



Cephalosporins and Related Antibiotics

Therapeutic Class Review (TCR)

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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 [®]) ¹	generic				X		X	X			
cephalexin (Keflex [®]) ^{2*}	generic			X			X	X			
Second Generation Cephalosporins											
cefaclor (Ceclor [®] , Ceclor CD [®]) ³	generic		X		X		X				
cefprozil (Cefzil [®]) ⁴	generic		X	X	X		X		X		
cefuroxime axetil tablets (Ceftin [®]) ⁵	generic		X	X	X	X	X	X	X	X	
cefuroxime axetil suspension (Ceftin) ⁶	GSK			X	X						X
Third Generation Cephalosporins											
cefdinir (Omnicef [®]) ⁷	generic	X	X	X	X		X		X		
cefditoren pivoxil (Spectracef [®]) ⁸	generic	X	X		X		X				
cefixime (Suprax [®]) ^{9†}	Lupin		X	X	X	X		X			
cefixime chewable tablets (Suprax Chewable) ¹⁰⁺	Lupin		X	X	X	X		X			
cefepodoxime proxetil (Vantin [®]) ^{11#}	generic	X	X	X	X	X	X	X	X		
ceftibuten (Cedax [®]) ¹²⁺⁺	Pernix Therapeutics		X	X	X						

FDA-Approved Indications (continued)

Drug	Manufacturer	CAP	AECB	AOM	Pharyngitis/ tonsillitis	Gonorrhea	Skin	UTI	Sinusitis	Lyme disease	Impetigo
Penicillin/Beta-Lactamase Inhibitor Combinations											
amoxicillin/clavulanate (Augmentin [®]) ^{13**}	Dr Reddys / generic			X			X	X	X		
amoxicillin/clavulanate ER (Augmentin XR [®]) ¹⁴	generic	X							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.

Cefpodoxime proxetil (Vantin) is additionally indicated for ano-rectal infections in women.

+ 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.

++Ceftibuten (Cedax) has been shown to have lower clinical efficacy (22 percent 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 *S. pneumoniae* was 23 percent less than control. Therefore, ceftibuten should be given empirically only when adequate antimicrobial coverage against *S. pneumoniae* has been previously administered.

OVERVIEW

Oral cephalosporins are divided into three 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 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*.¹⁵ 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 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.

The 2009 recommendations from the World Health Organization (WHO) suggest amoxicillin as the best first-line agent for the empirical treatment of non-severe pneumonia among children managed by first level health care providers.¹⁶ Trimethoprim-sulfamethoxazole (TMP/SMZ) may be considered an alternative in some settings. Treatment failure is defined as a child who develops signs warranting immediate referral or who does not have a decrease in respiratory rate after 48-72 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 three years of age.

Patients with an acute exacerbation of chronic obstructive pulmonary disease (COPD), will present with a change in the patient's baseline dyspnea, cough, a change in the sputum which is more than the day/day variation, acute in onset, and may warrant a change in the management of COPD. According to the 2011 update of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, all patients with symptoms of COPD exacerbation should be treated with additional bronchodilators with or without glucocorticosteroids. Treatment of acute exacerbations of chronic bronchitis (AECB) includes bronchodilator therapy, corticosteroids (oral or intravenous), and possibly supplemental oxygen. Systemic corticosteroids may improve an acute exacerbation of COPD by shortening recovery time, improving lung function and hypoxemia, and may reduce the risk of early relapse, treatment

failure, and length of hospital stay. Patients with a higher risk for poor outcome include those with presence of other comorbidities, severe COPD, frequent exacerbations (greater than three per year), and antimicrobial use within last three months. Patients with an increase in sputum purulence may benefit from antibiotics.¹⁷ For patients with mild exacerbation and no risk factors for poor outcome, oral antibiotic selection includes beta-lactams, tetracycline, and TMP/SMZ. Alternative treatments include any one of the following: macrolides, ketolides, second or third generation cephalosporins, or amoxicillin/clavulanate. For patients with moderate COPD exacerbation and at risk for poor outcomes, first-line oral antibiotic is amoxicillin/clavulanate. Alternative oral antibiotics are the fluoroquinolones (gemifloxacin, moxifloxacin, or levofloxacin).

