



# Department of Vermont Health Access

## Therapeutic Class Review First Generation Cephalosporins

### Overview/Summary

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

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.<sup>2,3</sup> 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).<sup>2,3</sup>

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.<sup>2</sup>

This review will focus on the oral first 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
Cefadroxil*	First generation cephalosporin	✓
Cephalexin* (Keflex <sup>®</sup> )	First generation cephalosporin	✓

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

The first 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 first generation cephalosporins that are noted

in Table 3. The first generation cephalosporins 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 First Generation Cephalosporins<sup>4-8</sup>**

Bacteria	Cefadroxil	Cephalexin
<b>Gram-Positive Aerobes</b>		
<i>Staphylococcus</i> spp.	✓ *	
<i>Staphylococcus aureus</i>		✓ *
<i>Streptococci</i> spp.	✓ †	
<i>Streptococcus pneumoniae</i>	✓	✓ ‡
<i>Streptococcus pyogenes</i>		✓
<b>Gram-Negative Aerobes</b>		
<i>Escherichia coli</i>	✓	✓
<i>Haemophilus influenzae</i>		✓
<i>Klebsiella</i> spp.	✓	✓
<i>Moraxella (Branhamella) catarrhalis</i>	✓	✓
<i>Proteus mirabilis</i>	✓	✓

\* Including penicillinase-producing strains.

† β-hemolytic.

‡ Penicillin-susceptible.

### Indications

**Table 3. Food and Drug Administration (FDA) Approved Indications<sup>4-8</sup>**

Indication	Cefadroxil	Cephalexin
<b>Dermatologic</b>		
Skin and skin structure infections	✓	✓
<b>Genitourinary</b>		
Genitourinary tract infections		✓
Urinary tract infections	✓	
<b>Musculoskeletal</b>		
Bone infections		✓
<b>Respiratory</b>		
Otitis media		✓
Pharyngitis and/or tonsillitis	✓	
Respiratory tract infections		✓

### Pharmacokinetics

**Table 4. Pharmacokinetics<sup>9-11</sup>**

Generic Name	Time to Peak Blood Levels (hours)	Protein Binding (%)	Renal Excretion (%)	Serum Half-Life (hours)
Cefadroxil	1.0 to 1.5	20	90	1 to 2
Cephalexin	1	15 to 20	90	0.9

### Clinical Trials

Overall, the first generation cephalosporins have demonstrated efficacy for their respective indications. Within-class comparisons between cefadroxil and cephalexin have failed to consistently demonstrate “superiority” of one agent over the other for the treatment of respiratory tract infections, skin and soft tissue infections or urinary tract infections.<sup>12-15</sup> Studies comparing the first generation cephalosporins to second or third generation cephalosporins have also failed to consistently demonstrate “superiority” of

one agent over the others for varying indications, though it is important to remember that the spectrum of activity differs between generations.<sup>16-21</sup> Randolph and colleagues compared cefadroxil and cefaclor for the treatment of group A  $\beta$ -hemolytic streptococcal pharyngitis and demonstrated a significantly greater number of patients with a good therapeutic response to cefadroxil.<sup>16</sup> Ballantyne et al compared cefadroxil and cefaclor in the treatment of skin and soft tissue infections and found no significant difference between groups in clinical efficacy, though adherence appeared to be better with cefadroxil based on the return of unused capsules.<sup>17</sup> No significant difference was observed between cefadroxil and cefuroxime or between cephalixin and cefdinir in the treatment of skin and soft tissue infections.<sup>18-20</sup> Gooch et al compared cefadroxil, cephalixin and cefuroxime 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 cephalixin.<sup>21</sup>

**Table 5. Clinical Trials**

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<b>Otitis Media</b>				
<p>Stechenberg et al<sup>22</sup></p> <p>Cephalexin 63.45±16.98 mg/kg/day in 4 divided doses</p> <p>vs</p> <p>ampicillin 73.13±17.41 mg/kg/day in 4 divided doses</p>	<p>DB, RCT</p> <p>Children with acute otitis media who presented to the emergency department</p>	<p>N=179</p> <p>14 days</p>	<p>Primary: Clinical response</p> <p>Secondary: Not reported</p>	<p>Primary: No significant differences were observed between groups.</p> <p>Significantly more patients in the cephalexin group responded poorly when <i>H influenza</i> was isolated compared to those in the ampicillin group (<math>P&lt;0.05</math>).</p> <p>Secondary: Not reported</p>
<b>Pharyngitis/Tonsillitis</b>				
<p>Randolph et al<sup>16</sup></p> <p>Cefadroxil 30 mg/kg once daily</p> <p>vs</p> <p>cefaclor 20 mg/kg TID</p>	<p>PRO, RCT</p> <p>Patients 3 to 21 years of age with clinical signs and symptoms of acute group A <math>\beta</math>-hemolytic streptococcal pharyngitis</p>	<p>N=250</p> <p>10 days</p>	<p>Primary: Clinical evaluation, microbiologic evaluations</p> <p>Secondary: Adverse event</p>	<p>Primary: On day 14 (<math>P=0.020</math>) and days 21 to 28 (<math>P=0.043</math>), a greater number of patients treated with cefadroxil had good therapeutic response to therapy compared to patients treated with cefaclor.</p> <p>Patients treated with cefadroxil had a lower failure or clinical recurrence compared to patients treated with cefaclor (4.6 vs 22.1%, respectively; no <math>P</math> value reported).</p> <p>Secondary: No significant drug-related adverse event reported.</p>
<p>Milatovic et al<sup>23</sup></p> <p>Cefadroxil 25 mg/kg BID (maximum 2 g/day)</p> <p>vs</p> <p>phenoxymethyl penicillin 25,000 U/kg TID (maximum 1.2 million U/day)</p>	<p>MC, RCT</p> <p>Pediatric patients 3 months to 18 years of age with acute tonsillo-pharyngitis caused by group A streptococci</p>	<p>N=150</p> <p>10 days</p>	<p>Primary: Microbiological failure rate, persistent clinical symptoms</p> <p>Secondary: Not reported</p>	<p>Primary: Microbiological failure rate was reported as 19.0 and 6.8% in patients treated with penicillin and cefadroxil, respectively (<math>P&lt;0.01</math>). Of the patients with microbiological failure, persistent clinical symptoms of infection were reported as 43.5 and 25.0% in these patients treated with penicillin and cefadroxil, respectively (<math>P</math> value not reported).</p> <p>Secondary: Not reported</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Disney et al <sup>24</sup>  Cephalexin 27 mg/kg/day divided in 4 doses  vs  penicillin 27 mg/kg/day divided in 4 doses	DB, MC, RCT, RETRO, XO  Patients 4 to 17 years of age with group A $\beta$ -hemolytic streptococcal tonsillo-pharyngitis	N=525  10 days	Primary: Symptomatic clinical failure, bacteriologic failure rate, combined failure rate  Secondary: Not reported	Primary: Symptomatic clinical failure rate was reported as 8 and 3% in patients treated with penicillin and cephalexin, respectively ( $P=0.01$ ); bacteriologic failure rate was reported as 11 and 7%, respectively ( $P=0.10$ ). Combined failure rate was 19 and 10% in patients treated with penicillin and cephalexin, respectively ( $P=0.004$ ).  Secondary: Not reported
<b>Respiratory Tract Infections</b>				
ZeLuff et al <sup>25</sup>  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 $P$ values were reported).  Microbiologic cure was reported in 98 and 96% of patients treated with cefadroxil and cefaclor, respectively (no $P$ 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.
Blaser et al <sup>12</sup>  Cefadroxil 500 mg BID  vs  cephalexin 250 mg QID	PRO, RCT  Patients 19 to 92 years of age with community-acquired pneumonia of mild to moderate severity	N=34  10 days	Primary: Clinical evaluation, microbiologic evaluation  Secondary: Adverse events	Primary: All 34 cases achieved clinical cure; no additional information in regards to differences in clinical cure rates were reported between cefadroxil and cephalexin (no $P$ values were reported).  Clearing of chest exam findings were reported in 79 and 73% of patients treated with cefadroxil and cephalexin, respectively (no $P$ values were reported).  Secondary: Drug-related adverse effects were minimal.
Verghese et al <sup>26</sup>  Cephalexin 250 mg QID	RCT  Patients with purulent	N=86  1 to 14 days	Primary: Clinical cure, clinical improvement	Primary: Clinical cure was reported as 70.8 and 50.0% in patients treated with cefixime and cephalexin, respectively ( $P<0.05$ ). Combined percentages for clinical cure and improvement were reported as 95.8 and 84.2% in patients treated with

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs cefixime 400 mg for 1 dose	exacerbation of chronic bronchitis		Secondary: Adverse events	cefixime and cephalexin, respectively ( $P=0.06$ ).  Secondary: Both treatments were well tolerated. Diarrhea occurred more often in patients treated with cefixime compared to patients treated with cephalexin ( $P=0.013$ ).
<b>Skin and Soft Tissue Infections</b>				
Ballantyne et al <sup>17</sup>  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; $P=0.41$ ). 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 $P$ value reported).  Secondary: Not reported
Ballantyne et al <sup>13</sup>  Cefadroxil 500 mg BID  vs  cefadroxil 1,000 mg once daily  vs  cefadroxil 1,000 mg BID  vs  cephalexin 500 mg QID  In study A, participants received either cefadroxil 1,000 mg BID or cephalexin; in study	MA (2 DB, MC)  Patients with various skin and soft-tissue infections, including furunculosis	N=224  10 days	Primary: Clinical evaluations, microbiologic evaluations  Secondary: Adverse events	Primary: In study A, improvement in clinical and bacteriologic evaluations were reported in patients treated with cefadroxil and cephalexin (100 vs 91%, respectively; no $P$ value reported).  In study B, improvement in clinical and bacteriologic evaluations was reported in patients treated with both cefadroxil doses and cephalexin (98 vs 97 vs 98%, respectively; no $P$ value reported).  Based on the studies in this MA, overall clinical and bacteriologic response to cefadroxil and cephalexin were both reported as 96%.  Secondary: No significant drug-related adverse events were reported.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
B, participants received either cefadroxil 500 mg BID or 1,000 mg once daily or cephalexin.				
Jacobs et al <sup>18</sup>  Cefuroxime 30 mg/kg/day divided every 12 hours  vs  cefadroxil 30 mg/kg/day divided every 12 hours	Investigator-blinded, MC, RCT  Patients 3 months to 12 years of age with skin or skin structure infections	N=238  Up to 20 days post-treatment	Primary: Clinical response, bacteriological response  Secondary: Not reported	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; $P=0.50$ )  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 ( $P=0.625$ ).  Secondary: Not reported
Tack et al <sup>19</sup>  Cephalexin 10 mg/kg QID  vs  cefdinir 7 mg/kg BID	DB, MC, RCT  Patients 6 months to 12 years of age diagnosed with an uncomplicated mild to moderate skin or skin-structure infection warranting systemic anti-microbial therapy and/or drainage	N=231  10 days	Primary: Clinical cure rate, microbiologic eradication rate  Secondary: Adverse events	Primary: Clinical cure rates were reported as 98.3 and 93.8% in patients treated with cefdinir and cephalexin, respectively ( $P=0.056$ ). Microbiologic eradication rates were reported as 99.4 and 97.4% in patients treated with cefdinir and cephalexin, respectively ( $P=0.14$ ).  Secondary: Drug-related adverse events were reported in 16 and 11% of patients treated with cefdinir and cephalexin, respectively ( $P=0.11$ ). The most common side effect was diarrhea.
Tack et al <sup>20</sup>	DB, MC, RCT	N=382	Primary: Pathogen	Primary: No significant difference was observed between groups in pathogen eradication

