

# 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,<sup>1</sup> are the most frequent reason for seeking medical attendance in the community.<sup>2</sup> Around 85% to 90% of global antibiotic consumption occurs in the community, with 80% of this consumption for the treatment of respiratory tract infections.<sup>3</sup> *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.<sup>4</sup> These studies related consumption of  $\beta$ -lactams (mainly second-generation oral cephalosporins) and macrolides (mainly long half-life macrolides) with penicillin/erythromycin resistance in *S. pneumoniae*

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(with temporal<sup>5</sup> and geographical<sup>6</sup> associations) and with ampicillin/amoxicillin resistance in *H. influenzae* (this study showed higher accountability for aminopenicillins with or without clavulanic acid).<sup>7</sup> Other studies showed that macrolide consumption (mainly long half-life macrolides) was linked to erythromycin resistance in *S. pyogenes*.<sup>8,9</sup>

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. pneumoniae*,<sup>10,11</sup> and because of the co-selection of resistance, the penicillin/erythromycin resistance in *S. pneumoniae* is associated with ampicillin resistance in *H. influenzae*.<sup>10</sup> Further, this resistance in *S. pneumoniae* and in *H. influenzae* is significantly related to erythromycin resistance in *S. pyogenes* from a geographical perspective.<sup>10</sup> The geographical relationship between macrolide resistance in *S. pneumoniae* and in *S. pyogenes* in Spain emphasizes the idea of resistance as a global problem, since *S. pneumoniae* is isolated mainly from adults, from lower respiratory tract samples, with MLS<sub>B</sub> as the prevalent resistance phenotype, while *S. pyogenes* is isolated mainly from children, from pharyngotonsillitis, with M-efflux as the prevalent resistance phenotype.<sup>10,11</sup>

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. pyogenes*

*S. pyogenes* is highly susceptible to penicillin (strains with minimum inhibitory concentration [MIC] >0.12 µg/mL have not been found) and should be considered susceptible to all β-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. pyogenes* varies among countries, from 6.9% in the US (56% MLS<sub>B</sub> phenotype)<sup>12</sup> to 25.6% in Hong Kong.<sup>13</sup> In a recent study performed in Eastern Europe, the rate of erythromycin resistance in *S. 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.<sup>14</sup> The predominant (75%) resistance phenotype was MLS<sub>B</sub> (58.9% of the constitutive phenotype plus 16.1% of the inducible phenotype).<sup>14</sup> 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<sub>B</sub> phenotype (7.0%, 10.5%, 14.0%, and 35.5%, respectively, among resistant strains in the corresponding SAUCE studies).<sup>15</sup>

Since both mechanisms of resistance (M-efflux and MLS<sub>B</sub>) imply resistance to 14- and 15-membered macrolides, erythromycin resistance implies resistance to azithromycin and clarithromycin.<sup>16</sup>

## *H. influenzae*

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

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.<sup>18</sup> In the US, ampicillin resistance averaged about 30% in the period 2001–2005.<sup>19</sup> In a European surveillance (2004–2005) including isolates from 11 countries, mean ampicillin resistance was 16.4%, resistance due to β-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.<sup>20</sup> 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 β-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).<sup>15</sup> However the rate of BLNAR and BLPACR among strains exhibiting high MIC of ampicillin ( $\geq 1 \mu\text{g/mL}$ ) or amoxicillin/clavulanic acid ( $\geq 2/1 \mu\text{g/mL}$ ) 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% BLPACR).<sup>21</sup> The situation in Japan is the most worrisome since in nationwide global surveillances the percentage of BLNAR and BLPACR strains was 29.1% and 6.7%, respectively, in adults in 2007<sup>22</sup> and 59.3% and 6.4%, respectively, in children in 2004.<sup>23</sup>

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).<sup>15</sup> In contrast, rates of susceptibility to cefaclor changed from 97.8% (by applying CLSI breakpoints) to 25.8% (PK/PD breakpoints).<sup>15</sup> 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,<sup>15</sup> 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.<sup>24</sup>

## *S. pneumoniae*

Except for fluoroquinolones (worldwide nonsusceptibility rates to levofloxacin are as low as  $<2.5\%$ <sup>25</sup>), 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.<sup>26</sup> Penicillin (with CLSI-defined breakpoints for oral penicillin) is the best epidemiological marker since nonsusceptibility rates to  $\beta$ -lactams and to macrolides are clustered in penicillin-intermediate and/or in penicillin-resistant *S. pneumoniae*.<sup>27</sup> In this sense, in a 2001–2002 surveillance study (mainly including noninvasive isolates) in Spain the reported nonsusceptibility rates to  $\beta$ -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.<sup>27</sup>

