Cephalosporins and Related Antibiotics Review

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Cephalosporins and Related Antibiotics Review

FDA-Approved Indications

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

Drug	Manufacturer	CAP	AECB	AOM	Pharyngitis/ tonsillitis	Gonorrhea	Skin	UTI	Sinusitis	Lyme disease	Impetigo
First Generation Cephalosporins											
cefadroxil (Duricef®)	generic				X		X	X			
cephalexin (Keflex®)*	generic			X			X	X			
Second Generation Cephalosporins											
cefaclor (Ceclor®, Ceclor CD®)	generic		X		X		X				
cefaclor (Raniclor™)	Pedinol	X		X	X		X	X			
cefprozil (Cefzil®)	generic		X	X	X		X		X		
cefuroxime axetil (Ceftin®)	generic		X	X	X	X	X	X	X	X	X
Third Generation Cephalosporins											
cefdinir (Omnicef®)	generic	X	X	X	X		X		X		
cefditoren pivoxil (Spectracef®)	Cornerstone Biopharma	X	X		X		X				
cefixime (Suprax®)	Lupin		X	X	X	X		X			
cefpodoxime proxetil (Vantin®)	generic	X	X	X	X	X	X	X	X		
ceftibuten (Cedax®)	Sciele		X	X	X						
Penicillin/Beta-Lactamase Inhibitor Combinations											
amoxicillin/clavulanate (Augmentin®)**	generic			X			X	X	X		
amoxicillin/clavulanate ER (Augmentin XR®)	GlaxoSmithKline	X							X		
amoxicillin/clavulanate (Augmentin ES-600®)***	generic			X							

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

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

*** Amoxicillin/clavulanate (Augmentin ES-600) is indicated for the treatment of pediatric patients with recurrent or persistent acute otitis media due to *Streptococcus. pneumoniae* (penicillin MICs ≤2 mcg/mL), *Hemophilus influenzae* (including beta-lactamase–producing strains), or *Moraxella catarrhalis* (including beta-lactamase–producing strains) characterized by the following risk factors: antibiotic exposure for acute otitis media within the preceding three months, and either of the following: age ≤ two years and daycare attendance.

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Overview

Oral cephalosporins are divided into three generations of agents. The first generation oral cephalosporins are most active against gram-positive organisms. The second generation oral cephalosporins are active against some gram-positive and gram-negative organisms. The third generation oral cephalosporins have enhanced activity against many of the gram-negative organisms and are more effective against many of the resistant bacteria. Many of the newer third generation oral cephalosporins also have activity against gram-positive organisms. Amoxicillin/clavulanic acid products (generics, Augmentin XR) have a similar spectrum of activity as the second and third generation oral cephalosporins and will be included in this review.

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 macrolide [e.g., erythromycin, clarithromycin (Biaxin®), azithromycin (Zithromax®) – strong recommendation] or doxycycline (weak recommendation) for those adult patients who are otherwise healthy without risk factors for multi-drug resistant *S. pneumoniae*.[1] For adult outpatients with comorbidities including chronic heart, lung, renal, hepatic disorders, diabetics, alcoholism, malignancies, asplenia, immunosuppression or use of any antibiotic within the last three 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 one of the following: high dose amoxicillin 1 gm 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.

The 2005 recommendations from IDSA for the oral treatment of impetigo include cephalexin and amoxicillin/clavulanate.[2] Other treatment options include dicloxacillin, clindamycin, and erythromycin, although some strains of *S. aureus* and *S. pyogenes* may be resistant. Muprocin ointment, applied topically, is recommended for impetigo in patients with limited number of lesions. For skin infections with methicillin-sensitive *Staphylococcus. aureus*, cephalexin is an alternative to the oral drug of choice, dicloxacillin.

For the management of acute sinusitis, adults with mild disease and no recent antimicrobial use should be initiated on amoxicillin/clavulanate, amoxicillin, cefpodoxime, cefuroxime, and cefdinir according to the 2004 guidelines from the Sinus and Allergy Health Partnership.[3] If patients fail to improve after three days, a respiratory fluoroquinolone (levofloxacin or moxifloxacin) is considered appropriate therapy. For adults with mild disease and recent antimicrobial use or adults with moderate disease, consider a respiratory fluoroquinolone (levofloxacin or moxifloxacin), amoxicillin/clavulanate or ceftriaxone as first line therapies. For children with mild disease and recent antimicrobial disease or with moderate disease, amoxicillin/clavulanate is initial therapy for acute sinusitis. The 2007 guidelines from the American Academy of Otolaryngology-Head and Neck Surgery Foundation support the use of amoxicillin as first line treatment for acute bacterial rhinosinusitis in most adults.[4]

The 2002 IDSA guidelines for acute pharyngitis recommend penicillin V orally for ten days.[5] Oral penicillin has proven efficacy and safety with a narrow spectrum of activity. In children, amoxicillin is commonly used due to the taste of the suspension. Erythromycin is a suitable alternative for patients allergic to penicillin. First generation oral cephalosporins are acceptable for patients who do not have immediate-type hypersensitivity to beta-lactams.