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Cephalexin 500 mg QID for 10 days  vs  cefdinir 300 mg BID for 10 days	Patients 13 years of age and older with acute skin and skin structure infections	7 to 16 days post-therapy	eradication rate, clinical success rate  Secondary: Not reported	rate (93% for cefdinir and 89% for cephalexin; $P=0.105$ ).  No significant difference was observed in the rate of superinfection between groups ( $P=0.22$ ).  No significant differences between groups was observed in clinical success rates (88% for cefdinir and 87% for cephalexin; $P=0.617$ ).  Secondary: Not reported
Bucko et al <sup>27</sup>  Cefadroxil 500 mg BID  vs  cefditoren 200 mg BID  vs  cefditoren 400 mg BID  vs  cefuroxime 250 mg BID  In study A, participants received cefditoren 200 mg or cefuroxime; in study B, participants received cefditoren 400 mg or cefadroxil.	MA (2 DB, MC, PG)  Patients with uncomplicated skin and skin structure infections	N=1,685  10 days	Primary: Clinical evaluation, microbiologic evaluation  Secondary: Adverse events	Primary: Clinical cure rates were reported as 85, 83, 88 and 85% for patients treated with cefditoren 200 mg, cefditoren 400 mg, cefuroxime, and cefadroxil, respectively (no $P$ values reported).  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 ( $P=0.018$ ).  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.
Gooch et al <sup>21</sup>  Cefadroxil 500 mg BID	DB, MC, PG, RCT  Patients with	N=330  10 days	Primary: Clinical and bacteriological response	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%

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs cephalixin 500 mg BID vs cefuroxime 250 mg BID	mild to moderate infections of the skin or skin structures		Secondary: Adverse events	of patients treated with cefuroxime, cephalixin, and cefadroxil, respectively ( $P=0.026$ , cefuroxime vs cephalixin).  Secondary: There was no significant difference in reported drug-related gastrointestinal adverse events by patients treated with cefuroxime, cephalixin, or cefadroxil (9.3 vs 7.2 vs 9.8%, respectively).
Wible et al <sup>28</sup>  Cefadroxil 15 mg/kg every 12 hours or 500 mg every 12 hours (patients 12 to 17 years of age)  vs  linezolid 10 mg/kg every 12 hours or 600 mg every 12 hours (patients 12 to 17 years of age)	DB, PRO, RCT  Patients 5 to 17 years of age with skin infections	N=508  10 to 21 days after last dose of study medication	Primary: Clinical cure, microbiological cure  Secondary; Not reported	Primary: No significant difference was observed between groups in clinical cure (90% for cefadroxil and 91% for linezolid; $P=0.737$ ).  No significant difference was observed between groups for microbiological cure 90.5% for cefadroxil and 90.4% for linezolid; $P=0.993$ ).  <i>S aureus</i> was eradicated in 88.8% of cefadroxil and 89.6% of linezolid treated microbiologically evaluable patients ( $P$ value not reported).  Secondary: Not reported
Kiani <sup>29</sup>  Cephalixin 500 mg BID for 10 days  vs  azithromycin 500 mg on day 1 then 250 mg once daily for days 2 through 5	DB, DD, MC, RCT  Patients 16 years of age and older with acute skin and skin structure infections	N=179  30 days	Primary: Clinical response, bacterial eradication  Secondary: Not reported	Primary: The distribution of clinical response (cured, improved, failed) was similar between groups ( $P=0.37$ ).  A satisfactory response occurred in 94.0% of patients in the azithromycin group and 95.8% of patients in the cephalixin group ( $P$ value not reported).  Clinical cure rates at the end of treatment were 53.0% in the azithromycin group and 59.4% in the cephalixin group ( $P$ value not reported).  Clinical improvement occurred in 41.0% of azithromycin patients and 36.5% of cephalixin patients ( $P$ value not reported).  The bacterial eradication rates were similar between groups (94.2% for the azithromycin group and 90.3% for the cephalixin group; $P=0.34$ ).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
<p>Parish et al<sup>30</sup></p> <p>Cephalexin 500 mg BID or 12.5 mg/kg BID (patients &lt;13 years of age) for 10 days</p> <p>vs</p> <p>retapamulin ointment 1% BID for 5 days</p>	<p>DB, DD, MC, NI, RCT</p> <p>Patients 9 months of age and older with underlying inflammatory skin disease and evidence of secondary infection</p>	<p>N=546</p> <p>Up to 19 days</p>	<p>Primary: Clinical response rate (success or failure) at follow-up (seven to nine days post-therapy)</p> <p>Secondary: Clinical response at end of therapy (days seven to nine for retapamulin or 12 to 14 for cephalexin), microbiological response at follow-up and end of therapy</p>	<p>Secondary: Not reported</p> <p>Primary: No significant difference between groups was observed in clinical response at follow-up (<i>P</i> value not reported).</p> <p>Secondary: Clinical success rates were similar between groups at end of therapy (<i>P</i> value not reported).</p> <p>No significant difference between groups was observed in microbiological response at follow-up or end of therapy (<i>P</i> value not reported).</p>
<p>Parish et al<sup>31</sup></p> <p>Clarithromycin 250 mg BID for 5 to 14 days</p> <p>vs</p> <p>cefadroxil 500 mg BID for 5 to 14 days (Study 1) or erythromycin 250 mg QID for maximum of 14 days (Study 2)</p>	<p>DB, MC, RCT</p> <p>Patients with skin or skin structure infections</p>	<p>N=299 (efficacy, Study 1)</p> <p>N=538 (safety, Study 1)</p> <p>N=141 (efficacy, Study 2)</p> <p>N=261 (safety, Study 2)</p>	<p>Primary: Clinical and bacteriological response</p> <p>Secondary: Not reported</p>	<p>Primary: In study 1, clinical cure rates were 77% in the clarithromycin group and 79% in the cefadroxil group (<i>P</i> value not reported).</p> <p>In study 1, overall bacteriologic eradication rates were 89% in the clarithromycin group and 92% in the cefadroxil group (<i>P</i> value not reported).</p> <p>In study 2, clinical cure rates were 79% in the clarithromycin group and 82% in the erythromycin group (<i>P</i> value not reported).</p> <p>In study 2, overall bacteriologic eradication rates were 95% in both the clarithromycin and erythromycin groups.</p> <p>Secondary: Not reported.</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
		48 hours post-treatment		
<b>Surgical Prophylaxis</b>				
Song et al <sup>32</sup>  Cefuroxime plus metronidazole  vs  gentamicin plus metronidazole  vs  first generation or second generation cephalosporin  vs  third generation cephalosporin  vs  other antibiotic agents as mono or combination therapy	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, 1.07; 95% CI, 0.54 to 2.12).  Secondary: Not reported
<b>Urinary Tract Infections</b>				
Bolding et al <sup>14</sup>  Cefadroxil 1,000 mg BID  vs	DB, RCT  Females 18 to 63 years of age with urinary tract	N=26  10 to 13 days	Primary: Clinical cure rate  Secondary: Adverse event	Primary: Clinical cure rates were achieved in 100 and 92% of patients treated with cephalexin and cefadroxil, respectively, within five to nine days; no <i>P</i> value reported. One patient treated with cefadroxil was not cured due to an <i>E coli</i> urinary tract infection.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
cephalexin 500 mg QID	infections			Secondary: One patient taking cefadroxil reported side effects of nausea and vomiting which may be associated with concurrent therapy with propoxyphene-acetaminophen. Patients treated with cefadroxil reported less vaginal itching or irritation compared to patients treated with cephalexin (no <i>P</i> value reported).
Elhanan et al <sup>15</sup>  Fosfomycin 3 g single-dose  vs  cephalexin 500 mg QID for 5 days	RCT  Women ≥16 years of age with acute uncomplicated cystitis (symptoms of dysuria, frequency/urgency of urination, absence of fever/flank pain, pyuria, ≥10 <sup>5</sup> CFU/mL of an organism sensitive to both antibiotics)	N=112  5 days to 1 month	Primary: Clinical cure, microbiological cure  Secondary: Not reported	Primary: At the five day follow-up, 91% of patients receiving fosfomycin and 91% of patients receiving cephalexin were considered clinically cured ( <i>P</i> =NS); at one month, 86 and 78% were considered cured, respectively ( <i>P</i> =NS).  In terms of microbiological cure, 91% of fosfomycin-treated patients compared to 83% of cephalexin-treated patients were cured at five days; 81% of fosfomycin-treated patients compared to 68% of cephalexin-treated patients were cured at one month ( <i>P</i> value not reported).  Secondary: Not reported
Zalmanovici Trestioreanu et al <sup>33</sup>  Nitrofurantoin  vs  SMX/TMP  vs  β-lactams (amoxicillin,	MA  Outpatient women 16 to 65 years of age with uncomplicated UTI defined by the presence of urinary complaints (and the absence of	N=6,016  ≥3 days	Primary: Short-term symptomatic cure and long-term symptomatic cure  Secondary: Short-term bacteriological cure, long-term bacterial cure, proportion of	Primary: There was no statistically significant difference in short-term and long-term symptomatic cure with any of the treatment comparisons: fluoroquinolones vs SMX/TMP (RR, 1.00; 95% CI, 0.97 to 1.03; <i>P</i> =0.89 and RR, 0.99; 95% CI, 0.94 to 1.05), β-lactams vs SMX/TMP (RR, 0.95; 95% CI, 0.81 to 1.39; <i>P</i> =0.56 and RR, 1.06; 95% CI, 0.93 to 1.21; <i>P</i> =0.40), nitrofurantoin vs β-lactams (RR, 1.19; 95% CI, 0.93 to 1.51 and RR, 0.98; 95% CI, 0.83 to 1.14), fluoroquinolones vs β-lactams (RR, 1.15; 95% CI, 0.99 to 1.32; <i>P</i> =0.064 and RR, 1.01; 95% CI, 0.96 to 1.05) and nitrofurantoin vs SMX/TMP (RR, 0.99; 95% CI, 0.95 to 1.04; <i>P</i> =0.82 and RR, 1.01; 95% CI, 0.94 to 1.09; <i>P</i> =0.81).  Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
cefadroxil, cefpodoxime pivmecillinam*)  vs  nalidixic acid  vs  fluoroquinolones (amifloxacin*, ciprofloxacin, norfloxacin, ofloxacin)	upper UTI signs) and leucocyturia or bacteriuria		patients that developed resistance ≤8 weeks after treatment period, numbers of days to symptom resolution, days of work-loss, adverse event resulting in discontinuation of therapy, proportion of patients that developed rash, diarrhea, any adverse event or complications	<p>In the ITT population comparing fluoroquinolones and SMX/TMP, there was a significant difference in short-term bacteriologic cure that slightly favored fluoroquinolones (RR, 1.03; 95% CI, 1.00 to 1.07; <i>P</i>=0.025). The result was no longer significant when patients with susceptible pathogens were compared (RR, 1.03; 95% CI, 0.98 to 1.07; <i>P</i>=0.23). This result was similar for long-term bacteriologic cure comparing fluoroquinolones and SMX/TMP (RR, 1.06; 95% CI, 1.00 to 1.12; <i>P</i>=0.046). When comparing fluoroquinolones vs β-lactams, short-term bacteriologic cure was significantly greater in patients treated with fluoroquinolones in the ITT population (RR, 1.22; 95% CI, 1.13 to 1.31; <i>P</i>&lt;0.00001) and the patients with susceptible pathogens (RR, 1.20; 95% CI 1.07 to 1.35; <i>P</i>=0.0018). There were no significant differences in short-term and long-term bacteriologic cure comparing the other treatment groups.</p> <p>Significantly less patients developed rashes with fluoroquinolones vs SMX/TMP (RR, 0.08; 95% CI, 0.71 to 1.29; <i>P</i>=0.0035) or β-lactams (RR, 0.10; 95% CI, 0.02 to 0.56; <i>P</i>=0.0083) and with nitrofurantoin vs SMX/TMP (RR, 0.17; 95% CI, 0.04 to 0.76; <i>P</i>=0.020). There were no significant differences in rashes comparing the other treatment groups.</p> <p>Data either could not be analyzed or was missing for number of days to symptom resolution or days of work loss. There were no significant differences in any of the other secondary outcomes when comparing treatment groups.</p>
Brumfitt et al <sup>34</sup>  TMP 200 mg BID for 7 days  vs  SMX/TMP 800/160 mg BID for 7 days  vs  ampicillin 1 g BID for 7 days	PRO  Pregnant patients with bacteriuria, hospitalized patients and patients in general practice	N=96  6 weeks	Primary: Cure rates  Secondary: Not reported	Primary: In pregnancy, the cure rates were equal with TMP and SMX/TMP (85%) compared to 65% with ampicillin and 78% with cephalexin ( <i>P</i> value not significant).  In hospitalized patients, there was no difference in cure rates between the treatments, which were 73, 84, 67 and 62% with TMP, SMX/TMP, ampicillin and cephalexin ( <i>P</i> value not reported).  In general practice, TMP was associated with a 96% cure rate compared to 81, 89 and 62% with SMX/TMP, ampicillin and cephalexin. Results for cephalexin were significantly lower than the other treatments ( <i>P</i> <0.02).  Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs cephalexin 1 g BID 7 days				
Ioannidis et al <sup>35</sup>  Azithromycin at various doses given for 3 to 5 days  vs  comparator antibiotics including amoxicillin/clavulanate, cefaclor, clarithromycin, roxithromycin*, amoxicillin, erythromycin, and penicillin	MA  Patients with acute otitis media, sinusitis, or pharyngitis	N=7,610  10 days	Primary: Clinical failure rate in the group of patients treated with azithromycin versus the comparator antibiotic  Secondary: Not reported	Primary: Azithromycin had similar clinical failure rates compared to the comparator antibiotics. The difference in clinical failure rates was <0.5% and no significant difference was found between groups ( <i>P</i> values not reported).  No significant difference was observed in bacteriologic outcomes ( <i>P</i> values not reported).  Secondary: Not reported
<b>Miscellaneous</b>				
Falagas et al <sup>36</sup>  Linezolid  vs  glycopeptides (vancomycin and teicoplanin*) or $\beta$ -lactams (amoxicillin/clavulanate, ampicillin/sulbactam, cefadroxil, ceftriaxone, oxacillin, dicloxacillin)	MA  Patients with complicated skin and soft tissue infections, Gram-positive infections, uncomplicated skin and soft tissue infections, nosocomial pneumonia, community-acquired	N=6,093  Up to 28 days	Primary: Treatment success, all-cause mortality and adverse effects  Secondary: Treatment duration, microbiological assessment and eradication of Gram-positive cocci	Primary: For all infections, linezolid had significantly higher treatment success with the ITT patients (OR, 1.23; 95% CI, 1.06 to 1.42; <i>P</i> value not reported) and clinically assessed patients (OR, 1.41; 95% CI, 1.11 to 1.81; <i>P</i> =0.006) compared to the glycopeptides or $\beta$ -lactams. When only the blinded RCTs were analyzed, there was no significant difference between the treatments in the ITT patients (OR, 1.14; 95% CI, 0.95 to 1.38; <i>P</i> value not reported) and in clinically assessed patients (OR, 1.15; 95% CI, 0.89 to 1.48; <i>P</i> =0.29). Additionally, there was no significant difference in treatment success in the clinically assessed patients when linezolid was compared to vancomycin alone (OR, 1.44; 95% CI, 0.90 to 2.30) or $\beta$ -lactams (OR, 11.34; 95% CI, 0.99 to 1.81).  For the skin and soft tissue infections in the clinically assessed patients, linezolid had significantly higher treatment success compared to glycopeptides or $\beta$ -lactams (OR, 1.67; 95% CI, 1.31 to 2.12; <i>P</i> <0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	pneumonia or MRSA infections			<p>For bacteremia in the clinically assessed patients, linezolid had significantly higher treatment success compared to glycopeptides or <math>\beta</math>-lactams (OR, 2.07; 95% CI, 1.13 to 3.78; <math>P=0.02</math>).</p> <p>There was no significant difference between linezolid and glycopeptides or <math>\beta</math>-lactams for the treatment of pneumonia in the clinically assessed patients (OR, 1.03; 95% CI, 0.75 to 1.42; <math>P=0.84</math>). This was similar for the subset of patients with nosocomial pneumonia (OR, 1.05; 95% CI, 0.75 to 1.46; <math>P</math> value not reported).</p> <p>There was no significant difference in mortality between linezolid and glycopeptides or <math>\beta</math>-lactams in the ITT patients (OR, 0.97; 95% CI, 0.79 to 1.19; <math>P</math> value not reported).</p> <p>There were more adverse events with linezolid compared to glycopeptides or <math>\beta</math>-lactams in the ITT patients; although, the difference was not significant (OR, 1.40; 95% CI, 0.95 to 2.06; <math>P=0.09</math>). Linezolid was associated with significantly more thrombocytopenia in the ITT patients compared to glycopeptides or <math>\beta</math>-lactams (OR, 11.75; 95% CI, 3.66 to 37.57; <math>P&lt;0.0001</math>).</p> <p>Secondary: For all Gram-positive infections in the microbiologically assessed patients, linezolid had significantly higher treatment success compared to glycopeptides or <math>\beta</math>-lactams (OR, 1.34; 95% CI, 1.05 to 1.72; <math>P=0.02</math>).</p> <p>Linezolid was associated with higher rates eradication rates for <i>S aureus</i> in the microbiologically assessed patients compared to the other antibiotics (OR, 1.81; 95% CI, 1.40 to 2.34; <math>P&lt;0.00001</math>).</p> <p>There was no significant differences in eradication rate for MRSA between linezolid and the other antibiotics (OR, 1.69; 95% CI, 0.84 to 3.41; <math>P=0.014</math>). There was also no significant difference between linezolid and vancomycin in patients with MRSA pneumonia (OR, 1.26; 95% CI, 0.54 to 2.96; <math>P</math> value not reported).</p> <p>There was no significant difference in eradication of enterococci species between</p>

