Drugs 2002; 62 (2): 319-336
0012-6667/02/0002-0319/$27.50/0

Cefditoren Pivoxil

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Contents

Abstract

▲ Cefditoren pivoxil is an orally absorbed prodrug that is rapidly hydrolysed by intestinal esterases to the microbiologically active cephalosporin cefditoren. Cefditoren has a broad spectrum of activity against Gram-positive and Gram-negative bacteria, including common respiratory and skin pathogens.

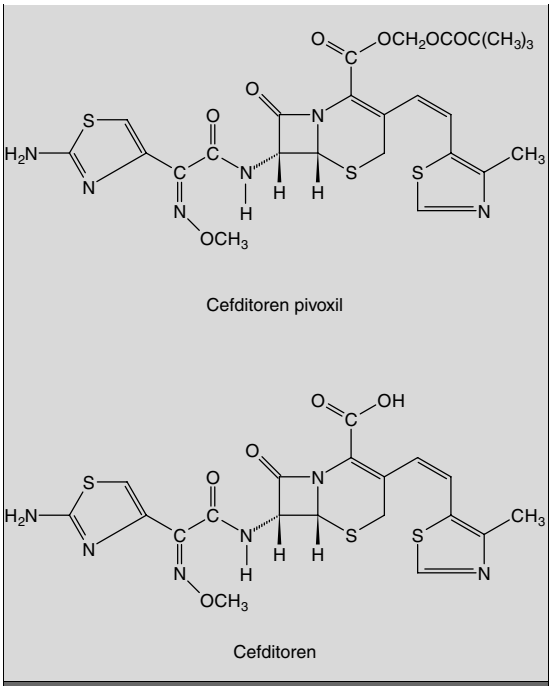
▲ Cefditoren has shown excellent *in vitro* activity against the Gram-positive pathogens penicillin-susceptible and -intermediate *Streptococcus pneumoniae*, *S. pyogenes* and methicillin-susceptible *Staphylococcus aureus*. Cefditoren was inactive against methicillin-resistant *S. aureus*. Of the important Gram-negative pathogens, cefditoren had potent antibacterial effects against β-lactamase-positive and -negative *Haemophilus influenzae*, *H. parainfluenzae* and β-lactamase-positive and -negative *Moraxella catarrhalis*. Cefditoren does not have antibacterial activity against *Pseudomonas aeruginosa* or atypical respiratory pathogens and has only variable activity against anaerobes.

▲ In healthy volunteers, single doses of cefditoren pivoxil 200 and 400mg achieved maximal plasma concentrations of 2.6 to 3.1 mg/L and 3.8 to 4.6 mg/L, respectively. Cefditoren penetrates rapidly into bronchopulmonary and tonsillar tissue as well as inflammatory and noninflammatory blister fluid.

▲ In two, randomised, double-blind trials involving patients with acute exacerbations of chronic bronchitis (AECB), cefditoren 200 and 400mg twice daily for 10 days produced clinical cure rates of 88 to 89% within 48 hours of treatment completion. Clinical cure rates in patients with AECB were similar to those of either clarithromycin 500mg twice daily or cefuroxime axetil 250mg twice daily. In patients with streptococcal pharyngitis, a 10-day course of cefditoren pivoxil 200mg twice daily produced clinical cure rates of 94% at 4 to 7 days after treatment, which were similar to those observed for phenoxymethylpenicillin potassium 250mg four times daily. In uncomplicated skin and skin structure infections, a 10-day course of cefditoren pivoxil 200 or 400mg twice daily produced the same clinical cure rate of 89% within 48 hours of treatment completion. These cefditoren pivoxil dosage regimens were as effective as a 10-day course of either cefadroxil 500mg twice daily or cefuroxime axetil 250mg twice daily in treating uncomplicated skin and skin structure infections, including those caused by *S. aureus* and *S. pyogenes*.

▲ The most common adverse events associated with therapeutic doses of cefditoren pivoxil are diarrhoea, nausea, headache, abdominal pain and vaginal candidiasis.

Features and properties of cefditoren pivoxil (ME1207)	
Indications	
Treatment of acute exacerbations of chronic bronchitis, pharyngitis/tonsillitis, and uncomplicated skin and skin structure infections	
Mechanism of action	
Cephalosporin antibacterial agent	Cell wall biosynthesis inhibitor
Dosage and administration	
Usual dosage in clinical trials	200 or 400mg twice daily depending on type of infection
Route of administration	Oral (with meals)
Duration of administration	10 days
Pharmacokinetic profile	
Peak plasma concentration	
200mg postprandial dose	2.6 to 3.1 mg/L
400mg postprandial dose	3.8 to 4.6 mg/L
Time to peak plasma concentration	1.5 to 3.0h
Elimination half-life	1.4 to 1.7h
Adverse events	
Most frequent	Diarrhoea, nausea, headache, abdominal pain, vaginal candidiasis



Chemical structure of cefditoren pivoxil and cefditoren

Cefditoren pivoxil is an orally absorbed ester prodrug of cefditoren, an active aminothiazolyl cephalosporin. Cefditoren has a broad spectrum of activity against both Gram-positive and Gram-negative bacteria, and is stable to hydrolysis in the presence of a variety of β-lactamases.

1. Antibacterial Activity

Mechanism of Action

Cephalosporins, like other β-lactam antimicrobials, are bactericidal by inducing cell lysis. They are selectively toxic to bacteria because they target a cellular component not present in eukaryotic cells, the peptidoglycan cell wall. The structural integrity of peptidoglycan is crucial to the survival of bacteria but β-lactam antibiotics impede its formation by binding to and inactivating penicillin binding proteins (PBPs), a group of enzymes that catalyse cell wall biosynthesis. This inhibitory mechanism has only a bacteriostatic effect but a more dramatic consequence of β-lactam exposure results from the loss of lipoteichoic acids from the cell wall to the growth medium.[1] Lipoteichoic acids inhibit murein hydrolase activity[2] and their absence from the cell wall triggers uncontrolled autolytic activity. Physiologically, autolysins 'nick' the cell wall in designated places so that the bacterial cell can grow or divide. Therefore, unchecked autolytic activity coupled with the loss of peptidoglycan biosynthetic capacity renders the bacterial cell susceptible to osmotic shock.[3,4]

For an antibacterial effect to be exerted clinically, a cephalosporin must have a high binding affinity for the specific PBPs of a causative bacterial pathogen. Binding affinities are usually expressed in terms of IC_{50} values, the concentration required to reduce enzyme activity by 50% or the concentration required to reduce the binding of a known agonist by 50%. A cephalosporin that exhibits low IC_{50} values for a specific PBP of a causative bacterial pathogen will have a greater chance of producing a clinical cure than one with high IC_{50} values, assuming that both drugs have a similar pharmacokinetic profile.

- In penicillin-susceptible clinical isolates of *Streptococcus pneumoniae*, cefditoren IC_{50} values for PBP1A, PBP2X and PBP2B were 0.41, 0.31 and 0.78 mg/L, respectively. These values were similar to IC_{50} values for amoxicillin, ampicillin and cefuroxime (except for PBP2B) but lower than values reported for cefprozil and cefaclor. In penicillin-resistant strains of *S. pneumoniae*, cefditoren IC_{50} values were 3.44 mg/L (PBP1A), 2.27 mg/L (PBP2X) and 3.69 mg/L (PBP2B), which were matched by amoxicillin and cefuroxime. In contrast, the IC_{50} values for cefprozil and cefaclor were 21- to 134-fold higher.[5] The binding affinities of cefditoren for PBPs of *Staphylococcus aureus* were 0.43 (PBP1), 0.20 (PBP2), 0.12 (PBP3) and 7.20 mg/L (PBP4).[6]
- Cefditoren IC_{50} values for six PBPs derived from *Haemophilus influenzae* clinical isolates were lowest for PBP4 (0.025 mg/L) and highest for PBP1, 3 and 7 (>3.130 mg/L). The IC_{50} values of

cefditoren in this Japanese study were lower than those of cefaclor for all PBPs and lower than those of cefdinir for PBP3, 4, 5 and 7.[7] In a separate Japanese study, the binding affinities of cefditoren for PBPs derived from *H. influenzae* reference strains were also variable and ranged from <0.008 mg/L (PBP3A) to >1 mg/L (PBP2, 4, and 5) across eight separate PBP assays.[6] The affinities of cefditoren for seven PBPs derived from reference strains of *Escherichia coli* were lowest for PBP3 (<0.04 mg/L) and highest for PBP5 and PBP6 (both >25 mg/L).[6]

In Vitro Activity

In this profile, the *in vitro* antibacterial activity refers to the minimum inhibitory concentrations (MICs) determined by agar and broth dilution techniques. The MIC is an absolute value and is defined as the highest dilution of antibacterial tested that completely inhibits visible surface growth of the inoculum after a standard period of incubation (usually 16 to 18 hours).[8] It should be noted that the comparisons made between various antibacterial agents in this section are based only on the MIC_{90} values and do not take into account their respective breakpoints. Unless antibacterials have the same breakpoint, MIC_{90} values cannot be truly compared in a clinical sense because crucial pharmacokinetic parameters are not taken into account. A more appropriate *in vitro* method of directly comparing antibiotics may be in terms of percentages of clinically susceptible isolates. However, in this profile, most of the *in vitro* studies did not provide such data and report only the MIC_{90} values. Many studies have measured cefditoren activity against penicillin-susceptible (MIC ≤0.06 mg/L), penicillin-intermediate (MIC 0.12 to 1 mg/L) and penicillin-resistant (MIC ≥2 mg/L) strains so that its clinical potential can be evaluated.[9]

Emphasis is given to studies that have followed the quality control guidelines recommended by the National Committee for Clinical Laboratory Standards (NCCLS). In fact, a collaborative study involving seven laboratories has validated cefditoren MIC quality control ranges against four strain-specific pathogens (*S. pneumoniae*, *S. aureus*, *H. influenzae* and *E. coli*) using the methods outlined by the NCCLS.[10] Validation of cefditoren MIC ranges for these bacteria is useful because it provides a baseline from which future cefditoren potency can be evaluated.

