with high dose amoxicillin/clavulanate (90 mg/kg/day of amoxicillin component, with 6.4 mg/kg/day of clavulanate in two divided doses). Those patients who have failed first-line treatment should be initiated on amoxicillin/clavulanate (90 mg/kg/day of amoxicillin component divided in two doses). Patients who have failed to improve while receiving amoxicillin should not be treated with SMX/TMP or erythromycin/sulfisoxazole. Patients who fail treatment with amoxicillin/clavulanate should be treated with parenteral ceftriaxone. For patients with fever and severe symptoms (including severe vomiting) that precludes the administration of oral antibacterial agents, a three-day course of ceftriaxone, administered intravenously or intramuscularly, should be initiated at the onset of symptoms. Ceftriaxone should also be initiated via intravenous route for three days in a patient who fails amoxicillin/clavulanate. <p><u>Special populations</u></p> <ul style="list-style-type: none"> In patients with a history of non-type-I penicillin allergy, cefdinir, cefpodoxime or cefuroxime are considered alternatives to amoxicillin. In patients with a history of type-1 penicillin allergy, azithromycin or clarithromycin can be used. Other options include erythromycin/sulfisoxazole, SMX/TMP or clindamycin. Parenteral therapy with ceftriaxone may be used in patients who

Clinical Guideline	Recommendations
<p>Infectious Diseases Society of America: Practice Guidelines for the Diagnosis and Management of Group A Streptococcal Pharyngitis (2002)⁶²</p>	<p>cannot tolerate oral therapy.</p> <ul style="list-style-type: none"> • Penicillin is the drug of choice for the treatment of group A streptococcal pharyngitis. • Amoxicillin may be used in place of penicillin based mainly on taste. • Erythromycin is an alternative in patients with a penicillin allergy. • First generation cephalosporins are acceptable alternatives in patients with a non-type 1 penicillin allergy. • Clindamycin may be used in patients who are unable to tolerate β-lactam antibiotics and who are infected with erythromycin-resistant group A <i>Streptococcus</i>. • For patients with multiple, recurrent episodes of pharyngitis, a 10-day course of clindamycin or amoxicillin/clavulanic acid is recommended. Alternatively, one dose of intramuscular benzathine penicillin G or benzathine penicillin G plus a four-day course of rifampin can be used.
<p>American Heart Association: Prevention of Rheumatic Fever and Diagnosis and Treatment of Acute Streptococcal Pharyngitis (2009)⁶³</p>	<p><u>Primary prevention (treatment of Streptococcal tonsillopharyngitis)</u></p> <ul style="list-style-type: none"> • The oral antibiotics of choice are penicillin V and amoxicillin. • Penicillin V, amoxicillin or benzathine penicillin G is recommended. • In patients allergic to penicillin, a narrow spectrum cephalosporin, clindamycin, azithromycin or clarithromycin may be used. • In symptomatic patients who fail an initial course of penicillin, retreatment with a narrow spectrum cephalosporin, clindamycin, amoxicillin/clavulanate or a combination of penicillin plus rifampin is recommended. • In clinical trials, a once-daily amoxicillin (Moxatag[®]) was shown to be effective for group A streptococcal pharyngitis. It has the advantage of being dosed once-daily which may enhance adherence. <p><u>Secondary prevention (prevention of recurrent attacks of rheumatic fever)</u></p> <ul style="list-style-type: none"> • Benzathine penicillin G, penicillin V or sulfadiazine are recommended. • In patients allergic to penicillin, a macrolide or azalide are recommended.
<p>Institute for Clinical Systems Improvement: Diagnosis and Treatment of Respiratory Illness in Children and Adults (2011)⁶⁴</p>	<p><u>Pharyngitis</u></p> <ul style="list-style-type: none"> • Penicillin is the drug of choice. Amoxicillin is an acceptable alternative due to poor palatability of penicillin suspension. • Penicillin-allergic patients should be treated with cephalosporins, erythromycin or clindamycin. • Alternative medications include macrolides, cephalexin, clindamycin, amoxicillin/clavulanate, and rocephin. • Prevention of recurrent rheumatic fever requires continuous antimicrobial prophylaxis. <p><u>Bacterial sinusitis</u></p> <ul style="list-style-type: none"> • Antibiotics should be reserved for patients who fail decongestant therapy, those presenting with symptoms and signs of more severe disease, and those with complications of acute sinusitis. • Amoxicillin is the first-line drug of choice. • SMX/TMP is a potential first-line antibiotic, though clinicians may avoid its use due to concerns regarding resistant <i>S pneumoniae</i>. It should generally be reserved for patients who are allergic to amoxicillin.

Clinical Guideline	Recommendations
	<ul style="list-style-type: none"> For patients allergic to both penicillin and SMX/TMP, macrolides may be prescribed. Cephalosporins may be considered, but there is about a 10% cross-reaction between cephalosporins and amoxicillin. In general, fluoroquinolones should not be used since they are generally inactive against pneumococci. Amoxicillin/clavulanate or a macrolide may be used in a patient who fails an initial round of treatment. A fluoroquinolone with pneumococcal coverage may be considered, except in patients who are skeletally immature. Additional second-line agents for patients infected with penicillin and SMX/TMP resistant bacteria include cefuroxime, cefpodoxime, cefprozil, cefdinir, cefaclor, clarithromycin, azithromycin, levofloxacin or moxifloxacin (except in patients who are skeletally immature).
<p>American Academy of Pediatrics: Management of Sinusitis (2001)⁶⁵</p>	<ul style="list-style-type: none"> Amoxicillin is considered first-line therapy for acute bacterial sinusitis due to its general effectiveness, safety, tolerability, and narrow spectrum. For children younger than two years of age with uncomplicated bacterial sinusitis that is mild to moderate in severity who do not attend day care and have not recently been treated with an antibiotic, amoxicillin is recommended at 45 mg/kg/day in two divided doses or 90 mg/kg/day in two divided doses. If the patient has an allergic reaction to amoxicillin that is not a type 1 hypersensitivity reaction, then cefdinir, cefuroxime, or cefpodoxime can be used. In cases of serious allergic reaction to amoxicillin, then clarithromycin, azithromycin, or clindamycin can be used. If the patient has an inadequate response, has recently been treated with an antibiotic, has a moderate or severe illness, or attends daycare, high dose amoxicillin/clavulanate (80 to 90 mg/kg/day in two divided doses) should be used instead. Alternatives include cefdinir, cefuroxime, or cefpodoxime.
<p>Infectious Diseases Society of America: Practice Guidelines for the Management of Bacterial Meningitis (2004)⁶⁶</p>	<p><u>Antimicrobial therapy based on the presumptive pathogen identified by positive Gram stain</u></p> <ul style="list-style-type: none"> <i>S pneumoniae</i> - vancomycin plus third-generation cephalosporin; alternative agents are meropenem or a fluoroquinolone. <i>Neisseria meningitides</i> - third generation cephalosporin; alternative agents include penicillin G, ampicillin, chloramphenicol, fluoroquinolones, or aztreonam. <i>Listeria monocytogenes</i> and <i>Streptococcus agalactiae</i> - ampicillin or penicillin G; alternative agents include SMX/TMP or meropenem (for <i>L monocytogenes</i>) and a third generation cephalosporin (for <i>S agalactiae</i>). <i>H influenzae</i> - third generation cephalosporin; alternative agents include chloramphenicol, cefepime, meropenem, or a fluoroquinolone. <i>Escherichia coli</i> - third generation cephalosporin; alternative agents include cefepime, meropenem, aztreonam, fluoroquinolone, or SMX/TMP. <p><u>Empiric therapy based on age and predisposing condition</u></p> <ul style="list-style-type: none"> Age <one month, <i>S agalactiae</i>, <i>E coli</i>, <i>L monocytogenes</i>, <i>Klebsiella</i> species: ampicillin plus cefotaxime or ampicillin plus aminoglycoside. Age one to 23 months, <i>S pneumoniae</i>, <i>N meningitides</i>, <i>S agalactiae</i>, <i>H influenzae</i>, <i>E coli</i>: vancomycin plus third generation cephalosporin