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				linezolid and the other antibiotics (OR, 0.95; 95% CI, 0.33 to 2.73; $P=0.93$ ).

\*Agent not available in the United States.

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

Study abbreviations: CI=confidence interval, DB=double blind, DD=double-dummy, ITT=intent-to-treat, MA=meta analysis, MC=multi-center, NI=non-inferiority, OL=open label, OR=odds ratio,

PG=parallel group, PRO=prospective, SB=single blinded, RCT=randomized controlled trial, RETRO=retrospective, XO=cross-over

Miscellaneous abbreviations: CFU=colony forming unit, MRSA=methicillin-resistant *Staphylococcus aureus*

**Special Populations****Table 6. Special Populations**<sup>4-8</sup>

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Cefadroxil	No dosage adjustment required in the elderly population.  Recommended dosage in children is 30 mg/kg/day in one or two divided doses.	Dose should be given every 12 hours in patients with creatinine clearance 25 to 50 mL/minute; every 24 hours if creatinine clearance is 10 to 25 mL/minute; every 36 hours if creatinine clearance is 0 to 10 mL/minute.	No dosage adjustment required.	B	Yes
Cephalexin	No dosage adjustment required in the elderly population.  Recommended dosage in children is 25 to 50 mg/kg/day in divided doses; for streptococcal pharyngitis in patients >1 year of age and for skin and skin structure infections, the dose may be divided every 12 hours; in severe infections the dose may be doubled; the dose for otitis media is 75 to 100 mg/kg/day in four divided doses.	Use with caution in patients with markedly impaired renal function.  Dosage may be lower than what is usually suggested.  Careful clinical observation and laboratory studies should be conducted.	No dosage adjustment required.	B	Yes

**Adverse Drug Events****Table 7. Adverse Drug Events (%)**<sup>4-8</sup>

Adverse Event	Cefadroxil	Cephalexin
<b>Central Nervous System</b>		
Agitation	-	✓
Confusion	-	✓
Dizziness	-	✓
Fever	✓	✓
Hallucinations	-	✓
Headache	-	✓
Seizures	✓	✓
<b>Dermatological</b>		
Erythema multiforme	✓	✓

Adverse Event	Cefadroxil	Cephalexin
Pruritis	✓	-
Rash	✓	✓
Stevens-Johnson syndrome	✓	✓
Toxic epidermal necrolysis	✓	✓
Urticaria	✓	✓
<b>Gastrointestinal</b>		
Abdominal pain	✓	✓
Colitis	-	✓
Diarrhea	✓	✓
Dyspepsia	✓	✓
Gastritis	-	✓
Nausea/vomiting	✓	✓
Pseudomembranous colitis	✓	✓
<b>Genitourinary</b>		
Anal pruritus	-	✓
Genital moniliasis	✓	✓
Genital pruritus	✓	✓
Vaginal discharge	-	✓
Vaginitis	✓	✓
<b>Hematological</b>		
Agranulocytosis	✓	✓
Aplastic anemia	✓	✓
Eosinophilia	✓	✓
Hemolytic anemia	✓	✓
Hemorrhage	✓	✓
Leukopenia	-	✓
Neutropenia	✓	✓
Pancytopenia	✓	✓
Positive Coomb's test	✓	-
Prothrombin time increased	✓	✓
Thrombocytopenia	✓	✓
<b>Hepatic</b>		
Cholestasis	✓	-
Cholestatic jaundice	-	✓
Elevated liver enzymes	✓	✓
Hepatic dysfunction	✓	-
Hepatic failure, idiosyncratic	✓	-
Hepatitis, transient	-	✓
<b>Musculoskeletal</b>		
Arthralgia	✓	✓
Arthritis	-	✓
Joint disorder	-	✓
<b>Renal</b>		
Blood urea nitrogen increased	✓	✓
Creatinine increased	✓	✓
Interstitial nephritis, reversible	-	✓
Renal insufficiency	✓	✓
Toxic nephropathy	✓	✓
<b>Miscellaneous</b>		
Anaphylaxis	✓	✓
Angioedema	✓	✓
Fatigue	-	✓

Adverse Event	Cefadroxil	Cephalexin
Serum sickness-like reaction	✓	-
Superinfection	✓	-

✓ Percent not specified.

- Event not reported.