Tentative MIC [and zone diameter (5μg disk test)] breakpoints for cefditoren have been proposed based on *in vitro* pharmacodynamic parameters and are as follows: ≤0.25 mg/L (≥26mm) for penicillin-susceptible *S. pneumoniae*; ≥1 mg/L (≤20mm) for penicillin-resistant *S. pneumoniae*; and ≤0.5 or ≤1 mg/L for *H. influenzae*.[9] Although excellent negative linear regressions were observed for scatter diagrams that plotted MICs against disk zone diameters for *S. pneumoniae*, poor correlations were observed for *H. influenzae* scatter diagrams.[9,11]

Although it is important to assess the activity of antimicrobial agents over a fixed inoculum concentration range, it is of clinical importance that inoculum concentrations that ranged from 1×10^3 to 10^8 colony forming units (cfu)/ml did not affect the MICs of cefditoren against *S. pneumoniae*, *H. influenzae* and *Neisseria meningitidis*.[12,13]

The *in vitro* activity of cefditoren and other comparative β-lactam agents against *S. pneumoniae* is shown in figure 1. The *in vitro* activity of cefditoren against a number of Gram-negative bacteria is presented in figure 2.

Gram-Positive Bacteria

Streptococci

- Cefditoren has shown excellent activity against clinical isolates of *S. pneumoniae*, with reported MIC_{90} values ranging from 0.015 to 0.03 mg/L and 0.5 to 2 mg/L for penicillin-susceptible and -resistant strains, respectively.[9,14-16] Importantly, 67.5% of penicillin-intermediate pneumococci with MICs of 0.5 to 1.0 mg/L were cefditoren susceptible (MICs ≤0.25 mg/L).[9] Figure 1 shows a representative study comparing the in vitro activity of cefditoren and various other antibacterials against *S. pneumoniae*.[14]

• Data from two studies showed that the activity of cefditoren (MIC_{90} 0.015mg/L, n = 336 isolates;[14] MIC_{90} 0.03 mg/L, n = 153 isolates[9]) against penicillin-susceptible strains is similar to that of ampicillin, amoxicillin/clavulanic acid and cefotaxime but greater than that of cefpodoxime (MIC_{90} 0.06 mg/L). However, in penicillin-resistant strains (n = 56 and 48 isolates), cefditoren was 2-fold more active than all β-lactam agents tested, including amoxicillin with or without clavulanic acid.

• MIC_{90} values of cefditoren against macrolide-sensitive and -resistant pneumococci were identical (both 1 mg/L), and were 4- to >16-fold lower than those for cefdinir, cefprozil, cefuroxime, cefpodoxime and cefixime.[17]

• Clinical isolates of *S. pyogenes* from the US, UK and Japan were also susceptible to cefditoren, with MIC_{90}s ranging from ≤0.006 to 0.03 mg/L.[6,12,18,19] Cefditoren had greater activity than the other cephalosporins tested, including ceftazidime (MIC_{90} 0.5 mg/L)[19] and cefaclor (MIC_{90} 0.2 mg/L).[18]

• Cefditoren had good activity against *S. pyogenes* derived from 32 fresh sinus aspiration isolates and 68 lower respiratory tract isolates, with MIC_{90} values of 0.03 mg/L for both types of isolate. Cefditoren had greater antibacterial activity than other

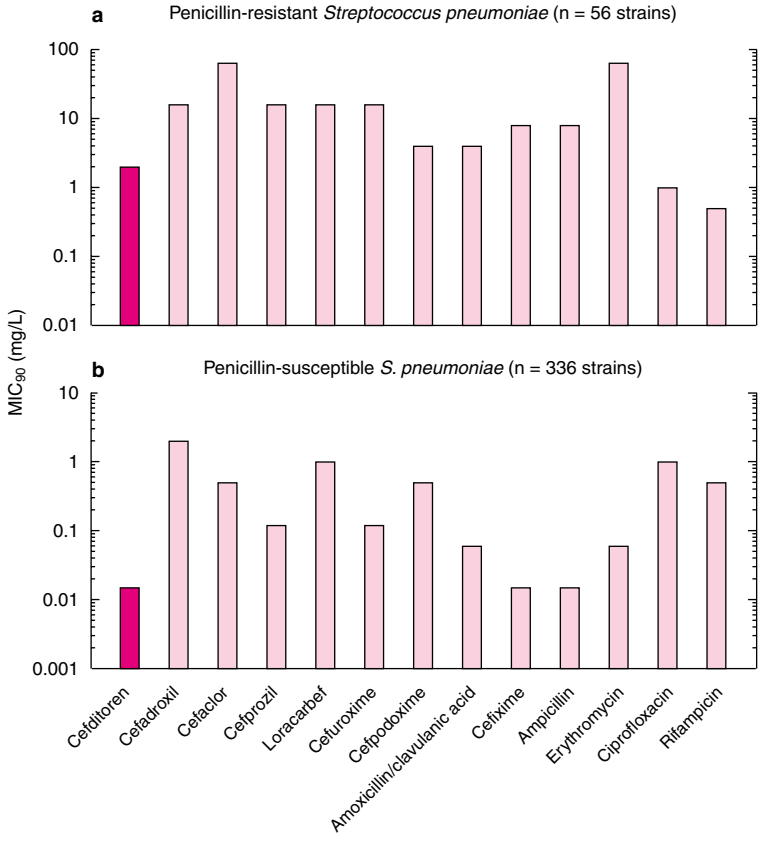


Fig. 1. *In vitro* activity of cefditoren and various other antibacterials tested against (**a**) 56 strains of penicillin-resistant *Streptococcus pneumoniae* and (**b**) 336 strains of penicillin-susceptible *S. pneumoniae*.[14] **MIC**$_{90}$ = minimum concentrations required to inhibit 90% of strains.

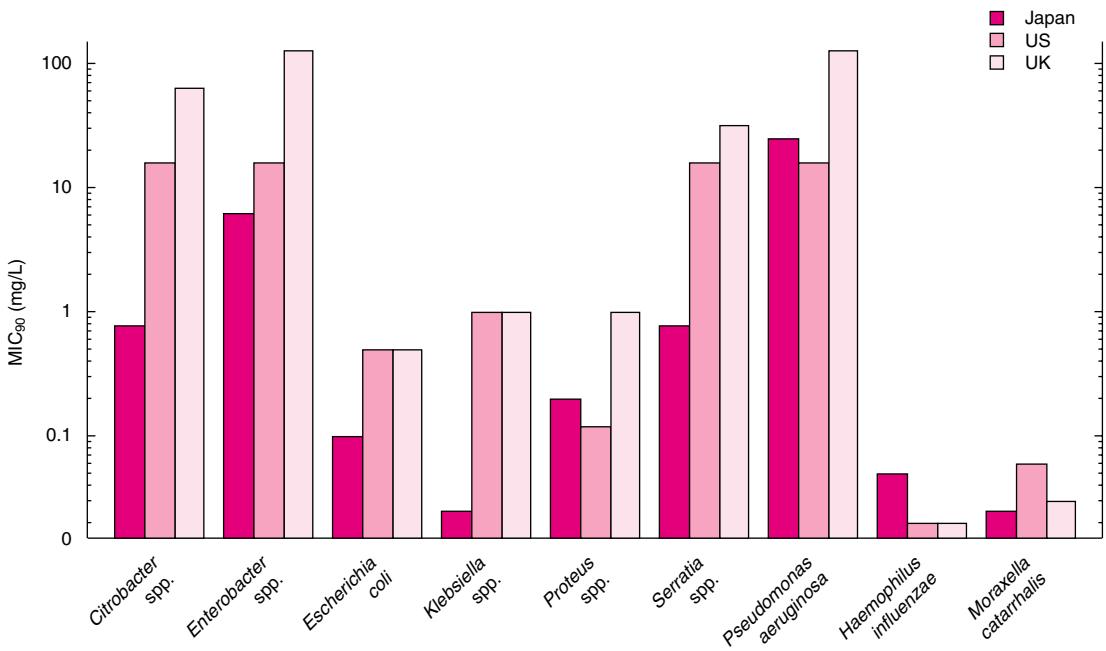


Fig. 2. *In vitro* activity of cefditoren against clinical isolates containing Gram-negative pathogens from the US, UK and Japan. Data from Japan for *Citrobacter* spp. are derived from cefditoren activity against *C. freundii*. Data from Japan and the US for *Enterobacter* spp., *Klebsiella* spp., *Proteus* spp. and *Serratia* spp. are specifically derived from cefditoren activity against *E. cloacae*, *K. pneumoniae*, *P. mirabilis* and *S. marcescens*, respectively.[6,12,14,24] **MIC**90 = minimum concentrations required to inhibit 90% of strains.

cephalosporins tested (MIC_{90} range 0.06 to 1 mg/L) and amoxicillin/clavulanic acid (MIC_{90} 0.06 mg/L).[16]

• Against 165 strains of *S. viridans*, cefditoren was ≥8-fold more active than either cefixime or ampicillin (MIC_{90} 1 *vs* ≥8 mg/L) and >32-fold more active than cefaclor.[11] Indeed, cefditoren had an MIC_{90} of 0.5 mg/L against 358 recent clinical isolates of *S. viridans* collected throughout the US, which was 4-fold lower than that for penicillin and 8-fold lower than those for amoxicillin/clavulanic acid and cefuroxime.[20] A study conducted in Spain (n = 120 isolates) reported cefditoren MICs that ranged from ≤0.03 to 0.12 mg/L and 1 to 8 mg/L against penicillin-susceptible and -resistant viridans group streptococci isolated from blood, respectively.[21]