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The American Academy of Pediatrics guidelines from 2004 recommend high dose amoxicillin (90 mg/kg/day) as first line therapy for the treatment of AOM in children.[6] 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, cefpodoxime, cefdinir and cefuroxime.

In 2007, the Centers for Disease Control and Prevention (CDC) recommend cephalosporins instead of fluoroquinolones for treatment of gonorrhea in the Sexually Transmitted Disease (STD) guidelines and updates.[7] The oral option for first line therapy is cefixime, although data show that cefpodoxime and cefuroxime also have favorable outcomes in gonorrhea treatment. The change in recommendations is supported by documented spread of fluoroquinolone resistance among *N. gonorrhoeae* in the United States.[8] A total of 82,064 episodes of urethral gonorrhea in males were evaluated from 1988 to 2003 across the US in public clinics. Treatment changed over the 16-year time period. The percentage of men treated with penicillin in 1988 was 39.5 percent with a decline to zero percent in 1994; penicillin resistance peaked in 1991 with 19.6 percent of isolates being reported as resistant to penicillin. Penicillin resistance declined to 6.5 percent in 2003. Fluoroquinolone resistance among *N. gonorrhea* isolates was first reported in 1991. In 2003, resistance was reported in 4.1, 14.4 and 6.5 percent of isolates were resistance to ciprofloxacin, tetracycline and penicillin, respectively. Resistance to ceftriaxone, cefixime, spectinomycin, and azithromycin is rare.

Pharmacology

Beta-lactams, such as cephalosporins and amoxicillin, work by binding to the penicillin-binding proteins which inhibit cell wall synthesis.[9] The drugs are usually bactericidal, depending on organism susceptibility, dose, tissue concentrations, and the rate at which organisms are multiplying. They 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, Hemophilus influenzae, Salmonella, Shigella,* and *Klebsiella*. Clavulanic acid generally does not inhibit beta-lactamases produced by *Enterobacter, Serratia, Citrobacter, Pseudomonas,* and *Acinetobacter.*

Resistance to the cephalosporins has emerged over the past decade especially in the acute care setting. Extended-spectrum beta-lactamases (ESBLs) were identified clinically with *E. coli* and *Klebsiella pneumoniae.*[10] Beta-lactamases are now categorized based on functional class, determined by the antibiotics that they inhibit. The second method of classification is based on the molecular structure.[11] The ESBLs are plasmid-mediated beta-lactamase enzymes that are derived from either a Temonier (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.[12] The ESBL-producing organisms are then resistant to many antimicrobials including ampicillin, ticarcillin, piperacillin, and some cephalosporins including ceftazidime. While high doses of beta-lactam/beta-lactamase inhibitor combination may be effective, the treatment of choice for ESBL-producing gram-negative bacteria is a carbapenem. Occasionally, fluoroquinolones, trimethoprim-sulfamethoxazole, and aminoglycosides are treatment options depending on *in vitro* susceptibility.[13,14,15,16]

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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* coverage. 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).[17]

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	+	+	+	+	+	+	+	+	+
Strep. pneumoniae	+	+	+	+	+	+	+	±	+
Viridens strep	±	+	+	+	O	+	+	O	+
Enterococcus faecalis	+	O	O	O	O	O	O	O	O
Staph. aureus - MSSA	+	+	+	+	+	+	O	O	+
Staph. epidermidis	+	±	±	±	±	±	O	O	±
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
C. freundii		O	O	O	O	O	O	O	O
C. diversus		O	O	O	O			+	
Citrobacter species	O		O	±	O	±	+	+	+
Aeromonas species	+						+	+	
Acinetobacter species	O	O	O	O	O	O	O	O	
Ps. 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. ducreyl	+						+		
ANEROBES:									
Actinomyces	+								
Bacteroides fragilis	+		O	O	O	O	O	O	
P. melaninogenica	+			+	+	+	+		
Peptostreptococcus sp.	+		+	+	+	+	+		

