Cefditoren in upper and lower community-acquired respiratory tract infections

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Abstract: This article reviews and updates published data on cefditoren in the evolving scenario of resistance among the most prevalent isolates from respiratory tract infections in the community (Streptococcus pyogenes, Haemophilus influenzae, and Streptococcus pneumoniae). By relating the in vitro activity of cefditoren (in national and multinational surveillance and against isolates with emerging resistant genotypes/phenotypes) to its pharmacokinetics, the cefditoren pharmacodynamic activity predicting efficacy (in humans, animal models, and in vitro simulations) is analyzed prior to reviewing clinical studies (tonsillopharyngitis, sinusitis, acute exacerbations of chronic bronchitis, and community-acquired pneumonia) and the relationship between bacterial eradication and clinical efficacy. The high in vitro activity of cefditoren against the most prevalent respiratory isolates in the community, together with its pharmacokinetics (enabling a twice daily regimen) leading to adequate pharmacodynamic indexes covering all S. pyogenes, H. influenzae, and at least 95% S. pneumoniae isolates, makes cefditoren an antibiotic that will play a significant role in the treatment of respiratory tract infections in the community. In the clinical setting, studies carried out with cefditoren showed that treatments with the 400 mg twice daily regimen were associated with high rates of bacteriological response, even against penicillin-nonsusceptible S. pneumoniae, with good correlation between bacteriological efficacy/response and clinical outcome.

Keywords: cefditoren, Streptococcus pyogenes, Haemophilus influenzae, Streptococcus pneumoniae, community-acquired respiratory tract infections

Scenario for new antibiotics for the treatment of respiratory tract infections

Infections, mainly respiratory tract infections,¹ are the most frequent reason for seeking medical attendance in the community.² Around 85% to 90% of global antibiotic consumption occurs in the community, with 80% of this consumption for the treatment of respiratory tract infections.³ Streptococcus pyogenes causing pharyngotonsillitis, and Streptococcus pneumoniae and Haemophilus influenzae causing otitis and lower respiratory tract infections (acute exacerbations of chronic bronchitis and community-acquired pneumonia), are the most prevalent isolates in community-acquired respiratory tract infections, and can be considered index bacteria for assessing antibiotic resistance.

Several studies carried out in Spain have shown that antibiotic consumption is the main reason for resistance selection in the community.⁴ These studies related consumption of β-lactams (mainly second-generation oral cephalosporins) and macrolides (mainly long half-life macrolides) with penicillin/erythromycin resistance in S. pneumoniae...
(with temporal\(^3\) and geographical\(^6\) associations) and with ampicillin/amoxicillin resistance in \(H.\) \textit{influenzae} (this study showed higher accountability for aminopenicillins with or without clavulanic acid).\(^7\) Other studies showed that macrolide consumption (mainly long half-life macrolides) was linked to erythromycin resistance in \(S.\) \textit{pyogenes}.\(^8,9\)

The Spanish data show that the analysis of resistance in the community should be seen as a global problem, since geographical and temporal relationships between resistance in these target bacteria have been described, leading to the concepts of co-resistance selection and co-selection of resistance. Due to co-resistance selection, there is a significant association between penicillin and erythromycin resistance in \(S.\) \textit{pyogenes}.\(^10,11\) and because of the co-selection of resistance, the penicillin/erythromycin resistance in \(S.\) \textit{pneumoniae} is associated with ampicillin resistance in \(H.\) \textit{influenzae}.\(^10\) Further, this resistance in \(S.\) \textit{pneumoniae} and in \(H.\) \textit{influenzae} is significantly related to erythromycin resistance in \(S.\) \textit{pyogenes} from a geographical perspective.\(^10\) The geographical relationship between macrolide resistance in \(S.\) \textit{pneumoniae} and in \(S.\) \textit{pyogenes} in Spain emphasizes the idea of resistance as a global problem, since \(S.\) \textit{pneumoniae} is isolated mainly from adults, from lower respiratory tract samples, with MLS\(_B\) as the prevalent resistance phenotype, while \(S.\) \textit{pyogenes} is isolated mainly from children, from pharyngotonsillitis, with M-efflux as the prevalent resistance phenotype.\(^10,11\)

The need for new antibiotics is defined mainly by their antimicrobial activity against the prevalent resistance phenotypes, rather than the activity against phenotypes susceptible to antibiotics previously used in the community. The analysis of resistance prevalence and phenotypes reported in index bacteria will define the context in which new antibiotics should demonstrate in vitro activity.