Staphylococci

• Like other cephalosporins tested, cefditoren was inactive against reference strains of methicillin-resistant *S. aureus* (MRSA), with a reported MIC_{90} of >32 mg/L.[6,18,19] For clinical isolates of methicillin-susceptible *S. aureus* (MSSA), cefditoren had MIC_{90} values that ranged from 1 to 3.13 mg/L.[6,12,18,19]

• Cefditoren MIC_{90} values against MSSA (MIC_{90} 0.5 mg/L) and MRSA (MIC_{90} 8.0 mg/L) isolated from fresh sinus aspirations and the lower respiratory tract were 2- to 16-fold lower than those of other cephalosporins tested and 2- to 8-fold lower than those of amoxicillin/clavulanic acid.[16]

• In clinical isolates of methicillin-susceptible *S. epidermidis* (MSSE) from the US, cefditoren and cefotaxime had MIC_{90} values of 0.5 mg/L and 0.06 mg/L, respectively.[19] More recent data from a study conducted in Japan showed an MIC_{90} value of 3.13 mg/L for cefditoren against MSSE.[6] Methicillin-resistant strains were not inhibited by cefditoren (MIC_{90} >32 mg/L).[19]

Gram-Negative Bacteria

• In studies conducted in the US, UK and Japan, cefditoren showed excellent activity against *H. influenzae* (median MIC_{90} range 0.015 to 0.05 mg/L)[6,9,11,12] and *Moraxella catarrhalis* (median MIC_{90} range ≤0.025 and 0.06 mg/L)[6,11,12] [figure 2]. The activity of cefditoren was not reduced by β-lactamase-positive *H. influenzae* [9,11,12,14,16] but was reduced against ampicillin-nonsusceptible *H. influenzae*, with a reported 67-fold increase in the MIC_{90} value (from 0.03 to 2 mg/L).[9] The activity of cefditoren was also reduced by β-lactamase-positive *M. catarrhalis*, with MIC_{90} values increasing to 1 mg/L.[11,12,22,23]

• *H. parainfluenzae* is also susceptible to cefditoren, with MIC_{50} and MIC_{90} values of ≤0.008 and 0.015 mg/L, respectively. The other cephalosporins tested showed a wide range of activities, with cefotaxime and ceftriaxone demonstrating similar activity to cefditoren (MIC_{90} ≤0.03 mg/L) but cefprozil and cefaclor demonstrating poor activity (MIC_{90} values both 8 mg/L). Furthermore, cefditoren had greater activity than amoxicillin with (MIC_{90} 2 mg/L) or without (MIC_{90} >8 mg/L) clavulanic acid.[25]

• Cefditoren had variable activity against Enterobacteriaceae derived from clinical isolates from the US, UK and Japan (figure 2). Against *Citrobacter* spp., *Enterobacter* spp. and *Serratia* spp., cefditoren's MIC_{90} values ranged from 1 to >16 mg/L, with Japanese strains the most susceptible. Cefditoren had good activity against *E. coli* (MIC_{90} range 0.50 to 0.78 mg/L), *Klebsiella* spp. (MIC_{90} range ≤0.025 to 1 mg/L) and *Proteus* spp. (MIC_{90} range 0.12 to 1.00 mg/L).[6,12,24]

• *Pseudomonas aeruginosa* was not susceptible to cefditoren (MIC_{90} range >16 to >128 mg/L) irrespective of the geographical location that the clinical isolates were obtained from.[6,12,24] A UK study has shown that *N. meningitidis* was susceptible to cefditoren (MIC_{90} 0.015 mg/L), which was less active than cefixime (MIC_{90} ≤0.004 mg/L) but more active than cefaclor (MIC_{90} 0.5 mg/L), cefuroxime (MIC_{90} 0.12 mg/L), ceftazidime (MIC_{90} 0.06 mg/L) and amoxicillin/clavulanic acid (MIC_{90} 0.12 mg/L).[12] In addition, the same study reported that cefditoren had good activity against penicillin-susceptible (MIC_{90} 0.008 mg/L) and -resistant (MIC_{90} 0.12 mg/L) *N. gonorrhoeae* as well as β-lactamase-producing *N. gonorrhoeae* (MIC_{90} 0.060 mg/L).

Anaerobes

• Cefditoren showed good activity against some reference strains of Gram-positive anaerobes including *Peptostreptococcus* spp. and *Clostridium* spp.[6] The respective MIC_{90}s of cefditoren against *P. magnus*, *P. asaccharolyticus* and *P. prevotii* were calculated as 1.56, 0.78 and 0.39 mg/L. Cefditoren activities against *Clostridium* spp. varied, with *C. perfringens* (MIC_{90} ≤0.025 mg/L) the most susceptible and *C. difficile* the most resistant (MIC_{90} 25 mg/L).[6] The MIC_{90} values of cefditoren against *Clostridium* spp. reference strains were reflected in its activity against *Clostridium* spp.-containing clinical isolates.[12] The MIC_{90} values against *C. perfringens* and *C. difficile* were 1 and 64 mg/L, respectively. Amoxicillin was more active against both strains of *Clostridium*, with an MIC_{90} of 0.12 mg/L for *C. perfringens* and 2 mg/L for *C. difficile*.

• Variable activity was also observed for cefditoren activity against reference strains of *Bacteroides* spp., with MIC_{90} values ranging from 1.56 mg/L for both *B. fragilis* and *B. vulgatus* to 25 mg/L for *B. ovatus* and *B. thetaiotaomicron*.[6] When tested against clinical isolates of *B. fragilis* in Japan and the UK, cefditoren MIC_{90} values were 6.25[18] and 32 mg/L,[12] respectively.

Bactericidal Activity

• Cefditoren demonstrated similar rates and extents of kill to those of other comparable β-lactam agents at 2 × MIC against clinical isolates of *S. pneumoniae* irrespective of penicillin-susceptibility status.[26] At this concentration, cefditoren had a percentage kill that ranged from 90.2 to >99.9% for penicillin-susceptible, from 99.4 to ≥99.9% for penicillin-intermediate and from 98.8 to ≥99.9% for penicillin-resistant strains of *S. pneumoniae*. The upper level of these ranges corresponds to the

NCCLS definition of bactericidal activity, which is the minimum bactericidal concentration (MBC) that kills ≥99.9% of bacteria [i.e. a 3 $\log_{10}$ reduction in bacterial cfu/ml].[8] During a 24-hour incubation period at 2 and 4 × MIC, cefditoren and other comparable β-lactams suppressed the regrowth of penicillin-susceptible, -intermediate and -resistant clinical isolates of *S. pneumoniae*.[26]

• Cefditoren showed greater bactericidal activity than most other tested antibacterials against a range of respiratory tract pathogens isolated from sinus aspirations and the lower respiratory tract. Its MBC_{90} was consistently lower than that for other cephalosporins tested against *S. pneumoniae*, *S. pyogenes*, *M. catarrhalis*, *S. aureus* and *H. influenzae*. Amoxicillin/clavulanic acid matched the MBC_{90} values of cefditoren only against penicillin-susceptible *S. pneumoniae* and β-lactamase-positive and -negative *M. catarrhalis*. With the exception of methicillin-susceptible and -resistant strains of *S. aureus*, cefditoren achieved MBC_{90} values of 1 to 2 × MIC_{90} for all aforementioned pathogens.[16]

• Time-kill studies have demonstrated that cefditoren has time-dependent bactericidal activity against clinical isolates of *S. pneumoniae*.[26,27] Cefditoren caused 99.9% killing of all nine *S. pneumoniae* strains tested at its MIC (≤0.5 mg/L) after an exposure time of 24 hours and 90% killing of all strains after an exposure time of 12 hours. Furthermore, cefditoren, but not other comparable β-lactam agents, brought about a 99% reduction in viability of all strains at 4 × MIC after an exposure time of 6 hours.[27] At concentrations 4 to 8 × MIC, cefditoren caused a ≥99.9% kill of susceptible strains of *S. aureus* (β-lactamase-positive), *S. pyogenes*, *S. pneumoniae*, *H. influenzae* (β-lactamase-positive), *M. catarrhalis* (β-lactamase-positive), *E. coli* (β-lactamase positive) and *K. pneumoniae* after a 3- to 12-hour exposure time.[12]

Postantibiotic Effect

• The postantibiotic effect (PAE) of cefditoren against upper and lower respiratory tract pathogens was measured by incubating each inoculum in a known drug concentration for 1 hour before removing the antimicrobial agent by centrifugation. After the removal of cefditoren at 4 × MIC, the mean PAE exceeded 1 hour against penicillin-susceptible and -resistant strains of *S. pneumoniae*. Similar results were observed with other comparable β-lactam agents.[28]

• Using the same methodology, the PAE also exceeded 1 hour against *S. pyogenes* and β-lactamase-negative *M. catarrhalis* strains. Neither cefditoren nor other comparable cephalosporins exhibited any PAE against β-lactamase-negative and β-lactamase-positive *H. influenzae*.[28]

• A UK study showed that there was little difference between the PAEs of cefditoren after inocula were exposed to antimicrobial concentrations of 4 or 8 × MIC for 1 hour.[12] When cefditoren was chemically removed from the test cultures by a broad-spectrum β-lactamase, the drug demonstrated PAEs against *S. pneumoniae* (range 1.1 to 1.8 hours), *S. aureus* (range 0.9 to 1.7 hours), *S. saprophyticus* (range 2.3 to 4.7 hours) and *M. catarrhalis* (range 1.0 to 1.7 hours). The range of PAEs of cefditoren against other bacteria were as follows: ampicillin-susceptible and β-lactamase-positive *H. influenzae* (range –0.9 to –0.2 hours); penicillin-susceptible and β-lactamase-positive *N. gonorrhoeae* (range –0.4 to 0.3 hours); *E. coli* (range 0.4 to 1.3 hours); *K. pneumoniae* (range –0.5 to 0.1 hours); and *P. mirabilis* (range –0.2 to 0.2 hours).