According to the 2007 American Academy of Otolaryngology guidelines on the treatment of adult sinusitis, adults with mild or moderate acute bacterial rhinosinusitis (ABRS) may be observed with watchful waiting. For those with severe ABRS, or if the patient worsens or fails to improve with watchful waiting, therapy with amoxicillin should begin.¹⁸ If treatment failure is observed following seven days of antibiotic therapy, a nonbacterial cause or infection with drug-resistant bacteria should be considered and should prompt a switch to alternate antibiotic therapy and re-evaluation of the patient. Optimal therapy of multidrug-resistant *S. pneumoniae* and beta-lactamase-producing *H. influenzae* and *M. catarrhalis* would 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. IDSA guidelines published online in March 2012 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 for 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).¹⁹

In the treatment of group A β -hemolytic streptococcal (GAS) tonsillopharyngitis, the American Heart Association recommends penicillin V oral or injectable benzathine penicillin for first line treatment for the prevention of Rheumatic Fever.²⁰ 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 new 2012 IDSA guidelines for acute pharyngitis recommend penicillin or amoxicillin orally for ten days for those non-allergic to these agents. For those patients allergic to penicillin, the recommendation is to use a first-generation cephalosporin for 10 days, or clindamycin or clarithromycin for 10 days, or azithromycin for five days.²¹ The IDSA updated full publication was released in fall 2012.

The current 2004 American Academy of Pediatrics guidelines recommend high dose amoxicillin (90 mg/kg/day) as first line therapy for the treatment of AOM in children.²² 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.

Genitourinary Infections

Urinary tract infections (UTI) occur more commonly in women.²³ Acute cystitis is a symptomatic bladder infection characterized by frequency, urgency, dysuria, and suprapubic pain in a woman with a normal genitourinary tract. The 2011 updated guidelines from IDSA for the management of acute uncomplicated cystitis consider the optimal approach to antibiotic selection and resistance patterns and the potential for the selection of drug-resistant organisms and colonization or infection for multi-drug resistant organisms. The empiric antibiotic selection for acute uncomplicated cystitis is nitrofurantoin 100 mg twice daily for five days. Nitrofurantoin has been shown to provide comparable efficacy to trimethoprim/sulfamethoxazole (TMP/SMX) given for three 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 three days when local uropathogens are less than 20 percent resistant or if the infecting strain is known to be sensitive. The fluoroquinolones, ofloxacin, ciprofloxacin and levofloxacin, are highly efficacious, but use of fluoroquinolones 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 three to seven days are appropriate regimens when the other recommended agents can not be used (B-I). In general, beta-lactams have inferior efficacy and more adverse effects compared to other antimicrobials for UTIs.

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.²⁴ If the indwelling catheter has been in place for more than two 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 antimicrobial therapy should be given for patients with a delayed response to therapy regardless if the patient remains catheterized or not. 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 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.

The 2010 Sexually Transmitted Disease (STD) guidelines from the Centers for Disease Control and Prevention (CDC) recommend cephalosporins instead of fluoroquinolones for treatment of gonorrhea.²⁵ The recommended treatment options for uncomplicated gonorrhea of the cervix, rectum, or urethra are ceftriaxone intramuscular (IM), cefixime oral, or injectable cephalosporin plus azithromycin 1 g orally for one dose or doxycycline orally 100 mg twice daily for seven days. The oral option for first line therapy is cefixime, although data show that cefpodoxime and cefuroxime also have favorable outcomes in gonorrhea treatment. For uncomplicated gonorrhea infections in the pharynx, ceftriaxone IM plus azithromycin or doxycycline are recommended.