**\(S.\) \textit{pyogenes}**

\(S.\) \textit{pyogenes} is highly susceptible to penicillin (strains with minimum inhibitory concentration [MIC] \(>0.12\) \(\mu\)g/mL have not been found) and should be considered susceptible to all \(\beta\)-lactams. In contrast, resistance to erythromycin is widely reported, with geographical variations in prevalence rates and predominant resistance phenotypes. The rate of erythromycin resistance in \(S.\) \textit{pyogenes} varies among countries, from 6.9\% in the US (56\% MLS\(_B\) phenotype)\(^2\) to 25.6\% in Hong Kong.\(^13\) In a recent study performed in Eastern Europe, the rate of erythromycin resistance in \(S.\) \textit{pyogenes} was low (<10\%) in Romania and Baltic countries, intermediate (10\%–20\%) in Poland and the Czech Republic, and high (>25\%) in Hungary and Slovakia.\(^14\) The predominant (75\%) resistance phenotype was MLS\(_B\) (58.9\% of the constitutive phenotype plus 16.1\% of the inducible phenotype).\(^14\) In Spain, although the rates of erythromycin resistance have decreased in SAUCE (Susceptibility to the Antimicrobials Used in the Community in España) studies over recent years (26.7\% in 1996–1997, 20.4\% in 1998–1999, 24.3\% in 2001–2002, and 19.0\% in 2006–2007), no temporal decreasing trend for erythromycin resistance was found in contrast to an increasing trend in the percentage of the MLS\(_B\) phenotype (7.0\%, 10.5\%, 14.0\%, and 35.5\%, respectively, among resistant strains in the corresponding SAUCE studies).\(^15\)

Since both mechanisms of resistance (M-efflux and MLS\(_B\)) imply resistance to 14- and 15-membered macrolides, erythromycin resistance implies resistance to azithromycin and clarithromycin.\(^16\)

**\(H.\) \textit{influenzae}**

Resistance to \(\beta\)-lactams in \(H.\) \textit{influenzae} is defined using ampicillin as a marker of resistance. Most ampicillin-resistant isolates are \(\beta\)-lactamase producers: TEM-1, TEM-2 and, with lower frequency, ROB-1. The remaining ampicillin-resistant isolates are resistant due to mutations in the \textit{ftsI} gene causing alterations in the amino acid sequences of penicillin-binding protein 3 (PBP3). Resistance phenotypes showing mutations in the \textit{ftsI} gene are BLNAR (\(\beta\)-lactamase negative ampicillin resistant) and BLPACR (\(\beta\)-lactamase positive amoxicillin/clavulanic acid resistant), which exhibits both resistance mechanisms (\(\beta\)-lactamase production and mutations in the \textit{ftsI} gene). These phenotypes should be considered also resistant to amoxicillin/clavulanic acid, ampicillin/sublactam, piperacillin/tazobactam, cefaclor, and cefuroxime.\(^17\)