Resistance Issues

• Cefditoren had a slower rate of hydrolysis to a wide range of β-lactamases than either cephaloridine or benzylpenicillin. In particular, the relative rate of cefditoren hydrolysis was <1% that of benzylpenicillin after *E. coli*-derived penicillinase (type I, III, IV and V) exposure[29] and also after *H. influenzae*-derived β-lactamase (type 39, 42, 44 and 46) exposure.[7] Similar results to that of cefditoren exposure to *E. coli*-derived penicillinase (cefteram and cefixime) and *H. influenzae*-derived β-lactamase (cefdinir) were observed for other cephalosporins tested.

• In a genetically defined panel of *E. coli* isolates that had various β-lactamase or outer membrane porin changes, cefditoren demonstrated antibacterial activity that was greater than or similar to that of other comparable β-lactam agents tested.[30] The MIC of cefditoren (0.25 mg/L) was unaffected by the ubiquitous TEM-1 β-lactamase as well as many of the SHV and PSE group of enzymes. However, many of the other TEM β-lactamases as well as the OXA group of enzymes increased the cefditoren MIC up to 64-fold (TEM-3, -4 and -42), with a similar elevation in MICs observed for the other β-lactam agents. In contrast, the ROB-I β-lactamase, which is produced by *H. influenzae*, increased the MICs of cefditoren, cefixime (0.5 mg/L), cefpodoxime (0.5 mg/L) and amoxicillin/ clavulanic acid 2-fold. ROB-I β-lactamases caused a 4- and 64-fold greater MIC elevation for cefuroxime and amoxicillin, respectively.

In Vivo Activity

• Time above the MIC is the most important pharmacokinetic/pharmacodynamic determinant of *in vivo* activity of cephalosporins.[31] In the thigh-infection model of neutropenic and normal mice, the duration of time that plasma cefditoren concentrations needed to exceed the MIC in order to be effective against *S. pneumoniae* was similar to that of other cephalosporins, with respect to each drug's dosage interval. Furthermore, time above the MIC for effective net static effects was similar for all *S. pneumoniae* strains tested, regardless of susceptibility status. The mean time above MIC for total and free drug was 55 (range 44 to 67%) and 33% (range 23 to 43%), respectively. Effective cefditoren therapy may correlate with total serum concentrations that are above the MIC for 50 to 55% of the dosage interval.[32]

• In experimental lung infections in immunocompromised mice (n = 6/group) caused by intranasal *H. influenzae* (3.1×10^7 cfu/0.025ml), subcutaneous doses of cefditoren (equivalent to a single 100mg dose in humans) initiated 1.5 hours after infection significantly reduced bacterial counts to 5.62 ± 0.18 (standard error) $\log_{10}$ cfu/lung compared with control (7.13 ± 0.04 $\log_{10}$ cfu/lung; $p < 0.01$) 24 hours after the first dose. Similarly, subcutaneous injections of cefditoren that modelled a single 200mg human dose reduced bacterial counts to 5.12 ± 0.15 $\log_{10}$ cfu/lung compared with control (see above). Cefditoren was more effective than cefdinir at the modelled 100mg dose (6.57 ± 0.27 $\log_{10}$ cfu/lung; $p < 0.01$); the effectiveness of cefdinir at the modelled 200mg dose was not determined.[33]

• Against subcutaneous abscesses of *S. aureus* (4.6×10^4 cfu/0.1ml) in mice (n = 5/group), a subcutaneous injection of cefditoren (modelled 100mg human dose) administered 1 hour after infection at sites remote from the abscess site was less effective than subcutaneous cefdinir (modelled 100mg human dose) and control. Compared with control values of 6.82 ± 0.11 $\log_{10}$ cfu/abscess at 24 hours after the first dose, the viable bacteria counts for cefditoren and cefdinir were 7.55 ± 0.29 and 4.20 ± 0.32 $\log_{10}$ cfu/abscess, respectively.[33]

• In experimental systemic infections in male mice (n = 24) inoculated with intraperitoneal *S. aureus* (2.6×10^7 cfu/mouse), *E. coli* (2.0×10^6 cfu/mouse) and *K. pneumoniae* (1.5×10^5 cfu/mouse), the administration of oral cefditoren pivoxil 1 hour after infection demonstrated variable protective efficacy. The ED_{50} (the dose required to protect 50% of animals) for cefditoren compared with cefdinir against each infection was as follows: *S. aureus* (14.5 *vs* 0.09 mg/kg); *E. coli* (1.45 *vs* 2.20 mg/kg); and *K. pneumoniae* (5.22 *vs* 1.30 mg/kg).[33]

• In a murine model of infection (n = 8) caused by an intraperitoneal challenge dose of *S. aureus* (4.3×10^8 cfu/mouse), the administration of oral cefditoren pivoxil (ED_{50} 0.33 mg/mouse) 1 hour after infection had a greater protective effect than either cefaclor (ED_{50} >2 mg/mouse) or cefteram (ED_{50} >2 mg/mouse). In another group of eight mice, oral cefditoren (ED_{50} 0.027 mg/mouse) was shown to have a similar protective effect to cefaclor (ED_{50} 0.04 mg/mouse), cefixime (ED_{50} 0.032 mg/mouse)

and cefteram (ED_{50} 0.032 mg/mouse) after intraperitoneal challenge with *E. coli* (3.0×10^7 cfu/mouse).[34]

Effects on Intestinal Bacterial Microflora

• Quantitative ecological disturbances of the aerobes Enterobacteriaceae, Streptococcaceae, *Staphylococcus* spp. and yeasts were observed in beagle dogs that received oral cefditoren pivoxil 12 mg/kg/day for 14 consecutive days. In particular, cefditoren pivoxil reduced Enterobacteriaceae counts to 4.2 ± 0.32 (standard deviation) $\log_{10}$ cfu/g of wet faeces on the eighth day of treatment compared with 7.9 ± 0.52 $\log_{10}$ cfu/g of wet faeces before treatment. A similar result was observed when an increased dose of 250 mg/kg/day was given. At the lower dosage of 12 mg/kg/day, cefditoren pivoxil caused only a transient decrease in anaerobic counts but at a dosage of 250 mg/kg/day, cefditoren pivoxil eradicated many of these bacteria. However, for both dosage regimens, the counts of all tested bacteria had started to recover by day 21. Qualitative ecological disturbances were observed for *C. difficile*, which became detectable after the fifth day of treatment (4.6 $\log_{10}$ cfu/g of wet faeces) and seventh day of treatment (3.7 ± 0.95 $\log_{10}$ cfu/g of wet faeces) for the 12 and 250 mg/kg/day dosage regimens, respectively. Only in the 250 mg/kg/day dosage regimen did *C. difficile* become undetectable after day 21.[35]

2. Pharmacokinetic Profile

Following oral administration of cefditoren pivoxil, the prodrug passively diffuses through the intestinal membrane where it is hydrolysed by esterases to cefditoren (the active metabolite) and pivalate. The prodrug is neither detected in plasma[36] after administration nor is it microbiologically active.[37]

Absorption and Distribution

• The peak plasma cefditoren concentration (C_{max}) and area under the plasma concentration-time curve (AUC) increased linearly with dose after single preprandial oral cefditoren pivoxil doses of 100, 200 and 300mg in healthy male volunteers. A single preprandial dose of 100 or 200mg produced a C_{max} of 1.44 and 2.46 mg/L, respectively, within 1.5 hours and an AUC of 4.03 and 7.93 mg • h/L. A postprandial dose of 200mg raised the C_{max} to 2.72 mg/L and the AUC to 10.82 mg • h/L.[37] A single dose of 400mg given to healthy volunteers produced a C_{max} of 4.1 mg/L and a corresponding AUC of 14.6 mg • h/L.[38] Across phase I studies, a single, postprandial, oral dose of cefditoren pivoxil 200mg, C_{max} values ranged from 2.62 to 3.1 mg/L.[37,39,40] Similarly, the 400mg dosage achieved a C_{max} range of 3.84 to 4.57 mg/L.[41-44] C_{max} is usually achieved 1.5 to 3 hours after oral administration.[37,41-43]

• Repeated doses of oral cefditoren pivoxil 200mg twice daily for 7 days resulted in C_{max} values of 2.5 mg/L and C_{min} values of almost 0 mg/L when measured 1.5 and 12 hours after each dose.[37] No accumulation of cefditoren is observed in subjects with normal renal function.[40]

• The estimated bioavailability of cefditoren pivoxil is 14% under fasting conditions.[40] However, the bioavailability of cefditoren pivoxil is increased to ≈16% if it is taken with a low-fat meal (693 calories: 14g fat; 122g carbohydrates; and 23g protein),[40] a common feature of cephalosporin prodrug esters.[45] Importantly, a moderate- (648 calories: 27g fat; 73g carbohydrates; and 29g protein) or high-fat meal (858 calories: 64g fat; 43g carbohydrates; and 31g protein) further increases the bioavailability of cefditoren pivoxil, with ≈50 and 70% increases in C_{max} and AUC compared with the fasted state.[40] Therefore, the maximal bioavailability of cefditoren is ≈25%, which compares with cefdinir (>36%), cefpodoxime (50%), cefixime (40 to 50%), cefprozil (95%) and ceftibuten (70 to 90%).[45,46] Limited data suggest that food has little effect on the rate of cefditoren absorption.[37]