Skin/Skin Structure Infections

The 2011 recommendations from IDSA for the treatment of impetigo is the use of mupirocin 2% topical ointment. For complicated skin soft tissue infections (cSSTI), the oral recommendation is to use

linezolid 600 mg by mouth twice daily for children ≥ 12 years of age and 10 mg/kg by mouth every eight hours for children < 12 years of age.²⁶ For skin infections with methicillin-sensitive *Staphylococcus aureus*, cephalexin is an alternative to the oral drug of choice, dicloxacillin. In the treatment of MRSA SSTIs oral therapy is only recommended for active infection and not for decolonization.

PHARMACOLOGY

Beta-lactams, such as cephalosporins and amoxicillin, work by binding to the penicillin-binding proteins which inhibit cell wall synthesis.²⁷ 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*.²⁸ 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.²⁹ The ESBLs are plasmid-mediated beta-lactamase enzymes that are derived from either a Temonier (TEM) or sulphhydryl 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.³⁰ 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, TMP/SMZ, and aminoglycosides are treatment options depending on *in vitro* susceptibility.^{31, 32, 33, 34}

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).³⁵

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	+	+	+	+	+	+	+	±	+
Viridans strep	±	+	+	+	0	+	+	0	+
Enterococcus faecalis	+	0	0	0	0	0	0	0	0
Staph. aureus - MSSA	+	+	+	+	+	+	0	0	+
Staph. epidermidis	+	±	±	±	±	±	0	0	±

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	
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. ducreyi	+						+		

Spectrum of Activity (continued)

Organism	amoxicillin/ clavulanate	cefadroxil	cephalexin	cefaclor	cefprozil	cefuroxime	cefixime	ceftibuten	cefdinir cefditoren cefepodoxime
Anaerobes									
Actinomyces	+								
Bacteroides fragilis	+		0	0	0	0	0	0	
P. melaninogenica	+			+	+	+	+		
Peptostreptococcus sp.	+		+	+	+	+	+		

PHARMACOKINETICS

Drug	Bioavailability (%)	Half-Life (hr)	Metabolites	Excretion (%)
First Generation Cephalosporins				
cefadroxil ³⁶	--	--	None	Renal: > 90
cephalexin (Keflex) ³⁷	--	1	--	Renal
Second Generation Cephalosporins				
cefaclor (Ceclor) ³⁸	--	0.6-0.9	Not appreciably metabolized	Renal
cefprozil (Cefzil) ³⁹	95	1.3	--	Renal: 60
cefuroxime axetil (Ceftin) ⁴⁰	--	1.2-1.9	--	Renal: > 50
Third Generation Cephalosporins				
cefdinir (Omnicef) ⁴¹	300 mg caps: 21 600 mg caps: 16 suspension: 25	1.7	Not appreciably metabolized	Renal
cefditoren pivoxil (Spectracef) ⁴²	14	1.6	Not appreciably metabolized	Renal
cefixime (Suprax) ⁴³	40-50	3-9	None	Renal
cefpodoxime proxetil (Vantin) ⁴⁴	50	2.1-2.8	Minimal metabolism	Renal
ceftibuten (Cedax) ⁴⁵	undetermined	2-2.4	Minimal activity of cis-ceftibuten trans-ceftibuten	Renal: 56 Feces: 39
Penicillin/Beta-Lactamase Inhibitor Combinations				
amoxicillin/clavulanate (Augmentin) ⁴⁶	--	1.3/1.0	None	Renal: 50-70/ 25-40
amoxicillin/clavulanate ER (Augmentin XR) ⁴⁷	--	1.3/1.0	None	Renal: 60-80/ 30-50

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

Effect of Food

The absorption of cefixime and ceftibuten may be delayed by food, but total absorption is not significantly affected. Cefpodoxime proxetil is a prodrug, absorbed from the gastrointestinal tract and de-esterified to its active metabolite, cefpodoxime. The absorption of cefpodoxime is increased by 21 to 33 percent when given with food. 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 percent compared to administration in the fasted state.

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.

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.⁴⁸ 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 cefuroxime axetil (Ceftin) oral suspension contains phenylalanine.⁴⁹

Penicillin/Beta-Lactamase Combinations^{50, 51}

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 about some of the amoxicillin/clavulanate products containing phenylalanine; the products include; Augmentin chewable tablets and Augmentin 200 mg/5 mL or 400 mg/5 mL oral suspension.