The epidemiology of ampicillin resistance varies geographically and temporally. In a global surveillance including 15 countries (in 2003–2004), ampicillin resistance ranged from 8.7\% in South Africa to 29.6\% in Asia.\(^18\) In the US, ampicillin resistance averaged about 30\% in the period 2001–2005.\(^19\) In a European surveillance (2004–2005) including isolates from 11 countries, mean ampicillin resistance was 16.4\%, resistance due to \(\beta\)-lactamase production ranging from 17.6\% in France to 0\% in Germany and Netherlands, and BLNAR isolates ranging from 33.9\% in Spain to 0\% in France and Netherlands.\(^20\) In Spain (SAUCE studies: 1996–1997, 1998–1999, 2001–2002, 2006–2007) ampicillin resistance seems to be decreasing over time (38.6\%, 30.0\%, 25.1\%, and 16.1\%, respectively), both resistance due to \(\beta\)-lactamase production (25.7\%, 23.0\%, 20.0\%, and 15.7\%, respectively) and to the BLNAR phenotype.
(13.5%, 12.0%, 4.4%, and 0.7%, respectively). However the rate of BLNAR and BLP ACR among strains exhibiting high MIC of ampicillin (≥1 µg/mL) or amoxicillin/clavulanic acid (≥2/1 µg/mL) is higher, as shown in a Spanish multicenter study carried out in 2005–2007 where among the 196 strains with high MICs identified, 165 showed mutations in the ftsI gene (73% BLNAR and 27% BLP ACR). The situation in Japan is the most worrisome since in nationwide global surveil-lances the percentage of BLNAR and BLP ACR strains was 29.1% and 6.7%, respectively, in adults in 2007 and 59.3% and 6.4%, respectively, in children in 2004.

According to the SAUCE study in 2006–2007, similar susceptibility rates to ampicillin or amoxicillin/clavulanic acid were obtained by applying CLSI (Clinical and Laboratory Standards Institute) and PK/PD breakpoints (pharmacodynamic [PD] breakpoints predicting eradication that are obtained through the relationship between pharmacokinetic [PK] parameters and MIC). In contrast, rates of susceptibility to cefaclor changed from 97.8% (by applying CLSI breakpoints) to 25.8% (PK/PD breakpoints). Similarly, percentages of susceptibility to macrolides were high by applying CLSI breakpoints (99.3% and 100% to clarithromycin and azithromycin, respectively) but sharply decreased to 5.1% and 23.8%, respectively, when PK/PD breakpoints were considered, probably due to the presence of efflux pumps in virtually all H. influenzae strains. This suggests that current CLSI breakpoints for H. influenzae for macrolides should be reviewed.

**S. pneumoniae**

Except for fluoroquinolones (worldwide nonsusceptibility rates to levofoxacin are as low as <2.5%25), antibiotic resistance in S. pneumoniae also depends on geographic location and time, antibiotic pressure (consumption) and the introduction of the 7-valent conjugate vaccine (PCV7 including serotypes most associated with penicillin/erythromycin nonsusceptibility) being the principal influencing factors. In a worldwide surveillance study, penicillin nonsusceptibility was 66% in South Africa, 47.3% in Asia-Pacific, 44.1% in the Middle East, 42.1% in North America, 37.9% in Latin America, and 27.9% in Europe. Penicillin (with CLSI-defined breakpoints for oral penicillin) is the best epidemiological marker since nonsusceptibility rates to β-lactams and to macrolides are clustered in penicillin-intermediate and/or in penicillin-resistant S. pneumoniae. In this sense, in a 2001–2002 surveillance study (mainly including noninvasive isolates) in Spain the reported nonsusceptibility rates to β-lactams and macrolides were around 0% and 15%, respectively, among penicillin-susceptible strains, around 80% for cefaclor, 50% for cefuroxime axetil, and 60% for macrolides among penicillin-intermediate strains, and around 35% for amoxicillin/clavulanic acid, 100% for cefaclor and cefuroxime axetil, 15% for cefotaxime, and 60% for macrolides among penicillin-resistant strains.

Focusing on invasive isolates, the increase in the prevalence of certain serotypes and of penicillin nonsusceptibility, which was reported in the 1980s and 1990s in relation to antibiotic consumption, reversed in the 2000s when PCV7 was introduced for immunization of children. The SAUCE studies in Spain (1996–1997, 1998–1999, 2001–2002, 2006–2007) have shown a decreasing trend for penicillin nonsusceptibility rates (60.0%, 50.2%, 43.9%, and 22.9%, respectively) in contrast to erythromycin nonsusceptibility, which has shown lower variations (36.5%, 34.9%, 34.5%, and 22.9%, respectively), the MLSr resistance phenotype decreasing over time (from 98.4% in 1996–1997 to 81.3% in 2006–2007). Of all invasive isolates received in the Spanish Reference Laboratory for Pneumococci in 2009, 85.3% belonged to serotypes not included in PCV7, around 20% being nonsusceptible to penicillin (=50% of them serotype 19A). Although serotypes 1 and 19A showed significant increasing trends, only serotype 19A was linked to penicillin nonsusceptibility. In this sense, in parallel to the increasing trend for serotype 19A there was an increasing trend for penicillin nonsusceptibility in serotype 19A which reached around 80% in 2008 and was associated with amoxicillin and cefotaxime nonsusceptibility in around 20% of isolates.