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	<p>(ceftriaxone or cefotaxime).</p> <ul style="list-style-type: none"> • Age two to 50 years, <i>N meningitides</i>, <i>S pneumoniae</i>: vancomycin plus third generation cephalosporin (ceftriaxone or cefotaxime). • Age >50 years, <i>S pneumoniae</i>, <i>N meningitides</i>, <i>L monocytogenes</i>, <i>aerobic gram-negative bacilli</i>: vancomycin plus ampicillin plus third generation cephalosporin (ceftriaxone or cefotaxime). • Basilar skull fracture, <i>S pneumoniae</i>, <i>H influenza</i>, group A β-hemolytic streptococci: vancomycin plus third generation cephalosporin (ceftriaxone or cefotaxime). • Penetrating head trauma, <i>S aureus</i>, coagulase-negative staphylococci, aerobic gram-negative bacilli: vancomycin plus cefepime, vancomycin plus ceftazidime, vancomycin plus meropenem. • Post-neurosurgery, aerobic gram-negative bacilli, <i>S aureus</i>, coagulase-negative staphylococci: vancomycin plus cefepime, vancomycin plus ceftazidime, vancomycin plus meropenem. • Cerebrospinal fluid shunt, coagulase-negative staphylococci, <i>S aureus</i>, aerobic gram-negative bacilli, <i>Propionibacterium acnes</i>: vancomycin plus cefepime, vancomycin plus ceftazidime, vancomycin plus meropenem. <p><u>Specific antimicrobial therapy based on pathogen and susceptibility</u></p> <ul style="list-style-type: none"> • <i>S pneumoniae</i>: <ul style="list-style-type: none"> ○ Penicillin minimum inhibitory concentration (MIC) <0.1 $\mu\text{g/mL}$: penicillin G or ampicillin, alternative therapies include third generation cephalosporin (ceftriaxone or cefotaxime), chloramphenicol. ○ Penicillin MIC 0.1 to 1.0 $\mu\text{g/mL}$: third generation cephalosporin (ceftriaxone or cefotaxime), alternative agents include cefepime, meropenem. ○ Penicillin MIC ≥ 2 $\mu\text{g/mL}$: vancomycin plus third generation cephalosporin (ceftriaxone or cefotaxime, consider addition of rifampin if MIC of ceftriaxone is >2$\mu\text{g/mL}$), alternative agent is fluoroquinolone (gatifloxacin or moxifloxacin). ○ Cefotaxime or ceftriaxone MIC ≥ 1 $\mu\text{g/mL}$: vancomycin plus third generation cephalosporin (ceftriaxone or cefotaxime, consider addition of rifampin if MIC of ceftriaxone is >2 $\mu\text{g/mL}$), alternative agent is fluoroquinolone (gatifloxacin or moxifloxacin). • <i>N meningitides</i>: <ul style="list-style-type: none"> ○ Penicillin MIC <0.1 $\mu\text{g/mL}$: penicillin G or ampicillin, alternative agents include third generation cephalosporin (ceftriaxone or cefotaxime), chloramphenicol. ○ Penicillin MIC 0.1 to 1.0 $\mu\text{g/mL}$: third generation cephalosporin (ceftriaxone or cefotaxime), alternative agents include chloramphenicol, fluoroquinolone, meropenem. • <i>L monocytogenes</i>: ampicillin or penicillin G (addition of aminoglycoside should be considered), alternative agents include SMX/TMP, meropenem. • <i>S agalactiae</i>: ampicillin or penicillin G (addition of aminoglycoside should be considered), alternative agents include third generation cephalosporin (ceftriaxone or cefotaxime). • <i>E coli</i> or <i>Enterobacteriaceae</i>: third generation cephalosporin,

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	<p>alternative agents include aztreonam, fluoroquinolone, meropenem, SMX/TMP, ampicillin.</p> <ul style="list-style-type: none"> • <i>P aeruginosa</i>: cefepime or ceftazidime (addition of aminoglycoside should be considered), alternative agents include aztreonam, ciprofloxacin, meropenem (addition of aminoglycoside should be considered). • <i>H influenza</i>: <ul style="list-style-type: none"> ○ β-lactamase negative: ampicillin, alternative agents include third generation cephalosporin (ceftriaxone or cefotaxime), cefepime, chloramphenicol, fluoroquinolone. ○ β-lactamase positive: third generation cephalosporin, alternative agents include cefepime, chloramphenicol, fluoroquinolone. • <i>S aureus</i> <ul style="list-style-type: none"> ○ Methicillin susceptible: nafcillin or oxacillin, alternative agents include vancomycin, meropenem. ○ Methicillin resistant: vancomycin (consider addition of rifampin), alternative agents include SMX/TMP, linezolid. • <i>Staphylococcus epidermidis</i>: vancomycin (consider addition of rifampin), alternative agent is linezolid. • <i>Enterococcus</i> species: <ul style="list-style-type: none"> ○ Ampicillin susceptible: ampicillin plus gentamicin. ○ Ampicillin resistant: vancomycin plus gentamicin. ○ Ampicillin and vancomycin resistant: linezolid.
<p>Infectious Diseases Society of America: Practice Guidelines for the Diagnosis and Management of Skin and Soft-Tissue Infections (2005)⁶⁷</p>	<p><u>General observations</u></p> <ul style="list-style-type: none"> • Minor skin and soft-tissue infections may be empirically treated with semisynthetic penicillins, first or second generation oral cephalosporins, macrolides, or clindamycin; however, resistance to clindamycin has been found in almost 50% of methicillin-resistant <i>S aureus</i> (MRSA) strains. • In patients with severe infection or infection that has progressed while on empirical antibiotic treatment, selection of therapeutic agents should be based on results of the gram stain, culture and drug susceptibility analysis. • In the case of <i>S aureus</i>, the clinician should assume the organism is resistant due to the high prevalence of community-associated MRSA strains. Agents effective against MRSA should be used in patients who have severe infections requiring hospitalization or those who have not responded to attempts to eradicate the infection (vancomycin, linezolid, daptomycin). Step-down treatment to other agents may be possible based on susceptibility tests. • An increase in the macrolide resistance of <i>Streptococcus pyogenes</i> has been noted, while 99.5% of strains remain susceptible to clindamycin and 100% to penicillin. • Osteomyelitis typically requires treatment for four to six weeks. <p><u>Animal bites</u></p> <ul style="list-style-type: none"> • The decision to administer oral or intravenous antibiotic therapy is determined by the depth and severity of the wound and the time elapsed since the bite. • Appropriate first-line therapy includes oral amoxicillin/clavulanate, doxycycline, or penicillin VK plus dicloxacillin. Other options include fluoroquinolones, SMX/TMP, and cefuroxime. The patient may also