• The mean volume of distribution at steady state of cefditoren is 9.3 ± 1.6L. Binding of cefditoren to plasma proteins averages 88% from *in vitro* [40] and *in vivo* [32] determinations. Penetration into red blood cells is negligible.[40]

• A single 400mg oral dose of cefditoren pivoxil achieved good penetration of cefditoren into noninflammatory and inflammatory blister fluid in 12 healthy volunteers. The principal pharmacokinetic parameters of cefditoren in the noninflammatory blister fluid compared with plasma were as follows: C_{max} (1.08 *vs* 3.27 mg/L); time to reach peak plasma concentrations (4.2 *vs* 2.8h); AUC_8 (4.23 *vs* 10.8 mg • h/L); and AUC_{12} (6.29 *vs* 11.4 mg • h/L). Generally, the AUC of cefditoren in blister fluid was 40 to 56% that of the serum AUC values and remained relatively high for 12 hours.[47]

• A randomised study measured the tissue penetration of cefditoren into the bronchial mucosa and epithelial lining fluid in 24 patients undergoing fibre-optic bronchoscopy (figure 3). During the collection interval of 2 to 3 hours after a single 400mg oral dose of cefditoren pivoxil, cefditoren concentrations in the bronchial mucosa and epithelial lining fluid were 0.908 ± 0.609 mg/L and 0.342 ± 0.250 mg/L, respectively, compared with 1.33 ± 0.95 mg/L in the plasma.[48]

• In fasted patients undergoing tonsillectomy, the mean tonsil tissue cefditoren concentration 2 to 4 hours after a single 200mg dose of cefditoren pivoxil was 0.18 ± 0.07 μg/g. Cefditoren tonsil tissue concentrations were 12 ± 3% of serum cefditoren concentrations.[40]

Metabolism and Elimination

• Cefditoren is not metabolised to any appreciable extent. Rather, it is eliminated from the plasma by excretion into the urine, with a renal clearance of 4 to 5 L/h. Cefditoren has an elimination half-life ($t_{1/2}$) of 1.4 to 1.7 hours in healthy young adults.[39,40,42,43]

• More than 70% of the pivalate is absorbed after multiple doses of cefditoren pivoxil, which is eliminated by renal excretion (>99%) as pivaloylcarnitine.[40]

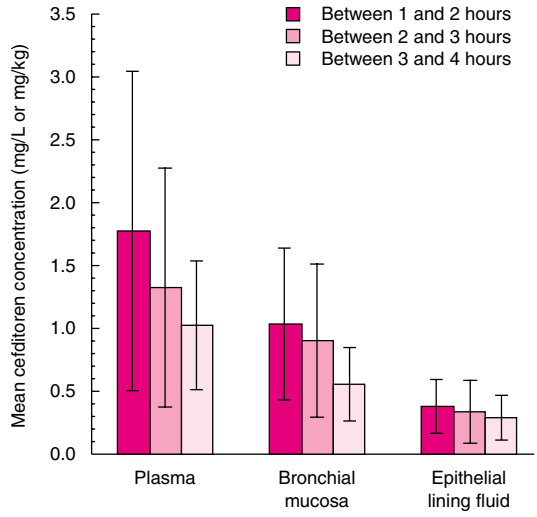


Fig. 3. Penetration of cefditoren into respiratory tissue and epithelial lining fluid in patients undergoing fibre-optic bronchoscopy (n = 24). Cefditoren concentrations are expressed as mean values ± standard deviation over three 1-hour collecting intervals.[48]

Influence of Age, Gender and Disease on Pharmacokinetics

• Both age and gender have statistically significant effects on cefditoren pharmacokinetics, but the changes in drug disposition are not considered clinically relevant. Compared with volunteers between the ages of 25 and 40 years who received a 7-day regimen of cefditoren pivoxil 400mg twice daily, patients aged ≥65 years had a 26% higher C_{max}, 33% higher AUC and 16% longer $t_{1/2}$. The results are readily explained in terms of older patients having a 24% lower creatinine clearance rate than younger patients. Compared with men, women had a 14% higher C_{max} and 16% higher AUC. The mean renal clearance in women was 13% lower than in men.[43]

• In a phase I study of 24 healthy volunteers who received cefditoren pivoxil 400mg twice daily for 7 days, moderate (30 to 49 ml/min/1.73m^2) or severe (<30 ml/min/1.73m^2) renal impairment increased cefditoren systemic exposure. On day 1, C_{max} values increased from 3.8 mg/L in patients

with normal renal function to 6.3 and 5.4 mg/L in patients with moderate and severe renal impairment, respectively ($p \leq 0.05$). The corresponding AUC values increased from 11.4 mg • h/L to 29.3 and 32.3 mg • h/L ($p \leq 0.05$). The $t_{1/2}$ was prolonged in patients with renal impairment, increasing to 3.2 hours (moderate impairment) and 5.3 hours (severe impairment) compared with 1.4 hours in patients with normal renal function (values not statistically analysed). In six patients with end-stage renal disease, there was no statistically significant difference in pharmacokinetic parameters between patients who underwent concurrent haemodialysis and those who did not [e.g. AUC_∞ values 41.1 *vs* 59.3 mg • h/L].[44]

• Only small effects on pharmacokinetics were observed in six patients with mild (Child-Pugh Class A) and six patients with moderate (Child-Pugh Class B) hepatic impairment who received cefditoren pivoxil 400mg twice daily for 7 days. For each of the pharmacokinetic parameters tested, statistical significance testing at the 5% confidence level failed to differentiate between patients with hepatic impairment and patients with normal hepatic function.[41]

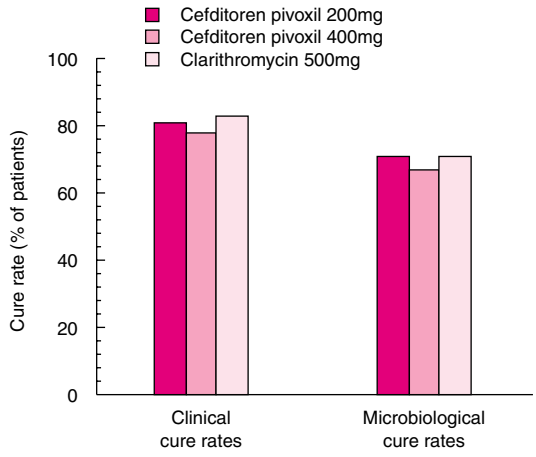


Fig. 4. Data from a randomised, double-blind clinical trial (n = 903) illustrating the cure rates of AECB achieved 7 to 14 days after a 10-day treatment course of cefditoren pivoxil either 200 or 400mg twice daily. The cure rates achieved by the trial comparator, clarithromycin (500mg twice daily for 10 days), are also shown.[49] Clinical cure was defined as the percentage of clinically evaluable patients who had resolution of pretreatment signs and symptoms, returned to preinfection baseline or improved without need for additional antimicrobial therapy. The microbiological cure rate was defined as the percentage of patients showing either eradication of all pretreatment causative respiratory pathogens or culture unavailable because of clearance of infection. **AECB** = acute exacerbation of chronic bronchitis.

3. Therapeutic Trials

Several phase III trials have been completed for cefditoren pivoxil; all have been published as abstracts. The trial endpoints were the clinical and microbiological cure rates. The clinical cure was defined as the percentage of patients who had resolution or improvement of pretreatment signs and symptoms without need for additional antimicrobial therapy. The definition of the microbiological cure rate varied between trials.

• In a double-blind, multicentre trial involving 903 patients with acute exacerbation of chronic bronchitis (AECB), oral cefditoren pivoxil 200 or 400mg twice daily for 10 days had a clinical cure rate of 89% (185 of 209 patients) and 88% (176 of 199), respectively, within 48 hours after completion of treatment (figure 4). Clinical cure rates 7 to 14 days after completion of therapy were 81% (172 of 213) and 78% (164 of 210) for the two dosage regimens. In comparison, the oral administration of the macrolide clarithromycin (500mg twice daily for 10 days) produced clinical cure rates of 90% (196 of 218) within 48 hours after completion of treatment and 83% (186 of 223) 7 to 14 days after completing therapy. In the same study, cefditoren 200 or 400mg twice daily had a microbiological cure rate of, respectively, 76% (159 of 208 patients) and 74% (147 of 198) within 48 hours of completing treatment, and 71% (152 of 215) and 67% (141 of 210) 7 to 14 days after completing treatment. Clarithromycin 500 mg/day produced microbiological cure rates of 82% (177 of 217) within 48 hours and 71% (158 of 222) 7 to 14 days after therapy.[49]

• A 10-day course of oral cefditoren pivoxil either 200 or 400mg twice daily was as effective as a 10-day course of oral cefuroxime axetil 250mg twice daily for treating AECB in a double-blind, randomised clinical trial (no statistical difference between groups). Clinical cure rates with cefditoren pivoxil 200 or 400mg within 48 hours after completion of treatment were 88% (131 of 149 patients) and 89% (128 of 144), respectively, compared with 89% (143 of 160) for cefuroxime axetil 250mg.[50] The clinical cure rates of the two cefditoren pivoxil dosage regimens 7 to 14 days after completing therapy were 82% (109 of 133) and 86% (112 of 130), compared with 79% (110 of 139) in the cefuroxime axetil group.[51] Overall microbiological cure rates were also similar, with cefditoren pivoxil 200 and 400mg dosages effective within 48 hours of treatment completion in 80% (118 of 148 patients) and 76% (110 of 144) of patients compared with 78% (124 of 160) effectiveness in the cefuroxime axetil group.[50] Similarly, the overall microbiological cure rates 7 to 14 days after therapy were 73% (135 of 186) and 77% (143 of 185) for the lower and upper cefditoren pivoxil dosages and 72% (135 of 188) for the cefuroxime axetil group.[51]