### **Contraindications/Precautions**

The first generation cephalosporins are contraindicated in patients with a known allergy to the cephalosporin group of antibiotics.<sup>4-8</sup>

Before therapy with a first 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 first generation cephalosporin is to be given to penicillin-sensitive patients, caution should be exercised because cross-sensitivity among  $\beta$ -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.<sup>4-8</sup>

*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.<sup>4-8</sup>

Prolonged administration may result in an overgrowth of non-susceptible organisms.<sup>4-8</sup>

The first 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.<sup>4-8</sup>

Cefadroxil and cephalexin should be used with caution in patients with markedly impaired renal function (creatinine clearance <50 mL/minute). Careful monitoring and laboratory testing is recommended.<sup>4-8</sup>

Cefadroxil and cephalexin should be used with caution in patients with a history of gastrointestinal disease and/or colitis.<sup>4-8</sup>

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.<sup>4-8</sup>

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.<sup>4-8</sup>

### **Drug Interactions**

No clinically significant drug interactions were noted in the clinical literature.<sup>4-8,37</sup>

**Dosage and Administration**

**Table 8. Dosing and Administration**<sup>4-8</sup>

Generic Name	Usual Adult Dose	Usual Pediatric Dose	Availability
Cefadroxil	<p><u>Pharyngitis and tonsillitis and skin and skin structure infections:</u> 1 g daily either once daily or divided BID</p> <p><u>Uncomplicated lower urinary tract infections:</u> 1 or 2 g once daily or divided BID</p> <p><u>Other urinary tract infections:</u> 2 g divided BID</p>	<p><u>Pharyngitis, tonsillitis, and impetigo:</u> 30 mg/kg/day as a single dose or divided every 12 hours</p> <p><u>Skin and skin structure infections and urinary tract infections:</u> 30 mg/kg/day divided every 12 hours</p>	<p>Capsule: 500 mg</p> <p>Powder for oral suspension: 250 mg/5 mL 500 mg/5 mL</p> <p>Tablet: 1 g</p>
Cephalexin	<p><u>Infections (genitourinary tract, bone, and respiratory tract infections):</u> 1 to 4 g daily in divided doses; usual adult dose is 250 mg every 6 hours; the 750 mg strength should be administered such that the total daily dose falls within 1 to 4 g</p> <p><u>Streptococcal pharyngitis, skin and skin structure infections, uncomplicated cystitis in patients &gt;15 years of age:</u> 500 mg every 12 hours</p>	<p><u>Infections (genitourinary tract, bone, respiratory tract, and skin and skin structure infections):</u> 25 to 50 mg/kg/day in divided doses; for streptococcal pharyngitis in patients &gt;1 year of age and for skin and skin structure infections, the dose may be divided every 12 hours</p> <p><u>Serious infections:</u> Dose may be doubled; adjust as needed</p> <p><u>Otitis media:</u> 75 to 100 mg/kg/day in 4 divided doses</p>	<p>Capsule: 250 mg 500 mg 750 mg*</p> <p>Powder for oral suspension: 125 mg/5 mL 250 mg/5 mL</p> <p>Tablets: 250 mg 500 mg</p>

\*Solely available as a branded product.

**Clinical Guidelines**

The clinical guidelines contained in Table 9 are summarized globally and are not limited to the role of the first 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 9. Clinical Guidelines**

Clinical Guideline	Recommendations
<p>Infectious Diseases Society of America/ American Thoracic Society: <b>Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults (2007)</b><sup>38</sup></p>	<p><u>General recommendations</u></p> <ul style="list-style-type: none"> <li>• Selection of antimicrobial regimens for empirical therapy is based on prediction of the most likely pathogens(s) and knowledge of local susceptibility patterns.</li> <li>• Once the etiology of community acquired pneumonia has been identified via microbiological testing, antimicrobial therapy should be directed at that pathogen.</li> </ul> <p><u>Empiric therapy - outpatient treatment</u></p> <ul style="list-style-type: none"> <li>• For previously healthy patients with no risk factors for drug resistant</li> </ul>

Clinical Guideline	Recommendations
	<p><i>Streptococcus pneumoniae</i> infection, a macrolide (azithromycin, clarithromycin, or erythromycin) can be used. Doxycycline may also be an alternate option.</p> <ul style="list-style-type: none"> <li>• 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 <math>\beta</math>-lactam (ceftriaxone, cefpodoxime, or cefuroxime) plus a macrolide or doxycycline, or amoxicillin/clavulanate.</li> </ul> <p><u>Empiric therapy - inpatient, non-intensive care unit treatment</u></p> <ul style="list-style-type: none"> <li>• A respiratory fluoroquinolone or a combination of a <math>\beta</math>-lactam plus a macrolide is recommended.</li> <li>• Preferred <math>\beta</math>-lactam agents include cefotaxime, ceftriaxone, and ampicillin; ertapenem may also be used for selected patients.</li> <li>• A respiratory fluoroquinolone should be used for penicillin allergic patients.</li> </ul> <p><u>Empiric therapy - inpatient, intensive care unit treatment</u></p> <ul style="list-style-type: none"> <li>• A <math>\beta</math>-lactam (cefotaxime, ceftriaxone, or ampicillin/sulbactam) plus either azithromycin or a respiratory fluoroquinolone.</li> <li>• For penicillin-allergic patients, a respiratory fluoroquinolone and aztreonam are recommended.</li> <li>• For <i>Pseudomonas</i> infection, use an antipneumococcal, antipseudomonal <math>\beta</math>-lactam (piperacillin/tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin.</li> <li>• The antipneumococcal, antipseudomonal <math>\beta</math>-lactams listed above can also be used with either an aminoglycoside and azithromycin, or an aminoglycoside and an antipneumococcal fluoroquinolone.</li> <li>• For penicillin-allergic patients, substitute aztreonam for the above <math>\beta</math>-lactam for <i>Pseudomonas</i> infection.</li> </ul> <p><u>Pathogen-directed therapy</u></p> <ul style="list-style-type: none"> <li>• <i>S pneumoniae</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.</li> <li>• <i>S pneumoniae</i> (penicillin resistant)- agents chosen based on susceptibility; alternative agents include vancomycin, linezolid and high-dose amoxicillin (3 g/day).</li> <li>• <i>Haemophilus influenzae</i> (non-<math>\beta</math>-lactamase producing)- amoxicillin preferred; alternative agents include fluoroquinolone, doxycycline, azithromycin, clarithromycin.</li> <li>• <i>H influenzae</i> (<math>\beta</math>-lactamase producing)- second- or third-generation cephalosporin or amoxicillin/clavulanate preferred; alternative agents include fluoroquinolone, doxycycline, azithromycin, clarithromycin.</li> <li>• <i>Mycoplasma pneumoniae/Chlamydia pneumoniae</i>- macrolide, tetracycline preferred; alternative agent is fluoroquinolone.</li> </ul>

Clinical Guideline	Recommendations
	<ul style="list-style-type: none"> <li>• <i>Legionella</i> species- fluoroquinolone, azithromycin preferred; alternative agent is doxycycline.</li> <li>• <i>Chlamydia psittaci</i>- tetracycline preferred; alternative agent is a macrolide.</li> <li>• <i>Coxiella burnetii</i>- tetracycline preferred; alternative agent is a macrolide.</li> <li>• <i>Francisella tularensis</i>- doxycycline preferred; alternative agents include gentamicin or streptomycin.</li> <li>• <i>Yersinia pestis</i>- streptomycin, gentamicin; recommended alternative agents include doxycycline or fluoroquinolone.</li> <li>• <i>Bacillus anthracis</i> (inhalation)- ciprofloxacin, levofloxacin, doxycycline preferred (usually with a second agent); alternative agents include other fluoroquinolones, rifampin, clindamycin, chloramphenicol, or a <math>\beta</math>-lactam if susceptible.</li> <li>• <i>Enterobacteriaceae</i>- third generation cephalosporin, carbapenem; alternative agents include a <math>\beta</math>-lactam/<math>\beta</math>-lactamase inhibitor or a fluoroquinolone.</li> <li>• <i>Pseudomonas aeruginosa</i>- antipseudomonal <math>\beta</math>-lactam plus ciprofloxacin or levofloxacin or aminoglycoside preferred; alternative agents include aminoglycoside plus ciprofloxacin or levofloxacin.</li> <li>• <i>Burkholderia pseudomallei</i>- carbapenem, ceftazidime preferred; alternative agents include fluoroquinolone or sulfamethoxazole/trimethoprim (SMX/TMP).</li> <li>• <i>Acinetobacter</i> species- carbapenem preferred; alternative agents include cephalosporin and aminoglycoside, ampicillin/sulbactam, colistin.</li> <li>• <i>Staphylococcus aureus</i> (methicillin susceptible)- antistaphylococcal penicillin preferred; alternative agents include cefazolin and clindamycin.</li> <li>• <i>S aureus</i> (methicillin resistant)- vancomycin or linezolid preferred; alternative agent is SMX/TMP.</li> <li>• <i>Bordetella pertussis</i>- macrolide preferred; alternative agent is SMX/TMP.</li> <li>• Anaerobe (aspiration)- <math>\beta</math>-lactam/<math>\beta</math>-lactamase inhibitor or clindamycin preferred; alternative agent is carbapenem.</li> <li>• Influenza virus- oseltamivir or zanamivir preferred.</li> <li>• <i>Mycobacterium tuberculosis</i>- isoniazid plus rifampin plus ethambutol plus pyrazinamide preferred.</li> <li>• <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.</li> <li>• <i>Histoplasmosis</i>- itraconazole preferred; alternative agent is amphotericin B.</li> <li>• <i>Blastomycosis</i>- itraconazole preferred; alternative agent is amphotericin B.</li> <li>• Suspected H1N1 pandemic influenza should be treated with oseltamivir and antibacterial agents targeting <i>S pneumonia</i> and <i>S aureus</i>.</li> </ul>
<p>American College of Chest Physicians:  <b>Management of Community-Acquired Pneumonia in the Home: An American College of Chest Physicians Clinical Position Statement (2005)</b><sup>39</sup></p>	<ul style="list-style-type: none"> <li>• The oral route for medications is recommended if the patient can tolerate it, and if the availability and activity of the agents are adequate.</li> <li>• Severity of illness, patient age, comorbidities, concomitant medications, and ease of administration are all factors that can impact the empiric treatment decision.</li> <li>• 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.</li> </ul>

Clinical Guideline	Recommendations
	<ul style="list-style-type: none"> <li>• Amoxicillin/clavulanate and some second generation cephalosporins (cefuroxime, cefpodoxime, or cefprozil) are alternatives for low-risk patients.</li> <li>• 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 <math>\beta</math>-lactam/macrolide combination or an antipneumococcal fluoroquinolone.</li> <li>• Double therapy with either a <math>\beta</math>-lactam/macrolide combination or a <math>\beta</math>-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.</li> </ul>
<p>Infectious Diseases Society of America/ American Thoracic Society: <b>Guidelines for the Management of Adults with Hospital-acquired, Ventilator-associated, and Healthcare-associated Pneumonia (2004)</b><sup>40</sup></p>	<ul style="list-style-type: none"> <li>• 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.</li> <li>• 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 <math>\beta</math>-lactam to treat <i>P aeruginosa</i> pneumonia.</li> <li>• De-escalation of antibiotics should be considered once results are available of lower respiratory tract cultures and patient's clinical response.</li> <li>• 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.</li> <li>• The following initial empiric therapy is recommended for hospital-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.</li> <li>• 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 <math>\beta</math>-lactam/ <math>\beta</math>-lactamase inhibitor (piperacillin/tazobactam) plus antipseudomonal fluoroquinolone (ciprofloxacin or levofloxacin) or aminoglycoside (amikacin, gentamicin or tobramycin) plus linezolid or vancomycin.</li> </ul>
<p>American Academy of Pediatrics and American Academy of Family Physicians, Subcommittee on Management of Acute Otitis Media: <b>Diagnosis and Management of Acute Otitis Media (2004)</b><sup>41</sup></p>	<ul style="list-style-type: none"> <li>• Treatment of existing pain, generally with acetaminophen or ibuprofen, is recommended regardless of initiation of antibacterial treatment.</li> <li>• 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.</li> <li>• Approximately 80% of patients with acute otitis media will respond to treatment with high-dose amoxicillin.</li> <li>• Patients with a fever <math>\geq 102^{\circ}\text{F}</math> 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</li> </ul>