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	<p>require an additional agent that is active against anaerobes, such as metronidazole or clindamycin.</p> <ul style="list-style-type: none"> • Intravenous options include ampicillin/sulbactam, piperacillin/tazobactam, second generation cephalosporins, and carbapenems. Second- and third-generation cephalosporins may be used but require the addition of an antianaerobic agent. <p><u>Animal contact</u></p> <ul style="list-style-type: none"> • Though no randomized controlled trials exist for treatment of cutaneous anthrax, most data indicate that penicillin is effective. Less evidence supports the use of tetracyclines, chloramphenicol and erythromycin. • Bioterrorism-related anthrax should be treated with a fluoroquinolone until susceptibility tests are available, as inhalation may also have occurred. • Cat scratch disease and bacillary angiomatosis may be treated with azithromycin, erythromycin or doxycycline. Other alternatives include rifampin, SMX/TMP and ciprofloxacin. • Erysipeloid cutaneous infections should be treated with penicillin or amoxicillin; cephalosporins, clindamycin and fluoroquinolones are effective alternatives. • Glanders may be treated with ceftazidime, gentamicin, imipenem, doxycycline, or ciprofloxacin. • Streptomycin has been the drug of choice for bubonic plague. Tetracycline and chloramphenicol are also appropriate. Fluoroquinolones are alternative agents. • Ciprofloxacin has been suggested for both treatment and prevention of plague (bubonic and pneumonic) due to biowarfare agents. • Streptomycin is considered the drug of choice for tularemia. Acutely ill patients should receive streptomycin or gentamicin. Mild to moderate disease may be treated with oral tetracycline or doxycycline. <p><u>Cellulitis</u></p> <ul style="list-style-type: none"> • Cellulitis is commonly treatable with oral antibiotics, such as dicloxacillin, cephalexin, clindamycin or erythromycin. • For severe infection, the treatment of choice is either a penicillinase-resistant semisynthetic penicillin or a first generation cephalosporin. • In patients with severe penicillin allergy, clindamycin or vancomycin is indicated. • To reduce the risk of recurrence, it is important to keep the affected area well-hydrated and to reduce edema with elevation or compression stockings. Prophylactic treatment with monthly intramuscular benzathine penicillin, oral erythromycin, or penicillin V is also an option. <p><u>Erysipelas</u></p> <ul style="list-style-type: none"> • Oral or intravenous penicillin is the first-line treatment depending on severity. • In the presence or suspicion of staphylococcal infection, a penicillinase-resistant semisynthetic penicillin or a first generation cephalosporin is indicated.

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	<p><u>Human bites</u></p> <ul style="list-style-type: none"> • Clenched-fist injuries typically require hospitalization and intravenous ampicillin/sulbactam, cefoxitin or one of the carbapenems. • Fluoroquinolones plus clindamycin or SMX/TMP plus metronidazole can be used in patients with severe penicillin allergy. <p><u>Impetigo</u></p> <ul style="list-style-type: none"> • Penicillinase-resistant penicillins or first generation cephalosporins are the preferred agents. • Erythromycin is indicated in the presence of pyoderma, but use is limited by erythromycin-resistant strains of <i>S aureus</i> and <i>S pyogenes</i>. • Topical therapy with mupirocin is equivalent to oral systemic antibiotics. <p><u>Necrotizing infections</u></p> <ul style="list-style-type: none"> • Antimicrobial therapy (coverage against aerobes and anaerobes) should be directed at the specific pathogen and appropriate doses should be used until operative procedures are no longer needed. • The combination of ampicillin/sulbactam, clindamycin and ciprofloxacin is first-line therapy for community-acquired mixed infection. The carbapenems, or a combination of cefotaxime plus metronidazole or clindamycin, are also appropriate. In cases of penicillin allergy, alternatives include clindamycin or metronidazole plus an aminoglycoside or fluoroquinolone. • Clindamycin and penicillin should be used in necrotizing fasciitis and/or streptococcal toxic shock syndrome caused by group A streptococci. The efficacy of intravenous gamma globulin in these cases is still under investigation. • <i>Streptococcus</i> infection should be treated with high-dose penicillin or ampicillin plus clindamycin. • <i>S aureus</i> infection, often associated with pyomyositis, should be treated with nafcillin, oxacillin, or cefazolin. Vancomycin should be reserved for resistant strains or can be used in cases of severe penicillin allergy, as well as linezolid, quinupristin/dalfopristin or daptomycin. Clindamycin is limited by its potential of cross-resistance. • In gas gangrene, the efficacy of hyperbaric oxygen is inconclusive. Standard antibiotic treatment is penicillin plus clindamycin. <p><u>Soft-tissue infections caused by community-acquired MRSA</u></p> <ul style="list-style-type: none"> • They are often susceptible to non-β-lactam antibiotics, and standard treatment includes doxycycline, clindamycin, SMX/TMP, rifampin, or fluoroquinolones, specifically levofloxacin, gatifloxacin or moxifloxacin. <p><u>Surgical site infections</u></p> <ul style="list-style-type: none"> • Surgical site infections often resolve without the use of antibiotics. • In patients with a temperature >38.5°C, pulse rate >100 beats/minute or erythema diameter >5 cm from incision with induration or necrosis, a short course of antibiotics is recommended. • For wounds of the perineum or operation on the gastrointestinal tract

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	<p>or female genital tract, cefotetan or ampicillin/sulbactam or a fluoroquinolone plus clindamycin is recommended.</p> <ul style="list-style-type: none"> • For clean wounds on the trunk, head, neck or extremities, cefazolin, oxacillin or clindamycin are recommended. <p><u>Immunocompromised patients</u></p> <ul style="list-style-type: none"> • In neutropenic patients, empiric broad-spectrum antibacterial therapy is recommended at the first sign of infection including fever. • For gram-negative infections, monotherapy with carbapenems, cephalosporins with antipseudomonal activity, and piperacillin/tazobactam, are all appropriate. Recommended combination therapy regimens are (1) an aminoglycoside plus either an antipseudomonal penicillin or an extended-spectrum cephalosporin, or (2) an extended-spectrum penicillin plus ciprofloxacin. Adjunct treatment with granulocyte colony-stimulating factor or granulocyte-monocyte colony-stimulating factor is recommended. • For gram-positive infections, vancomycin is not recommended for empirical antibiotic therapy because of resistance; linezolid or daptomycin are appropriate alternatives to vancomycin. • For <i>Nocardia</i> infection, first-line therapy is SMX/TMP. Other sulfonamide antibiotics and imipenem are also appropriate. • Empirical antifungal therapy is a common practice in neutropenic patients with persistent fever. Amphotericin B, caspofungin and voriconazole are appropriate. • Amphotericin B and its lipid formulations have been the gold standard to treatment for yeast and fungal infections in neutropenic patients. Caspofungin and voriconazole appear to be as effective as amphotericin B and with less serious acute toxicity but are more expensive. • Treatment of non-tubercular mycobacterial infections of the skin and soft tissues requires combination therapy that should include a macrolide. • Cutaneous <i>Nocardia</i> infections should be treated with SMX/TMP, the treatment of choice. Other sulfa antibiotics and imipenem are also effective. • Initial therapy for Cryptococcal cellulitis is fluconazole, which is also used to complete therapy after patients have shown an initial response to amphotericin B and 5-flucytosine induction therapy. • Amphotericin B is recommended in patients with cellular immune deficiency and disseminated histoplasmosis. Itraconazole may replace amphotericin B after one to two weeks to complete at least six to 12 months of treatment. • Prevention of viral reactivation with oral acyclovir, famciclovir or valacyclovir is an important component of the treatment of cutaneous varicella zoster virus. • Acyclovir is the treatment of choice for herpes simplex virus infections, though famciclovir and valacyclovir are also highly effective. • Prolonged ganciclovir therapy is the treatment of choice for cutaneous cytomegalovirus.
<p>Infectious Diseases Society of America:</p>	<ul style="list-style-type: none"> • Aerobic gram-positive cocci are the usual pathogens responsible for acute infections due to breaks in the skin. The most common