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Pharmacokinetics

Drug	Bioavailability (%)	Half-Life (hr)	Metabolites	Excretion (%)
First Generation Cephalosporins				
cefadroxil[18]	--	--	None	Renal: > 90
cephalexin (Keflex)[19]	--	1	--	Renal
Second Generation Cephalosporins				
cefaclor (Ceclor, Raniclor)[20,21]	--	0.6-0.9	Not appreciably metabolized	Renal
cefprozil (Cefzil)[22]	95	1.3	--	Renal: 60
cefuroxime axetil (Ceftin)[23]	--	1.2-1.9	--	Renal: > 50
Third Generation Cephalosporins				
cefdinir (Omnicef)[24]	300 mg caps: 21 600 mg caps: 16 suspension: 25	1.7	Not appreciably metabolized	Renal
cefditoren pivoxil (Spectracef)[25]	14	1.6	Not appreciably metabolized	Renal
cefixime (Suprax)[26]	40-50	3-9	None	Renal
cefpodoxime proxetil (Vantin)[27]	50	2.1-2.9	Minimal metabolism	Renal
ceftibuten (Cedax)[28,29,30]	61-90	2-3	Minimal activity of cis-ceftibuten trans-ceftibuten	Renal: 56 Feces: 39
Penicillin/Beta-Lactamase Inhibitor Combinations				
amoxicillin/ clavulanate (Augmentin)[31]	--	1.3/1.0	None	Renal: 50-70/ 25-40
amoxicillin/ clavulanate ER (Augmentin XR)[32]	--	1.3/1.0	None	Renal: 60-80/ 30-50
amoxicillin/ clavulanate (Augmentin-ES 600)[33]	--	1.4/1.1	None	Renal: 50-70/ 25-40

Contraindications/Warnings

Pseudomembranous colitis has been reported with nearly all antibacterial agents and 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.

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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 percent 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 of its components.

Cefditoren (Spectracef) is contraindicated in patients with carnitine deficiency or inborn errors of metabolism that may result in clinically significant carnitine deficiency. Cefditoren use causes renal excretion of carnitine.[34] Additionally, cefditoren tablets contain sodium caseinate, a milk protein. Patients with milk protein hypersensitivity (not lactose intolerance) should not be administered cefditoren.

Penicillin/Beta-Lactamase Combinations[35,36,37]

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 and Augmentin ES-600) 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.[38,39,40] Hepatic toxicity associated with the use of amoxicillin/clavulanate potassium is usually reversible.

Patients with phenylketonuria should be cautioned about Augmentin ES-600 suspension containing 7 mg phenylalanine.

Drug Interactions

Due to renal elimination as the primary method of excretion, drug interactions for this category of drugs are limited. Probenecid inhibits the renal excretion of the agents in this category. For the amoxicillin/clavulanate products, probenecid inhibits excretion of amoxicillin.[41,42,43]

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allopurinol and ampicillin[44,45,46]

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

antacids[47,48]

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.

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

carbamazepine[49]

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

H_2-Receptor Antagonists[50,51]

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

Drugs that reduce gastric acidity may result in a lower bioavailability of cefuroxime compared with that of fasting state and tend to cancel the effect of postprandial absorption.

Iron Supplements and Foods Fortified With Iron[52]

Extent of absorption of cefdinir was reduced by 80 percent with the coadministration of ferrous sulfate 60 mg. If iron supplements are required during cefdinir therapy, cefdinir should be taken at least two 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[53]

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

oral contraceptives[54,55,56]

In common with other broad-spectrum antibiotics, amoxicillin/clavulanate may reduce the efficacy of oral contraceptives.

warfarin[57]

Increased prothrombin time and INR, with or without clinical bleeding, has been reported when cefixime is administered concomitantly with warfarin.