Clinical Guideline	Recommendations
	<p>two divided doses).</p> <ul style="list-style-type: none"> <li>• 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).</li> <li>• Patients who have failed to improve while receiving amoxicillin should not be treated with SMX/TMP or erythromycin/sulfisoxazole.</li> <li>• Patients who fail treatment with amoxicillin/clavulanate should be treated with parenteral ceftriaxone.</li> <li>• 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.</li> </ul> <p><u>Special populations</u></p> <ul style="list-style-type: none"> <li>• In patients with a history of non-type-I penicillin allergy, cefdinir, cefpodoxime or cefuroxime are considered alternatives to amoxicillin.</li> <li>• 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.</li> <li>• Parenteral therapy with ceftriaxone may be used in patients who cannot tolerate oral therapy.</li> </ul>
<p>Infectious Diseases Society of America: <b>Practice Guidelines for the Diagnosis and Management of Group A Streptococcal Pharyngitis (2002)</b><sup>42</sup></p>	<ul style="list-style-type: none"> <li>• Penicillin is the drug of choice for the treatment of group A streptococcal pharyngitis.</li> <li>• Amoxicillin may be used in place of penicillin based mainly on taste.</li> <li>• Erythromycin is an alternative in patients with a penicillin allergy.</li> <li>• First generation cephalosporins are acceptable alternatives in patients with a non-type 1 penicillin allergy.</li> <li>• Clindamycin may be used in patients who are unable to tolerate <math>\beta</math>-lactam antibiotics and who are infected with erythromycin-resistant group A <i>Streptococcus</i>.</li> <li>• 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.</li> </ul>
<p>American Heart Association: <b>Prevention of Rheumatic Fever and Diagnosis and Treatment of Acute Streptococcal Pharyngitis (2009)</b><sup>43</sup></p>	<p><u>Primary prevention (treatment of Streptococcal tonsillopharyngitis)</u></p> <ul style="list-style-type: none"> <li>• The oral antibiotics of choice are penicillin V and amoxicillin.</li> <li>• Penicillin V, amoxicillin or benzathine penicillin G is recommended.</li> <li>• In patients allergic to penicillin, a narrow spectrum cephalosporin, clindamycin, azithromycin or clarithromycin may be used.</li> <li>• 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.</li> <li>• In clinical trials, a once-daily amoxicillin (Moxatag<sup>®</sup>) was shown to be effective for group A streptococcal pharyngitis. It has the advantage of being dosed once-daily which may enhance adherence.</li> </ul> <p><u>Secondary prevention (prevention of recurrent attacks of rheumatic fever)</u></p> <ul style="list-style-type: none"> <li>• Benzathine penicillin G, penicillin V or sulfadiazine are recommended.</li> <li>• In patients allergic to penicillin, a macrolide or azalide are recommended.</li> </ul>
<p>Institute for Clinical</p>	<p><u>Pharyngitis</u></p>

Clinical Guideline	Recommendations
<p>Systems Improvement:  <b>Diagnosis and Treatment of Respiratory Illness in Children and Adults (2011)</b><sup>44</sup></p>	<ul style="list-style-type: none"> <li>• Penicillin is the drug of choice. Amoxicillin is an acceptable alternative due to poor palatability of penicillin suspension.</li> <li>• Penicillin-allergic patients should be treated with cephalosporins, erythromycin or clindamycin.</li> <li>• Alternative medications include macrolides, cephalexin, clindamycin, amoxicillin/clavulanate, and rocephin.</li> <li>• Prevention of recurrent rheumatic fever requires continuous antimicrobial prophylaxis.</li> </ul> <p><u>Bacterial sinusitis</u></p> <ul style="list-style-type: none"> <li>• 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.</li> <li>• Amoxicillin is the first-line drug of choice.</li> <li>• 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.</li> <li>• 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.</li> <li>• In general, fluoroquinolones should not be used since they are generally inactive against pneumococci.</li> <li>• 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.</li> <li>• 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).</li> </ul>
<p>American Academy of Pediatrics:  <b>Management of Sinusitis (2001)</b><sup>45</sup></p>	<ul style="list-style-type: none"> <li>• Amoxicillin is considered first-line therapy for acute bacterial sinusitis due to its general effectiveness, safety, tolerability, and narrow spectrum.</li> <li>• 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.</li> <li>• 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.</li> <li>• 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.</li> </ul>
<p>Infectious Diseases Society of America:  <b>Practice Guidelines for the Management of Bacterial Meningitis (2004)</b><sup>46</sup></p>	<p><u>Antimicrobial therapy based on the presumptive pathogen identified by positive Gram stain</u></p> <ul style="list-style-type: none"> <li>• <i>S pneumoniae</i> - vancomycin plus third-generation cephalosporin; alternative agents are meropenem or a fluoroquinolone.</li> <li>• <i>Neisseria meningitides</i> - third generation cephalosporin; alternative agents include penicillin G, ampicillin, chloramphenicol, fluoroquinolones, or aztreonam.</li> </ul>

Clinical Guideline	Recommendations
	<ul style="list-style-type: none"> <li>• <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>).</li> <li>• <i>H influenza</i> - third generation cephalosporin; alternative agents include chloramphenicol, cefepime, meropenem, or a fluoroquinolone.</li> <li>• <i>Escherichia coli</i> - third generation cephalosporin; alternative agents include cefepime, meropenem, aztreonam, fluoroquinolone, or SMX/TMP.</li> </ul> <p><u>Empiric therapy based on age and predisposing condition</u></p> <ul style="list-style-type: none"> <li>• Age &lt;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.</li> <li>• Age one to 23 months, <i>S pneumoniae</i>, <i>N meningitides</i>, <i>S agalactiae</i>, <i>H influenza</i>, <i>E coli</i>: vancomycin plus third generation cephalosporin (ceftriaxone or cefotaxime).</li> <li>• Age two to 50 years, <i>N meningitides</i>, <i>S pneumoniae</i>: vancomycin plus third generation cephalosporin (ceftriaxone or cefotaxime).</li> <li>• Age &gt;50 years, <i>S pneumoniae</i>, <i>N meningitides</i>, <i>L monocytogenes</i>, aerobic gram-negative bacilli: vancomycin plus ampicillin plus third generation cephalosporin (ceftriaxone or cefotaxime).</li> <li>• Basilar skull fracture, <i>S pneumoniae</i>, <i>H influenza</i>, group A <math>\beta</math>-hemolytic streptococci: vancomycin plus third generation cephalosporin (ceftriaxone or cefotaxime).</li> <li>• Penetrating head trauma, <i>S aureus</i>, coagulase-negative staphylococci, aerobic gram-negative bacilli: vancomycin plus cefepime, vancomycin plus ceftazidime, vancomycin plus meropenem.</li> <li>• Post-neurosurgery, aerobic gram-negative bacilli, <i>S aureus</i>, coagulase-negative staphylococci: vancomycin plus cefepime, vancomycin plus ceftazidime, vancomycin plus meropenem.</li> <li>• 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.</li> </ul> <p><u>Specific antimicrobial therapy based on pathogen and susceptibility</u></p> <ul style="list-style-type: none"> <li>• <i>S pneumoniae</i>:             <ul style="list-style-type: none"> <li>○ Penicillin minimum inhibitory concentration (MIC) &lt;0.1 <math>\mu\text{g/mL}</math>: penicillin G or ampicillin, alternative therapies include third generation cephalosporin (ceftriaxone or cefotaxime), chloramphenicol.</li> <li>○ Penicillin MIC 0.1 to 1.0 <math>\mu\text{g/mL}</math>: third generation cephalosporin (ceftriaxone or cefotaxime), alternative agents include cefepime, meropenem.</li> <li>○ Penicillin MIC <math>\geq 2</math> <math>\mu\text{g/mL}</math>: vancomycin plus third generation cephalosporin (ceftriaxone or cefotaxime, consider addition of rifampin if MIC of ceftriaxone is &gt;2<math>\mu\text{g/mL}</math>), alternative agent is fluoroquinolone (gatifloxacin or moxifloxacin).</li> <li>○ Cefotaxime or ceftriaxone MIC <math>\geq 1</math> <math>\mu\text{g/mL}</math>: vancomycin plus third generation cephalosporin (ceftriaxone or cefotaxime, consider addition of rifampin if MIC of ceftriaxone is &gt;2 <math>\mu\text{g/mL}</math>), alternative agent is fluoroquinolone (gatifloxacin or moxifloxacin).</li> </ul> </li> <li>• <i>N meningitides</i>:             <ul style="list-style-type: none"> <li>○ Penicillin MIC &lt;0.1 <math>\mu\text{g/mL}</math>: penicillin G or ampicillin, alternative agents include third generation cephalosporin (ceftriaxone or cefotaxime), chloramphenicol.</li> </ul> </li> </ul>

Clinical Guideline	Recommendations
	<ul style="list-style-type: none"> <li>○ Penicillin MIC 0.1 to 1.0 µ/mL: third generation cephalosporin (ceftriaxone or cefotaxime), alternative agents include chloramphenicol, fluoroquinolone, meropenem.</li> <li>● <i>L monocytogenes</i>: ampicillin or penicillin G (addition of aminoglycoside should be considered), alternative agents include SMX/TMP, meropenem.</li> <li>● <i>S agalactiae</i>: ampicillin or penicillin G (addition of aminoglycoside should be considered), alternative agents include third generation cephalosporin (ceftriaxone or cefotaxime).</li> <li>● <i>E coli</i> or <i>Enterobacteriaceae</i>: third generation cephalosporin, alternative agents include aztreonam, fluoroquinolone, meropenem, SMX/TMP, ampicillin.</li> <li>● <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).</li> <li>● <i>H influenza</i>: <ul style="list-style-type: none"> <li>○ β-lactamase negative: ampicillin, alternative agents include third generation cephalosporin (ceftriaxone or cefotaxime), cefepime, chloramphenicol, fluoroquinolone.</li> <li>○ β-lactamase positive: third generation cephalosporin, alternative agents include cefepime, chloramphenicol, fluoroquinolone.</li> </ul> </li> <li>● <i>S aureus</i> <ul style="list-style-type: none"> <li>○ Methicillin susceptible: nafcillin or oxacillin, alternative agents include vancomycin, meropenem.</li> <li>○ Methicillin resistant: vancomycin (consider addition of rifampin), alternative agents include SMX/TMP, linezolid.</li> </ul> </li> <li>● <i>Staphylococcus epidermidis</i>: vancomycin (consider addition of rifampin), alternative agent is linezolid.</li> <li>● <i>Enterococcus</i> species: <ul style="list-style-type: none"> <li>○ Ampicillin susceptible: ampicillin plus gentamicin.</li> <li>○ Ampicillin resistant: vancomycin plus gentamicin.</li> <li>○ Ampicillin and vancomycin resistant: linezolid.</li> </ul> </li> </ul>
<p>Infectious Diseases Society of America: <b>Practice Guidelines for the Diagnosis and Management of Skin and Soft-Tissue Infections (2005)</b><sup>47</sup></p>	<p><b>General observations</b></p> <ul style="list-style-type: none"> <li>● 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.</li> <li>● 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.</li> <li>● 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.</li> <li>● 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.</li> <li>● Osteomyelitis typically requires treatment for four to six weeks.</li> </ul>

Clinical Guideline	Recommendations
	<p><u>Animal bites</u></p> <ul style="list-style-type: none"> <li>• 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.</li> <li>• 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 require an additional agent that is active against anaerobes, such as metronidazole or clindamycin.</li> <li>• 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.</li> </ul> <p><u>Animal contact</u></p> <ul style="list-style-type: none"> <li>• 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.</li> <li>• Bioterrorism-related anthrax should be treated with a fluoroquinolone until susceptibility tests are available, as inhalation may also have occurred.</li> <li>• Cat scratch disease and bacillary angiomatosis may be treated with azithromycin, erythromycin or doxycycline. Other alternatives include rifampin, SMX/TMP and ciprofloxacin.</li> <li>• Erysipeloid cutaneous infections should be treated with penicillin or amoxicillin; cephalosporins, clindamycin and fluoroquinolones are effective alternatives.</li> <li>• Glanders may be treated with ceftazidime, gentamicin, imipenem, doxycycline, or ciprofloxacin.</li> <li>• Streptomycin has been the drug of choice for bubonic plague. Tetracycline and chloramphenicol are also appropriate. Fluoroquinolones are alternative agents.</li> <li>• Ciprofloxacin has been suggested for both treatment and prevention of plague (bubonic and pneumonic) due to biowarfare agents.</li> <li>• 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.</li> </ul> <p><u>Cellulitis</u></p> <ul style="list-style-type: none"> <li>• Cellulitis is commonly treatable with oral antibiotics, such as dicloxacillin, cephalexin, clindamycin or erythromycin.</li> <li>• For severe infection, the treatment of choice is either a penicillinase-resistant semisynthetic penicillin or a first generation cephalosporin.</li> <li>• In patients with severe penicillin allergy, clindamycin or vancomycin is indicated.</li> <li>• 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.</li> </ul> <p><u>Erysipelas</u></p> <ul style="list-style-type: none"> <li>• Oral or intravenous penicillin is the first-line treatment depending on severity.</li> <li>• In the presence or suspicion of staphylococcal infection, a penicillinase-</li> </ul>