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<p>Diagnosis and Treatment of Diabetic Foot Infections (2004)⁶⁸</p>	<p>pathogens identified are <i>S aureus</i> and the b-hemolytic streptococci.</p> <ul style="list-style-type: none"> • Chronic wounds involve more complex pathogens including enterococci, Enterobacteriaceae, anaerobes, <i>P aeruginosa</i> and non-fermentative gram-negative rods. • Antibiotics are not recommended in uninfected wounds. • Most patients with mild to moderate infections can be treated as outpatients. • For severe infections, initial empiric antibiotic therapy should include coverage for gram-positive, gram-negative and anaerobic pathogens and should be administered parenterally. • Mild to moderate infections can usually be treated with narrow-spectrum agents which cover gram-positive cocci. • On the basis of available data, no single drug or drug combination appears to be “superior” to another. • Cephalosporins have been used and include cefoxitin, ceftizoxime, ceftriaxone and cephalexin. • Osteomyelitis typically requires four to six weeks of antibiotic therapy.
<p>American College of Obstetricians and Gynecologists: Practice Bulletin: Treatment of Urinary Tract Infections in Nonpregnant Women (2008)⁶⁹</p>	<ul style="list-style-type: none"> • Most urinary tract infections are caused by <i>E coli</i> (80 to 90%). • Other causes of urinary tract infections include <i>Staphylococcus saprophyticus</i>, <i>Proteus</i>, <i>Pseudomonas</i>, <i>Klebsiella</i> and <i>Enterobacter</i> species. • Treatment options include SMX/TMP (preferred), trimethoprim, ciprofloxacin, levofloxacin, norfloxacin, gatifloxacin (all three-day regimens), nitrofurantoin macrocrystals, nitrofurantoin monohydrate/macrocrystals (seven-day regimens) and fosfomycin tromethamine (single dose). • First generation cephalosporins and amoxicillin are less effective than the above agents due to resistance and rapid excretion from the urinary tract. • B-lactams are not first-line therapy in acute cystitis unless the causative organism is gram-positive, in which case amoxicillin or amoxicillin/clavulanate may be used. • Women with frequent recurrences may be treated with once daily nitrofurantoin, norfloxacin, ciprofloxacin, trimethoprim, SMX/TMP or any other agent listed above for six to 12 months and then be reassessed. • SMX/TMP is considered the preferred treatment for uncomplicated cystitis except in areas where resistance is common. • Fluoroquinolones should not be used first-line in areas where SMX/TMP resistance is uncommon. • Acute pyelonephritis in acutely ill patients should be treated with parenteral broad-spectrum antibiotics. If gram-positive organisms are suspected, amoxicillin, ampicillin or a cephalosporin may be used. In other cases β-lactams are no longer recommended. • First-line treatment for pyelonephritis is now a fluoroquinolone. SMX/TMP may be used in areas of low resistance. • Parenteral treatment options include an aminoglycoside with ampicillin or piperacillin, a first generation cephalosporin, aztreonam, piperacillin/tazobactam, or a parenteral fluoroquinolone alone or in combination.
<p>Infectious Diseases Society of America:</p>	<p><u>Acute uncomplicated bacterial cystitis</u></p> <ul style="list-style-type: none"> • Taking into consideration availability, allergy history and tolerance

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<p>International Clinical Practice Guidelines for the Treatment of Uncomplicated Acute Bacterial Cystitis and Acute Pyelonephritis in Women: A 2010 Update by the Infectious Disease Society of America and the European Society for Microbiology and Infectious Disease (2011)⁷⁰</p>	<p>the following antimicrobials are recommended: nitrofurantoin monohydrate/macrocrystals, SMX/TMP, fosfomycin, pivmecillinam*.</p> <ul style="list-style-type: none"> • Fluoroquinolones (ofloxacin, ciprofloxacin and levofloxacin) are recommended as alternative agents if the above agents cannot be used. Although highly efficacious, fluoroquinolones (ofloxacin, ciprofloxacin and levofloxacin) should be reserved for important uses other than acute cystitis due to increasing resistance. • β-lactams (amoxicillin/clavulanate, cefdinir, and cefpodoxime) are also recommended as alternative agents. Due to poor efficacy and antimicrobial resistance, amoxicillin and ampicillin should not be used as monotherapy. <p><u>Acute pyelonephritis</u></p> <ul style="list-style-type: none"> • In patients not requiring hospitalization and where the prevalence of resistance in the community is not known to exceed 10%, oral ciprofloxacin with or without an initial intravenous loading dose is appropriate. • An initial one-time intravenous dose of a long-acting parenteral antimicrobial, such as ceftriaxone or consolidated 24-hour dose of an aminoglycoside is recommended if prevalence of fluoroquinolone resistance exceeds 10%. • In patients not requiring hospitalization and where the prevalence of resistance in the community is not known to exceed 10%, a once-daily fluoroquinolone (e.g., ciprofloxacin, levofloxacin) is appropriate. • If the pathogen is known to be susceptible, oral SMX/TMP is recommended. When the susceptibility is not known, an initial intravenous dose of a long-acting parenteral antimicrobial, such as ceftriaxone or consolidated 24-hour dose of an aminoglycoside is recommended. • Oral β-lactam agents are less effective than other available agents. Therefore if an oral β-lactam agent is used, an initial intravenous dose of a long-acting parenteral antimicrobial, such as ceftriaxone or consolidated 24-hour dose of an aminoglycoside is recommended. • For women with pyelonephritis requiring hospitalization, 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 should be initial treatment.
<p>Centers for Disease Control and Prevention: Sexually Transmitted Diseases Treatment Guidelines (2010)⁷¹</p>	<p><u>Chancroid</u></p> <ul style="list-style-type: none"> • Azithromycin, ceftriaxone, ciprofloxacin (contraindicated in pregnant or lactating women) or erythromycin are recommended treatment strategies. <p><u>Genital herpes simplex virus</u></p> <ul style="list-style-type: none"> • First episodes should be treated with acyclovir, famciclovir, or valcyclovir. • Acyclovir, famciclovir or valcyclovir may be used as suppressive therapy, though famciclovir may be somewhat less effective for suppression of viral shedding. Ease of administration and cost are important considerations for prolonged treatment. • Episodic treatment requires initiation of therapy within one day of lesion onset or during the prodrome that precedes outbreak. • Intravenous acyclovir is recommended for severe disease.

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	<p><u>Granuloma inguinale</u></p> <ul style="list-style-type: none"> • Doxycycline is recommended. • Alternative agents include azithromycin, ciprofloxacin, erythromycin or SMX/TMP. • The addition of an aminoglycoside may be considered if improvement is not evident within the first few days of therapy. <p><u>Lymphogranuloma venereum</u></p> <ul style="list-style-type: none"> • Doxycycline is recommended. • An alternative agent is erythromycin. • Clinical data are lacking, though azithromycin is probably effective. • Fluoroquinolone treatment may also be effective, though extended treatment intervals are likely required. • Pregnant and lactating women should be treated with erythromycin. Azithromycin may be an alternative but clinical data are lacking. <p><u>Syphilis</u></p> <ul style="list-style-type: none"> • Penicillin G is the preferred drug for all stages of syphilis. Alternative agents include doxycycline and tetracycline. Limited studies suggest that ceftriaxone is effective. • Azithromycin may be effective in early syphilis but should only be used when treatment with penicillin G or doxycycline is not feasible. It should not be used in pregnant women and men who have sex with men. • Penicillin G is the only therapy recommended during pregnancy. Pregnant women with an allergy to penicillin should be desensitized. • Benzathine penicillin G is recommended for primary and secondary syphilis. • Infants ≥ 1 month of age with primary or secondary syphilis should be treated with benzathine penicillin G. • Early latent syphilis should be treated with benzathine penicillin G in patients with normal cerebrospinal fluid examinations. • Late latent syphilis or latent syphilis of unknown duration should be treated with benzathine penicillin G in patients with normal cerebrospinal fluid examinations. Alternative agents include doxycycline or tetracycline. • Patients with tertiary syphilis with no evidence of neurosyphilis should be treated with benzathine penicillin G. • Patients with neurosyphilis should be treated with aqueous crystalline penicillin G. An alternative regimen in patients in whom compliance can be assured is procaine penicillin plus probenecid. • Congenital syphilis: <ul style="list-style-type: none"> ○ Proven or highly probably disease with abnormal physical exam, serum quantitative serologic titer fourfold higher than the mother's titer or positive darkfield test of body fluids should be treated with aqueous crystalline penicillin G or procaine penicillin G. ○ Normal physical exam and serum quantitative tier same or less than fourfold the maternal tier and the mother was not treated, inadequately treated or has no documentation of treatment or the mother was treated with erythromycin or other non-penicillin regimen or the mother received <4

