INTRODUCTION

- Cephalosporins are used to treat a variety of infections. They have a broad spectrum of activity, are usually well tolerated, and are easy to administer (AHFS 2020).
- The cephalosporins are grouped into generations based on their spectrum of activity.
  - Generally, the first- and second-generation cephalosporins are used in the treatment of infections caused by susceptible staphylococci or streptococci. Use of first-generation cephalosporins in the treatment of gram-negative infections is generally limited as compared to second- and third-generation agents (AHFS 2020).
  - Third-generation cephalosporins are less active than first and second-generation cephalosporins against gram-positive aerobic bacteria, especially staphylococci. These agents may be used for infections caused by the following susceptible gram-negative bacteria: Escherichia coli, Haemophilus influenzae, Klebsiella pneumoniae, Proteus mirabilis, Enterobacter, Neisseria, and Serratia, among others. Cefdinir, cefixime, and cefpodoxime are inactive against most strains of Enterobacter (AHFS 2020).
  - Fourth and fifth generation cephalosporins are available in injectable formulations. They provide expanded gram-negative coverage, especially against bacteria resistant to third-generation cephalosporins. In addition, they have improved gram-positive coverage than third-generation cephalosporins (AHFS 2020).
- Enterobacteriaceae continue to develop more β-lactamase–mediated resistance. Additionally, other modes of resistance to the third-generation cephalosporins are becoming more prevalent. These resistance patterns are threatening the utility of this class of drugs (Lepak et al 2020).
- This review will focus on the oral third-generation cephalosporins as listed in Table 1. Review of each drug will focus on its Food and Drug Administration (FDA)-approved indications.
- Medispan class: Cephalosporins – third-generation

Table 1. Medications Included Within Class Review

<table>
<thead>
<tr>
<th>Drug*</th>
<th>Generic Availability</th>
</tr>
</thead>
<tbody>
<tr>
<td>cefdinir†</td>
<td>✔️</td>
</tr>
<tr>
<td>cefpodoxime‡</td>
<td>✔️</td>
</tr>
<tr>
<td>Spectracef (cefditoren pivoxil)</td>
<td>✔️</td>
</tr>
<tr>
<td>Suprax (cefixime) §</td>
<td>✔️</td>
</tr>
</tbody>
</table>

* Cedax (ceftibuten) is an FDA-approved third-generation cephalosporin which has been discontinued.
† Branded product, Omnicef, is no longer marketed.
‡ Branded product, Vantin, is no longer marketed.
§ Generic available for cefixime capsule and oral suspension; Suprax chewable tablets remain a branded product.

(Recources: Drugs@FDA 2020; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2020, Clinical Pharmacology 2020)

INDICATIONS

Table 2. FDA Approved Indications

<table>
<thead>
<tr>
<th>Indication</th>
<th>cefdinir</th>
<th>cefpodoxime</th>
<th>Spectracef (cefditoren)</th>
<th>Suprax (cefixime)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Bacterial Exacerbations of Chronic Bronchitis due to H. influenzae (including β-lactamase-producing strains), M. catarrhalis (including β-lactamase-producing strains), or S. pneumoniae (penicillin-susceptible strains only)</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Indication</td>
<td>cefdinir</td>
<td>cefpodoxime</td>
<td>Spectracef (cefditoren)</td>
<td>Suprax (cefixime)</td>
</tr>
<tr>
<td>---------------------------------------------------------------------------</td>
<td>----------</td>
<td>-------------</td>
<td>------------------------</td>
<td>------------------</td>
</tr>
<tr>
<td><strong>Acute Bacterial Otitis Media</strong> due to <em>H. influenzae</em> (including ß-lactamase-producing strains), <em>M. catarrhalis</em> (including ß-lactamase-producing strains), or <em>S. pyogenes</em></td>
<td>√ †</td>
<td>√ $</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Acute Maxillary Sinusitis</strong> caused by <em>H. influenzae</em> (including ß-lactamase producing strains), <em>S. pneumoniae</em> (penicillin-susceptible strains only), and <em>M. catarrhalis</em> (including ß-lactamase producing strains)</td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Acute, Uncomplicated Ano-rectal Infections</strong> in women due to <em>N. gonorrhoeae</em> (including penicillinase-producing strains)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Community-Acquired Pneumonia</strong> caused by <em>H. influenzae</em> (including ß-lactamase-producing strains), <em>H. parainfluenzae</em> (including ß-lactamase-producing strains), <em>S. pneumoniae</em> (penicillin-susceptible strains only), or <em>M. catarrhalis</em> (including ß-lactamase producing strains)</td>
<td>√</td>
<td>√ ‖</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Pharyngitis and Tonsillitis</strong> due to <em>S. pyogenes</em></td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Uncomplicated Gonorrhea (cervical/urethral)</strong> caused by <em>N. gonorrhoeae</em> (penicillinase- and non-penicillinase-producing strains)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Uncomplicated Skin and Skin-Structure Infections</strong> caused by <em>S. aureus</em> (including ß-lactamase-producing strains) or <em>S. pyogenes</em></td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Uncomplicated Urinary Tract Infections</strong> caused by <em>E. coli</em> and <em>P. mirabilis</em></td>
<td>√</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Also approved for *H. parainfluenzae* (including ß-lactamase producing strains)
† Approved for *S. pneumoniae* (penicillin-susceptible strains only), not for *S. pyogenes*
‡ *H. influenzae* (non-beta-lactamase-producing strains only)
§ Also approved for *S. pneumoniae* (excluding penicillin-resistant strains)
‖ Not for *H. parainfluenzae* or *M. catarrhalis*
¶ Also approved for *K. pneumoniae* or *S. saprophyticus*
** Not for *M. catarrhalis*


- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

**CLINICAL EFFICACY SUMMARY**

- Studies evaluating the third-generation cephalosporins for the treatment of acute exacerbations of chronic bronchitis did not consistently demonstrate significant differences in clinical response or eradication rate when compared to other cephalosporin agents (Alvarez-Sala et al 2006, Fogarty et al 2000, Phillips et al 1993, Van Herwaarden et al 1999, Zuck et al 1999). A study compared cefixime and cephalaxin in the treatment of hospitalized patients with exacerbations of chronic bronchitis and demonstrated significantly better clinical cure rates in patients treated with cefixime compared to cephalaxin (70.8% vs 50%; p < 0.05). The incidence of diarrhea was higher in the cefixime group (Verghese et al 1990).
- In the treatment of gonorrhea, cefixime and cefpodoxime have generally demonstrated comparable efficacy in the rate of bacteriologic cure (> 90%) in open-label and dose-response studies; cefixime also demonstrated comparable efficacy when compared to ceftriaxone (Handsfield et al 1991, Novak et al 1992, Plourde et al 1992, Portilla et al, 1992, Verdon et al 1993). In a meta-analysis in pregnant women, there was no significant difference between intramuscular ceftriaxone and oral cefixime for gonococcal infection cure based on 1 study and very low-quality evidence (Comunián-Carrasco et al 2018).
• A study compared cefixime and cefpodoxime in the treatment of acute otitis media. By day 15, bacteriologic cure was reported in 83% and 81% of patients treated with cefpodoxime and cefixime, respectively (p = 0.541) (Asmar et al 1994). Other head-to-head studies of the third-generation cephalosporins in the treatment of acute otitis media demonstrated no statistically significant differences in efficacy between the agents (Blumer et al 2000, MacLoughlin et al 1996, Piippo et al 1991). However, 1 study did show that high-dose amoxicillin/clavulanic acid for 10 days of therapy was more effective than 5 days of therapy with cefdinir (Casey et al 2012).
• In the treatment of lower respiratory tract infections including community-acquired pneumonia, no cephalosporin consistently demonstrated significant differences when the third-generation cephalosporins were compared with each other, cephalosporins in other generations, or amoxicillin/clavulanate (Drehobl et al 1997, Fogarty et al 2002, Lodha et al 2013, Sengupta et al 2004, van Zyle et al 2002).

**CLINICAL GUIDELINES**

• Organizations differ in their recommendations regarding the use of third-generation cephalosporins for the treatment of acute bacterial rhinosinusitis. The American College of Allergy, Asthma, and Immunology allows for the empiric use of third-generation cephalosporins for acute bacterial rhinosinusitis, while the Infectious Diseases Society of America discourages their use due to emerging resistance patterns (Chow et al 2012, Peters et al 2014). Combination therapy with clindamycin may be used as an alternative to amoxicillin in children and adults with non-type 1 hypersensitivity reactions to penicillins (Chow et al 2012, Rosenfeld et al 2015). Other authors state that third-generation cephalosporins and clindamycin are an appropriate alternative for treatment of acute bacterial rhinosinusitis in children with a history of any type of hypersensitivity reaction to amoxicillin (Wald et al 2013).
• For empiric treatment of outpatients with community acquired pneumonia, a β-lactam plus a macrolide or doxycycline may be used as an alternative to a respiratory fluoroquinolone in patients with risk factors for drug-resistant *S. pneumoniae*. While high-dose amoxicillin and amoxicillin-clavulanate are the preferred β-lactams, ceftriaxone, cefpodoxime, and cefturoxime are recommended alternatives (Metlay et al 2019).
• Although not first-line treatment, third-generation oral cephalosporins may also be considered as a part of the treatment regimen in patients with skin and soft-tissue diseases (Stevens et al 2014).
• For Group A streptococcal pharyngitis, penicillin or amoxicillin are the recommended therapies. In patients with penicillin allergies, first generation cephalosporins (non-anaphylaxis type reactions) for 10 days, clindamycin or clarithromycin for 10 days, or azithromycin for 5 days are recommended (Shulman et al 2012).
• Third-generation cephalosporins are also recommended as an alternative treatment for acute otitis media and acute cystitis (Gupta et al 2011, Lieberthal et al 2013). Cefixime is a treatment option for acute pyelonephritis in children > 1 month of age (Strohmeier et al 2014).
• Due to treatment failures, the CDC no longer recommends the routine use of cefixime as a first-line regimen for treatment of gonorrhea in the United States (CDC 2015). Cefixime should only be considered as an alternative regimen if ceftriaxone is not available, and only in combination with azithromycin. Other oral cephalosporins (eg, cefpodoxime) are not recommended because of inferior efficacy and less favorable pharmacodynamics.
• Third-generation cephalosporins may be an option for empiric treatment of bloody diarrhea in infants < 3 months of age and others with neurologic involvement (Shane et al 2017).
• In treatment of uncomplicated pyelonephritis, cefpodoxime or ceftibuten may be used in combination with an initial IV dose of a long-acting parenteral antimicrobial; oral fluoroquinolones also comprise the suggested regimens if resistance is below 10% (Bonkat et al 2020).
SAFETY SUMMARY