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.<sup>28,29</sup> The introduction of PCV7 has not only dramatically reduced the incidence of invasive pneumococcal disease but also markedly decreased PCV7 serotypes, thus affecting the rate of penicillin and erythromycin nonsusceptibility in invasive isolates both from children and adults.<sup>29,30</sup> 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  $\text{MLS}_B$  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 ( $\approx 50\%$  of them serotype 19A).<sup>31</sup> Although serotypes 1 and 19A showed significant increasing trends, only serotype 19A was linked to penicillin nonsusceptibility.<sup>31–33</sup> In this sense, in parallel to the increasing trend for serotype 19A<sup>28,32</sup> there was an increasing trend for penicillin nonsusceptibility in serotype 19A<sup>28</sup> which reached around 80% in 2008 and was associated with amoxicillin and cefotaxime nonsusceptibility in around 20% of isolates.<sup>32</sup>

The emergence of amoxicillin resistance in pre-existing penicillin-resistant clones has been reported among PCV7 and non-PCV7 serotypes,<sup>34,35</sup> with troublesome clones (Spain<sup>23F</sup>-1, Spain<sup>9V</sup>-3, Spain<sup>6B</sup>-2 and Spain<sup>14</sup>-5) exhibiting MIC values of amoxicillin higher than of penicillin.<sup>34</sup> 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).<sup>35</sup> These isolates showed MICs of penicillin, amoxicillin, and cefotaxime of  $\geq 16 \mu\text{g/mL}$ ,<sup>35,36</sup> representing a breakthrough increase in the magnitude of resistance to  $\beta$ -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.<sup>25</sup>

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  $\approx 80\%$ , to amoxicillin/clavulanic acid of  $\approx 95\%$ , to cefuroxime axetil of  $\approx 95\%$ , and to cefotaxime of  $\approx 100\%$ .<sup>15</sup>

## 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.<sup>37</sup> 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.<sup>37</sup> 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*.<sup>38</sup>

### In vitro activity

Cefditoren exhibited high intrinsic activity against *S. pyogenes*, with MIC<sub>50</sub>/MIC<sub>90</sub> values of  $\leq 0.03/\leq 0.03$   $\mu\text{g/mL}$ , both against macrolide-susceptible or -resistant strains, in a multicenter, multinational study performed in Europe.<sup>14</sup> The intrinsic activity of cefditoren was similar against *H. influenzae* (MIC<sub>50</sub>/MIC<sub>90</sub> =  $\leq 0.03/\leq 0.03$   $\mu\text{g/mL}$ ), as shown in a study carried out in 8 Central and Eastern European countries in 2005–2006.<sup>39</sup> 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 (MIC<sub>90</sub> values ranging from  $\leq 0.015$  to  $0.06$   $\mu\text{g/mL}$ ).<sup>21,40</sup>

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 MIC<sub>50</sub>/MIC<sub>90</sub> values of cefditoren of  $\leq 0.03/0.5$   $\mu\text{g/mL}$ .<sup>41</sup> After PCV7 introduction the prevalence of vaccine serotypes greatly decreased (together with a decrease in penicillin nonsusceptibility),<sup>28,29</sup> and in the most recent SAUCE study (2006–2007) MIC<sub>50</sub>/MIC<sub>90</sub> values of cefditoren were  $\leq 0.015/0.125$   $\mu\text{g/mL}$ .<sup>15</sup> In parallel there has been a high increase in the prevalence of non-PCV7 serotypes<sup>28,29</sup> 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.<sup>31</sup> Of these, 80% were susceptible to penicillin (MIC<sub>90</sub> of cefditoren  $\leq 0.06$   $\mu\text{g/mL}$ ) 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).<sup>31</sup> The intrinsic activity of cefditoren against these penicillin nonsusceptible non-PCV7 serotypes varied on serotype basis: MIC<sub>90</sub> of 1  $\mu\text{g/mL}$  for penicillin-resistant and 0.5  $\mu\text{g/mL}$  for penicillin-intermediate serotype 19A isolates, 0.5  $\mu\text{g/mL}$  for serotype 11A, 0.25  $\mu\text{g/mL}$  for serotypes 35B, 6A, and 15A, 0.12  $\mu\text{g/mL}$  for serotype 24F and 0.06  $\mu\text{g/mL}$  for serotype 23B isolates.<sup>31</sup>