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.^{52, 53}

allopurinol and ampicillin^{54, 55}

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^{56, 57}

Cefditoren (Spectracef) should not be administered with antacids as there is a reduction in mean C_{max} and mean area-under-the-curve (AUC) of cefditoren.

Concomitant administration of cefdinir (Omnicef) capsules with antacids delays C_{max} 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.

carbamazepine⁵⁸

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

H₂-Receptor Antagonists⁵⁹

It is not recommended to co-administer H₂-receptor antagonists with cefditoren. Mean C_{max} is reduced by 27 percent and mean AUC is reduced by 22 percent with concurrent administration of cefditoren and H₂-receptor antagonists.

Iron Supplements and Foods Fortified With Iron⁶⁰

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.

metformin⁶¹

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

oral contraceptives^{62, 63}

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

warfarin⁶⁴

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

ADVERSE EFFECTS

Drug	Diarrhea	Nausea	Vaginal fungal infections	Abdominal pain	Headache	Increase in ALT/AST	Eosinophilia	Rash
First Generation Cephalosporins								
cefadroxil ⁶⁵	reported	reported	reported	reported	nr	reported	reported	reported
cephalexin (Keflex) ⁶⁶	reported	reported	reported	reported	reported	reported	reported	reported
Second Generation Cephalosporins								
cefaclor ⁶⁷	reported	reported	reported	reported	reported	reported	reported	reported
cefprozil (Cefzil) ⁶⁸	2.9	3.5	1.6	1	<1	2/2	2.3	0.9
cefuroxime axetil tablets (Ceftin) ⁶⁹	3.7	3	0.1-1	0.1-1	0.1-1	1.6/2	1.1	0.1-1
cefuroxime axetil suspension (Ceftin) ⁷⁰	8.6	2.6	0.1-1	0.1-1	nr	nr	0.1-1	0.1-1
Third Generation Cephalosporins								
cefdinir (Omnicef) ⁷¹ n=3,841	15	3	4	1	2	0.7/0.4	0.7	0.9
cefditoren pivoxil (Spectracef) ⁷²	11-15	4-6	3-6	2	2-3	0.1-1	0.1-1	0.1-1
cefixime (Suprax) ⁷³	16	7	<2	3	<2	<2	<2	<2
cefopodoxime proxetil (Vantin) ⁷⁴ n=4,696	7	3.3	1-1.3	1.2	1	reported	reported	<1
ceftibuten (Cedax) ⁷⁵	3	4	0.1-1	1	3	>1/0.1-1	3	0.1-1
Penicillin/Beta-Lactamase Inhibitor Combinations								
amoxicillin/clavulanate (Augmentin) ⁷⁶	9	3	1	reported	reported	reported	reported	3
amoxicillin/clavulanate (Augmentin XR) ⁷⁷	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

Pediatrics

Safety and effectiveness of most of the agents in this review for pediatric patients have been established. Cefditoren (Spectracef) is approved patients age 12 years and older.⁷⁸

Cephalexin may be used in children over one year old.⁷⁹ Pediatric patients weighing greater than 4.5 kg may be treated with cefadroxil.⁸⁰ Safety and effectiveness data are available for children age six months and older for cefprozil, cefixime, ceftibuten, and cefdinir.^{81, 82, 83, 84, 85} Children as young as two months may be treated with cefpodoxime.⁸⁶ Cefaclor may be used in children as young as one month.⁸⁷ Cefuroxime axetil suspension (Ceftin) is approved for children ages three months to 12 years. Ceftin tablets and Ceftin for oral suspension are not bioequivalent and are therefore not substitutable on a milligram-per-milligram basis.⁸⁸

Safety and effectiveness of Augmentin XR has been shown for pediatric patients ≥ 40 kg who are able to swallow whole tablets.⁸⁹ 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.⁹⁰ Amoxicillin/clavulanate tablets may be used for children weighing at least 40 kg.