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	<p>weeks of treatment before delivery should be treated with aqueous crystalline penicillin G, procaine penicillin G, or benzathine penicillin G.</p> <ul style="list-style-type: none"> ○ Normal physical exam with serum quantitative titer the same or less than fourfold the maternal titer and the mother was treated during pregnancy, treatment was appropriate and administered for >4 weeks before delivery and the mother has no evidence of reinfection or relapse should be treated with benzathine penicillin G. ● Infants ≥ 1 month of age identified as having reactive serologic tests for syphilis should be treated with aqueous crystalline penicillin G. ● If the child has no clinical manifestations of the disease and the cerebrospinal fluid examination is normal, penicillin G at up to three weekly doses can be considered. ● Any child suspected of having congenital syphilis with neurologic involvement should be treated with aqueous crystalline penicillin G. ● Infants and children requiring treatment for syphilis who have a history of penicillin allergy or develop an allergic reaction should be desensitized. <p><u>Urethritis</u></p> <ul style="list-style-type: none"> ● Azithromycin or doxycycline is recommended. Alternative regimens include erythromycin, levofloxacin or ofloxacin. ● In the case of recurrent or persistent urethritis, if the patient was compliant with the initial regimen and re-exposure can be excluded, metronidazole or tinidazole plus azithromycin is recommended. <p><u>Cervicitis</u></p> <ul style="list-style-type: none"> ● Azithromycin or doxycycline is recommended. <p><u>Chlamydia</u></p> <ul style="list-style-type: none"> ● Azithromycin or doxycycline is recommended. ● Alternative agents include erythromycin, levofloxacin or ofloxacin. ● Azithromycin or amoxicillin is recommended in pregnant patients. An alternative agent is erythromycin. ● Infants with ophthalmia neonatorum should be treated with oral erythromycin. ● Infants with pneumonia caused by <i>Chlamydia trachomatis</i> should be treated with oral erythromycin. ● Children with chlamydial infection should be treated with oral erythromycin (patients weighing <45 kg), azithromycin (patients weighing ≥ 45 kg and <8 years), or azithromycin or doxycycline (patients ≥ 8 years of age). <p><u>Gonococcal infections</u></p> <ul style="list-style-type: none"> ● Patients infected with <i>Neisseria gonorrhoeae</i> are frequently coinfecting with <i>C trachomatis</i> and should be treated for both infections. ● Ceftriaxone is recommended. If ceftriaxone is not an option, other regimens include cefixime or single dose injectable cephalosporin regimens plus azithromycin or doxycycline. ● Gonococcal infections of the pharynx should be treated with ceftriaxone plus azithromycin or doxycycline.

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	<ul style="list-style-type: none"> • Gonococcal conjunctivitis should be treated with ceftriaxone. • Disseminated gonococcal infection should be treated with ceftriaxone. Alternative agents include cefotaxime or ceftizoxime. • Gonococcal meningitis and endocarditis should be treated with ceftriaxone. • Ophthalmia neonatorum should be treated with ceftriaxone. • Gonococcal scalp abscesses should be treated with ceftriaxone or cefotaxime. • Infants born to mothers with untreated gonorrhea should be treated with ceftriaxone. • Children weighing >45 kg should be treated with a regimen recommended for adults. • Children weighing ≤45 kg should be treated with ceftriaxone at an appropriate dose. • Ceftriaxone is recommended in children with bacteremia or arthritis. • Erythromycin ophthalmic ointment is recommended as prophylaxis against ophthalmia neonatorum at birth. If erythromycin is not available, infants at risk can be administered ceftriaxone. <p><u>Bacterial vaginosis</u></p> <ul style="list-style-type: none"> • Metronidazole orally or topically or topical clindamycin are recommended. • Alternative agents include oral tinidazole or oral or intravaginal clindamycin. • Intravaginal metronidazole is an option in patients who are unable to tolerate oral metronidazole. • Treatment of all pregnant women with symptoms is recommended. Oral metronidazole or clindamycin is recommended. <p><u>Trichomoniasis</u></p> <ul style="list-style-type: none"> • Oral metronidazole or tinidazole is recommended. <p><u>Vulvovaginal candidiasis</u></p> <ul style="list-style-type: none"> • Over-the-counter butoconazole, clotrimazole, miconazole or tioconazole are recommended. • Prescription agents include butoconazole, nystatin, terconazole or oral fluconazole. • Oral fluconazole weekly for six months is the recommended treatment for recurrent infection. • Severe vulvovaginal candidiasis should be treated with seven to 14 days of topical therapy or fluconazole in two consecutive doses (second dose 72 hours after initial dose). • Only topical therapies are recommended in pregnancy. <p><u>Pelvic inflammatory disease</u></p> <ul style="list-style-type: none"> • Mild to moderate pelvic inflammatory disease should be treated with parenteral or oral therapies. • Recommended parenteral regimen A: cefotetan or ceftiofuran plus doxycycline (oral or intravenous). • Recommended parenteral regimen B: clindamycin plus gentamicin. • Alternative parenteral regimens are ampicillin/sulbactam plus doxycycline (oral or intravenous).

Clinical Guideline	Recommendations
	<ul style="list-style-type: none"> • Outpatient oral therapy may be considered in patients with mild to moderate disease. Recommended regimens include ceftriaxone plus doxycycline with or without metronidazole, cefoxitin and probenecid plus doxycycline with or without metronidazole, or another parenteral 3rd generation cephalosporin plus doxycycline with or without metronidazole. • If parenteral cephalosporin therapy is not feasible, fluoroquinolones with or without metronidazole may be considered if the community prevalence and individual risk for gonorrhea are low. <p><u>Epididymitis</u></p> <ul style="list-style-type: none"> • Ceftriaxone plus doxycycline is recommended. For acute infections most likely caused by enteric organisms, levofloxacin or ofloxacin are recommended. <p><u>Human papillomavirus</u></p> <ul style="list-style-type: none"> • External genital warts: <ul style="list-style-type: none"> ○ Podofilox 0.5% solution or gel, imiquimod 5% cream or sinecatechins 15% ointment are recommended as patient-applied treatments. ○ Cryotherapy with liquid nitrogen or cryoprobe, podophyllin resin, trichloroacetic acid or bichloroacetic acid or surgical removal are recommended as provider-administered treatments. ○ Alternative regimens include intralesional interferon, photodynamic therapy and topical cidofovir. • Cervical warts: <ul style="list-style-type: none"> ○ Biopsy evaluation is recommended to exclude high-grade squamous intraepithelial lesions • Vaginal warts: <ul style="list-style-type: none"> ○ Cryotherapy with liquid nitrogen or trichloroacetic acid or bichloroacetic acid are recommended. • Urethral meatus warts: <ul style="list-style-type: none"> ○ Cryotherapy with liquid nitrogen or podophyllin in compound tincture of benzoin is recommended. • Anal warts: <ul style="list-style-type: none"> ○ Cryotherapy with liquid nitrogen, trichloroacetic acid or bichloroacetic acid or surgical removal is recommended. <p><u>Proctitis</u></p> <ul style="list-style-type: none"> • Ceftriaxone plus doxycycline is recommended. <p><u>Pediculosis pubis</u></p> <ul style="list-style-type: none"> • Permethrin or pyrethrins are recommended. • Alternative agents include malathion or ivermectin. <p><u>Scabies</u></p> <ul style="list-style-type: none"> • Permethrin or ivermectin are recommended. • Lindane is an alternative agent, not recommended as first-line. <p><u>Prophylaxis after sexual assault</u></p> <ul style="list-style-type: none"> • Hepatitis B vaccination. • Empirical regimen for Chlamydia, gonorrhea and trichomonas.