• Oral cefditoren pivoxil demonstrated excellent efficacy in the treatment of streptococcal pharyngitis in two combined multicentre trials that involved a total of 1011 patients (figure 5). In these double-blind studies, patients were randomised to receive either cefditoren pivoxil 200mg twice daily for 10 days or phenoxymethylpenicillin potassium 250mg four times daily for 10 days. The clinical cure rate with cefditoren pivoxil was 94% (347 of 369 patients) at 4 to 7 days after treatment and 89% (319 of 358) at 19 to 25 days after treatment. The clinical cure rates with phenoxymethylpenicillin potassium over the same time intervals were 90% (332 of 367) and 86% (305 of 356), respectively. A statistically significant (all $p < 0.05$) increase in bacteriological response rates was observed for cefditoren pivoxil compared with phenoxymethylpenicillin potassium after 4 to 7 days [90% (329 of 364) *vs* 83% (301 of 364)] and after 19 to 25 days [85% (301 of 356) *vs* 77% (269 of 351)].[52]

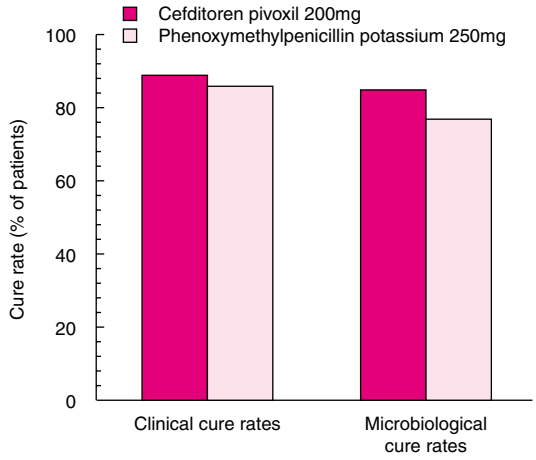


Fig. 5. Cure rates of streptococcal pharyngitis achieved 19 to 25 days after a 10-day treatment course of either cefditoren pivoxil 200mg twice daily or phenoxymethylpenicillin potassium 250mg four times daily. Data taken from the study by Gooch et al.,[52] which combined data from two randomised, double-blind clinical trials involving 1011 patients. Clinical cure was defined as the percentage of patients who had resolution or improvement of pretreatment signs and symptoms without need for additional antimicrobial therapy. The microbiological cure rate was defined as the percentage of patients for whom *Streptococcus pyogenes* was eradicated.

• In a double-blind, randomised, multicentre trial involving 857 patients with uncomplicated skin and skin structure infections, a clinical cure rate of 89% within 48 hours of completing treatment was reported after the administration of oral cefditoren pivoxil 200mg (230 of 257 patients) or 400mg (225 of 254) twice daily for 10 days. The comparator, cefuroxime axetil (250mg twice daily for 10 days), produced a similar clinical cure rate of 90% (232 of 258). The clinical cure rates of the two cefditoren pivoxil dosages 7 to 14 days after completing therapy were 84% [(223 of 265) and (216 of 257)], compared with 88% (234 of 265) in the cefuroxime axetil group. Within 48 hours of completing therapy, the microbiological cure rates were similar be-

tween the two cephalosporins, with cefditoren pivoxil 200 and 400mg effective in 85% (112 of 131 patients) and 82% (112 of 137) of patients compared with 87% (103 of 119) effectiveness in the cefuroxime axetil group. Likewise, the microbiological cure rates 7 to 14 days after completing therapy were 81% (110 of 135) and 85% (121 of 143) for the lower and upper cefditoren pivoxil dosages and 85% (103 of 121) for the cefuroxime axetil group. [53]

• A separate, double-blind, randomised study (n = 828), reported that cefditoren pivoxil 200 or 400mg twice daily for 10 days eradicated causative skin pathogens in 90% (140 of 155 patients) and 88% (141 of 161), respectively, within 48 hours of completing treatment. The eradication rate of the 200mg cefditoren pivoxil dosage was significantly higher than the rate observed with cefadroxil 500mg twice daily [81% (125 of 154); $p < 0.05$]. In particular, cefditoren pivoxil 200 and 400mg had an eradication rate for *S. aureus* of 86% (66 of 77) and 84% (73 of 87), respectively, and for *S. pyogenes* of 91% (10 of 11) and 100% (6 of 6). Cefadroxil had an eradication rate of 82% (68 of 83) for *S. aureus* and 100% (3 of 3) for *S. pyogenes*. Similar results were observed 7 to 14 days after therapy.[54]

• The results of the two aforementioned trials[53,54] that investigated skin and skin structure infections were combined so that the microbiological cure rate of cefditoren pivoxil could be evaluated with respect to comparators (figure 6). The overall clinical cure rates were 85, 83 and 87% for cefditoren pivoxil 200mg, cefditoren pivoxil 400mg and comparator groups, respectively, 7 to 14 days after therapy.[55]

4. Tolerability

• Cefditoren pivoxil has been administered to 4299 patients in clinical trials to date at the recommended therapeutic dose of 200 or 400mg twice daily for 10 days. Most adverse events have been

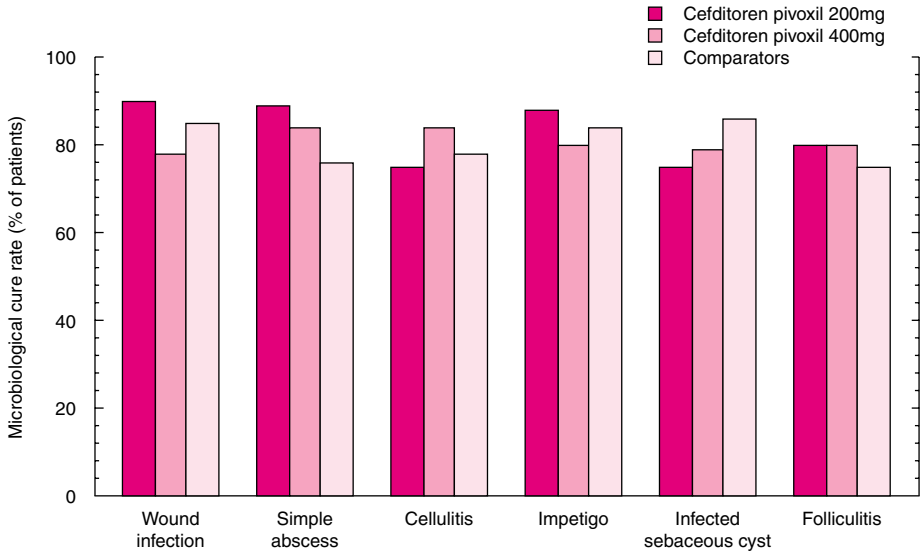


Fig. 6. Microbiological cure rates by infection type achieved 7 to 14 days after a treatment course of cefditoren pivoxil 200 or 400mg twice daily for 10 days. Comparators were 10-day courses of either cefuroxime axetil (250mg twice daily) or cefadroxil (500mg twice daily). Data taken from the study by Herbert et al.,[55] which combined data from two randomised, double-blind clinical trials involving 762 evaluable patients. The microbiological cure was defined as the eradication of the causative skin pathogen.

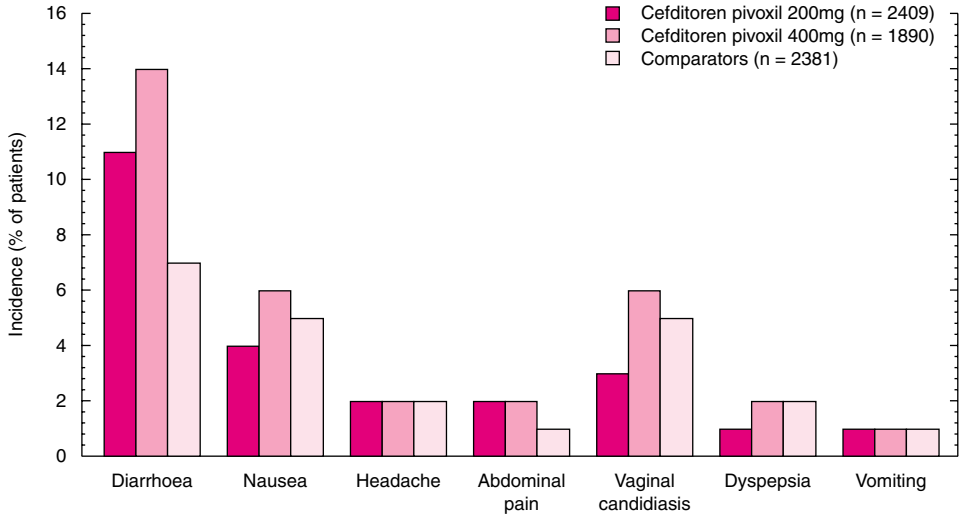


Fig. 7. Tolerability of cefditoren pivoxil 200 and 400mg twice daily for 10 days in 4299 adult and adolescent patients. Data were pooled from all clinical trails to date. These treatment-related adverse events were thought by clinical trial investigators to be possibly, probably or definitely attributable to cefditoren pivoxil. Also shown are tolerability data from 2381 patients who received comparator antibacterials, including amoxicillin/clavulanic acid, cefadroxil, cefuroxime axetil, cefpodoxime proxetil, clarithromycin and penicillin.[40]

mild in intensity and self-limiting. Figure 7 illustrates some of the common treatment-related adverse events that were thought by clinical trial investigators to be possibly, probably or definitely attributable to cefditoren pivoxil. No deaths or disabilities have been attributable to cefditoren pivoxil.[40]