Clinical Guideline	Recommendations
	<p>resistant semisynthetic penicillin or a first generation cephalosporin is indicated.</p> <p><u>Human bites</u></p> <ul style="list-style-type: none"> <li>• Clenched-fist injuries typically require hospitalization and intravenous ampicillin/sulbactam, cefoxitin or one of the carbapenems.</li> <li>• Fluoroquinolones plus clindamycin or SMX/TMP plus metronidazole can be used in patients with severe penicillin allergy.</li> </ul> <p><u>Impetigo</u></p> <ul style="list-style-type: none"> <li>• Penicillinase-resistant penicillins or first generation cephalosporins are the preferred agents.</li> <li>• 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>.</li> <li>• Topical therapy with mupirocin is equivalent to oral systemic antibiotics.</li> </ul> <p><u>Necrotizing infections</u></p> <ul style="list-style-type: none"> <li>• 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.</li> <li>• 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.</li> <li>• 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.</li> <li>• <i>Streptococcus</i> infection should be treated with high-dose penicillin or ampicillin plus clindamycin.</li> <li>• <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.</li> <li>• In gas gangrene, the efficacy of hyperbaric oxygen is inconclusive. Standard antibiotic treatment is penicillin plus clindamycin.</li> </ul> <p><u>Soft-tissue infections caused by community-acquired MRSA</u></p> <ul style="list-style-type: none"> <li>• They are often susceptible to non-<math>\beta</math>-lactam antibiotics, and standard treatment includes doxycycline, clindamycin, SMX/TMP, rifampin, or fluoroquinolones, specifically levofloxacin, gatifloxacin or moxifloxacin.</li> </ul> <p><u>Surgical site infections</u></p> <ul style="list-style-type: none"> <li>• Surgical site infections often resolve without the use of antibiotics.</li> <li>• In patients with a temperature <math>&gt;38.5^{\circ}\text{C}</math>, pulse rate <math>&gt;100</math> beats/minute or erythema diameter <math>&gt;5</math> cm from incision with induration or necrosis, a short course of antibiotics is recommended.</li> <li>• For wounds of the perineum or operation on the gastrointestinal tract or female genital tract, cefotetan or ampicillin/sulbactam or a fluoroquinolone plus clindamycin is recommended.</li> </ul>

Clinical Guideline	Recommendations
	<ul style="list-style-type: none"> <li>• For clean wounds on the trunk, head, neck or extremities, cefazolin, oxacillin or clindamycin are recommended.</li> </ul> <p><u>Immunocompromised patients</u></p> <ul style="list-style-type: none"> <li>• In neutropenic patients, empiric broad-spectrum antibacterial therapy is recommended at the first sign of infection including fever.</li> <li>• 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.</li> <li>• For gram-positive infections, vancomycin is not recommended for empirical antibiotic therapy because of resistance; linezolid or daptomycin are appropriate alternatives to vancomycin.</li> <li>• For <i>Nocardia</i> infection, first-line therapy is SMX/TMP. Other sulfonamide antibiotics and imipenem are also appropriate.</li> <li>• Empirical antifungal therapy is a common practice in neutropenic patients with persistent fever. Amphotericin B, caspofungin and voriconazole are appropriate.</li> <li>• 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.</li> <li>• Treatment of non-tubercular mycobacterial infections of the skin and soft tissues requires combination therapy that should include a macrolide.</li> <li>• Cutaneous <i>Nocardia</i> infections should be treated with SMX/TMP, the treatment of choice. Other sulfa antibiotics and imipenem are also effective.</li> <li>• 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.</li> <li>• 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.</li> <li>• Prevention of viral reactivation with oral acyclovir, famciclovir or valacyclovir is an important component of the treatment of cutaneous varicella zoster virus.</li> <li>• Acyclovir is the treatment of choice for herpes simplex virus infections, though famciclovir and valacyclovir are also highly effective.</li> <li>• Prolonged ganciclovir therapy is the treatment of choice for cutaneous cytomegalovirus.</li> </ul>
<p>Infectious Diseases Society of America: <b>Diagnosis and Treatment of Diabetic Foot Infections (2004)</b><sup>48</sup></p>	<ul style="list-style-type: none"> <li>• Aerobic gram-positive cocci are the usual pathogens responsible for acute infections due to breaks in the skin. The most common pathogens identified are <i>S aureus</i> and the b-hemolytic streptococci.</li> <li>• Chronic wounds involve more complex pathogens including enterococci, Enterobacteriaceae, anaerobes, <i>P aeruginosa</i> and non-fermentative gram-negative rods.</li> <li>• Antibiotics are not recommended in uninfected wounds.</li> <li>• Most patients with mild to moderate infections can be treated as</li> </ul>

Clinical Guideline	Recommendations
	<p>outpatients.</p> <ul style="list-style-type: none"> <li>• For severe infections, initial empiric antibiotic therapy should include coverage for gram-positive, gram-negative and anaerobic pathogens and should be administered parenterally.</li> <li>• Mild to moderate infections can usually be treated with narrow-spectrum agents which cover gram-positive cocci.</li> <li>• On the basis of available data, no single drug or drug combination appears to be “superior” to another.</li> <li>• Cephalosporins have been used and include cefoxitin, ceftizoxime, ceftriaxone and cephalexin.</li> <li>• Osteomyelitis typically requires four to six weeks of antibiotic therapy.</li> </ul>
<p>American College of Obstetricians and Gynecologists:  <b>Practice Bulletin:                      Treatment of Urinary Tract Infections in Nonpregnant Women (2008)</b><sup>49</sup></p>	<ul style="list-style-type: none"> <li>• Most urinary tract infections are caused by <i>E coli</i> (80 to 90%).</li> <li>• 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.</li> <li>• 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).</li> <li>• First generation cephalosporins and amoxicillin are less effective than the above agents due to resistance and rapid excretion from the urinary tract.</li> <li>• <math>\beta</math>-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.</li> <li>• 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.</li> <li>• SMX/TMP is considered the preferred treatment for uncomplicated cystitis except in areas where resistance is common.</li> <li>• Fluoroquinolones should not be used first-line in areas where SMX/TMP resistance is uncommon.</li> <li>• 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 <math>\beta</math>-lactams are no longer recommended.</li> <li>• First-line treatment for pyelonephritis is now a fluoroquinolone. SMX/TMP may be used in areas of low resistance.</li> <li>• 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.</li> </ul>
<p>Infectious Diseases Society of America:  <b>International Clinical Practice Guidelines for the Treatment of Uncomplicated Acute Bacterial Cystitis and Acute Pyelonephritis in Women: A 2010 Update by the</b></p>	<p><u>Acute uncomplicated bacterial cystitis</u></p> <ul style="list-style-type: none"> <li>• Taking into consideration availability, allergy history and tolerance the following antimicrobials are recommended: nitrofurantoin monohydrate/macrocrystals, SMX/TMP, fosfomycin, pivmecillinam*.</li> <li>• 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.</li> <li>• <math>\beta</math>-lactams (amoxicillin/clavulanate, cefdinir, and cefpodoxime) are also recommended as alternative agents. Due to poor efficacy and</li> </ul>

Clinical Guideline	Recommendations
<p><b>Infectious Disease Society of America and the European Society for Microbiology and Infectious Disease (2011)</b><sup>50</sup></p>	<p>antimicrobial resistance, amoxicillin and ampicillin should not be used as monotherapy.</p> <p><u>Acute pyelonephritis</u></p> <ul style="list-style-type: none"> <li>• 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.</li> <li>• 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%.</li> <li>• 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.</li> <li>• 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.</li> <li>• Oral <math>\beta</math>-lactam agents are less effective than other available agents. Therefore if an oral <math>\beta</math>-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.</li> <li>• 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.</li> </ul>
<p>Centers for Disease Control and Prevention: <b>Sexually Transmitted Diseases Treatment Guidelines (2010)</b><sup>51</sup></p>	<p><u>Chancroid</u></p> <ul style="list-style-type: none"> <li>• Azithromycin, ceftriaxone, ciprofloxacin (contraindicated in pregnant or lactating women) or erythromycin are recommended treatment strategies.</li> </ul> <p><u>Genital herpes simplex virus</u></p> <ul style="list-style-type: none"> <li>• First episodes should be treated with acyclovir, famciclovir, or valcyclovir.</li> <li>• 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.</li> <li>• Episodic treatment requires initiation of therapy within one day of lesion onset or during the prodrome that precedes outbreak.</li> <li>• Intravenous acyclovir is recommended for severe disease.</li> </ul> <p><u>Granuloma inguinale</u></p> <ul style="list-style-type: none"> <li>• Doxycycline is recommended.</li> <li>• Alternative agents include azithromycin, ciprofloxacin, erythromycin or SMX/TMP.</li> <li>• The addition of an aminoglycoside may be considered if improvement is not evident within the first few days of therapy.</li> </ul> <p><u>Lymphogranuloma venereum</u></p> <ul style="list-style-type: none"> <li>• Doxycycline is recommended.</li> <li>• An alternative agent is erythromycin.</li> <li>• Clinical data are lacking, though azithromycin is probably effective.</li> </ul>

Clinical Guideline	Recommendations
	<ul style="list-style-type: none"> <li>• Fluoroquinolone treatment may also be effective, though extended treatment intervals are likely required.</li> <li>• Pregnant and lactating women should be treated with erythromycin. Azithromycin may be an alternative but clinical data are lacking.</li> </ul> <p><u>Syphilis</u></p> <ul style="list-style-type: none"> <li>• Penicillin G is the preferred drug for all stages of syphilis. Alternative agents include doxycycline and tetracycline. Limited studies suggest that ceftriaxone is effective.</li> <li>• 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.</li> <li>• Penicillin G is the only therapy recommended during pregnancy. Pregnant women with an allergy to penicillin should be desensitized.</li> <li>• Benzathine penicillin G is recommended for primary and secondary syphilis.</li> <li>• Infants <math>\geq 1</math> month of age with primary or secondary syphilis should be treated with benzathine penicillin G.</li> <li>• Early latent syphilis should be treated with benzathine penicillin G in patients with normal cerebrospinal fluid examinations.</li> <li>• 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.</li> <li>• Patients with tertiary syphilis with no evidence of neurosyphilis should be treated with benzathine penicillin G.</li> <li>• 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.</li> <li>• Congenital syphilis:             <ul style="list-style-type: none"> <li>○ 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.</li> <li>○ 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 &lt;4 weeks of treatment before delivery should be treated with aqueous crystalline penicillin G, procaine penicillin G, or benzathine penicillin G.</li> <li>○ 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 &gt;4 weeks before delivery and the mother has no evidence of reinfection or relapse should be treated with benzathine penicillin G.</li> </ul> </li> <li>• Infants <math>\geq 1</math> month of age identified as having reactive serologic tests for syphilis should be treated with aqueous crystalline penicillin G.</li> <li>• 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.</li> <li>• Any child suspected of having congenital syphilis with neurologic</li> </ul>

