# Cephalosporins and Related Antibiotics
# Therapeutic Class Review (TCR)

**November 1, 2017**

**The literature review is current through March 19, 2019.**



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## FDA-APPROVED INDICATIONS

| Drug | Manufacturer | CAP | AECB | AOM | Pharyngitis/ tonsillitis | Gonorrhea | Skin | UTI | Sinusitis | Lyme disease | Impetigo |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **First Generation Cephalosporins** | | | | | | | | | | | |
| cefadroxil[1] | generic | | | | X | | X | X | | | X |
| cephalexin* (Keflex®, Daxbia™)[2,3] | generic, Crown, Pragma | X | | X | X | | X | X | X | | X |
| **Second Generation Cephalosporins** | | | | | | | | | | | |
| cefaclor[4] | generic | X | X | X | X | | X | X | | | |
| cefprozil†[5] | generic | | X | X | X | | X | | X | | |
| cefuroxime axetil tablets†[6] | generic | | X | X | X | X | X | X | X | X | |
| **Third Generation Cephalosporins** | | | | | | | | | | | |
| cefdinir[7] | generic | X | X | X | X | | X | | X | | |
| cefditoren pivoxil (Spectracef®)[8] | generic, Vansen | X | X | | X | | X | | | | |
| cefixime‡ (Suprax®)[9] | generic, Lupin | | X | X | X | X | | X | | | |
| cefpodoxime proxetil§[10] | generic | X | X | X | X | X | X | X | X | | |
| ceftibuten‖ (Cedax®)[11] | Pernix | | X | X | X | | | | | | |
| **Penicillin/Beta-Lactamase Inhibitor Combinations** | | | | | | | | | | | |
| amoxicillin/clavulanate¶ (Augmentin®)[12] | generic, Dr Reddys/ Neopharma | | | X | | | X | X | X | | |
| amoxicillin/clavulanate ER (Augmentin XR®)[13] | generic, Dr Reddys | X | | | | | | | X | | |

(AECB = Acute Exacerbation of Chronic Bronchitis; AOM = Acute Otitis Media; CAP= Community Acquired Pneumonia; UTI = Urinary Tract Infection)

* Cephalexin is additionally indicated for bone infections, acute prostatitis, and respiratory tract infections, both upper and lower, due to susceptible organisms.

† On November 22, 2016, the FDA removed the indication for secondary bacterial infection of acute bronchitis (SBIAB) for cefprozil; the agency no longer approves products for the treatment of SBIAB.[14,15]

‡ Otitis media should be treated using the cefixime suspension or chewable tablet due to higher serum concentrations achieved with these dosage forms compared to cefixime tablets or capsules.

§ Cefpodoxime proxetil is additionally indicated for ano-rectal infections in women.

‖ Ceftibuten (Cedax) has been shown to have lower clinical efficacy (22% lower than control) in acute bacterial exacerbations of chronic bronchitis clinical trials where *Moraxella catarrhalis* was isolated from infected sputum at baseline. In addition, although ceftibuten used empirically was equivalent to comparators in the treatment of clinically and/or microbiologically documented acute otitis media (AOM), the efficacy against *Streptococcus pneumoniae* was 23% less than control. Therefore, ceftibuten should be given empirically only when adequate antimicrobial coverage against *S. pneumoniae* has been previously administered.

¶ Amoxicillin/clavulanate (Augmentin) tablets are additionally indicated for lower respiratory tract infections due to susceptible organisms.

## OVERVIEW

Oral cephalosporins are divided into 3 generations of agents. First generation oral cephalosporins are active against gram-positive organisms. Second generation oral cephalosporins are active against some gram-positive and gram-negative organisms. Third generation oral cephalosporins have enhanced activity against many gram-negative organisms and are more effective against many resistant bacteria. Many newer third generation oral cephalosporins also have activity against gram-positive organisms. Amoxicillin/clavulanic acid products (generics, Augmentin XR) have similar spectrums of activity, as the second and third generation oral cephalosporins, and are included in this review.

### Respiratory Infections

The 2007 joint guidelines from the American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) for the treatment of community acquired pneumonia (CAP) recommend a macrolide (e.g., erythromycin, clarithromycin [Biaxin®], azithromycin [Zithromax®]) – strong recommendation) or doxycycline (weak recommendation) for adult patients who are otherwise healthy without risk factors for multi-drug resistant *S. pneumoniae*.[16] For adult outpatients with comorbidities including chronic heart, lung, renal, hepatic disorders, diabetes, alcoholism, malignancies, asplenia, immunosuppression or have used any antibiotic within the last 3 months, or other risk factors for multi-drug resistant *S. pneumoniae*, first-line therapy for CAP may include a respiratory fluoroquinolone (moxifloxacin [Avelox®], gemifloxacin [Factive®] or levofloxacin [Levaquin®] 750 mg daily – strong recommendation) or a beta-lactam plus a macrolide (as listed above) as a strong recommendation. Beta-lactam selection for CAP may include 1 of the following: high dose amoxicillin (1 g three times daily) or amoxicillin/clavulanate. Other beta-lactam alternatives include injectable ceftriaxone, oral cefpodoxime, or oral cefuroxime. Doxycycline may also be used as an alternative to macrolides in combination with a beta-lactam. IDSA has assigned this guideline an archived status; it is currently undergoing an update with a projected completion of Fall 2019.

The 2014 recommendations from the World Health Organization (WHO) suggest amoxicillin as the best first-line agent for the treatment of childhood pneumonia in an outpatient setting, preferably administered as amoxicillin 250 mg twice daily for 5 days.[17] Trimethoprim-sulfamethoxazole (TMP/SMZ) may be considered an alternative in some settings. Treatment failure is in a child is defined as development of signs warranting immediate referral or no decrease in respiratory rate after 48 to 72 hours of therapy. If failure occurs, and no indication for immediate referral exists, possible explanations for failure should be systematically evaluated, including non-adherence to therapy and alternative diagnoses. If failure of the first-line agent remains a possible explanation, second-line agents include high-dose amoxicillin-clavulanic acid, with or without a macrolide, for children over 3 years of age.

Patients with an acute exacerbation of chronic obstructive pulmonary disease (COPD) will present with a change in baseline dyspnea, cough, a change in the sputum which is more than the day to day variation, acute in onset; these changes may warrant a change in the management of COPD. According to the 2019 update of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, a COPD exacerbation is defined as an acute worsening of respiratory symptoms resulting in additional therapy.[18] Exacerbations can be caused by several factors, the most common being respiratory tract infections. A 5 to 7 day course of antibiotics can reduce recovery time, risk of early relapse, risk of

treatment failure, and duration of hospitalization. Specific recommendations on choice of antibiotic were not addressed in the guidelines.