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Adverse Effects

Drug	Diarrhea	Nausea	Vaginal fungal infections	Abdominal pain	Headache	Increase in ALT/AST	Eosinophilia	Rash
First Generation Cephalosporins								
cefadroxil[58]	reported	reported	reported	reported	nr	reported	reported	reported
cephalexin (Keflex)[59]	reported	reported	reported	reported	reported	reported	reported	reported
Second Generation Cephalosporins								
cefaclor (generic, Raniclor)[60,61]	reported	reported	reported	reported	reported	reported	reported	reported
cefprozil (Cefzil)[62]	2.9	3.5	1.6	1	<1	2/2	2.3	0.9
cefuroxime axetil (Ceftin)[63]	8.6	2.6	0.1-1	0.1-1	nr	0.1-1	0.1-1	0.1-1
Third Generation Cephalosporins								
cefdinir (Omnicef)[64] n=3,841	15	3	4	1	2	0.7/0.4	0.7	0.9
cefditoren pivoxil (Spectracef)[65]	11-15	4-6	3-6	2	2-3	0.1-1	0.1-1	0.1-1
cefixime (Suprax)[66]	30	7	<2	3	<2	<2	<2	<2
cefpodoxime proxetil (Vantin)[67] n=4,696	7	3.3	1-1.3	1.2	1	reported	reported	< 1
ceftibuten (Cedax)[68]	3	4	0.1-1	1	3	1/>0.1, <1	3	0.1-1
Penicillin/Beta-Lactamase Inhibitor Combinations								
amoxicillin/clavulanate (Augmentin)[69]	9	3	1	<1	<1	reported	reported	3
amoxicillin/clavulanate (Augmentin ES-600)[70]	2.9	reported	1.4	reported	reported	reported	reported	1.4
amoxicillin/clavulanate (Augmentin XR)[71]	15.6	2.2	2.1	1.6	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. nr=not reported. ALT=alanine aminotransferase AST=aspartate aminotransferase

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Special Populations

Pediatrics

Safety and effectiveness of most of the agents in this review for pediatric patients have been established. Two exceptions include Augmentin XR and cefditoren (Spectracef). Augmentin XR is only approved for patients older than 16 years old.[72] Cefditoren (Spectracef) is approved patients age 12 years and older.[73]

Cephalexin may be used in children over one year old.[74] Pediatric patients weighing greater than 4.5 kg may be treated with cefadroxil.[75] Safety and effectiveness data are available for children age six months and older for cefprozil, cefixime and cefdinir.[76,77,78] Children as young as two months may be treated with cefpodoxime.[79] Ceftibuten (Cedax) is approved for use in children weighing over 10 kg.[80] Cefaclor may be used in children as young as one month.[81]

Amoxicillin/clavulanate (Augmentin ES-600) is approved for children from three months to 12 years for the treatment of otitis media and sinusitis.[82] 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.[83]

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.[84] Some investigators have found that cefdinir and cefixime are among those antibiotics that were most palatable.[85,86] 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.

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Dosages

Drug	Sinusitis	Bronchitis	Skin Infections	Otitis Media	Duration/Age	Availability
First Generation Cephalosporins						
cefadroxil	--	--	1 gm given in one or two divided doses daily **Pediatrics**: 30 mg/kg/day in one or two doses daily	--	10 days; 4.5 kg and up	Capsule: 500 mg Tablet: 1 gm Suspension: 250, 500 mg per 5 mL
cephalexin (Keflex)	--	--	500 mg Q12h **Pediatrics**: 25-50 mg/kg/day in divided in two doses daily	75-100 mg/kg/day in divided doses given Q6hrs	10 days/ 10-40 kg	capsules: 250, 500, 750 mg suspension: 125, 250 mg per 5 mL
Second Generation Cephalosporins						
cefaclor (Ceclor, Ceclor CD, Raniclor)	--	--	250-500 mg Q8h **Pediatrics**: 20-40 mg/kg/day in 3 divided doses; given Q8hrs for 7-10 days	20-40 mg/kg/day in 3 divided doses; given Q8hrs	10 days; > 1mo – 12 yrs	chewable tablets (Raniclor): 250, 375 mg capsules: 250, 500 mg suspension: 125, 187, 250, 375 mg per 5 mL ER tablets: 500 mg
cefprozil (Cefzil)	250 mg Q12h or 500 mg Q12h for 10 days	500 mg Q12h for 10 days	250 mg Q12h or 500 mg daily or 500 mg Q12h for 10 days **Pediatrics**: 20 mg/kg/day for 10 days	15 mg/kg Q12hrs	10 days/ 6 mo-12 yr	tablets: 250, 500 mg suspension: 125 and 250 per 5 mL suspension
cefuroxime axetil (Ceftin)	250 mg Q12h for 10 days	250 or 500 mg Q12h for 10 days	250 or 500 mg Q12h for 10 days **Pediatrics Impetigo**: 15 mg/kg Q12h for 10 days	15 mg/kg Q12hrs	10 days/ 3 mo-12 yr	tablets: 250, 500 mg suspension: 125, 250 mg per 5 mL