Clinical Guideline	Recommendations
<p>Infectious Diseases Society of America: The Clinical Assessment, Treatment, and Prevention of Lyme Disease, Human Granulocytic Anaplasmosis, and Babesiosis: Clinical Practice Guidelines by the Infectious Diseases Society of America (2006)^{72†}</p>	<ul style="list-style-type: none"> • Emergency contraception. • Ceftriaxone or cefixime plus metronidazole plus azithromycin or doxycycline is the recommended regimen. <p><u>Early Lyme disease</u></p> <ul style="list-style-type: none"> • Doxycycline, amoxicillin or cefuroxime for 10 to 21 days are the preferred treatment options for adult patients with early localized or early disseminated Lyme disease associated with erythema migrans, in the absence of specific neurologic manifestations or advanced atrioventricular heart block. • Children under the age of eight should be treated with amoxicillin or cefuroxime. Children eight years of age and older may be treated with doxycycline. • Macrolides should be reserved for patients who are intolerant to doxycycline, amoxicillin or cefuroxime. • First generation cephalosporins are ineffective and should not be used. • When erythema migrans cannot be differentiated from bacterial cellulitis, it is reasonable to treat with cefuroxime or amoxicillin/clavulanate. • Ceftriaxone is effective but is not “superior” to oral agents and is more likely to cause serious adverse events. • Doxycycline should be avoided in pregnant patients. <p><u>Lyme meningitis and other manifestations of early neurologic Lyme disease</u></p> <ul style="list-style-type: none"> • Ceftriaxone is recommended. • Alternatives include parenteral cefotaxime or penicillin G. • Oral doxycycline may be used in patients intolerant to β-lactams. • Ceftriaxone is recommended in children. An alternative agent is cefotaxime or penicillin G. • Children eight years of age and older may be treated with oral doxycycline. • Antibiotics may not hasten the resolution of seventh cranial nerve palsy associated with Lyme disease but are recommended to prevent further sequelae. <p><u>Lyme carditis</u></p> <ul style="list-style-type: none"> • Patients with atrioventricular heart block and/or myopericarditis may be treated with oral or parenteral antibiotic therapy. • Ceftriaxone is recommended as initial management for hospitalized patients. <p><u>Borrelial lymphocytoma</u></p> <ul style="list-style-type: none"> • Recommended regimens are the same as for erythema migrans. <p><u>Late Lyme disease with Lyme arthritis</u></p> <ul style="list-style-type: none"> • Doxycycline, amoxicillin or cefuroxime are recommended in patients without neurological manifestations. • Children under the age of eight should be treated with amoxicillin or cefuroxime. Children eight years of age and older may be treated with doxycycline. • Adult patients with Lyme arthritis and evidence of neurological manifestations should be treated with parenteral ceftriaxone.

Clinical Guideline	Recommendations
	<p>Cefotaxime or penicillin G are acceptable alternatives.</p> <ul style="list-style-type: none"> • Patient with persistent joint swelling may be treated with a second four-week course of oral antibiotics or a two to four week course of ceftriaxone. <p><u>Late neurological Lyme disease</u></p> <ul style="list-style-type: none"> • Parenteral ceftriaxone is recommended for adults and children. • Cefotaxime or penicillin G are alternatives. <p><u>Acrodermatitis chronic atrophicans</u></p> <ul style="list-style-type: none"> • Recommended regimens are the same as for erythema migrans. <p><u>Long-term treatment</u></p> <ul style="list-style-type: none"> • Antibiotic therapy is not recommended for patients with long-term (≥ 6 months) subjective symptoms. <p><u>Human granulocytic anaplasmosis</u></p> <ul style="list-style-type: none"> • Doxycycline is recommended. • Children <8 years of age without concomitant Lyme disease may be treated with an abbreviated course of doxycycline. If the child has concomitant Lyme disease, amoxicillin or cefuroxime are recommended after the course of doxycycline. • In patients not suited for treatment with doxycycline, rifampin is recommended. Patients with concomitant Lyme disease should also be treated with amoxicillin or cefuroxime. <p><u>Babesiosis</u></p> <ul style="list-style-type: none"> • Atovaquone plus azithromycin or clarithromycin plus quinine is recommended. • Clarithromycin plus quinine is recommended in patients with severe disease.
<p>Global Initiative for Chronic Obstructive Lung Disease: Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2010)⁷³</p>	<p><u>Management of exacerbations of Chronic Obstructive Pulmonary Disease (COPD) with a bacterial component</u></p> <ul style="list-style-type: none"> • Predominant bacteria include <i>H influenzae</i>, <i>S pneumoniae</i> and <i>M catarrhalis</i>. • Patients with severe COPD requiring mechanical ventilation may be more frequently infected with <i>P aeruginosa</i>. • Patients with mild exacerbations and no risk for poor outcome may be treated with oral penicillin, ampicillin, amoxicillin, tetracycline or SMX/TMP. Alternative agents include amoxicillin/clavulanate, a macrolide, a second or third generation cephalosporin or a ketolide. • Patients with moderate exacerbations and risk factors for poor outcomes should be treated with amoxicillin/clavulanate. Alternative agents are fluoroquinolones. Parenteral options include β-lactam/β-lactamase inhibitor, second or third generation cephalosporin, or fluoroquinolones. • Patients with severe exacerbations with risk factors for <i>P aeruginosa</i> should be treated with high dose oral or parenteral fluoroquinolones or parenteral β-lactam with <i>P aeruginosa</i> activity.
<p>American Heart Association: Prevention of Infectious Endocarditis (2007)⁷⁴</p>	<ul style="list-style-type: none"> • Antibiotic prophylaxis is recommended for patients at the highest risk of adverse outcome from endocarditis, including those with: <ul style="list-style-type: none"> ○ Prosthetic cardiac valve or prosthetic material used for cardiac valve repair.