According to the 2015 American Academy of Otolaryngology – Head and Neck Surgery guidelines on the treatment of adult sinusitis, its watch and wait strategy has now been extended to all patients with uncomplicated acute bacterial rhinosinusitis (ABRS) regardless of severity.[19] Previously it referred only to those patients with mild or moderate ABRS. For those with ABRS, the recommendation for first-line therapy is amoxicillin with or without clavulanate (previously it was amoxicillin alone in this group). If treatment failure is observed following 7 days of antibiotic therapy, a nonbacterial cause or infection with drug-resistant bacteria should be considered and should prompt a switch to an alternative antibiotic and reevaluation of the patient. Optimal therapy of multidrug-resistant *S. pneumoniae* and beta-lactamase–producing *H. influenzae* and *M. catarrhalis* should include high-dose amoxicillin-clavulanate (4 g per day amoxicillin equivalent) or a respiratory fluoroquinolone (levofloxacin, moxifloxacin, or gemifloxacin), which would also cover less common pathogens. Patients with penicillin allergy could receive a fluoroquinolone. The Infectious Diseases Society of America (IDSA) guidelines published in March 2012 (reaffirmed in May 2015) recommend amoxicillin-clavulanic acid versus amoxicillin alone as first-line empirical therapy for children with acute rhinosinusitis (strong, moderate), and amoxicillin-clavulanic acid versus amoxicillin alone for empiric treatment in adults with ABRS (weak, low). An alternative for children with allergy to penicillins is levofloxacin. Doxycycline may be used as an alternative to amoxicillin-clavulanic acid in adults. Other agents are no longer recommended due to higher resistance rates (macrolides, sulfamethoxazole-trimethoprim, second and third generation cephalosporins).[20]

When treating group A ß-hemolytic streptococcal (GAS) tonsillopharyngitis, the American Heart Association recommends oral penicillin V or injectable benzathine penicillin as first-line to prevent rheumatic fever.[21] Oral penicillin has proven efficacy, low cost, and safety with a narrow spectrum of activity. Group A streptococci resistant to penicillin have not been documented. For penicillin-allergic individuals, acceptable alternatives include a narrow-spectrum oral cephalosporin, such as cefadroxil or cephalexin, oral clindamycin, or various oral macrolides or azalides. The 2012 IDSA guidelines for acute pharyngitis recommend penicillin or amoxicillin orally for 10 days. For those patients allergic to penicillin, the IDSA recommends a first-generation a 10 day course of a cephalosporin, clindamycin, or clarithromycin, or 5 days of azithromycin therapy. IDSA has assigned this guideline an archived status; however, a newer version has not been issued.[22]

The 2013 American Academy of Pediatrics guidelines recommend high-dose amoxicillin (90 mg/kg/day) as first-line therapy for the treatment of acute otitis media (AOM) in children.[23] For patients with amoxicillin hypersensitivity (not urticaria or anaphylaxis), cefdinir, cefpodoxime, and cefuroxime can be used for AOM. For patients with AOM who do not improve on high-dose amoxicillin, treatment alternatives include amoxicillin/clavulanate or ceftriaxone. Alternative therapies are clindamycin and ceftriaxone.

## Genitourinary Infections

Urinary tract infections (UTI) occur more commonly in women.[24] Acute cystitis is a symptomatic bladder infection characterized by frequency, urgency, dysuria, and suprapubic pain in patients with a normal genitourinary tract. The 2011 updated guidelines from IDSA for the management of acute uncomplicated cystitis consider resistance patterns and ecological adverse effects of antimicrobial therapy in drug selection. The empiric antibiotic selection for acute uncomplicated cystitis is

nitrofurantoin 100 mg twice daily for 5 days. Nitrofurantoin has been shown to provide comparable efficacy to trimethoprim/sulfamethoxazole (TMP/SMZ) given for 3 days (Strength of recommendation: A [good evidence to support]; quality of evidence: I [evidence from greater than one randomized controlled trial]). Empiric antibiotic selection may include TMP/SMZ double-strength (160/800 mg) twice daily for 3 days when local uropathogens are less than 20% resistant or if the infecting strain is known to be sensitive. The fluoroquinolones, ofloxacin, ciprofloxacin, and levofloxacin, are highly efficacious, but their use has been linked to infections with methicillin-resistant *Staphylococcus aureus* (MRSA) and with increasing fluoroquinolone resistance in gram negative bacilli. Fluoroquinolones are considered alternatives for acute cystitis (A-III). Cephalosporins (cefdinir, cefaclor, and cefpodoxime) and amoxicillin-clavulanate given for 3 to 7 days are appropriate regimens when the other recommended agents cannot be used (B-I). In general, beta-lactams have inferior efficacy and more adverse effects compared to other antimicrobials for UTIs. IDSA has assigned this guideline an archived status; it is currently undergoing an update with a projected completion of 2022.

A complicated urinary tract infection which may involve the bladder or kidneys is a symptomatic infection in patients with functional or structural abnormalities of the genitourinary tract. The 2010 guidelines from the IDSA for diagnosis, prevention, and treatment of catheter-associated urinary tract infections recommend that a urine culture be obtained prior to the initiation of antibiotics.[25] If the indwelling catheter has been in place for more than 2 weeks and it is still indicated, the catheter should be replaced. Seven days of antimicrobial treatment should be given to patients who have prompt resolution of symptoms, and 10 to 14 days of therapy for patients with a delayed response, regardless if the catheter remains in place. Five days of levofloxacin therapy may be considered in patients with mild illness. Three days of antimicrobial therapy may be considered for women ≤ 65 years of age that develop a catheter-associated UTI without upper urinary tract symptoms after an indwelling catheter has been removed. Specific recommendations for antibiotics were not cited in the IDSA guidelines. IDSA has assigned this guideline an archived status; however, a newer version has not been issued.

The 2015 Sexually Transmitted Disease (STD) guidelines from the Centers for Disease Control and Prevention (CDC) recommend annual screening for *N. gonorrhoeae* in all sexually active women under age 25, and for older women at increased risk for infection. Due to increased treatment failure with several antibiotics, including cefixime and ceftriaxone; cefixime is no longer recommended as first-line therapy. With this in mind, the only recommended regimen is dual treatment with ceftriaxone and azithromycin.[26] The recommended treatment options for uncomplicated gonorrhea of the cervix, rectum, or urethra are ceftriaxone 250 mg intramuscular (IM) in a single dose plus azithromycin 1 g orally for 1 dose. If ceftriaxone is not available, the alternative is cefixime 400 mg orally (single dose) plus azithromycin 1 g orally (single dose). In the event of azithromycin contraindication, doxycycline 100 mg orally twice a day for 7 days may be used as the second antimicrobial in combination with ceftriaxone or cefixime. For uncomplicated gonorrhea infections in the pharynx, ceftriaxone 250 mg IM plus azithromycin 1 g is the recommended regimen. The American Congress of Obstetricians and Gynecologists (ACOG) also recommend treatment with ceftriaxone and azithromycin in their opinion summary published in November 2015 (reaffirmed 2018).[27]

## Skin/Skin Structure Infections

The 2014 recommendation from IDSA for the treatment of impetigo, either bullous or nonbullous, is the use of either topical mupirocin or retapamulin twice daily for 5 days.[28] Oral therapy for impetigo is recommended as a 7-day regimen with an agent active against *S. aureus*; either oral dicloxacillin or

cephalexin. When MRSA is suspected or confirmed, then oral doxycycline, clindamycin, or TMP/SMZ is recommended. For purulent skin soft tissue infections (pSSTI), the oral recommendation in the presence of MRSA is one of the following options: intravenous (IV) nafcillin or oxacillin, or IV cefazolin if patient is penicillin allergic. Oral options include dicloxacillin; or cephalexin in those with penicillin allergy. For the treatment of MRSA SSTIs, vancomycin IV is the drug of choice and linezolid is no longer recommended.