• The most common treatment-related adverse events of cefditoren pivoxil 200mg (and 400mg) twice daily were as follows: diarrhoea 11% (and 14%); nausea 4% (and 6%); headache 2% (and 2%); abdominal pain 2% (and 2%), vaginal candidiasis 3% (and 6%); dyspepsia 1% (and 2%); and vomiting 1% (and 1%).[40]

• In 244 and 242 geriatric patients who received cefditoren pivoxil 200 and 400mg twice daily, respectively, no clinically significant differences were observed regarding the drug's tolerability or effectiveness compared with that in younger patients.[40]

• Treatment discontinuation related to adverse events occurred in 2% of patients who received cefditoren pivoxil 200mg twice daily and 3% of patients who received 400mg twice daily in clinical trials. Discontinuations were mainly due to gastrointestinal disturbance, with diarrhoea and nausea the most common symptoms. Diarrhoea led to a discontinuation of therapy in 0.7% of patients who received cefditoren pivoxil 200mg twice daily and 1.4% of patients who received 400mg twice daily.[40]

• As with many antibacterial agents, pseudomembranous colitis has been reported with cefditoren pivoxil. Cefditoren disturbs the ecological balance of colonic bacterial microflora, which permits the overgrowth of clostridia (see section 1). In particular, the toxin produced by *C. difficile* is a primary cause of antibacterial-associated colitis.[40]

5. Drug Interactions

• In a small crossover study of 24 healthy adults who received a single oral dose of cefditoren pivoxil 400mg alone, or concurrently with an intravenous injection of the histamine H_2 receptor

antagonist famotidine (20mg), the cefditoren C_{max} was reduced from 4.01 to 2.96 mg/L and the AUC reduced from 13.95 to 10.97 mg • h/L (both $p \leq 0.05$). Likewise, the coadministration of an antacid containing magnesium hydroxide and aluminium hydroxide also reduced the systemic exposure to cefditoren. The C_{max} value was lowered to 3.43 mg/L and the AUC lowered to 12.43 mg • h/L ($p \leq 0.05$).[42]

- No statistically significant differences were observed in the pharmacokinetic parameters of ethinyl estradiol (the estrogenic component in most oral contraceptives) when cefditoren pivoxil (400mg twice daily) was given concurrently to 24 women for 13 days. Indeed, the concentration versus time plot for ethinyl estradiol alone, or concurrently with cefditoren, was superimposable.[56]
- A phase I, randomised, crossover study (n = 24) showed that the renal tubule blocking drug probenecid caused a substantial increase in plasma exposure to cefditoren by reducing its renal clearance. Compared with a single 200mg dose of cefditoren pivoxil alone, the coadministration of a single dose of probenecid 1g increased the cefditoren C_{max} from 2.62 to 3.92 mg/L, AUC from 7.95 to 18.17 mg • h/L and $t_{1/2}$ from 1.41 to 2.15 hours. Renal clearance was reduced from 4.8 to 1.2 L/h.[39]
- The administration of cefditoren pivoxil induced changes in laboratory parameters in some patients that could be of possible clinical significance. The incidence of these changes after the administration of the 200mg (and 400mg) dosage schedule were as follows: haematuria 2.9% (and 3.2%), increased urine white blood cells 2.3% (and 2.5%), decreased haematocrit 1.7% (and 2.2%) and increased glucose 1.6% (and 0.8%).[40]
- Cephalosporins, including cefditoren pivoxil, are known to occasionally induce a positive direct Coomb's test. Also, a false-positive urinary glucose result can occur if testing with reducing reagents that contain ferrous (Fe^{2+}) ions (e.g. Benedict's or Fehling's solution or with CLINITEST® tablets). There are no such problems with enzyme-linked assays for glycosuria (e.g. CLINISTIX® and TES-TAPE®). False-negative results may occur with the ferricyanide test; therefore, it is recommended that the glucose oxidase or hexokinase method are used in the determination of blood/plasma glucose levels in patients receiving cefditoren pivoxil.[40]
- When cefditoren pivoxil was given as a 200mg twice daily regimen for 10 days, the mean decrease in plasma carnitine levels was 18.1 ± 7.2 μmol/L – a 39% decrease in plasma carnitine levels. Following a cefditoren pivoxil 400mg twice daily regimen for 14 days, plasma carnitine levels fell by 63% (33.3 ± 9.7 μmol/L). However, plasma carnitine levels returned to control ranges within 7 to 10 days of drug discontinuation. No clinical effects of carnitine decrease have been associated with short-term treatment.[40]

6. Cefditoren Pivoxil: Current Status

Cefditoren pivoxil is a cephalosporin prodrug with a broad spectrum of activity against Gram-positive and Gram-negative bacteria. Phase III trials have demonstrated that it is a safe and effective treatment for pharyngitis/tonsillitis, AECB, and uncomplicated skin and skin structure infections.

In the US, cefditoren pivoxil received Food and Drug Administration approval in September of 2001 for treating the following mild to moderate bacterial infections in adults and adolescents (12 years or older): a dosage of 200mg twice daily for 10 days is indicated for the treatment of pharyngitis/tonsillitis caused by susceptible strains of *S. pyogenes*; a dosage of 200mg twice daily for 10 days is indicated for uncomplicated skin and skin structure infections caused by susceptible strains of *S. aureus* and *S. pyogenes*; and a dosage of 400mg twice daily for 10 days is indicated for the treatment of AECB caused by susceptible strains of *H. influenzae*, *H. parainfluenzae*, *M. catarrhalis* and penicillin-susceptible strains of *S. pneumonia*. Cefditoren pivoxil should be administered with meals so that bioavailability is maximised.

No dosage adjustment is necessary in patients with mild renal impairment. However, it is recom-

mended that not more than 200mg twice daily be given to patients with moderate impairment and 200mg once daily to those with severe impairment. A suitable dosage regimen in patients with end-stage renal impairment has not been determined. No dosage adjustment is necessary in patients with mild to moderate hepatic impairment (Child-Pugh Class A or B). The pharmacokinetic profile in patients with severe hepatic impairment (Child-Pugh Class C) has not been studied.[40]

Cefditoren pivoxil is contraindicated in patients with known allergy to the cephalosporin class of antibiotics or any of its components. It is also contraindicated in patients with carnitine deficiency or inborn errors of metabolism that may result in clinically significant carnitine deficiency. Cefditoren pivoxil tablets contain sodium caseinate; therefore, patients with milk protein hypersensitivity should not be prescribed this antimicrobial agent.[40]

References

1. Tomasz A, Höltje JV. Murein hydrolases and the lytic and killing action of penicillin. Microbiology 1977: 209-15
2. Höltje JV, Tomasz A. Lipoteichoic acid: a specific inhibitor of autolysin activity in pneumococcus. Proc Nat Acad Sci USA 1975; 72 (5): 1690-4
3. Donowitz GR, Mandell GL. Cephalosporins. Mandell GL, Douglas RG, Bennett JE. Principles and practice of infectious diseases. 3rd ed. 1990 New York: Churchill Livingston: 246-57
4. Tomasz A. The mechanism of the irreversible antimicrobial effects of penicillins: how the β-lactam antibiotics kill and lyse bacteria. Annu Rev Microbiol 1979; 33: 113-37
5. Nagai K, Davies T, Jacobs M, et al. Affinity of penicillin-binding proteins (PBP) 1A, 2X and 2B for amoxicillin (AX), cefditoren (CD) and other β-lactams among 18 *Streptococcal pneumoniae* (Sp) clinical isolates [abstract no. 647a]. 41st Interscience Conference on Antimicrobial Agents and Chemotherapy; 2001 Dec 16-19; Chicago (IL)
6. Watanabe Y, Hatano K, Matsumoto Y, et al. *In vitro* antibacterial activity of FK041, a new orally active cephalosporin. J Antibiot (Tokyo) 1999; 52: 649-59
7. Shimizu M, Takata T, Masuyoshi S, et al. Antibacterial activity, bactericidal effect and β-lactamase stability of CDTR, and its binding affinity to PBPs against clinical isolate of *Haemophilus influenzae.* Jpn J Chemother 1995; 43 (9): 815-20
8. Ackerman BH, Dello Buono FA. *In vitro* testing of antibiotics. Pharmacotherapy 1996; 16 (2): 201-21
9. Fuchs PC, Barry AL, Brown SD. Susceptibility of *Streptococcus pneumoniae* and *Haemophilus influenzae* to cefditoren, and provisional interpretive criteria. Diag Microbiol Infect Dis 2000; 37: 265-9
10. Jones RN, Biedenbach DJ, and the Quality Control Working Group. Validation of cefditoren MIC quality control ranges by a multi-laboratory study (2001). Diagn Microbiol Infect Dis 2001; 40: 71-3
11. Johnson DM, Biedenbach DJ, Beach ML, et al. Antimicrobial activity and *in vitro* susceptibility test development for cefditoren against *Haemophilus influenzae*, *Moraxella catarrhalis*, and Streptococcus species. Diagn Microbiol Infect Dis 2000; 37 (2): 99-105
12. Felmingham D, Robbins MJ, Ghosh G, et al. An *in vitro* characterization of cefditoren, a new oral cephalosporin. Drugs Exp Clin Res 1994; 20: 127-47
13. Soriano F, Coronel P, Gimeno M, et al. Inoculum effect and bactericidal activity of cefditoren and other antibiotics against *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*. Eur J Clin Microbiol Infect Dis 1996; 15: 761-3
14. Jones RN, Biedenbach DJ, Croco MAT, et al. *In vitro* evaluation of a novel orally administered cephalosporin (cefditoren) tested against 1249 recent clinical isolates of *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae.* Diagn Microbiol Infect Dis 1998; 31: 573-8
15. Kelly LM, Jacobs MR, Appelbaum PC. Comparison of agar dilution, microdilution, E-test, and disk diffusion methods for testing activity of cefditoren against *Streptococcus pneumoniae.* J Clin Microbiol 1999; 37: 3296-9
16. Dubois J, St Pierre C. Superior inhibitory and bacterial activity of cefditoren against respiratory tract pathogens [poster no. 370]. 40th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2000 Sep 17-20; Toronto (ON)
17. Ednie LM, Pankuch GA, Jacobs MR, et al. Activity of cefditoren compared with other agents against quinolone and macrolide susceptible and resistant pneumococci [poster no. 378]. 40th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2000 Sep 17-20; Toronto (ON)
18. Miyazaki S, Miyazaki Y, Tsuji A, et al. *In vitro* antibacterial activity of ME1207, a new oral cephalosporin. Antimicrob Agents Chemother 1991; 35: 1691-4
19. Chin N-X, Zhang Y-X, Neu HC. *In vitro* activity of a new cephalosporin ME-1206 compared with other agents. Diagn Microbiol Infect Dis 1991; 14: 417-24
20. Sahm DF, Draghi D, Blosser RS, et al. Comparative activities of cefditoren and other antimicrobials against recent clinical isolates of non-pneumococcal streptococci collected throughout the Unites States [poster no. 375]. 40th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2000 Sep 17-20; Toronto (ON)
21. Alcaide F, Linares J, Pallares R, et al. *In vitro* activities of 22 β-lactam antibiotics against penicillin-resistant and penicillin-susceptible viridans group streptococci isolated from blood. Antimicrob Agents Chemother 1995; 39: 2243-7
22. Sahm DF, Karlowsky JA, Draghi D, et al. Comparative activities of cefditoren and other antimicrobials against recent clinical isolates of *H. influenzae* and *M. catarrhalis* collected throughout the United States [poster no. 369]. 40th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2000 Sep 17-20; Toronto (ON)