The emergence of amoxicillin resistance in pre-existing penicillin-resistant clones has been reported among PCV7 and non-PCV7 serotypes, with troublesome clones (Spain23F-1, Spain9V-3, Spain48-2 and Spain14-5) exhibiting MIC values of amoxicillin higher than of penicillin. In addition, in 2008 a published article described in 9 Romanian isolates of the sequence type ST321 (or the nearest matched type with only a single or double locus variance), belonging to serotypes 23F or 19A, the presence of a new cluster in regions 595–600 of PBP2X together with a new murM allele (with absence of mutations in the conserved domain of PBP1A). These isolates showed MICs of penicillin, amoxicillin, and cefotaxime of ≈16 µg/mL, representing a breakthrough increase in the magnitude of resistance to β-lactams.
Also of great concern is the existence of isolates showing multiple resistance defined as full resistance to 2 or more of the 6 classes of antibacterials represented by penicillin, erythromycin, cefuroxime, tetracyclines, trimethoprim/sulfamethoxazole, and levofloxacin. Multiple resistance in *S. pneumoniae* has been reported at rates as high as 19.1% in North America, 27.7% in Western Europe, and 80.4% in the Far East.25

According to the SAUCE study in 2006–2007, no differences in susceptibility rates were found by applying PK/PD and CLSI breakpoints, with susceptibility rates to macrolides of =80%, to amoxicillin/clavulanic acid of =95%, to cefuroxime axetil of =95%, and to cefotaxime of =100%.15

**Cefditoren: in vitro activity, pharmacokinetics, and pharmacodynamics**

Cefditoren is the active form of cefditoren pivoxil, an oral third-generation aminothiazolyl cephalosporin with structural components similar to those of first- and third-generation cephalosporins.37 In cefditoren, the group attached at the C-7 position of the cephem skeleton affords activity against Gram-negative microorganisms, whereas the one attached at the C-3 position (not seen in other nonfirst-generation cephalosporins) affords activity against Gram-positive bacteria.37 According to the study by Yamada et al on the structure of the PBP2X of *S. pneumoniae* complexed with cefditoren, the unique methylthiazole group of the C-3 side chain of the cephem skeleton fits well into the PBP binding pocket, a feature that is likely to play a role in the high activity of cefditoren against *S. pneumoniae*.38

**In vitro activity**

Cefditoren exhibited high intrinsic activity against *S. pyogenes*, with MIC₅₀/MIC₉₀ values of =0.03/≤0.03 µg/mL, both against macrolide-susceptible or -resistant strains, in a multicenter, multinational study performed in Europe.14 The intrinsic activity of cefditoren was similar against *H. influenzae* (MIC₅₀/ MIC₉₀ = =0.03/≤0.03 µg/mL), as shown in a study carried out in 8 Central and Eastern European countries in 2005–2006.39 This in vitro activity against *H. influenzae* was not influenced by the phenotype/genotype of the isolates, with similar intrinsic activity to cefotaxime against ampicillin-susceptible, beta-lactamase positive, BLNAR, and BLPACR strains (MIC₉₀ values ranging from =0.015 to 0.06 µg/mL).21,40