## PHARMACOLOGY[29]

Beta-lactams, such as cephalosporins and amoxicillin, work by binding to the penicillin-binding proteins which inhibit cell wall synthesis.[30] The drugs are usually bactericidal, depending on organism susceptibility, dose, tissue concentrations, and the rate at which organisms are multiplying. Beta-lactams are most effective against rapidly growing organisms forming cell walls.

The clavulanic acid component of the Augmentin product line inactivates the beta-lactamase enzyme produced by some bacteria. Clavulanic acid inhibits beta-lactamases from *Escherichia coli, Haemophilus influenzae, Salmonella, Shigella,* and *Klebsiella*. It generally does not inhibit beta-lactamases produced by *Enterobacter, Serratia, Citrobacter, Pseudomonas,* and *Acinetobacter.*

Resistance to cephalosporins has emerged, especially in the acute care setting. Extended-spectrum beta-lactamases (ESBLs) have been identified clinically with *E. coli* and *Klebsiella pneumoniae.*[31] Beta-lactamases are now categorized based on functional class, determined by the antibiotics that they inhibit. A second method of classification is based on the molecular structure.[32] The ESBLs are plasmid-mediated beta-lactamase enzymes that are derived from either a Temoneira (TEM) or sulphydryl variable (SHV) type of beta-lactamase enzyme. Over 100 varieties of TEM and SHV beta-lactamases have been identified. The most common forms of ESBL are mutants of TEM-1, TEM-2, and SHV-1 beta-lactamases. Both TEM-1 and SHV-1 enzymes cause resistance to ampicillin.[33] The ESBL-producing organisms are resistant to many antimicrobials including ampicillin, ticarcillin, piperacillin, and some cephalosporins, including ceftazidime. While high doses of a beta-lactam/beta-lactamase inhibitor combination may be effective, the treatment of choice for ESBL-producing gram-negative bacteria is a carbapenem. Occasionally, fluoroquinolones, TMP/SMZ, and aminoglycosides are treatment options depending on *in vitro* susceptibility.[34,35,36,37]

## Spectrum of Activity

In general, the first generation oral cephalosporins have more gram-positive coverage. Third generation oral cephalosporins have broad spectrum gram-negative coverage, as well as coverage of penicillin-susceptible *S. pneumoniae*. The cephalosporins and related antibiotics do not have activity against atypical pathogens, *Listeria monocytogenes,* or methicillin-resistant *Staphylococcus aureus* (MRSA) to name a few. Cephalosporins do not have activity against *Enterococcus.* Local susceptibility patterns may differ from the chart below (adapted from reference).[38]

Key: + = usually effective clinically or > 60 % susceptible, ± = clinical trials lacking or 30-60 % susceptible, 0 = not clinically effective or < 30 % susceptible, blank = data not available.

| Organism | amoxicillin/ clavulanate | cefadroxil | cephalexin | cefaclor | cefprozil | cefuroxime | cefixime | ceftibuten | cefdinir cefditoren cefpodoxime |
|---|---|---|---|---|---|---|---|---|---|
| **Gram Positive** | | | | | | | | | |
| Strep. Group A,B,C,G | + | + | + | + | + | + | + | + | + |
| *S. pneumoniae* | + | + | + | + | + | + | + | ± | + |
| Viridans strep | ± | + | + | + | O | + | + | O | + |
| *Enterococcus faecalis* | + | O | O | O | O | O | O | O | O |
| *S. aureus* - MSSA | + | + | + | + | + | + | O | O | + |
| *S. epidermidis* | + | ± | ± | ± | ± | ± | O | O | ± |

***Spectrum of Activity (continued)***

| Organism | amoxicillin/ clavulanate | cefadroxil | cephalexin | cefaclor | cefprozil | cefuroxime | cefixime | ceftibuten | cefdinir cefditoren cefpodoxime |
|---|---|---|---|---|---|---|---|---|---|
| **Gram Negative** | | | | | | | | | |
| *N. gonorrhoeae* | + | O | O | ± | ± | ± | + | ± | + |
| *N. meningitides* | + | O | O | ± | ± | ± | ± | ± | |
| *M. catarrhalis* | + | O | O | ± | + | + | + | + | + |
| *H. influenzae* | + | | O | + | + | + | + | + | + |
| *E. coli* | + | + | + | + | + | + | + | + | + |
| Klebsiella species | + | + | + | + | + | + | + | + | |
| Enterobacter species | O | O | O | O | O | O | O | ± | O |
| Serratia species | O | O | O | O | O | O | ± | ± | O |
| Salmonella species | + | O | O | | | | + | + | + |
| Shigella species | + | O | O | | | | + | + | + |
| Proteus mirabilis | + | + | + | + | + | ± | + | + | + |
| Proteus vulgaris | + | O | O | O | O | O | + | + | ± |
| Providencia species | + | O | O | O | O | + | + | + | |
| Morganella species | ± | O | O | O | O | ± | O | O | O |
| Citrobacter species | O | | O | ± | O | ± | + | + | + |
| Aeromonas species | + | | | | | | + | + | |
| Acinetobacter species | O | O | O | O | O | O | O | O | |
| *P. aeruginosa* | O | O | O | O | O | O | O | O | O |
| *B. cepacia* | O | O | O | O | O | O | O | + | |
| *S. maltophilia* | O | O | O | O | O | O | O | O | |
| *Y. enterocolitica* | ± | | | | | | + | + | |
| *P. multocida* | + | | O | | | | + | | + |
| *H. ducreyi* | + | | | | | | + | | |

***Spectrum of Activity (continued)***

| Organism | amoxicillin/ clavulanate | cefadroxil | cephalexin | cefaclor | cefprozil | cefuroxime | cefixime | ceftibuten | cefdinir cefditoren cefpodoxime |
|---|---|---|---|---|---|---|---|---|---|
| **Anaerobes** | | | | | | | | | |
| Actinomyces | + | | | | | | | | |
| *Bacteroides fragilis* | + | | O | O | O | O | O | O | |
| *P. melaninogenica* | + | | | + | + | + | + | | |
| Peptostreptococcus species | + | | + | + | + | ± | + | | |