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.⁹¹ Some investigators have found that cefdinir and cefixime are among those antibiotics that were most palatable.^{92, 93} 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^{94, 95, 96, 97, 98, 99, 100, 101, 102, 103, 104, 105, 106}

Drug	CAP	Sinusitis	Bronchitis	Skin Infections	Otitis Media	Pharyngitis / Tonsillitis	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	--	1 gm given in one or two divided doses daily for 10 days Pediatrics: 30 mg/kg/day in one or two doses daily for 10 days	Capsule: 500 mg Tablet: 1 gm Suspension: 250, 500 mg per 5 mL
cephalexin (Keflex)	--	--	--	500 mg Q12h Pediatrics: 25-50 mg/kg/day divided in two doses daily (children 10-40 kg)	Pediatrics: 75-100 mg/kg/day in divided doses given Q6hrs (children 10-40 kg)	500 mg Q12h for 10 days Pediatrics: 25-50 mg/kg/day divided in two doses daily for 10 days (children 10-40 kg)	capsules: 250, 500, 750 mg tablet: 250, 500 mg suspension: 125, 250 mg per 5 mL
Second Generation Cephalosporins							
cefaclor (Ceclor, Ceclor CD) ¹⁰⁷	250-500 mg Q8h ER tablets: 500 mg Q12h for 7-10 days	--	ER tablets: 500 mg Q12h for 7 days	250-500 mg Q8h Pediatrics: 20-40 mg/kg/day in 3 divided doses; given Q8h for 7-10 days (ages > 1month – 12 years)	Pediatrics: 20-40 mg/kg/day in 3 divided doses; given Q8hrs (ages > 1month – 12 years)	250-500 mg Q8h Pediatrics: 20-40 mg/kg/day in 3 divided doses; given Q8h for 7-10 days (ages > 1mo – 12 years)	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 Pediatrics: 7.5-15 mg/kg Q12h (ages 6 months-12 years)	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 (ages 2-12 years)	Pediatrics: 15 mg/kg Q12h (ages 6 mo-12 years)	500 mg Q24h for 10 days (ages ≥13 years) Pediatrics: 7.5 mg/kg Q12h 10 days (ages 2-12 years)	tablets: 250, 500 mg suspension: 125 and 250 per 5 mL

Dosages (continued)

Drug	CAP	Sinusitis	Bronchitis	Skin Infections	Otitis Media	Pharyngitis / Tonsillitis	Availability
Second Generation Cephalosporins (continued)							
cefuroxime axetil tablets (Ceftin)	--	250 mg Q12h for 10 days including pediatric patients who can swallow a whole tablet	250 or 500 mg Q12h for 10 days	250 or 500 mg Q12h for 10 days	Pediatrics: 250 mg Q12h for 10 days for those children who can swallow a whole tablet	250 mg Q12h for 10 days	generic tablets: 250, 500 mg
cefuroxime axetil oral suspension (Ceftin)	--	Pediatrics: 15 mg/kg Q12h for 10 days (ages 3 months - 12 years)	--	Pediatrics – Impetigo: 15 mg/kg Q12h for 10 days (ages 3 months - 12 years)	Pediatrics: 15 mg/kg Q12h for 10 days (ages 3 months - 12 years)	Pediatrics: 10 mg/kg Q12h for 10 days (ages 3 months - 12 years)	Branded suspension: 125, 250 mg per 5 mL
Third Generation Cephalosporins							
cefdinir (Omnicef)	300 mg Q12h for 10 days (ages ≥13 years)	300 mg Q12h or 600 mg Q24h for 10 days (ages ≥13 years) Pediatrics: 7 mg/kg Q12h or 14 mg/kg Q24h for 10 days (ages 6 months – 12 years)	300 mg Q12h for 5 to 10 days or 600 mg Q24h for 10 days (ages ≥13 years)	300 mg Q12h for 10 days Pediatrics: 7 mg/kg Q12h for 10 days (ages 6 months – 12 years)	Pediatrics: 7 mg/kg Q12h for 5 – 10 days or 14 mg/kg Q24h for 10 days (ages 6 months – 12 years)	300 mg Q12h for 5 to 10 days or 600 mg Q24h for 10 days (ages ≥13 years) Pediatrics: 7 mg/kg Q12h for 5 – 10 days or 14 mg/kg Q24h for 10 days (ages 6 months – 12 years)	capsules: 300 mg suspension: 125, 250 mg per 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, 400 mg