For *S. pneumoniae* the multicenter, multinational ARISE study carried out in Europe in the pre-PCV7 era (thus including a large number of isolates from serotypes 6, 9, 14, and 23, traditionally linked to resistance) showed MIC₅₀/MIC₉₀ values of cefditoren of =0.03/0.5 µg/mL.41 After PCV7 introduction the prevalence of vaccine serotypes greatly decreased (together with a decrease in penicillin nonsusceptibility),28,29 and in the most recent SAUCE study (2006–2007) MIC₅₀/MIC₉₀ values of cefditoren were =0.015/0.125 µg/mL.15 In parallel there has been a high increase in the prevalence of non-PCV7 serotypes28,29 which occupied the niche left by PCV7 serotypes, leading to a prevalence of 85.3% of non-PCV7 serotypes isolates among invasive isolates in 2009 in Spain.31 Of these, 80% were susceptible to penicillin (MIC₉₀ of cefditoren ≤0.06 µg/mL) and 20% were nonsusceptible (of these, 56.3% for serotype 19A, 9.8% for serotype 24F, 7.0% for serotype 35B, 5.4% for serotype 6A, and 4.4% for serotypes 11A, 15A, and 23B each).31 The intrinsic activity of cefditoren against these penicillin nonsusceptible non-PCV7 serotypes varied on serotype basis: MIC₉₀ of 1 µg/mL for penicillin-resistant and 0.5 µg/mL for penicillin-intermediate serotype 19A isolates, 0.5 µg/mL for serotype 11A, 0.25 µg/mL for serotypes 35B, 6A, and 15A, 0.12 µg/mL for serotype 24F and 0.06 µg/mL for serotype 23B isolates.31

The intrinsic activity of cefditoren was markedly higher than that of other β-lactams against isolates with resistance patterns highly troubling as strains belonging to clones Spain23F-1, Spain9V-3, Spain19A-2, and Spain14-5. Against these strains cefditoren showed MIC₉₀ values ≤1 µg/mL, 1 dilution lower than values for cefotaxime.34 The intrinsic activity of cefditoren against the exceptional strains of sequence type ST321 (serotypes 23F or 19A) with a new cluster in regions 595–600 of PBP2X and a new murM allele warrants special attention.35 These isolates, representing the isolates most resistant to β-lactams described in the literature, were inhibited by 2 µg/mL of cefditoren in contrast to MICs ≥16 µg/mL of penicillin, amoxicillin, and cefotaxime.35

No inoculum effect was observed with cefditoren when testing several clinical isolates of *S. pneumoniae* and *H. influenzae* by determining its in vitro activity using inoculum sizes of 10⁴ to 10⁵ colony forming units (cfu)/mL compared with the one obtained with inocula of 10⁷ to 10⁸ cfu/mL.42

**Pharmacokinetics**

When orally administered to humans the prodrug cefditoren pivoxil is completely and rapidly hydrolyzed to cefditoren, the bioavailability being low in the fasting state (15%–20%). However when administered after high fat meals the bioavailability of cefditoren increases, Cₘₐₓ and AUC values being 50% and 70%, respectively, higher than those determined.
in the fasting state.\textsuperscript{37} In a phase I study in Caucasians administered 400 mg cefditoren pivoxil single dose in the fed state, $C_{\text{max}}$ was 3.7 ± 0.7 μg/mL, $T_{\text{max}}$ was 2 hours, $\text{AUC}_{\infty}$ was 12.5 ± 1.6 μg h/mL, and $t_{1/2}$ was 1.54 ± 0.20 hours.\textsuperscript{43}

**Pharmacodynamics**

By relating pharmacokinetic variables and susceptibility data (ie, antibiotic drug exposure relative to in vitro MIC), PK/PD breakpoints indicate the highest MIC that produces the adequate value for the relevant PK/PD parameter predicting bacterial killing, eradication, and clinical outcome. In the case of cefditoren, pharmacodynamics in relation to community-acquired respiratory tract infections should be studied especially for *S. pneumoniae*, since *H. influenzae* and *S. pyogenes* are uniformly and highly susceptible to cefditoren. For cefditoren, as for β-lactams, the time (t) (expressed as percentage of the dosing interval) that antibiotic concentrations exceed the value of MIC (t > MIC) is the index predicting efficacy with a cut-off value of 40% for clinical cure in humans,\textsuperscript{44,45} although a t > MIC of 33% has been used as bacteriostatic endpoint and susceptibility is defined by the FDA and CLSI as inhibition by usually achievable concentrations of the recommended dose.\textsuperscript{17,46}