## PHARMACOKINETICS[39,40,41,42,43,44,45,46,47,48,49,50]

| Drug | Bioavailability (%) | Half-Life (hr) | Metabolites | Excretion (%) |
|---|---|---|---|---|
| **First Generation Cephalosporins** | | | | |
| cefadroxil | -- | -- | None | Renal: > 90 |
| cephalexin (Keflex, Daxbia) | -- | 1 | -- | Renal |
| **Second Generation Cephalosporins** | | | | |
| cefaclor | -- | 0.6-0.9 | Not appreciably metabolized | Renal |
| cefprozil | 95 | 1.3 | -- | Renal: 60 |
| cefuroxime axetil | -- | 1.2-1.9 | -- | Renal: > 50 |
| **Third Generation Cephalosporins** | | | | |
| cefdinir | 300 mg caps: 21<br>600 mg caps: 16<br>suspension: 25 | 1.7 | Not appreciably metabolized | Renal |
| cefditoren pivoxil (Spectracef) | 14 | 1.6 | Not appreciably metabolized | Renal |
| cefixime (Suprax) | 40-50 | 3-9 | None | Renal |
| cefpodoxime proxetil | 50 | 2.1-2.8 | Minimal metabolism | Renal |
| ceftibuten (Cedax) | undetermined | 2-2.4 | Minimal activity of cis-ceftibuten trans-ceftibuten | Renal: 56<br>Feces: 39 |
| **Penicillin/Beta-Lactamase Inhibitor Combinations** | | | | |
| amoxicillin/ clavulanate (Augmentin) | -- | 1.3/1 | None | Renal: 50-70/25-40 |
| amoxicillin/ clavulanate ER (Augmentin XR) | -- | 1.3/1 | None | Renal: 60-80/30-50 |

Cefixime (Suprax) chewable tablets and oral suspension result in average peak concentrations approximately 25% to 50% higher than the tablets, when tested in normal adult volunteers. Because of the lack of bioequivalence, the tablet or capsule should not be substituted for the suspension or chewable tablets for the treatment of otitis media. Cefixime chewable tablets are bioequivalent to cefixime suspension. Cefixime 400 mg capsules are bioequivalent to cefixime 400 mg tablets under fasting conditions.

### Effect of Food

The absorption of cefixime and ceftibuten may be delayed by food, but total absorption is not significantly affected. Cefixime 400 mg capsules are bioequivalent to cefixime 400 mg tablets under fasting conditions; however, food reduces the absorption following administration of the capsule by approximately 15% based on AUC and 25% based on Cmax.

Cefpodoxime proxetil is a prodrug that is absorbed from the gastrointestinal tract and de-esterified to its active metabolite, cefpodoxime. Following oral administration of 100 mg of cefpodoxime proxetil to

fasting subjects, approximately 50% of the administered cefpodoxime dose is absorbed systemically. Over the recommended dosing range (100 to 400 mg), approximately 29% to 33% of the administered cefpodoxime dose is excreted unchanged in the urine in 12 hours. There is minimal metabolism of cefpodoxime *in vivo*. When taken with food, the absorption is increased. When a 200 mg tablet dose is taken with food, the AUC can be 21% to 33% higher than under fasting conditions, and the peak plasma concentration average is 3.1 mcg/mL in fed subjects versus 2.6 mcg/mL in fasted subjects. Time to peak concentration is not significantly different between fed and fasted subjects. When a 200 mg dose of the suspension is taken with food, the extent of absorption (mean AUC) and mean peak plasma concentration in fed subjects were not significantly different from fasted subjects, but the rate of absorption is slower with food (48% increase in Tmax).

The rate and extent of absorption of cefdinir may be reduced when given with a high-fat meal, but not to a clinically significant magnitude; therefore, cefdinir may be taken without regard to meals.

Administration of cefditoren pivoxil following a high-fat meal may result in an increase in bioavailability of up to 70% compared to administration in the fasted state.

## CONTRAINDICATIONS/WARNINGS[51,52,53,54,55,56,57,58,59,60,61]

Pseudomembranous colitis has been reported with nearly all antibacterial agents and severity may range from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Before therapy with cephalosporins or penicillin products is initiated, inquiry should be made to determine if the patient has had a previous hypersensitivity reaction to cephalosporins or penicillins. Cross hypersensitivity among beta-lactam antibiotics has been documented and may occur in up to 10% of patients with a history of penicillin allergy.

### Cephalosporins

Cephalosporins are contraindicated in patients with known allergy to the cephalosporin class of antibiotics or any component.

Cefditoren (Spectracef) use causes renal excretion of carnitine. It is contraindicated in patients with carnitine deficiency or inborn errors of metabolism that may result in clinically significant carnitine deficiency. Additionally, cefditoren tablets contain sodium caseinate, a milk protein. Patients with milk protein hypersensitivity (not lactose intolerance) should not be administered cefditoren.

Phenylketonurics should be cautioned that cefixime (Suprax) contains aspartame, a source of phenylalanine.

### Penicillin/Beta-Lactamase Combinations

Hypersensitivity reactions including skin rashes, pruritus, urticaria, angioedema, serum sickness-like reactions (urticaria or skin rash accompanied by arthritis, arthralgia, myalgia, and frequently fever), erythema multiforme (rarely Stevens-Johnson syndrome), acute generalized exanthematous pustulosis, hypersensitivity vasculitis, and an occasional case of exfoliative dermatitis (including toxic epidermal necrolysis), have been reported with penicillins. These reactions may be controlled with antihistamines and, if necessary, systemic corticosteroids. Whenever such reactions occur, the drug

should be discontinued. Serious and occasional fatal hypersensitivity (anaphylactic) reactions can occur with oral penicillin.

Amoxicillin/clavulanate (Augmentin, Augmentin XR) is contraindicated in patients with a history of allergic reactions to any penicillin. Amoxicillin/clavulanate is also contraindicated in patients with a previous history of cholestatic jaundice/hepatic dysfunction associated with treatment with amoxicillin/clavulanate. Amoxicillin/clavulanate (Augmentin XR) tablets are contraindicated in patients with severe renal impairment (creatinine clearance [CrCl] < 30 mL/min) and in patients on hemodialysis.

Amoxicillin/clavulanate should be used with caution in patients with evidence of hepatic dysfunction. Hepatic toxicity associated with the use of amoxicillin/clavulanate potassium is usually reversible.

Patients with phenylketonuria should be cautioned that some of the amoxicillin/clavulanate products contain phenylalanine; the products include Augmentin chewable tablets and Augmentin 200 mg/5 mL or 400 mg/5 mL oral suspension.

## DRUG INTERACTIONS[62,63,64,65,66,67,68,69,70,71,72,73]

Due to renal elimination as the primary method of excretion, drug interactions for this category of drugs are limited. However, probenecid inhibits the renal excretion of the agents in this category. For the amoxicillin/clavulanate products, probenecid inhibits excretion of amoxicillin.

### allopurinol and ampicillin

An increased incidence of rashes has been reported in patients receiving both allopurinol and ampicillin. No increased incidence of rashes has been reported in clinical trials with amoxicillin/clavulanate (Augmentin products); however, the sample size on both drugs was small.