Dosages (continued)

Drug	CAP	Sinusitis	Bronchitis	Skin Infections	Otitis Media	Pharyngitis / Tonsillitis	Availability
Third Generation Cephalosporins (continued)							
cefixime (Suprax) *Suprax chew tabs follow same dosing as the susp.	--	--	400 mg daily or 200 mg Q12h for 10 days Pediatrics: 8 mg/kg daily or 4mg/kg Q12h (ages 6 months – 12 years)	--	Pediatrics: 8 mg/kg daily for 10 days or 4mg/kg Q12h (ages 6 months – 12 years)	400 mg daily or 200 mg Q12h for 10 days Pediatrics: 8 mg/kg daily or 4mg/kg Q12h for 10 days (ages 6 months – 12 years)	chewable tablets: 100, 200 mg tablet: 400 mg suspension: 100 and 200 mg per 5 mL
cefepodoxime (Vantin)	200 mg Q12h for 14 days	200 mg Q12h for 10 days Pediatrics: 5 mg/kg Q12h for 10 days (ages 2 months – 12 years)	200 mg Q12h for 10 days	400 mg Q12h for 7-14 days	Pediatrics: 5 mg/kg Q12h for 5 days (ages 2 months – 12 years)	100 mg Q12h for 5 – 10 days Pediatrics: 5 mg/kg Q12h for 5 – 10 days (ages 2 months – 12 years)	tablets: 100, 200 mg suspension: 50 and 100 mg per 5 mL
ceftibuten (Cedax)	--	--	400 mg daily for 10 days (ages ≥12 years)	--	400 mg daily for 10 days (ages ≥12 years) Pediatrics: 9 mg/kg daily for 10 days (maximum 400 mg daily) (ages 6 months – 12 years)	400 mg daily for 10 days (ages ≥12 years) Pediatrics: 9 mg/kg daily for 10 days (maximum 400 mg daily) (ages 6 months – 12 years)	capsule: 400 mg suspension: 90 mg per 5 mL

Dosages (continued)

Drug	CAP	Sinusitis	Bronchitis	Skin Infections	Otitis Media	Pharyngitis / Tonsillitis	Availability
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: 25-45 mg/kg Q12h or 20-40 mg/kg Q8h for 10 days	Pediatrics: 25-45 mg/kg Q12h or 20-40 mg/kg Q8h for 10 days (ages > 3 mo to 40 kg)	--	tablets: 250/125, 500/125, 875/125 mg chewable tablets: 125/31.25 and 250/62.5 (brand only); 200/28.5, 400/57 mg suspensions: 125/31.25 and 250/62.5 per 5 mL (brand only); 200/28.5, 400/57 mg per 5 mL
amoxicillin/ clavulanate (Augmentin XR)	2 tablets Q12h for 7-10 days (including pediatric patients weighing ≥40 kg and are able to swallow a whole tablet)	2 tablets Q12h for 10 days (including pediatric patients weighing ≥40 kg and are able to swallow a whole tablet)	--	--	--	--	1,000/62.5 mg tablet

DOSING CONSIDERATIONS

First Generation Cephalosporins^{108, 109}

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, the 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^{110, 111}

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^{112, 113, 114, 115, 116}

Adult patients with CrCl<30 mL/min should receive cefdinir (Omnicef) 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 cefditoren 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 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. 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 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 should not be substituted for the **cefixime chewable tablets or** suspension in the treatment of otitis media. **Cefixime chew 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 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 within 30 to 49 mL/min, the dose of ceftibuten should be 4.5 mg/kg or 200 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^{117, 118}

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 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 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. 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 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.

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.¹¹⁹ 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) in UTIs

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.¹²⁰ 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.¹²¹ 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.¹²² 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 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.¹²³ 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, which may promote patient adherence.

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