The intrinsic activity of cefditoren was markedly higher than that of other  $\beta$ -lactams against isolates with resistance patterns highly troubling as strains belonging to clones Spain<sup>23F</sup>-1, Spain<sup>9V</sup>-3, Spain<sup>6B</sup>-2, and Spain<sup>14</sup>-5. Against these strains cefditoren showed MIC<sub>90</sub> values  $\leq 1$   $\mu\text{g/mL}$ , 1 dilution lower than values for cefotaxime.<sup>34</sup> 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.<sup>35</sup> These isolates, representing the isolates most resistant to  $\beta$ -lactams described in the literature, were inhibited by 2  $\mu\text{g/mL}$  of cefditoren in contrast to MICs  $\geq 16$   $\mu\text{g/mL}$  of penicillin, amoxicillin, and cefotaxime.<sup>35</sup>

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  $10^4$  to  $10^5$  colony forming units (cfu)/mL compared with the one obtained with inocula of  $10^7$  to  $10^8$  cfu/mL.<sup>42</sup>

### 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, C<sub>max</sub> and AUC values being 50% and 70%, respectively, higher than those determined



in the fasting state.<sup>37</sup> In a phase I study in Caucasians administered 400 mg cefditoren pivoxil single dose in the fed state,  $C_{\max}$  was  $3.7 \pm 0.7 \mu\text{g/mL}$ ,  $T_{\max}$  was 2 hours,  $\text{AUC}_{\infty}$  was  $12.5 \pm 1.6 \mu\text{g} \times \text{h/mL}$ , and  $t_{1/2}$  was  $1.54 \pm 0.20$  hours.<sup>43</sup>

### 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  $\beta$ -lactams, the time (t) (expressed as percentage of the dosing interval) that antibiotic concentrations exceed the value of MIC ( $t > \text{MIC}$ ) is the index predicting efficacy with a cut-off value of 40% for clinical cure in humans,<sup>44,45</sup> although a  $t > \text{MIC}$  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.<sup>17,46</sup>

Data from a phase I study in Caucasians showed that the 400 mg twice daily regimen of cefditoren pivoxil gave a value of  $t > \text{MIC}$  for total drug of about 55% for MIC of  $0.5 \mu\text{g/mL}$ , 68% for MIC of  $0.25 \mu\text{g/mL}$ , 81% for MIC of  $0.12 \mu\text{g/mL}$ , and 94% for MIC of  $0.06 \mu\text{g/mL}$ .<sup>43</sup> 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.<sup>47</sup> For cefditoren, which exhibits 88% protein binding,<sup>37</sup> 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 ( $1\text{--}2 \mu\text{g/mL}$ ) showed that cefditoren  $t > \text{MIC}$  of  $\approx 35\%$  (free  $t > \text{MIC}$  of  $\approx 20\%$ ) produced 100% survival in contrast to placebo (0% survival).<sup>48</sup> Free  $t > \text{MIC}$  of  $\approx 20\%$  was also related to  $>99.9\%$  reduction in bacterial load (of 2 isolates serotypes 6B and 15A with MIC =  $0.25 \mu\text{g/mL}$ ) in an in vitro pharmacodynamic simulation with physiological albumin concentrations and 86% protein binding rate in the device.<sup>49</sup> In a cefditoren Monte Carlo simulation (using data determined in the phase I study<sup>43</sup>) considering 33%  $t > \text{MIC}$

(bacteriostatic endpoint) as endpoint value (approximately the value obtained in the mice model for total drug), strains with MICs up to  $0.5 \mu\text{g/mL}$  were covered by cefditoren.<sup>46</sup> When applying free drug 33%  $t > \text{MIC}$  (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  $0.25 \mu\text{g/mL}$  were covered.<sup>46</sup> If the classical theoretical value of free  $t > \text{MIC}$  of 40% was considered, strains up to  $0.12 \mu\text{g/mL}$  were covered by cefditoren in the Monte Carlo simulation.<sup>46</sup>

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

An interesting pharmacodynamic result for cefditoren in the above-mentioned mice model was the decrease in the required  $t > \text{MIC}$  values producing efficacy when animals were passively immunized (with nonprotective levels of specific antibodies) prior to infection. The required values of  $t > \text{MIC}$  linked to efficacy decreased from  $\approx 35\%$  (free  $t > \text{MIC}$  of  $\approx 20\%$ ) in nonimmunized animals to  $\approx 25\%$  (free  $t > \text{MIC}$  of  $\approx 15\%$ ) in the immunized ones.<sup>48</sup> 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<sup>55,56</sup> 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.<sup>57</sup>