### probenecid

Use of probenecid with cefuroxime increases systemic exposure to the antibiotic and is not recommended.

### antacids

Cefditoren (Spectracef) should not be administered with antacids as there is a reduction in mean Cmax and mean area-under-the-curve (AUC) of cefditoren, in other words, a lower gastric acidity results in lower bioavailability of cefuroxime axetil.

Concomitant administration of cefdinir capsules with antacids delays Cmax by 1 hour and reduces AUC by approximately 40%. If antacids are required during cefdinir therapy, cefdinir should be taken at least 2 hours before or after the antacid.

### carbamazepine

Elevated carbamazepine levels have been reported with concurrently administered cefixime (Suprax). Monitoring of carbamazepine plasma concentrations may be helpful.

## $H_2$-Receptor Antagonists

It is not recommended to co-administer $H_2$-receptor antagonists with cefditoren. Mean Cmax of cefditoren is reduced by 27% and mean AUC is reduced by 22% with concurrent administration of cefditoren and $H_2$-receptor antagonists.

## Iron Supplements and Foods Fortified With Iron

The bioavailability of cefdinir is reduced by approximately 80% with the co-administration of ferrous sulfate 60 mg. If iron supplements are required during cefdinir therapy, cefdinir should be taken at least 2 hours before or after the iron supplement. Iron-fortified foods have not been studied. Iron-fortified infant formula had no significant effect on cefdinir pharmacokinetics.

## metformin

Patient monitoring and dose adjustment of metformin is recommended in patients concomitantly taking cephalexin (Keflex, Daxbia) and metformin, based on data from a single-dose healthy volunteer study.

## oral contraceptives

As with other broad-spectrum antibiotics, amoxicillin/clavulanate and cefuroxime may reduce the efficacy of oral contraceptives.

## warfarin

Increased prothrombin time and international normalization ratio (INR), with or without clinical bleeding, have been reported when cefixime is administered concomitantly with warfarin.

## ADVERSE EFFECTS[74,75,76,77,78,79,80,81,82,83,84,85]

| Drug | Diarrhea | Nausea | Vaginal fungal infections | Abdominal pain | Headache | Increase in ALT/AST | Eosinophilia | Rash |
|---|---|---|---|---|---|---|---|---|
| **First Generation Cephalosporins** | | | | | | | | |
| cefadroxil | reported | reported | reported | reported | nr | reported | reported | reported |
| cephalexin (Keflex, Daxbia) | reported | reported | reported | reported | reported | reported | reported | reported |
| **Second Generation Cephalosporins** | | | | | | | | |
| cefaclor | reported | reported | reported | reported | reported | reported | reported | reported |
| cefprozil | 2.9 | 3.5 | 1.6 | 1 | < 1 | 2/2 | 2.3 | 0.9 |
| cefuroxime axetil tablets | 3.7 | 3 | 0.1-1 | 0.1-1 | 0.1-1 | 1.6/2 | 1.1 | 0.1-1 |
| **Third Generation Cephalosporins** | | | | | | | | |
| cefdinir n=3,841 | 15 | 3 | 4 | 1 | 2 | 0.7/0.4 | 0.7 | 0.9 |
| cefditoren pivoxil (Spectracef) | 11-15 | 4-6 | 3-6 | 2 | 2-3 | 0.1-1 | 0.1-1 | 0.1-1 |
| cefixime (Suprax) | 16 | 7 | < 2 | 3 | < 2 | < 2 | < 2 | < 2 |
| cefpodoxime proxetil n=4,696 | 7 | 3.3 | 1-1.3 | 1.2 | 1 | reported | reported | < 1 |
| ceftibuten (Cedax) | 3 | 4 | 0.1-1 | 1 | 3 | > 1/0.1-1 | 3 | 0.1-1 |
| **Penicillin/Beta-Lactamase Inhibitor Combinations** | | | | | | | | |
| amoxicillin/clavulanate (Augmentin) | 9 | 3 | 1 | reported | reported | reported | reported | 3 |
| amoxicillin/clavulanate (Augmentin XR) | 14.5 | 2.1 | 3.3 | nr | reported | reported | reported | reported |

Adverse effects are reported as a percentage. Adverse effects data are obtained from prescribing information and should not be considered comparative or all inclusive. nr=not reported. ALT=alanine aminotransferase AST=aspartate aminotransferase

## SPECIAL POPULATIONS[86,87,88,89,90,91,92,93,94,95,96]

### Pediatrics

Safety and effectiveness of most agents in this review have been established in the pediatric population. Cefditoren (Spectracef) is approved for patients age 12 years and older.

Cephalexin may be used in children over 1 year old.[97] Pediatric patients weighing greater than 4.5 kg may be treated with cefadroxil. Safety and effectiveness data are available for children age 6 months and older for cefprozil, cefixime, ceftibuten, and cefdinir. Children as young as 2 months may be treated with cefpodoxime. Cefaclor may be used in children as young as 1 month.

Safety and effectiveness of amoxicillin/clavulanate (Augmentin XR) have been shown for pediatric patients ≥ 40 kg who are able to swallow whole tablets. Amoxicillin/clavulanate 125 mg/5 mL suspension may be used in infants less than 12 weeks of age; the dosage is 30 mg/kg divided every 12 hours.

Compliance with antibiotic therapy is essential for bacterial eradication and treatment of the infection. Palatability, administration frequency, and duration of therapy influence compliance in the pediatric patient.[98] Some investigators have found that cefdinir and cefixime are among those antibiotics that were most palatable.[99,100] Shorter courses of therapy are seen with cefdinir and cefpodoxime for AOM in children.

### Pregnancy

All agents in this category are Pregnancy Category B.

### Renal Impairment

Cephalosporins and penicillin/beta-lactamase inhibitor combinations are primarily renally excreted. Renal impairment generally requires dose reduction or interval extension. Specific dosing recommendations are listed in the dosing considerations section.