Data from a phase I study in Caucasians showed that the 400 mg twice daily regimen of cefditoren pivoxil gave a value of t > MIC for total drug of about 55% for MIC of 0.5 μg/mL, 68% for MIC of 0.25 μg/mL, 81% for MIC of 0.12 μg/mL, and 94% for MIC of 0.06 μg/mL.\textsuperscript{43} Classically the unbound fraction of an antimicrobial has been considered the active fraction in vitro; however the reversibility of protein binding implies that limitation of activity may be far from absolute, even in highly protein bound agents.\textsuperscript{47} For cefditoren, which exhibits 88% protein binding,\textsuperscript{37} this could be postulated as a limitation to its in vivo intrinsic activity. Considering that protein binding rates in humans and mice are equal for cefditoren, the extrapolation to humans of pharmacodynamic data obtained in animal models acquires special interest. A pneumococcal sepsis model in mice infected by strains with exceptionally high cefditoren MIC (1–2 μg/mL) showed that cefditoren t > MIC of ~35% (free t > MIC of ~20%) produced 100% survival in contrast to placebo (0% survival).\textsuperscript{48} Free t > MIC of ~20% was also related to >99.9% reduction in bacterial load (of 2 isolates serotypes 6B and 15A with MIC = 0.25 μg/mL) in an in vitro pharmacodynamic simulation with physiological albumin concentrations and 86% protein binding rate in the device.\textsuperscript{49} In a cefditoren Monte Carlo simulation (using data determined in the phase I study\textsuperscript{43}) considering 33% t > MIC (bacteriostatic endpoint) as endpoint value (approximately the value obtained in the mice model for total drug), strains with MICs up to 0.5 μg/mL were covered by cefditoren.\textsuperscript{46} When applying free drug 33% t > MIC (a value higher than the one required in the mice model for 100% survival and in the pharmacodynamic simulation for >99.9% reduction in bacterial load), strains up to 0.25 μg/mL were covered.\textsuperscript{46} If the classical theoretical value of free t > MIC of 40% was considered, strains up to 0.12 μg/mL were covered by cefditoren in the Monte Carlo simulation.\textsuperscript{46}

According to these data, the cefditoren breakpoint for nonsusceptibility should be within the range ≤0.12 μg/mL and ≤0.5 μg/mL. This latter value has been proposed by several authors considering cefditoren MIC\textsuperscript{90} values lower than the breakpoints values for parenteral third-generation cephalosporins and the pharmacokinetics of cefditoren,\textsuperscript{50–52} and was the breakpoint approved by the Spanish Agency during the registration procedure in Europe (susceptibility ≤0.5 μg/mL).\textsuperscript{53} The most conservative breakpoint (≤0.12 μg/mL) has been proposed by the FDA.\textsuperscript{54} With this breakpoint, 94.9% of *S. pneumoniae* isolates in Spain in 2006–2007 are covered.\textsuperscript{15}

An interesting pharmacodynamic result for cefditoren in the above-mentioned mice model was the decrease in the required t > MIC values producing efficacy when animals were passively immunized (with nonprotective levels of specific antibodies) prior to infection. The required values of t > MIC linked to efficacy decreased from ~35% (free t > MIC of ~20%) in nonimmunized animals to ~25% (free t > MIC of ~15%) in the immunized ones.\textsuperscript{48} This is interesting in the context where specific antibodies (at nonprotective levels) are likely to be present before *S. pneumoniae* infection, since colonization is to some extent a B-cell immunizing event\textsuperscript{55,56} and preventive measures such as pneumococcal vaccination are increasingly been used in the community. The benefit of these findings would not be the decrease of administered doses, but rather the coverage by current regimens of the exceptional strains with high MIC values.