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Drug	Sinusitis	Bronchitis	Skin Infections	Otitis Media	Duration/Age	Availability
Third Generation Cephalosporins						
cefdinir (Omnicef)	300 mg Q12h or 600 mg Q24h for 10 days	300 mg Q12h for 5 to 10 days or 600 mg Q24h for 10 days	300 mg Q12h or 600 mg Q24h for 10 days **Pediatrics**: 7 mg/kg Q12h or 14 mg/kg daily for 10 days	7 mg/kg Q12hrs or 14 mg/kg Q24hrs	5 to 10 days/ 6 mo– 12 yrs 10 days/ 6 mo-12 yr	capsules: 300 mg suspension: 125, 250 mg per 5 mL
cefditoren pivoxil (Spectracef)	--	400 mg twice daily for 10 days	200 mg twice daily for 10 days	--	--	tablets: 200, 400 mg
cefixime (Suprax)	--	400 mg daily for 10 days	--	8 mg/kg daily	10 days/ 6 mo– 12 yrs	100 and 200 mg per 5 mL suspension 400 mg tablets
cefpodoxime (Vantin)	200 mg Q12h for 10 days	200 mg Q12h for 10 days	400 mg Q12h for 7-14 days	5 mg/kg Q12hrs	5 days/ 2 mo-12 yr	tablets: 100, 200 mg suspension: 50 and 100 mg per 5 mL
ceftibuten (Cedax)	--	400 mg daily for 10 days	--	9 mg/kg daily	10 days/ 6 mo-12 yr	capsule: 400 mg suspension: 90 mg per 5 mL
Penicillin/Beta-Lactamase Inhibitor Combinations						
amoxicillin/ clavulanate (Augmentin)	500 mg Q12h or 250 mg Q8h for 10 days	--	500 mg Q12h or 250 mg Q8h for 10 days **Pediatrics**: 45 mg/kg Q12h or 40 mg/kg Q8h for 10 days	45 mg/kg Q12h or 40 mg/kg Q8h	10 days/ > 3 mo – 40 kg	tablets: 250/125, 500/125, 875/125 mg chewable tablets: 125/31.25, 200/28.5, 250/62.5, 400/57 mg suspensions: 125/31.25, 200/28.5, 250/62.5, 400/57 mg per 5 mL
a/amoxicillin/ clavulanate (Augmentin XR)	2 tablets Q12h for 10 days	--	--	--	--	1,000/62.5 mg tablet
amoxicillin/ clavulanate (Augmentin ES-600)	--	--	--	**Pediatrics:** 90 mg/kg/day divided and given Q12h	10 days/ ≥ 3 mo – 40kg	600/42.9 mg per 5 mL suspension

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Dosing Considerations

First Generation Cephalosporins[87,88]

Cefadroxil should be administered to adults as 1-2 gm 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 two doses. Cefadroxil should be given as 500 mg every 24 hours for patients with CrCl 10-24 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 six hours. Cephalexin 500 mg may be administered every 12 hours. For pediatric patients with infections other than otitis media, dose of cephalexin is 25 to 50 mg/kg daily given in divided doses. Cephalexin for patients with CrCl=11-40 mL/min should be administered as a loading dose of 250-500 mg, followed by a dose of 250-500 mg every eight to 12 hours. For patients with CrCl≤10 mL/min, a loading dose of cephalexin 250-500 mg then 250 mg every 12 to 24 hours has been recommended.

Second Generation Cephalosporins[89,90,91]

Cefaclor (Raniclor) should be used with caution when administering in patients with severe renal impairment.

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

Cefuroxime axetil tablets and suspension are not bioequivalent and should not be substituted on a mg-per-mg basis. Cefuroxime is renally excreted and will accumulate in renal insufficiency; safety and efficacy of cefuroxime in renal failure patients have not been established. Cefuroxime suspension should be administered with food whereas tablets may be given without regard to meals.

Third Generation Cephalosporins[92,93,94,95,96]

Cefdinir patients with CrCl<30 mL/min should receive 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 CrCl=30-49 mL/min should receive no more than cefditoren 200 mg twice daily. For patients with CrCl<30 mL/min, the dosage should be cefditoren 200 mg once daily. There are no dosage recommendations for cefditoren for patients on hemodialysis.

Cefixime (Suprax) doses for patients with CrCl 21-60 mL/min should be reduced to 300 mg daily (75 percent 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.