## DOSAGES[101,102,103,104,105,106,107,108,109,110,111,112]

| Drug | CAP | Sinusitis | Bronchitis | Skin Infections | Otitis Media | Pharyngitis / Tonsillitis | Availability |
|---|---|---|---|---|---|---|---|
| **First Generation Cephalosporins** | | | | | | | |
| cefadroxil | -- | -- | -- | 1 g given in 1 or 2 divided doses daily<br>**Pediatrics**:<br>30 mg/kg/day in 1 or 2 doses daily | -- | 1 g given in 1 or 2 divided doses daily for 10 days<br>**Pediatrics**:<br>30 mg/kg/day in 1 or 2 doses daily for 10 days | capsule: 500 mg<br>tablet: 1 g<br>suspension: 250 mg/5 mL, 500 mg/5 mL |
| cephalexin (Keflex) | 250-500 mg given every 6 hours<br>**Pediatrics:**<br>25-100 mg/kg/day given every 6 hours | -- | -- | 500 mg every 12 hours<br>**Pediatrics**:<br>25-50 mg/kg/day divided in 2 doses daily<br>(children 10-40 kg) | **Pediatrics**:<br>75-100 mg/kg/day in divided doses given every 6 hours<br>(children 10-40 kg) | 500 mg every 12 hours for 10 days<br>**Pediatrics**:<br>25-50 mg/kg/day divided in 2 doses daily for 10 days<br>(children 10-40 kg) | capsules:<br>250 mg (generic only), 500 mg (generic only), 750 mg<br>tablet (generic only):<br>250 mg, 500 mg<br>suspension (generic only): 125 mg/5 mL, 250 mg/5 mL |
| cephalexin (Daxbia) | 1 to 4 g given in 2 to 4 divided doses<br>**Pediatrics (> 1 year of age):**<br>25-100 mg/kg/day in equally divided doses | -- | -- | 1 to 4 g given in 2 to 4 divided doses<br>**Pediatrics**:<br>25-100 mg/kg/day in equally divided doses | **Pediatrics**:<br>75-100 mg/kg/day in divided doses given every 6 hours<br>(children 10-40 kg) | 1 to 4 g given in 2 to 4 divided doses<br>**Pediatrics**:<br>25-100 mg/kg/day given in equally divided doses | capsules:<br>333 mg (brand only) |
| **Second Generation Cephalosporins** | | | | | | | |
| cefaclor | 250-500 mg every 8 hours<br><br>ER tablets:<br>500 mg every 12 hours for 7-10 days | -- | ER tablets:<br>500 mg every 12 hours for 7 days | 250-500 mg every 8 hours<br>**Pediatrics**:<br>20-40 mg/kg/day in 3 divided doses; given every 8 hours for 7-10 days<br>(ages > 1 month – 12 years) | **Pediatrics**:<br>20-40 mg/kg/day in 3 divided doses; given every 8 hours<br>(ages > 1 month – 12 years) | 250-500 mg every 8 hours<br>**Pediatrics**:<br>20-40 mg/kg/day in 3 divided doses; given every 8 hours for 7-10 days<br>(ages > 1 month – 12 years) | capsules: 250 mg, 500 mg<br>suspension:<br>125 mg/5 mL, 250 mg/5 mL, 375 mg/5 mL<br>ER tablets: 500 mg |

ER = extended-release

***Dosages (continued)***

| Drug | CAP | Sinusitis | Bronchitis | Skin Infections | Otitis Media | Pharyngitis / Tonsillitis | Availability |
|---|---|---|---|---|---|---|---|
| **Second Generation Cephalosporins *(continued)*** | | | | | | | |
| cefprozil | -- | 250 mg every 12 hours<br>or<br>500 mg every 12 hours<br>for 10 days<br>**Pediatrics:**<br>7.5-15 mg/kg every 12 hours<br>(ages 6 months-12 years) | 500 mg every 12 hours<br>for 10 days | 250 mg every 12 hours or<br>500 mg daily or<br>500 mg every 12 hours for 10 days<br>**Pediatrics**:<br>20 mg/kg/day for 10 days<br>(ages 2-12 years) | **Pediatrics:**<br>15 mg/kg every 12 hours<br>(ages 6 month-12 years) | 500 mg every 24 hours<br>for 10 days<br>(ages ≥ 13 years)<br>**Pediatrics**:<br>7.5 mg/kg every 12 hours 10 days<br>(ages 2-12 years) | tablets: 250 mg, 500 mg<br>suspension: 125 mg/5 mL, 250 mg/5 mL |
| cefuroxime axetil tablets | 500 mg every 12 hours for at least 5 days | 250 mg every 12 hours for 10 days including pediatric patients who can swallow a whole tablet | 250 or 500 mg every 12 hours for 10 days | 250 or 500 mg every 12 hours for 10 days | **Pediatrics:**<br>250 mg every 12 hours for 10 days for those children who can swallow a whole tablet | 250 mg every 12 hours for 10 days | tablets: 250 mg, 500 mg |

***Dosages (continued)***

| Drug | CAP | Sinusitis | Bronchitis | Skin Infections | Otitis Media | Pharyngitis / Tonsillitis | Availability |
|---|---|---|---|---|---|---|---|
| **Third Generation Cephalosporins** | | | | | | | |
| cefdinir | 300 mg every 12 hours for 10 days (ages ≥ 13 years) | 300 mg every 12 hours or 600 mg every 24 hours for 10 days (ages ≥ 13 years) **Pediatrics:** 7 mg/kg every 12 hours or 14 mg/kg every 24 hours for 10 days (ages 6 months to 12 years) | 300 mg every 12 hours for 5 to 10 days or 600 mg every 24 hours for 10 days (ages ≥ 13 years) | 300 mg every 12 hours for 10 days **Pediatrics**: 7 mg/kg every 12 hours for 10 days (ages 6 months – 12 years) | **Pediatrics:** 7 mg/kg every 12 hours for 5 to 10 days or 14 mg/kg every 24 hours for 10 days (ages 6 months to 12 years) | 300 mg every 12 hours for 5 to 10 days or 600 mg every 24 hours for 10 days (ages ≥ 13 years) **Pediatrics:** 7 mg/kg every 12 hours for 5 to 10 days or 14 mg/kg every 24 hours for 10 days (ages 6 months to 12 years) | capsules: 300 mg suspension: 125 mg/5 mL, 250 mg/5 mL |
| cefditoren pivoxil (Spectracef) | 400 mg twice daily for 14 days | -- | 400 mg twice daily for 10 days | 200 mg twice daily for 10 days | -- | 200 mg twice daily for 10 days | tablets: 200 mg, 400 mg (generic only) dose pack: 400 mg (Spectracef only) |
| cefixime (Suprax)* | -- | -- | 400 mg daily or 200 mg every 12 hours **Pediatrics:** 8 mg/kg daily or 4mg/kg every 12 hours (ages 6 months to 12 years) | -- | **Pediatrics:** 8 mg/kg daily for 10 days or 4mg/kg every 12 hours (ages 6 months to 12 years) | 400 mg daily or 200 mg every 12 hours **Pediatrics:** 8 mg/kg daily or 4mg/kg every 12 hours (ages 6 months to 12 years) | chewable tablets (brand only): 100 mg, 200 mg tablet: 400 mg capsule (brand only): 400 mg suspension: 100 mg/5 mL, 200 mg/5 mL, 500 mg/5 mL (brand only) |