Cefditoren has shown a postantibiotic effect greater than 1 hour for *S. pneumoniae* and *S. pyogenes*, which also supports the twice daily regimen for the treatment of respiratory tract infections.\textsuperscript{57}

**Efficacy clinical studies with cefditoren in the treatment of upper respiratory tract infections**

During the clinical development of cefditoren, 3 comparative multicenter studies were performed with cefditoren...
Efficacy clinical studies with cefditoren in the treatment of community-acquired lower respiratory tract infections

Seven studies were carried out in the clinical development of cefditoren in the treatment of lower respiratory tract infections, 4 studies in community-acquired pneumonia (CAP) and 3 studies in acute exacerbation of chronic bronchitis (AECB). A pooled analysis of data was performed including a total of 4159 randomized patients. Comparators were amoxicillin/clavulanic acid or cefpodoxime in CAP studies, and cefuroxime or clarithromycin in AECB studies. Pooled data from CAP studies revealed no significant differences in response rates between cefditoren and comparators, percentages ranging from 89.2% to 91.8% at the end of therapy and from 85.9% to 90.4% at the end of follow-up.

For microbiological assessment, data from CAP and AECB studies were pooled. Globally, the bacteriologically evaluable population consisted of 1910 patients with 1223 target pathogens isolated prior to treatment initiation, including 406 *S. pneumoniae* isolates (56 of them nonsusceptible to oral penicillin) and 595 *H. influenzae* isolates. No significant differences were found in the rate of bacteriological responders for *S. pneumoniae*, percentages ranging from 88.5% to 92.0%. Among penicillin nonsusceptible (MIC ≥ 0.12 µg/mL) *S. pneumoniae* isolates, all 20 (100%) strains in the cefditoren 400 mg group, 84.2% (16 out of 19) strains in the cefditoren 200 mg group, and 94.1% (16 out of 17) strains in the comparator group were eradicated or presumed eradicated. Among penicillin-resistant (MIC ≥ 2 µg/mL) isolates, 17 (94.4%) of 18 isolates in both ceftoxitin arms were eradicated or presumed eradicated, compared with 10 (90.9%) of 11 in the comparator group. Differences in the rate of responders for *H. influenzae* were also not significant (range 82.7% to 86.6%).

Bacterial eradication as a goal of antibacterial treatment, and subsequent clinical efficacy

The correlation between bacterial eradication and clinical outcome in respiratory tract infections can be explored in streptococcal tonsillopharyngitis as an upper respiratory tract infection and AECB as a lower respiratory tract infection,
since noninvasive samples for culture are easily collected over time. As noted in the previous section, in the pooled analysis of studies on tonsillopharyngitis bacteriological efficacy was associated with a higher clinical response rate. Cefditoren (a β-lactamase-resistant cephalosporin) showed a tendency of higher bacteriological response for S. pyogenes than penicillin (susceptible to β-lactamases produced by commensal flora),

In this context, this article reviews and updates published data on cefditoren in the evolving situation of resistance among the most prevalent isolates from respiratory tract infections in the community. By relating its in vitro activity (from surveillance and in vitro studies including isolates with emerging resistant genotypes/phenotypes) to its pharmacokinetics, the cefditoren pharmacodynamic activity predicting therapeutic efficacy (in humans, animal models, and in vitro simulations) was analyzed prior to reviewing clinical studies and the relationship between bacterial eradication and therapeutic efficacy. The wide range of studies carried out with cefditoren constitutes one of the most extensive and continuous sources of data defining the role of a new antibiotic in the community and provides information to clinicians (on cefditoren and comparators) of relevance to establish empirical therapy.
The high in vitro activity of cefditoren against the most prevalent respiratory isolates in the community, together with its pharmacokinetics (allowing a twice daily regimen) leading to adequate pharmacodynamic indexes covering all S. pyogenes, H. influenzae, and 94.9% S. pneumoniae isolates, makes cefditoren an antibiotic that will play a significant role in the treatment of respiratory tract infections in the community. In the clinical setting, studies carried out with cefditoren showed that treatments with the 400 mg twice daily regimen were associated with high rates of bacteriological response, even against penicillin nonsusceptible S. pneumoniae, with good correlation between bacteriological efficacy/response and clinical outcome.

Disclosure

The authors declare no conflicts of interest.

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Cefditoren and respiratory tract infections