23. Beyer J, Shortridge V, Flamm R, et al. *In vitro* activity of cefditoren against clincal isolates of *S. pneumoniae*, *H. influenzae*, and *M. Catarrhalis* [poster no. 376]. 40th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2000 Sep 17-20; Toronto (ON)
24. Jones RN, Biedenbach DJ, Johnson DM. Cefditoren activity against nearly 1000 non-fastidious bacterial isolates and the development of *in vitro* susceptibility test methods. Diagn Microbiol Infect Dis 2000; 37: 143-6
25. Jacobs MR, Bajaksouzian S, Palavecino-Fasola EL, et al. Activity of cefditoren against *Haemophilus* species and *Moraxella catarrhalis* [abstract]. 37th Interscience Conference on Antimicrobial Agents and Chemotherapy;1997 Sep 28-Oct 1: Toronto (ON), 132
26. Draghi D, Selman LJ, Karlowsky JA, et al. Bactericidal activity of cefditoren and comparator agents against penicillin-susceptible, -intermediate, and -resistant isolates of *Streptococcus pneumonia* [poster no. 373]. 40th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2000 Sep 17-20; Toronto (ON)
27. Spangler SK, Jacobs MR, Appelbaum PC. Time-kill studies on susceptibility of nine penicillin-susceptible and -resistant pneumococci to cefditoren compared with nine other β-lactams. J Antimicrob Chemother 1997; 39: 141-8
28. Dubois J, St-Pierre C. *In vitro* study of the post-antibiotic effect and the bactericidal activity of cefditoren and ten other oral antimicrobial agents against upper and lower respiratory tract pathogens. Diagn Microbiol Infect Dis 2000; 37: 187-93
29. Tamura A, Okamoto R, Mitsuhashi S, et al. Antibacterial activity and β-lactamase stability of ME1207. Chemotherapy1992; 40: 1-6
30. Ehrhardt AF, Moland ES, Sanders CC. Impact of specific β-lactamase and β-lactamase/porin combinations on the *in vitro* activity of cefditoren in a genetically defined panel [poster no. 374]. 40th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2000 Sep 17-20; Toronto (ON)
31. Craig WA. Interrelationship between pharmacokinetics and pharmacodynamics in determining dosage regimens for broad-spectrum cephalosporins. Diagn Microbiol Infect Dis 1995; 22: 89-96
32. Craig WA, Andes DR. *In vivo* pharmacodynamic activity of cefditoren (CDTR) against *Streptococcus pneumoniae* [poster no. 2248]. 41st Interscience Conference on Antimicrobial Agents and Chemotherapy; Dec 16-19; Chicago 2001
33. Tawara S, Hatano K, Wakai Y, et al. *In vivo* antibacterial activity of FK041, a new orally active cephalosporin. J Antibiot Tokyo 1999; 52: 660-5
34. Sakagami K, Atsumi K, Tamura A, et al. Synthesis and oral activity of ME1207, a new orally active cephalosporin [letter]. J Antibiot Tokyo 1990; 43: 1047-50
35. Tamura A, Ida T, Saito S, et al. The effect of ME1207, a new oral cephalosporin, on-time intestinal microflora of beagle dogs. Chemotherapy 1992; 40: 65-74
36. Shiba K, Maezawa H, Yoshida M, et al. Effects of antacids on pharmacokinetics of cefditoren pivoxil and its metabolism in humans. Chemotherapy 1992; 40 (11): 1310-9
37. Li JT, Hou F, Lu H, et al. Phase I clinical trial of cefditoren pivoxil (ME 1207): pharmacokinetics in healthy volunteers. Drugs Exp Clin Res 1997; 23: 145-50
38. Kuti JL, Quintiliani R. Cefditoren pivoxil. Formulary 2001; 36: 265-75
39. Mayer M, Mulford D, Witt G. Effect of probenicid on the pharmacokinetics of cefditoren [poster no. 945]. 41st Interscience Conference on Antimcrobial Agents and Chemotherapy; 2001 Dec 16-19; Chicago (IL)
40. TAP Pharmaceutical Products Inc. Spectracef™ tablets. Aug 2001. (Data on file)
41. Mayer M, Mulford D, Witt G. Effect of hepatic impairment on the pharmacokinetics of cefditoren [poster no. 312]. 40th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2000 Sep 17-20; Toronto (ON)
42. Mayer M, Mulford D, Witt G. Effect of an H_2 receptor antagonist or an antacid on the pharmacokinetics of cefditoren [poster no. 313]. 40th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2000 Sep 17-20; Toronto (ON)
43. Mulford D, Mayer M, Witt G. Effect of age and gender on the pharmacokinetics of cefditoren [poster no. 310]. 40th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2000 Sep 17-20; Toronto (ON)
44. Mulford D, Mayer M, Witt G. Effect of renal impairment on the pharmacokinetics of cefditoren [poster no. 311]. 40th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2000 Sep 17-20; Toronto (ON)
45. Kneer J. Pharmacokinetic properties of new oral cephalosporins. Med Mal Infect 1992 Jun; 22: 556-64
46. Medeiros AA. Comparison of oral cephalosporins and their activity against β-lactamase-producing bacteria. Infect Dis Clin Pract 1998 Nov; 7: 273-9
47. Mayer M, Mulford D, Witt G. Pharmacokinetics of cefditoren in blister fluid and plasma [abstract no. 656]. 40th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2000 Sep 17-20; Toronto (ON)
48. Kinzig-Schippers M, Hinder M, Göhler K, et al. Tissue penetration of cefditoren (CEE) into bronchial mucosa (BM) and epithelial lining fluid (ELF) in patients undergoing fiberoptic bronchoscopy [poster no. 946]. 41st Interscience Conference on Antimicrobials Agents and Chemotherapy; 2001 Dec 16-19; Chicago (IL)
49. Tucker R, Rhudy J, Hunt B, et al. Safety and efficacy of cefditoren in acute exacerbation of chronic bronchitis (AECB) [abstract no. 836]. 40th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2000 Sep 17-20; Toronto (ON)
50. Bettis R, Agre K, Williamson S, et al. Safety and efficacy of cefditoren in acute bacterial exacerbation of chronic bronchitis. 39th Interscience Conference on Antimicrobial Agents and Chemotherapy, 1999 Sep 26-29; San Francisco (CA), 711
51. Henry DC, Poling TL, Bettis RB, et al. A double-blind, randomized study of cefditoren *vs* cefuroxime for AECB. J Respir Dis 2001; 22 (8): 69-74
52. Gooch W, Marsh D, Stickler T, et al. Cefditoren is safe and effective treatment for streptococcal pharyngitis [abstract no. 837]. 40th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2000 Sep 17-20; Toronto (ON)

53. Millikan L, Hahn H, Hom R, et al. Cefditoren is safe and effective treatment for uncomplicated skin and skin structure infections [abstract no. 1450]. 40th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2000 Sep 17-20; Toronto (ON)
54. Herbert A, Bucko A, Bell V. Cefditoren pivoxil (CDTR) is safe and effective in the eradication of common pathogens in uncomplicated skin and skin structure infections (USSI) [abstract no. 1451]. 40th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2000 Sep 17-20; Toronto (ON)
55. Herbert A, Millikan L, Hunt B, et al. Effectiveness of cefditoren pivoxil (CDTR) in various types of uncomplicated skin and skin structure infections (USSI) [abstract no. 1452]. 40th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2000 Sep 17-20; Toronto (ON)
56. Mulford D, Mayer M, Witt G. Effect of cefditoren on the pharmacokinetics of ethinyl estradiol [poster no. 314]. 40th Interscience Conference on Antimicrobial Agents and Chemotherapy; 2000 Sep 17-20; Toronto (ON)

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