Clinical Guideline	Recommendations
	<p>involvement should be treated with aqueous crystalline penicillin G.</p> <ul style="list-style-type: none"> <li>• Infants and children requiring treatment for syphilis who have a history of penicillin allergy or develop an allergic reaction should be desensitized.</li> </ul> <p><u>Urethritis</u></p> <ul style="list-style-type: none"> <li>• Azithromycin or doxycycline is recommended. Alternative regimens include erythromycin, levofloxacin or ofloxacin.</li> <li>• 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.</li> </ul> <p><u>Cervicitis</u></p> <ul style="list-style-type: none"> <li>• Azithromycin or doxycycline is recommended.</li> </ul> <p><u>Chlamydia</u></p> <ul style="list-style-type: none"> <li>• Azithromycin or doxycycline is recommended.</li> <li>• Alternative agents include erythromycin, levofloxacin or ofloxacin.</li> <li>• Azithromycin or amoxicillin is recommended in pregnant patients. An alternative agent is erythromycin.</li> <li>• Infants with ophthalmia neonatorum should be treated with oral erythromycin.</li> <li>• Infants with pneumonia caused by <i>Chlamydia trachomatis</i> should be treated with oral erythromycin.</li> <li>• Children with chlamydial infection should be treated with oral erythromycin (patients weighing &lt;45 kg), azithromycin (patients weighing ≥45 kg and &lt;8 years), or azithromycin or doxycycline (patients ≥8 years of age).</li> </ul> <p><u>Gonococcal infections</u></p> <ul style="list-style-type: none"> <li>• Patients infected with <i>Neisseria gonorrhoeae</i> are frequently coinfecting with <i>C trachomatis</i> and should be treated for both infections.</li> <li>• Ceftriaxone is recommended. If ceftriaxone is not an option, other regimens include cefixime or single dose injectable cephalosporin regimens plus azithromycin or doxycycline.</li> <li>• Gonococcal infections of the pharynx should be treated with ceftriaxone plus azithromycin or doxycycline.</li> <li>• Gonococcal conjunctivitis should be treated with ceftriaxone.</li> <li>• Disseminated gonococcal infection should be treated with ceftriaxone. Alternative agents include cefotaxime or ceftizoxime.</li> <li>• Gonococcal meningitis and endocarditis should be treated with ceftriaxone.</li> <li>• Ophthalmia neonatorum should be treated with ceftriaxone.</li> <li>• Gonococcal scalp abscesses should be treated with ceftriaxone or cefotaxime.</li> <li>• Infants born to mothers with untreated gonorrhea should be treated with ceftriaxone.</li> <li>• Children weighing &gt;45 kg should be treated with a regimen recommended for adults.</li> <li>• Children weighing ≤45 kg should be treated with ceftriaxone at an appropriate dose.</li> <li>• Ceftriaxone is recommended in children with bacteremia or arthritis.</li> <li>• Erythromycin ophthalmic ointment is recommended as prophylaxis against ophthalmia neonatorum at birth. If erythromycin is not available,</li> </ul>

Clinical Guideline	Recommendations
	<p>infants at risk can be administered ceftriaxone.</p> <p><u>Bacterial vaginosis</u></p> <ul style="list-style-type: none"> <li>• Metronidazole orally or topically or topical clindamycin are recommended.</li> <li>• Alternative agents include oral tinidazole or oral or intravaginal clindamycin.</li> <li>• Intravaginal metronidazole is an option in patients who are unable to tolerate oral metronidazole.</li> <li>• Treatment of all pregnant women with symptoms is recommended. Oral metronidazole or clindamycin is recommended.</li> </ul> <p><u>Trichomoniasis</u></p> <ul style="list-style-type: none"> <li>• Oral metronidazole or tinidazole is recommended.</li> </ul> <p><u>Vulvovaginal candidiasis</u></p> <ul style="list-style-type: none"> <li>• Over-the-counter butoconazole, clotrimazole, miconazole or tioconazole are recommended.</li> <li>• Prescription agents include butoconazole, nystatin, terconazole or oral fluconazole.</li> <li>• Oral fluconazole weekly for six months is the recommended treatment for recurrent infection.</li> <li>• 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).</li> <li>• Only topical therapies are recommended in pregnancy.</li> </ul> <p><u>Pelvic inflammatory disease</u></p> <ul style="list-style-type: none"> <li>• Mild to moderate pelvic inflammatory disease should be treated with parenteral or oral therapies.</li> <li>• Recommended parenteral regimen A: cefotetan or cefoxitin plus doxycycline (oral or intravenous).</li> <li>• Recommended parenteral regimen B: clindamycin plus gentamicin.</li> <li>• Alternative parenteral regimens are ampicillin/sulbactam plus doxycycline (oral or intravenous).</li> <li>• 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 3<sup>rd</sup> generation cephalosporin plus doxycycline with or without metronidazole.</li> <li>• 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.</li> </ul> <p><u>Epididymitis</u></p> <ul style="list-style-type: none"> <li>• Ceftriaxone plus doxycycline is recommended. For acute infections most likely caused by enteric organisms, levofloxacin or ofloxacin are recommended.</li> </ul> <p><u>Human papillomavirus</u></p> <ul style="list-style-type: none"> <li>• External genital warts:             <ul style="list-style-type: none"> <li>○ Podofilox 0.5% solution or gel, imiquimod 5% cream or sinecatechins 15% ointment are recommended as patient-applied treatments.</li> </ul> </li> </ul>

Clinical Guideline	Recommendations
	<ul style="list-style-type: none"> <li>○ Cryotherapy with liquid nitrogen or cryoprobe, podophyllin resin, trichloroacetic acid or bichloroacetic acid or surgical removal are recommended as provider-administered treatments.</li> <li>○ Alternative regimens include intralesional interferon, photodynamic therapy and topical cidofovir.</li> <li>● Cervical warts:             <ul style="list-style-type: none"> <li>○ Biopsy evaluation is recommended to exclude high-grade squamous intraepithelial lesions</li> </ul> </li> <li>● Vaginal warts:             <ul style="list-style-type: none"> <li>○ Cryotherapy with liquid nitrogen or trichloroacetic acid or bichloroacetic acid are recommended.</li> </ul> </li> <li>● Urethral meatus warts:             <ul style="list-style-type: none"> <li>○ Cryotherapy with liquid nitrogen or podophyllin in compound tincture of benzoin is recommended.</li> </ul> </li> <li>● Anal warts:             <ul style="list-style-type: none"> <li>○ Cryotherapy with liquid nitrogen, trichloroacetic acid or bichloroacetic acid or surgical removal is recommended.</li> </ul> </li> </ul> <p><u>Proctitis</u></p> <ul style="list-style-type: none"> <li>● Ceftriaxone plus doxycycline is recommended.</li> </ul> <p><u>Pediculosis pubis</u></p> <ul style="list-style-type: none"> <li>● Permethrin or pyrethrins are recommended.</li> <li>● Alternative agents include malathion or ivermectin.</li> </ul> <p><u>Scabies</u></p> <ul style="list-style-type: none"> <li>● Permethrin or ivermectin are recommended.</li> <li>● Lindane is an alternative agent, not recommended as first-line.</li> </ul> <p><u>Prophylaxis after sexual assault</u></p> <ul style="list-style-type: none"> <li>● Hepatitis B vaccination.</li> <li>● Empirical regimen for Chlamydia, gonorrhea and trichomonas.</li> <li>● Emergency contraception.</li> <li>● Ceftriaxone or cefixime plus metronidazole plus azithromycin or doxycycline is the recommended regimen.</li> </ul>
<p>Infectious Diseases Society of America:  <b>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)</b><sup>52†</sup></p>	<p><u>Early Lyme disease</u></p> <ul style="list-style-type: none"> <li>● 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.</li> <li>● 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.</li> <li>● Macrolides should be reserved for patients who are intolerant to doxycycline, amoxicillin or cefuroxime.</li> <li>● First generation cephalosporins are ineffective and should not be used.</li> <li>● When erythema migrans cannot be differentiated from bacterial cellulitis, it is reasonable to treat with cefuroxime or amoxicillin/clavulanate.</li> <li>● Ceftriaxone is effective but is not “superior” to oral agents and is more likely to cause serious adverse events.</li> <li>● Doxycycline should be avoided in pregnant patients.</li> </ul>

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	<p><u>Lyme meningitis and other manifestations of early neurologic Lyme disease</u></p> <ul style="list-style-type: none"> <li>• Ceftriaxone is recommended.</li> <li>• Alternatives include parenteral cefotaxime or penicillin G.</li> <li>• Oral doxycycline may be used in patients intolerant to <math>\beta</math>-lactams.</li> <li>• Ceftriaxone is recommended in children. An alternative agent is cefotaxime or penicillin G.</li> <li>• Children eight years of age and older may be treated with oral doxycycline.</li> <li>• Antibiotics may not hasten the resolution of seventh cranial nerve palsy associated with Lyme disease but are recommended to prevent further sequelae.</li> </ul> <p><u>Lyme carditis</u></p> <ul style="list-style-type: none"> <li>• Patients with atrioventricular heart block and/or myopericarditis may be treated with oral or parenteral antibiotic therapy.</li> <li>• Ceftriaxone is recommended as initial management for hospitalized patients.</li> </ul> <p><u>Borrelial lymphocytoma</u></p> <ul style="list-style-type: none"> <li>• Recommended regimens are the same as for erythema migrans.</li> </ul> <p><u>Late Lyme disease with Lyme arthritis</u></p> <ul style="list-style-type: none"> <li>• Doxycycline, amoxicillin or cefuroxime are recommended in patients without neurological manifestations.</li> <li>• 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.</li> <li>• Adult patients with Lyme arthritis and evidence of neurological manifestations should be treated with parenteral ceftriaxone. Cefotaxime or penicillin G are acceptable alternatives.</li> <li>• 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.</li> </ul> <p><u>Late neurological Lyme disease</u></p> <ul style="list-style-type: none"> <li>• Parenteral ceftriaxone is recommended for adults and children.</li> <li>• Cefotaxime or penicillin G are alternatives.</li> </ul> <p><u>Acrodermatitis chronic atrophicans</u></p> <ul style="list-style-type: none"> <li>• Recommended regimens are the same as for erythema migrans.</li> </ul> <p><u>Long-term treatment</u></p> <ul style="list-style-type: none"> <li>• Antibiotic therapy is not recommended for patients with long-term (<math>\geq 6</math> months) subjective symptoms.</li> </ul> <p><u>Human granulocytic anaplasmosis</u></p> <ul style="list-style-type: none"> <li>• Doxycycline is recommended.</li> <li>• Children <math>&lt; 8</math> 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.</li> <li>• In patients not suited for treatment with doxycycline, rifampin is recommended. Patients with concomitant Lyme disease should also be</li> </ul>