Clinical Guideline	Recommendations
	<ul style="list-style-type: none"> ○ Previous infective endocarditis. ○ Congenital heart disease: <ul style="list-style-type: none"> ▪ Unrepaired cyanotic congenital heart disease including palliative shunts and conduits. ▪ Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first six months after the procedure. ▪ Repaired congenital heart disease with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibits endothelialization). ○ Cardiac transplantation recipients who develop cardiac valvulopathy. ● Antibiotic prophylaxis is no longer recommended based solely on an increased lifetime risk of developing infectious endocarditis. ● Antibiotic prophylaxis should be administered as a single dose before the procedure. ● Prophylaxis is recommended for all patients described above who are undergoing a dental procedure which involves manipulation of the gingival tissue or the periapical region of the teeth or perforation of the oral mucosa. ● Recommended regimens include: <ul style="list-style-type: none"> ○ Oral: amoxicillin 2 g (adults) or 50 mg/kg (children). ○ Unable to take oral medication: ampicillin or ceftriaxone or cefazolin. ○ Allergic to penicillins or ampicillin, oral: cephalexin or clindamycin or azithromycin or clarithromycin. ● Allergic to penicillins or ampicillin and unable to take oral medications: cefazolin or ceftriaxone or clindamycin. ● Antibiotic prophylaxis with a regimen described above for patients described above is recommended prior to an invasive procedure of the respiratory tract that involves incision or biopsy of the respiratory mucosa such as tonsillectomy and adenoidectomy. ● For patients described above who undergo an invasive respiratory tract procedure to treat an established infection it is recommended that the regimen contain an agent effective against <i>S viridans</i>. If the infection is known or suspected to be caused by <i>S aureus</i> the regimen should include an antistaphylococcal penicillin or cephalosporin or vancomycin in patients who can't tolerate a penicillin. Vancomycin is also recommended if the infection is known or suspected to be caused by MRSA. ● The administration of prophylactic antibiotics is no longer recommended solely to prevent endocarditis in patients undergoing a genitourinary or gastrointestinal tract procedure. ● Patients described above with infections of the genitourinary or gastrointestinal tract or for those receiving antibiotic therapy to prevent wound infection or sepsis associated with a gastrointestinal or genitourinary tract procedure, the regimen should include an agent active against enterococci, such as penicillin, ampicillin, piperacillin or vancomycin. ● For patients described above scheduled for an elective cystoscopy or other urinary tract manipulation who have an enterococcal urinary

Clinical Guideline	Recommendations
	<p>tract infection or colonization, antibiotic therapy to eradicate enterococci from the urine before the procedure is reasonable. If the procedure is not elective, empiric or specific antimicrobial therapy may be administered to the patient containing an agent active against enterococci.</p> <ul style="list-style-type: none"> • Amoxicillin or ampicillin is preferred for enterococcal coverage in these patients. Vancomycin may be used in patients unable to tolerate penicillin. • In patients described above who undergo a surgical procedure involving infected skin, skin structure or musculoskeletal tissue, it is reasonable that the therapeutic regimen for the treatment of the infection contain an agent active against staphylococci and β-hemolytic streptococci such as an antistaphylococcal penicillin or a cephalosporin. Vancomycin and clindamycin are options in patients unable to tolerate a β-lactam or who are known or suspected to have an infection caused by a methicillin-resistant staphylococcus.
<p>American Academy of Pediatric Dentistry: Clinical Guideline on Antibiotic Prophylaxis for Dental Patients at Risk for Infection (2008)⁷⁵</p>	<ul style="list-style-type: none"> • Infective endocarditis prophylaxis for dental procedures is reasonable only for patients with underlying cardiac conditions associated with the highest risk of adverse outcome from infective endocarditis. • For patients with those conditions, prophylaxis is recommended for procedures involving manipulation of gingival tissue or periapical region of teeth or perforation of the oral mucosa. • Prophylaxis is not recommended based solely on an increased lifetime risk of infective endocarditis. • Recommended regimens include: <ul style="list-style-type: none"> ○ Oral: amoxicillin 2 g (adults) or 50 mg/kg (children). ○ Unable to take oral medication: ampicillin or ceftriaxone or cefazolin. ○ Allergic to penicillins or ampicillin, oral: cephalexin or clindamycin or azithromycin or clarithromycin. ○ Allergic to penicillins or ampicillin and unable to take oral medications: cefazolin or ceftriaxone or clindamycin.
<p>Infectious Disease Society of America/ Surgical Infection Society: Diagnosis and Management of Complicated Intra-abdominal Infection in Adults and Children (2010)⁷⁶</p>	<p><u>Community-acquired infection of mild to moderate severity in adults</u></p> <ul style="list-style-type: none"> • Single agent therapy with ticarcillin/clavulanate, ceftiofloxacin, ertapenem, moxifloxacin or tigecycline or combination therapy of metronidazole with cefazolin, cefuroxime, ceftriaxone, levofloxacin or ciprofloxacin is preferred over regimens with substantial antipseudomonal activity. • Ampicillin/sulbactam, cefotetan and clindamycin are not recommended due to high rates of resistance. • Empiric therapy with antifungals or coverage for Enterococcus is not recommended. • Aminoglycosides are not recommended for routine use because of the risk of toxicity. • Agents recommended for higher severity infections are not recommended for mild to moderate community-acquired infections because of the risk of toxicity and development of resistance. <p><u>High-risk community-acquired infections in adults</u></p> <ul style="list-style-type: none"> • The empiric use of broad-spectrum agents with activity against gram-negative organisms including meropenem, imipenem/cilastatin,

Clinical Guideline	Recommendations
	<p>doripenem, piperacillin/tazobactam, ciprofloxacin or levofloxacin in combination with metronidazole or ceftazidime or cefepime in combination with metronidazole is recommended.</p> <ul style="list-style-type: none"> • Aztreonam plus metronidazole with the addition of an agent effective against gram-positive cocci is an alternative. • Quinolones should not be used unless hospital surveys indicate >90% susceptibility of E coli. • In the absence of evidence of resistant pathogens, aminoglycosides or another second agent effective against gram-negative facultative and anaerobic bacilli and/or agents effective against MRSA should not be used. • Empiric used of agents effective against enterococci is recommended. <p><u>Health care-associated infection in adults</u></p> <ul style="list-style-type: none"> • Multidrug regimens that include agents with expanded spectra of activity against gram-negative facultative and anaerobic bacilli, such as meropenem, imipenem/cilastatin, doripenem, piperacillin/tazobactam or ceftazidime may be required. Therapy should be tailored based on local microbiology results and culture and susceptibility reports when they become available. <p><u>Antifungal therapy</u></p> <ul style="list-style-type: none"> • For patients with severe-community acquired or health care-associated infections with cultures that show Candida, antifungal therapy is recommended. • Fluconazole is an appropriate first-line choice if C albicans is isolated. • For fluconazole resistant Candida species and critically ill patients, an echinocandin (casposfungin, micafungin or anidulafungin) is recommended. • Amphotericin B is not recommended due to its toxicity. <p><u>Anti-enterococcal therapy</u></p> <ul style="list-style-type: none"> • Empiric therapy for enterococci is recommended for patients with health care-associated infections when enterococci are recovered, patients with post-operative infections, patients that have received cephalosporins or other antimicrobial agents selecting for Enterococcus species, immunocompromised patients and patients with valvular heart disease or prosthetic intravascular materials. • Therapy should be directed against E faecalis and can include ampicillin/piperacillin and vancomycin. • Empiric therapy for vancomycin-resistant E faecium is not recommended unless patient is at very high risk or patient is known to be colonized with E faecium. <p><u>Anti-MRSA therapy</u></p> <ul style="list-style-type: none"> • Empiric therapy for MRSA should be provided to patients with health care-associated infections with known colonization with MRSA or are at high risk for MRSA infection because of prior treatment failure and significant antibiotic exposure. • Vancomycin is recommended for treatment if suspected or proven infection due to MRSA.