- The most common adverse effects seen with the cephalosporins are gastrointestinal disturbances, with diarrhea and nausea reported most frequently. Female patients can develop vaginal yeast infections. Changes in laboratory parameters such as increased blood urea nitrogen (BUN) and creatinine, decreased hematocrit and hemoglobin, increased liver enzymes, and increased glucose levels may also be seen.
- Dose adjustment of third-generation cephalosporins is recommended in renal impairment.
- Cephalosporins should not be given to patients who have experienced a previous allergic reaction to a cephalosporin. Caution should be utilized if administering to penicillin-allergic patients; however, the risk of a cross-reaction is less than 10 percent with the third-generation cephalosporins (The Medical Letter 2012).
- Patients should be monitored for Clostridium difficile-associated diarrhea.
- Antacids and H2-antagonists can inhibit the absorption of cephalosporins; administration should be separated by at least 2 hours.
- A false-positive reaction for ketones and glucose in the urine can be seen when using certain tests.
- Cefixime, cefdinir, cefditoren, and cefpodoxime are Pregnancy Category B (no evidence of risk in humans, but there remains a remote possibility; animal reproductive studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women).
- Cefixime chewable tablets contain aspartame, which may be harmful to patients with phenylketonuria.
- Cefditoren causes renal excretion of carnitine and is contraindicated in patients with carnitine deficiency or with inborn errors of metabolism that may result in carnitine deficiency.
- Cefditoren is contraindicated in patients with milk protein hypersensitivity.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

<table>
<thead>
<tr>
<th>Drug</th>
<th>Available Formulations</th>
<th>Route</th>
<th>Usual Recommended Frequency</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>cefdinir</td>
<td>Capsule, suspension</td>
<td>Oral</td>
<td>Every 12 or 24 hours</td>
<td>Dosing adjustments are recommended in renal impairment</td>
</tr>
<tr>
<td>cefpodoxime</td>
<td>Tablet, suspension</td>
<td>Oral</td>
<td>Every 12 hours</td>
<td></td>
</tr>
<tr>
<td>Spectracef (cefditoren)</td>
<td>Tablet</td>
<td>Oral</td>
<td>Every 12 hours</td>
<td></td>
</tr>
<tr>
<td>Suprax (cefixime)</td>
<td>Capsule, chewable tablet, suspension</td>
<td>Oral</td>
<td>Every 12 or 24 hours</td>
<td></td>
</tr>
</tbody>
</table>

See the current prescribing information for full details

CONCLUSION

- Current clinical evidence supports the efficacy of each third-generation cephalosporin for their FDA-approved indications, including the treatment of acute otitis media, upper and lower respiratory tract infections, pharyngitis, tonsillitis, uncomplicated urinary tract infections, and skin and soft-tissue infections.
- The safety and efficacy of the third-generation cephalosporins are generally comparable among agents, with the exception of variation in coverage of specific bacterial strains. No agent has consistently demonstrated superiority over another.
  - The overall place in therapy for third-generation cephalosporins in the treatment of various infections is limited by increasing resistance.
  - Local resistance patterns should be checked before prescribing a third-generation cephalosporin. More isolates of H. influenzae, S. pneumonia, and N. gonorrhoeae have become resistant.
- Cross-sensitivity reactions can occur with cephalosporins in patients with a penicillin allergy.

REFERENCES


Publication Date: June 22, 2020