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	<p>treated with amoxicillin or cefuroxime.</p> <p><u>Babesiosis</u></p> <ul style="list-style-type: none"> <li>• Atovaquone plus azithromycin or clarithromycin plus quinine is recommended.</li> <li>• Clarithromycin plus quinine is recommended in patients with severe disease.</li> </ul>
<p>Global Initiative for Chronic Obstructive Lung Disease: <b>Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2010)</b><sup>53</sup></p>	<p><u>Management of exacerbations of Chronic Obstructive Pulmonary Disease (COPD) with a bacterial component</u></p> <ul style="list-style-type: none"> <li>• Predominant bacteria include <i>H influenzae</i>, <i>S pneumoniae</i> and <i>M catarrhalis</i>.</li> <li>• Patients with severe COPD requiring mechanical ventilation may be more frequently infected with <i>P aeruginosa</i>.</li> <li>• 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.</li> <li>• Patients with moderate exacerbations and risk factors for poor outcomes should be treated with amoxicillin/clavulanate. Alternative agents are fluoroquinolones. Parenteral options include <math>\beta</math>-lactam/<math>\beta</math>-lactamase inhibitor, second or third generation cephalosporin, or fluoroquinolones.</li> <li>• Patients with severe exacerbations with risk factors for <i>P aeruginosa</i> should be treated with high dose oral or parenteral fluoroquinolones or parenteral <math>\beta</math>-lactam with <i>P aeruginosa</i> activity.</li> </ul>
<p>American Heart Association: <b>Prevention of Infectious Endocarditis (2007)</b><sup>54</sup></p>	<ul style="list-style-type: none"> <li>• Antibiotic prophylaxis is recommended for patients at the highest risk of adverse outcome from endocarditis, including those with:             <ul style="list-style-type: none"> <li>○ Prosthetic cardiac valve or prosthetic material used for cardiac valve repair.</li> <li>○ Previous infective endocarditis.</li> <li>○ Congenital heart disease:                 <ul style="list-style-type: none"> <li>▪ Unrepaired cyanotic congenital heart disease including palliative shunts and conduits.</li> <li>▪ 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.</li> <li>▪ 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).</li> </ul> </li> <li>○ Cardiac transplantation recipients who develop cardiac valvulopathy.</li> </ul> </li> <li>• Antibiotic prophylaxis is no longer recommended based solely on an increased lifetime risk of developing infectious endocarditis.</li> <li>• Antibiotic prophylaxis should be administered as a single dose before the procedure.</li> <li>• 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.</li> <li>• Recommended regimens include:             <ul style="list-style-type: none"> <li>○ Oral: amoxicillin 2 g (adults) or 50 mg/kg (children).</li> <li>○ Unable to take oral medication: ampicillin or ceftriaxone or</li> </ul> </li> </ul>

Clinical Guideline	Recommendations
	<p>cefazolin.</p> <ul style="list-style-type: none"> <li>○ Allergic to penicillins or ampicillin, oral: cephalexin or clindamycin or azithromycin or clarithromycin.</li> </ul> <ul style="list-style-type: none"> <li>• Allergic to penicillins or ampicillin and unable to take oral medications: cefazolin or ceftriaxone or clindamycin.</li> <li>• 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.</li> <li>• 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.</li> <li>• The administration of prophylactic antibiotics is no longer recommended solely to prevent endocarditis in patients undergoing a genitourinary or gastrointestinal tract procedure.</li> <li>• 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.</li> <li>• For patients described above scheduled for an elective cystoscopy or other urinary tract manipulation who have an enterococcal urinary 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.</li> <li>• Amoxicillin or ampicillin is preferred for enterococcal coverage in these patients. Vancomycin may be used in patients unable to tolerate penicillin.</li> <li>• 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 <math>\beta</math>-hemolytic streptococci such as an antistaphylococcal penicillin or a cephalosporin. Vancomycin and clindamycin are options in patients unable to tolerate a <math>\beta</math>-lactam or who are known or suspected to have an infection caused by a methicillin-resistant staphylococcus.</li> </ul>
<p>American Academy of Pediatric Dentistry: <b>Clinical Guideline on Antibiotic Prophylaxis for Dental Patients at Risk for Infection (2008)</b><sup>55</sup></p>	<ul style="list-style-type: none"> <li>• 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.</li> <li>• 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.</li> <li>• Prophylaxis is not recommended based solely on an increased lifetime risk of infective endocarditis.</li> <li>• Recommended regimens include: <ul style="list-style-type: none"> <li>○ Oral: amoxicillin 2 g (adults) or 50 mg/kg (children).</li> <li>○ Unable to take oral medication: ampicillin or ceftriaxone or</li> </ul> </li> </ul>

Clinical Guideline	Recommendations
	<p>cefazolin.</p> <ul style="list-style-type: none"> <li>○ Allergic to penicillins or ampicillin, oral: cephalexin or clindamycin or azithromycin or clarithromycin.</li> <li>○ Allergic to penicillins or ampicillin and unable to take oral medications: cefazolin or ceftriaxone or clindamycin.</li> </ul>
<p>Infectious Disease Society of America/ Surgical Infection Society: <b>Diagnosis and Management of Complicated Intra-abdominal Infection in Adults and Children (2010)</b><sup>56</sup></p>	<p><u>Community-acquired infection of mild to moderate severity in adults</u></p> <ul style="list-style-type: none"> <li>• Single agent therapy with ticarcillin/clavulanate, ceftioxin, ertapenem, moxifloxacin or tigecycline or combination therapy of metronidazole with cefazolin, cefuroxime, ceftriaxone, levofloxacin or ciprofloxacin is preferred over regimens with substantial antipseudomonal activity.</li> <li>• Ampicillin/sulbactam, cefotetan and clindamycin are not recommended due to high rates of resistance.</li> <li>• Empiric therapy with antifungals or coverage for Enterococcus is not recommended.</li> <li>• Aminoglycosides are not recommended for routine use because of the risk of toxicity.</li> <li>• 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.</li> </ul> <p><u>High-risk community-acquired infections in adults</u></p> <ul style="list-style-type: none"> <li>• The empiric use of broad-spectrum agents with activity against gram-negative organisms including meropenem, imipenem/cilastatin, doripenem, piperacillin/tazobactam, ciprofloxacin or levofloxacin in combination with metronidazole or ceftazidime or cefepime in combination with metronidazole is recommended.</li> <li>• Aztreonam plus metronidazole with the addition of an agent effective against gram-positive cocci is an alternative.</li> <li>• Quinolones should not be used unless hospital surveys indicate &gt;90% susceptibility of <i>E coli</i>.</li> <li>• 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.</li> <li>• Empiric used of agents effective against enterococci is recommended.</li> </ul> <p><u>Health care-associated infection in adults</u></p> <ul style="list-style-type: none"> <li>• 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.</li> </ul> <p><u>Antifungal therapy</u></p> <ul style="list-style-type: none"> <li>• For patients with severe-community acquired or health care-associated infections with cultures that show Candida, antifungal therapy is recommended.</li> <li>• Fluconazole is an appropriate first-line choice if C albicans is isolated.</li> <li>• For fluconazole resistant Candida species and critically ill patients, an echinocandin (caspofungin, micafungin or anidulafungin) is recommended.</li> <li>• Amphotericin B is not recommended due to its toxicity.</li> </ul>

Clinical Guideline	Recommendations
	<p><u>Anti-enterococcal therapy</u></p> <ul style="list-style-type: none"> <li>• 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.</li> <li>• Therapy should be directed against E faecalis and can include ampicillin/piperacillin and vancomycin.</li> <li>• 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.</li> </ul> <p><u>Anti-MRSA therapy</u></p> <ul style="list-style-type: none"> <li>• 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.</li> <li>• Vancomycin is recommended for treatment if suspected or proven infection due to MRSA.</li> </ul> <p><u>Cholecystitis and cholangitis in adults</u></p> <ul style="list-style-type: none"> <li>• For patients with suspected cholecystitis and cholangitis, antibiotic therapy is recommended when a biliary-enteric anastomosis is present.</li> <li>• In community-acquired acute cholecystitis of mild to moderate severity, cefazolin, cefuroxime or ceftriaxone is recommended.</li> <li>• 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.</li> <li>• 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.</li> </ul> <p><u>Pediatric infection</u></p> <ul style="list-style-type: none"> <li>• For pediatric patients with complicated intra-abdominal infections, acceptable broad-spectrum regimens include an aminoglycoside based regimen, a carbapenem (imipenem, meropenem, or ertapenem) a <math>\beta</math>-lactam/<math>\beta</math>-lactamase inhibitor combination (piperacillin/tazobactam or ticarcillin/clavulanate) or an advanced generation cephalosporin (cefotaxime, ceftriaxone, ceftazidime or cefepime) with metronidazole.</li> <li>• For children with severe reactions to <math>\beta</math>-lactam antibiotics, ciprofloxacin plus metronidazole or an aminoglycoside based regimen are recommended.</li> <li>• 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</li> </ul>

Clinical Guideline	Recommendations
<p>National Surgical Infection Prevention Project:  <b>Antimicrobial Prophylaxis for Surgery: An Advisory Statement from the National Surgical Infection Prevention Project (2004)</b><sup>57</sup></p>	<p>consistent with fungal infections, fluconazole and amphotericin should be used.</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"> <li>• Intravenous cefazolin or intravenous cefuroxime are recommended.</li> <li>• If the patient has a <math>\beta</math>-lactam allergy, intravenous vancomycin is appropriate and intravenous clindamycin is an alternative.</li> </ul> <p><u>Colorectal surgery</u></p> <ul style="list-style-type: none"> <li>• Oral neomycin plus oral erythromycin or oral neomycin plus oral metronidazole are recommended along with administration of a mechanical bowel preparation.</li> <li>• Intravenous cefotetan or intravenous cefoxitin are recommended for parental prophylaxis. Intravenous cefazolin plus oral metronidazole are recommended as a cost-effective alternative.</li> <li>• For patients with a confirmed allergy or adverse reaction to <math>\beta</math>-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.</li> </ul> <p><u>Gynecologic and obstetric surgery</u></p> <ul style="list-style-type: none"> <li>• Intravenous cefotetan is preferred for abdominal or vaginal hysterectomy. Intravenous cefazolin and intravenous cefoxitin are reasonable alternatives.</li> <li>• Intravenous metronidazole is an alternative, but may be less effective as monotherapy.</li> <li>• For patients with a <math>\beta</math>-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.</li> </ul>

\*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 first generation cephalosporins are used to treat a variety of infections including otitis media, pharyngitis and tonsillitis, respiratory tract infections, urinary tract infections and skin and soft tissue infections. Treatment guidelines identify first generation cephalosporins as acceptable alternatives to

penicillin in patients with a non-type 1 penicillin allergy for the treatment of group A streptococcal pharyngitis.<sup>42</sup> The Infectious Diseases Society of America recommends the first or second generation cephalosporins for the empiric treatment of minor skin and soft tissue infections, the treatment of cellulitis, erysipelas (in the presence or suspicion of *Staphylococcus aureus*) and impetigo.<sup>47</sup>

Clinical trials comparing the oral first generation cephalosporin agents cefadroxil and cephalexin have failed to consistently demonstrate “superiority” of one agent over the other for the treatment of respiratory tract infections, skin and soft tissue infections or urinary tract infections.<sup>12-15</sup> Studies comparing the first generation cephalosporins to second or third generation agents have also failed to consistently demonstrate “superiority” of one agent over the others for varying indications, though it is important to remember that the spectrum of activity differs between generations.<sup>16-21</sup>

Cefadroxil and cephalexin are both available generically in at least one dosage form or strength. A 750 mg strength capsule of cephalexin (Keflex<sup>®</sup>) is available as a branded agent only, though treatment guidelines and clinical trials do not demonstrate “superiority” or clinical necessity of this agent over other agents 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
Cephalexin	4,324	4,927	99.39%	\$66,776.46	\$13.55
Cephadroxil	30	30	0.61%	\$799.47	\$26.65
<b>Class Total:</b>	<b>4,354</b>	<b>4,957</b>	<b>100%</b>	<b>\$67,575.93</b>	<b>\$13.63</b>

**Recommendations**

In recognition of the established safety and efficacy of first generation cephalosporins, consensus clinical guideline recommendations, availability of generics and cost considerations, no changes are recommended to the current Department of Vermont Health Access (DVHA) approval criteria (below).

Keflex<sup>®</sup>:

- The patient has had a documented side effect, allergy, or treatment failure to generic cefadroxil and cephalexin.

Of note, the brand Duricef<sup>®</sup> has been discontinued; hence, it may be removed from the DVHA PDL.

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