***Dosages (continued)***

| Drug | CAP | Sinusitis | Bronchitis | Skin Infections | Otitis Media | Pharyngitis / Tonsillitis | Availability |
|---|---|---|---|---|---|---|---|
| **Third Generation Cephalosporins *(continued)*** | | | | | | | |
| cefpodoxime | 200 mg every 12 hours for 14 days | 200 mg every 12 hours for 10 days<br>**Pediatrics:**<br>5 mg/kg every 12 hours for 10 days (ages 2 months to 12 years) | 200 mg every 12 hours<br>for 10 days | 400 mg every 12 hours for 7 to14 days | **Pediatrics:**<br>5 mg/kg every 12 hours for 5 days (ages 2 months to 12 years) | 100 mg every 12 hours for 5 to 10 days<br>**Pediatrics:**<br>5 mg/kg every 12 hours for 5 to 10 days<br>(ages 2 months to 12 years) | tablets: 100 mg, 200 mg<br>suspension: 50 mg/5 mL, 100 mg/5 mL |
| ceftibuten (Cedax) | -- | -- | 400 mg daily<br>for 10 days<br>(ages ≥ 12 years) | -- | 400 mg daily for 10 days<br>(ages ≥ 12 years)<br>**Pediatrics:**<br>9 mg/kg daily for 10 days (maximum 400 mg daily)<br>(ages 6 months – 12 years) | 400 mg daily for 10 days<br>(ages ≥ 12 years)<br>**Pediatrics:**<br>9 mg/kg daily for 10 days (maximum 400 mg daily)<br>(ages 6 months – 12 years) | capsule: 400 mg<br>suspension: 180 mg/5 mL |

***Dosages (continued)***

| Drug | CAP | Sinusitis | Bronchitis | Skin Infections | Otitis Media | Pharyngitis / Tonsillitis | Availability |
|---|---|---|---|---|---|---|---|
| **Penicillin/Beta-Lactamase Inhibitor Combinations** | | | | | | | |
| amoxicillin/ clavulanate (Augmentin) | 250 mg or 500 mg every 8 hours or 500 mg or 875 mg every 12 hours<br>**Pediatrics**<br>**≥ 40 kg:**<br>250 or 500 mg every 8 hours or 500 mg or 875 mg every 12 hours | 500 mg every 12 hours<br>or<br>250 mg every 8 hours<br>for 10 days | -- | 500 mg every 12 hours<br>or<br>250 mg every 8 hours<br>for 10 days<br><br>**Pediatrics**:<br>25-45 mg/kg every 12 hours<br>or<br>20-40 mg/kg every 8 hours for 10 days | **Pediatrics:**<br>25-45 mg/kg every 12 hours<br>or<br>20-40 mg/kg every 8 hours<br>for 10 days<br><br>(ages > 3 months to 40 kg) | -- | Tablets (generic only): 250/125 mg, 500/125 mg, 875/125 mg<br>chewable tablets (generic only): 200/28.5 mg, 400/57 mg<br>suspensions (generic only): 125/31.25 mg/5 mL, 200/28.5 mg/5 mL, 400/57 mg/5 mL, 600/42.9 mg/5 mL<br>suspension (brand & generic): 250/62.5 mg/5 mL |
| amoxicillin/ clavulanate (Augmentin XR) | 2 tablets every 12 hours for 7-10 days (including pediatric patients weighing ≥ 40 kg and are able to swallow a whole tablet) | 2 tablets every 12 hours for 10 days (including pediatric patients weighing ≥ 40 kg and are able to swallow a whole tablet) | -- | -- | -- | -- | 1,000/62.5 mg tablet |

*Cefixime (Suprax) chewable tablets follow same dosing as the suspension

## DOSING CONSIDERATIONS[113,114,115,116,117,118,119,120,121,122,123]

### First Generation Cephalosporins

Cefadroxil should be administered to adults as 1 to 2 grams given as a single dose or in divided doses twice daily. For children, cefadroxil is administered as 30 mg/kg/day given as a single dose or divided in 2 doses. Cefadroxil should be given as 500 mg every 24 hours for patients with CrCl 10 to 24 mL/min or 500 mg every 36 hours for patients on dialysis.

Cephalexin should be administered to adults as 1 to 4 grams daily in divided doses given every 6 hours. Cephalexin 500 mg may be administered every 12 hours. For pediatric patients with infections other than otitis media, the dose of cephalexin is 25 to 50 mg/kg daily given in divided doses. Cephalexin for patients with CrCl of 11 to 40 mL/min should be administered as a loading dose of 250 to 500 mg, followed by a dose of 250 to 500 mg every 8 to 12 hours. For patients with CrCl 10 mL/min or less, a loading dose of cephalexin 250 to 500 mg then 250 mg every 12 to 24 hours has been recommended.

### Second Generation Cephalosporins

Cefprozil for patients with CrCl < 30 mL/min should be given twice daily at 50% of the normal dosage. For patients on hemodialysis, give cefprozil after the dialysis session.

Cefuroxime is renally excreted and will accumulate in renal insufficiency; dosage interval should be adjusted based on creatinine clearance; CrCl 10 to < 30 ml/min = standard dose every 24 hours, < 10 ml/min without hemodialysis = standard dose every 48 hours, hemodialysis = give a single additional standard dose at the end of dialysis. Cefuroxime tablets may be given without regard to meals.

### Third Generation Cephalosporins

Adult patients with CrCl < 30 mL/min should receive cefdinir 300 mg once daily; pediatric patients should receive 7 mg/kg (up to 300 mg) once daily. For patients on hemodialysis, give cefdinir 300 mg (or 7 mg/kg) every other day.

Cefditoren (Spectracef) doses should be administered with meals. Patients with moderate renal impairment (CrCl within 30 to 49 mL/min) should receive no more than 200 mg twice daily. For patients with severe renal impairment (CrCl < 30 mL/min), the cefditoren dosage should be 200 mg once daily. There are no dosage recommendations for cefditoren for patients with end stage renal disease.

Cefixime (Suprax) doses for patients with CrCl within 21 to 60 mL/min should be reduced to 300 mg daily (75% of full dose therapy). For patients with CrCl < 20 mL/min or on continuous ambulatory peritoneal dialysis, cefixime dose should be reduced to 200 mg daily. Children weighing more than 50 kg or older than 12 years should be treated with the recommended adult dose. Otitis media should be treated with the chewable tablet or suspension. Clinical studies of otitis media were conducted with the cefixime chewable tablets or suspension, and the cefixime chewable tablets or suspension result in higher peak blood levels than the tablet when administered at the same dose. Therefore, the tablet or capsule should not be substituted for the cefixime chewable tablets or suspension in the treatment of otitis media. Cefixime chewable tabs must be chewed or crushed before swallowing.

Cefpodoxime proxetil for patients with CrCl < 30 mL/min should be dosed every 24 hours. Hemodialysis patients should receive cefpodoxime 3 times per week after hemodialysis.

Ceftibuten (Cedax) suspension should be administered 2 hours before or 1 hour after a meal. For patients with CrCl within 30 to 49 mL/min, the dose of ceftibuten should be 4.5 mg/kg or 200 mg daily; CrCl within 5 to 29 mL/min should be given as ceftibuten 2.25 mg/kg or 100 mg daily. Patients on hemodialysis should receive ceftibuten 9 mg/kg or 400 mg after each dialysis session.