Clinical Guideline	Recommendations
	<p><u>Cholecystitis and cholangitis in adults</u></p> <ul style="list-style-type: none"> For patients with suspected cholecystitis and cholangitis, antibiotic therapy is recommended when a biliary-enteric anastomosis is present. In community-acquired acute cholecystitis of mild to moderate severity, cefazolin, cefuroxime or ceftriaxone is recommended. In acute cholangitis following bilio-enteric anastomosis of any severity and community-acquired acute cholecystitis of severe physiologic disturbance, advance age or immunocompromised state, a combination regimen with metronidazole and imipenem/cilastatin, meropenem, doripenem, piperacillin/tazobactam, ciprofloxacin, levofloxacin or cefepime is recommended. For health care-associated biliary infection of any severity, the above regimen (a combination regimen with metronidazole and imipenem/cilastatin, meropenem, doripenem, piperacillin/tazobactam, ciprofloxacin, levofloxacin or cefepime) with the addition of vancomycin is recommended. <p><u>Pediatric infection</u></p> <ul style="list-style-type: none"> For pediatric patients with complicated intra-abdominal infections, acceptable broad-spectrum regimens 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. For children with severe reactions to β-lactam antibiotics, ciprofloxacin plus metronidazole or an aminoglycoside based regimen are recommended. In neonates with necrotizing enterocolitis, the broad-spectrum antibiotics that may be useful are ampicillin, gentamicin and metronidazole; ampicillin, cefotaxime and metronidazole; or meropenem. For suspected MRSA, vancomycin may be used in place of ampicillin. If the cultures are consistent with fungal infections, fluconazole and amphotericin should be used.
<p>National Surgical Infection Prevention Project: Antimicrobial Prophylaxis for Surgery: An Advisory Statement from the National Surgical Infection Prevention Project (2004)⁷⁷</p>	<p>Sponsoring organizations include the following: American Academy of Orthopaedic Surgeons; American Association of Critical Care Nurses; American Association of Nurse Anesthetists; American College of Surgeons; American College of Osteopathic Surgeons; American Geriatrics Society; American Society of Anesthesiologists; American Society of Colon and Rectal Surgeons; American Society of Health-System Pharmacists; American Society of PeriAnesthesia Nurses; Ascension Health; Association of PeriOperative Registered Nurses; Association for Professionals in Infection Control and Epidemiology; Infectious Diseases Society of America; Medical Letter; Premier; Society for Healthcare Epidemiology of America; Society of Thoracic Surgeons; and Surgical Infection Society.</p> <p><u>Cardiothoracic and vascular surgery</u></p> <ul style="list-style-type: none"> Intravenous cefazolin or intravenous cefuroxime are recommended. If the patient has a β-lactam allergy, intravenous vancomycin is appropriate and intravenous clindamycin is an alternative.

Clinical Guideline	Recommendations
	<p><u>Colorectal surgery</u></p> <ul style="list-style-type: none"> • Oral neomycin plus oral erythromycin or oral neomycin plus oral metronidazole are recommended along with administration of a mechanical bowel preparation. • Intravenous cefotetan or intravenous ceftiofloxacin are recommended for parental prophylaxis. Intravenous cefazolin plus oral metronidazole are recommended as a cost-effective alternative. • For patients with a confirmed allergy or adverse reaction to β-lactams, intravenous clindamycin plus intravenous gentamicin, intravenous aztreonam or intravenous ciprofloxacin; intravenous metronidazole plus intravenous gentamicin or intravenous ciprofloxacin are recommended. A single dose of intravenous levofloxacin can be substituted for intravenous ciprofloxacin. <p><u>Gynecologic and obstetric surgery</u></p> <ul style="list-style-type: none"> • Intravenous cefotetan is preferred for abdominal or vaginal hysterectomy. Intravenous cefazolin and intravenous ceftiofloxacin are reasonable alternatives. • Intravenous metronidazole is an alternative, but may be less effective as monotherapy. • For patients with a β-lactam allergy, intravenous clindamycin plus intravenous gentamicin, intravenous aztreonam or intravenous ciprofloxacin; intravenous metronidazole plus intravenous gentamicin or intravenous ciprofloxacin; or intravenous clindamycin monotherapy are recommended. A single dose of intravenous levofloxacin can be substituted for intravenous ciprofloxacin.

*Agent not currently available in the United States.

†The 2006 Lyme disease guidelines by the Infectious Disease Society of America were the subject of an antitrust investigation by the Connecticut Attorney General in 2006 to examine potential conflicts of interest among panelist and whether the panelist failed to consider divergent medical opinion. An independent review panel was convened and, in 2010, agreed that no changes needed to be made to the 2006 guidelines.

Conclusions

The second generation cephalosporins are used to treat a variety of infections including skin and skin structure infections, genitourinary tract infections, respiratory tract infections and Lyme disease. Second generation cephalosporins have greater activity against *Haemophilus influenza* compared to the first generation cephalosporins and have enhanced activity against gram-negative bacteria in vitro. Treatment guidelines identify second generation cephalosporins as treatment options for community acquired pneumonia and alternative agents for patients with a non-type 1 penicillin allergy for the treatment of otitis media and pharyngitis.^{58,59,61,62} Cefaclor, cefprozil and cefuroxime are considered alternative agents for the treatment of sinusitis.⁶⁵ The Infectious Diseases Society of America recommends second generation cephalosporins as an option for the empiric treatment of minor skin and soft tissue infections.⁶⁷ Cefuroxime is identified as a first-line treatment option in patients with early Lyme disease and in patients with late Lyme disease without neurological manifestations.⁷² The Global Initiative for Chronic Obstructive Lung Disease recommends the use of a second or third generation cephalosporin as an alternative to penicillin, ampicillin, amoxicillin, tetracycline or sulfamethoxazole/trimethoprim in patients with chronic obstructive pulmonary disease and mild exacerbations with no risk of a poor outcome.⁷³

Clinical trials comparing the oral second generation cephalosporins to each other and to first and third generation cephalosporins have failed to consistently demonstrate “superiority” of one agent over the other, though it is important to remember that the spectrum of activity differs between generations.¹²⁻⁴⁴ One study summarized by Ball found significantly better clinical efficacy rates with cefprozil compared to cefuroxime for the treatment of lower respiratory tract infections.¹⁹ Gooch et al compared cefuroxime, cefadroxil and cephalexin in patients with mild to moderate skin and skin structure infections and found no

significant difference between cefuroxime and cefadroxil in clinical or bacteriological outcomes, though a significant difference in favor of cefuroxime was observed when compared to cephalexin.³⁹ Two studies compared cefaclor to cefaclor extended-release in the treatment of pneumonia and pharyngitis/tonsillitis. Derriennic and colleagues found similar clinical and bacteriologic response rates between agents in the treatment of pharyngitis/tonsillitis, and Casali and colleagues reported no significant differences between agents in favorable clinical response and pathogen eradication in patients with pneumonia.^{24,29}

All second generation agents are available generically in at least one dosage form or strength. The 250 mg/5 mL concentration of cefuroxime is only available as the branded agent Ceftin[®]. A 125 mg/5 mL concentration is available generically.

Appendix I: Utilization Within This Drug Class for DVHA: January 1, 2011 to June 30, 2011

Medication	Unique utilizers	# of Rx's	Market Share (%)	Plan Cost \$	Avg \$/Rx
Cefuroxime	253	265	67.60%	\$4,600.78	\$17.36
Cefprozil	65	65	16.58%	\$3,729.48	\$57.38
Ceftin [®]	43	47	11.99%	\$7,256.25	\$154.39
Cefaclor	15	15	3.83%	\$834.89	\$55.66
Class Total:	376	392	100%	\$16,421.40	\$41.89

Recommendations

At this time, all generic second-generation cephalosporins are preferred on the Department of Vermont Health Access (DVHA) preferred drug list (PDL). The brands, Ceftin[®], Cefzil[®], and Lorabid[®] are listed as PA required. However, two of these brands, Cefzil[®] and Lorabid[®], have been discontinued and hence should be removed from the DVHA PDL. No additional changes to the current approval criteria for the second-generation cephalosporins are recommended.

Ceftin[®] tablets:

- The patient has had a documented side effect, allergy, or treatment failure to at least two of the following medications: cefaclor/ER, cefprozil, and cefuroxime. If a product has an AB rated generic, one trial must be the generic formulation.

Ceftin[®] suspension:

- The patient has had a documented side effect, allergy, or treatment failure to at least two of the following medications: cefaclor suspension, cefprozil suspension and cefuroxime suspension. If a product has an AB rated equivalent that is preferred, one trial must be the preferred formulation.

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