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

Ceftibuten (Cedax) suspension should be administered two hours before or one hour after a meal. For patients with CrCl 30-49 mL/min, the dose of ceftibuten should be 4.5 mg/kg or 200

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mg daily; CrCl 5-29 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[97,98,99]

Amoxicillin/clavulanate may be given with or without food. Patients with CrCl 10-30 mL/min should receive amoxicillin/clavulanate 250 or 500 mg every 12 hours (based on the amoxicillin component), depending on the severity of infection. Give amoxicillin/clavulanate 250 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 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 ES-600) does not have the same amount of clavulanic acid as Augmentin and should not be substituted for Augmentin formulations.

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 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 percent 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/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 1980's and 1990's. There is little evidence that one drug is better than others for the approved indications. 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 percent, 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.

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cefditoren (Spectracef), cefuroxime (Ceftin), and cefadroxil

Cefditoren 200 and 400 mg twice daily were compared to cefuroxime 250 mg and cefadroxil 500 mg twice daily for ten days for the treatment of uncomplicated skin and skin structure infections.[100] Cellulitis, wound infections, and simple abscesses were the most common infections among the 1,685 enrolled patients enrolled in the two 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 percent), cefditoren 400 mg (83 percent), cefuroxime (88 percent), and cefadroxil (85 percent)]. 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 three 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.

cefditoren (Spectracef) and cefuroxime (Ceftin)

Cefditoren 200 mg twice daily for five days was compared to cefuroxime 250 mg twice daily for ten days in a randomized, double-blind, double-dummy trial of 541 patients with acute exacerbations of chronic bronchitis.[101] Patients were assessed during therapy, at the end, and at follow-up. Clinical success was seen in 79.9 percent of the cefditoren patients and 82.7 percent of the cefuroxime group. Sputum signs (decreasing volume and purulence) decreased from 80 percent to 10 percent of patients. At the end of treatment, the per-pathogen bacteriological response showed 72.8 percent (of 103 isolates) in the cefditoren group versus 67 percent (of 94 isolates) in the cefuroxime group. The per-pathogen bacteriological response correlated well with clinical success (83.5 percent of 164 baseline isolates from patients with clinical success were eradicated compared with three percent of 33 isolates from patients with clinical failure). Clinical success in patients infected with *H. influenzae,* the most frequent isolate, was 84 percent and 82.5 percent 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.[102] Adult patients (n=633) were randomized to amoxicillin/clavulanate 2,000/125 mg or 875/125 mg, both given twice daily for seven days. In the double-blind, non-inferiority trial, 25.3 percent of patients at enrollment had an identified pathogen isolated from sputum or blood culture. Pathogens (n=160) included *S. pneumoniae* (36.3 percent), methicillin-sensitive *S. aureus* (21.3 percent), and *H. influenzae* (20.6 percent) in the intent-to-treat population. Clinical success was evaluated at days 16 to 37 with 90.3 and 87.6 percent for amoxicillin/clavulanate 2,000/125 mg and 875/125 mg groups, respectively (treatment difference, 2.7 percent; 95% confidence interval (CI), -3.0 to 8.3). Bacterial eradication was 86.6 and 78.4 percent for the amoxicillin/clavulanate 2,000/125 mg and 875/125 mg groups, respectively (treatment difference, 8.1 percent; 95% CI, -5.8 to 22.1). Adverse event rates and clinical and bacterial eradication rates were similar between the two groups.

Two dosages of amoxicillin/clavulanate were compared in a clinical trial with 893 patients with AECB.[103] In the randomized, double-blind, controlled trial, patients were assigned to either amoxicillin/clavulanate 2,000/125 mg twice daily for five days or 875/125 mg given twice daily for seven days. A total of 141 patients had at least one 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 percent for the high- and low-dose groups, respectively (treatment difference, 1.8 percent; 95% CI, -2.2 to 5.7). In the subgroup of patients with isolated pathogens, bacteriological eradication

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was 76.7 and 73 percent for the high- and low-dose groups, respectively (treatment difference, 3.8 percent; 95% CI, -7.5 to 15.0). Tolerability and adverse events were similar.

Meta-Analysis

A meta-analysis of five randomized controlled trials with 1,030 adults with group A beta-hemolytic streptococcal tonsillopharyngitis was performed.[104] The likelihood of bacteriological eradication with five 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

The few comparative trials of cephalosporins and amoxicillin/clavulanate show them to be equal in efficacy. The agents are active against different microorganisms, and some may be given once daily.

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