### Penicillin/Beta-Lactamase Inhibitor Combinations[124,125]

Amoxicillin/clavulanate may be given with or without food. Patients with CrCl 10 to 30 mL/min should receive amoxicillin/clavulanate 250 mg or 500 mg every 12 hours (based on the amoxicillin component), depending on the severity of infection. Give amoxicillin/clavulanate 250 mg or 500 mg every 24 hours, depending on severity of infection, to patients with CrCl < 10 mL/min. Hemodialysis patients should receive amoxicillin/clavulanate 250 mg or 500 mg every 24 hours, with an additional dose both during and at the end of dialysis. Use caution with severe hepatic impairment.

Amoxicillin/clavulanate (Augmentin XR) is contraindicated in patients with CrCl < 30 mL/min.

## CLINICAL TRIALS

### Search Strategies

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies, including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Numerous clinical trials have been published for products in this class in the 1980s and 1990s. There is little evidence that one drug is better than others for the approved indications. Current usage patterns are somewhat based on spectrum of activity for empirical therapy and local resistance patterns when culture and sensitivity are known. Regional, including nationwide, variances in pathogens and susceptibility and resistance rates must be taken into consideration when evaluating studies. Many short-term clinical trials in outpatients with minor infections lose a significant portion of patients, such as greater than 25%, due to a lack of follow-up.

Many trials performed with the cephalosporins compare these products to macrolides and fluoroquinolones. While relative efficacy to these other antibiotics is important, these comparisons lend very little insight into relative efficacy and safety to agents within this class.

The literature review of significant trials comparing agents within this therapeutic class is complete as of March 19, 2019.

## cefditoren (Spectracef), cefuroxime, and cefadroxil

Cefditoren 200 mg and 400 mg twice daily were compared to cefuroxime 250 mg and cefadroxil 500 mg twice daily for 10 days for the treatment of uncomplicated skin and skin structure infections.[126] Cellulitis, wound infections, and simple abscesses were the most common infections among the 1,685 enrolled patients enrolled in 2 randomized, double-blind, multicenter, parallel-group studies. The first study compared cefditoren and cefuroxime; the second study compared cefditoren and cefadroxil. Baseline characteristics of the groups were similar. Clinical cure rates were similar among the groups (cefditoren 200 mg [85%], cefditoren 400 mg [83%], cefuroxime [88%], and cefadroxil [85%]). Cefditoren 200 mg eradicated significantly fewer pathogens than did cefuroxime (p=0.043), but significantly more than cefadroxil (p=0.018). Eradication rates of the pathogens were similar among all 3 antibiotics with the exception of favoring cefditoren for *Peptostreptococcus* species eradication over cefadroxil. More treatment-related adverse effects resulting in discontinuation were seen in the cefditoren 400 mg group compared to the cefditoren 200 mg and the other cephalosporins.

## cephalexin (Keflex)

Newer studies show no significant differences in efficacy between cephalexin and clindamycin, nor any benefit of sulfamethoxazole-trimethoprim added to cephalexin in the treatment of uncomplicated skin infections.[127,128]

## cefditoren (Spectracef) in bronchitis

Cefditoren 400 mg twice daily was evaluated for use in upper and lower community-acquired (CA) respiratory tract infections. This was a review of articles involving the most prevalent isolates in the community. The relationship between bacterial eradication and clinical efficacy was analyzed and led to the conclusion that cefditoren's high activity against *S. pyogenes, H. influenzae*, and approximately 95% of *S. pneumoniae* isolates make this an effective treatment regimen for CA-respiratory tract infections.[129]

Cefditoren 200 mg twice daily for 5 days was compared to cefuroxime 250 mg twice daily for 10 days in a randomized, double-blind, double-dummy trial of 541 patients with acute exacerbations of chronic bronchitis.[130] Patients were assessed during therapy, at the end, and at follow-up. Clinical success was seen in 79.9% of the cefditoren patients and 82.7% of the cefuroxime group. Sputum signs (decreasing volume and purulence) decreased from 80% to 10% of patients. At the end of treatment, the per-pathogen bacteriological response showed 72.8% (of 103 isolates) in the cefditoren group versus 67% (of 94 isolates) in the cefuroxime group. The per-pathogen bacteriological response correlated well with clinical success (83.5% of 164 baseline isolates from patients with clinical success were eradicated compared with 3% of 33 isolates from patients with clinical failure). Clinical success in patients infected with *H. influenzae,* the most frequent isolate, was 84% and 82.5% in the cefditoren and cefuroxime groups, respectively.

## amoxicillin/clavulanate (Augmentin and Augmentin XR)

Two dosage formulations of amoxicillin/clavulanic acid were compared in the treatment of CAP.[131] Adult patients (n=633) were randomized to amoxicillin/clavulanate 2,000/125 mg or 875/125 mg, both given twice daily for 7 days. In the double-blind, non-inferiority trial, 25.3% of patients at enrollment had an identified pathogen isolated from sputum or blood culture. Pathogens (n=160) included *S. pneumoniae* (36.3%), methicillin-sensitive *S. aureus* (21.3%), and *H. influenzae* (20.6%) in the intent-to-

treat population. Clinical success was evaluated at days 16 to 37 with 90.3% and 87.6% for amoxicillin/clavulanate 2,000/125 mg and 875/125 mg groups, respectively (treatment difference, 2.7%; 95% confidence interval [CI], -3 to 8.3). Bacterial eradication was 86.6% and 78.4% for the amoxicillin/clavulanate 2,000/125 mg and 875/125 mg groups, respectively (treatment difference, 8.1%; 95% CI, -5.8 to 22.1). Adverse event rates and clinical and bacterial eradication rates were similar between the 2 groups.

Two dosages of amoxicillin/clavulanate were compared in a clinical trial with 893 patients with AECB.[132] In the randomized, double-blind, controlled trial, patients were assigned to either amoxicillin/clavulanate 2,000/125 mg twice daily for 5 days or 875/125 mg given twice daily for 7 days. A total of 141 patients had at least 1 pathogen isolated. Both doses were clinically effective at the test of cure visit on days 14 to 21 with a response rate of 93% and 91.2% for the high- and low-dose groups, respectively (treatment difference, 1.8%; 95% CI, -2.2 to 5.7). In the subgroup of patients with isolated pathogens, bacteriological eradication was 76.7% and 73% for the high- and low-dose groups, respectively (treatment difference, 3.8%; 95% CI, -7.5 to 15). Tolerability and adverse events were similar.

## META-ANALYSIS

A meta-analysis of 5 randomized controlled trials with 1,030 adults with group A beta-hemolytic streptococcal tonsillopharyngitis was performed.[133] The likelihood of bacteriological eradication with 5 days of cefpodoxime, cefuroxime, cefotiam (not available in the US), and cefdinir was noninferior to 10 days of penicillin (odds ratio, 1.46; 95% CI, 0.96 to 2.22; p=0.08).

## SUMMARY

Cephalosporins and amoxicillin/clavulanate are active against different microorganisms. Some products may be given once daily, which may promote patient adherence. The emergence of cephalosporin resistant strains of various infectious species should be considered when making treatment decisions. Although treatment guidelines published by various organizations are updated as needed, head-to-head studies published in the United States are limited.

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