## 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

and penicillin V as comparator in pharyngotonsillitis in patients  $\geq 12$  years of age. The three studies included a total of 1322 randomized patients, with 1241 patients in the intention-to-treat (ITT) analysis and 1010 patients in the per-protocol (PP) population. In the pooled analysis of the three studies, no significant differences in clinical response were found between cefditoren and penicillin V, success rates ranging from 89.4% to 95.3%.<sup>58</sup> Eradication of *S. pyogenes* was higher with cefditoren at the end of therapy (90.4% vs 82.7%;  $P = 0.002$ ) and at the end of follow-up (84.7% vs 76.7%;  $P = 0.008$ ), although the statistical significance set at  $P < 0.001$  was not reached.<sup>58</sup>

Two additional studies have been recently published for cefditoren in the treatment of group A  $\beta$ -hemolytic streptococcal pharyngotonsillitis in children.<sup>59,60</sup> Ozaki et al reported a study comparing 3 mg/kg cefditoren-pivoxil 3 times daily for 5 days versus amoxicillin 10 mg/kg 3 times daily for 10 days in 258 patients (258 isolates with amoxicillin and cefditoren MIC  $\leq 0.06$   $\mu\text{g/mL}$ ).<sup>59</sup> Eradication was 100% with amoxicillin and 99% with cefditoren pivoxil, with no differences in the recurrence rate (15 patients in the amoxicillin arm and 8 patients in the cefditoren arm).<sup>59</sup> The second study compared the efficacy provided by 9 mg/kg cefditoren pivoxil (maximum dose 300 mg/day) 3 times daily for 5 days (77 patients) versus 10 days (149 patients) in children with history of at least 1 episode of group A  $\beta$ -hemolytic streptococcal pharyngotonsillitis.<sup>60</sup> Similar bacteriological failure occurred in both arms (9.1% vs 11.4%), but significantly higher recurrences were found in the 5 days treatment group (9.1% vs 0.7%;  $P = 0.03$ ).<sup>60</sup>

Three studies were carried out in adults with acute sinusitis during the clinical development of cefditoren, using cefuroxime or amoxicillin/clavulanic acid as comparators. The three studies included 1819 randomized patients: 1726 patients included in the ITT and 1589 patients in the PP population. In the pooled analysis of the three studies, no differences in clinical response were found between cefditoren and comparators both at the end of therapy (80.2% vs 84.8%) and at the end of follow-up (71.2% vs 77.4%).<sup>58</sup> An additional study in the treatment of bacterial rhinosinusitis in children was recently published comparing 4 to 6 mg/kg twice daily (maximum dose 300 mg/day) versus 80 to 90 mg/kg (on amoxicillin basis) amoxicillin/clavulanic acid (maximum dose 800 mg/day) twice daily for 14 days.<sup>61</sup> Rates of improvement were similar in both groups (78.8% vs 84.7%) with similar relapse rates (9.1% vs 11.1%) or recurrences (3.0% vs 5.6%) of sinus symptoms.<sup>61</sup>

## 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.<sup>62</sup> 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 of responders 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.<sup>62</sup> Pooled data from the AECB studies resulted in response rates ranging from 85.8% to 91.3% at the end of therapy and from 81.2% to 83.3% at the end of follow-up, without significant differences between groups.<sup>62</sup>

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.<sup>62</sup> 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  $\geq 0.12$   $\mu\text{g/mL}$ ) *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.<sup>62</sup> Among penicillin-resistant (MIC  $\geq 2$   $\mu\text{g/mL}$ ) isolates, 17 (94.4%) of 18 isolates in both cefditoren arms were eradicated or presumed eradicated, compared with 10 (90.9%) of 11 in the comparator group.<sup>62</sup> Differences in the rate of responders for *H. influenzae* were also not significant (range 82.7% to 86.6%).<sup>62</sup>

## 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.<sup>58</sup> Cefditoren (a  $\beta$ -lactamase-resistant cephalosporin) showed a tendency of higher bacteriological response for *S. pyogenes* than penicillin (susceptible to  $\beta$ -lactamases produced by commensal flora),<sup>58</sup> reinforcing the concept of “co-pathogenicity” with  $\beta$ -lactamase-producing bacteria. It has been hypothesized that  $\beta$ -lactamase from  $\beta$ -lactamase-producing isolates such as *H. influenzae* may protect non- $\beta$ -lactamase-producing isolates such as *S. pyogenes* from the action of the antibiotic.<sup>63,64</sup> In this sense, a previous meta-analysis also showed higher bacteriological failures with penicillins versus cephalosporins.<sup>65</sup> Co-pathogenicity was also explored in vitro in a pharmacodynamic simulation of free concentrations over 24 hours obtained with 875 mg amoxicillin 3 times daily, 875/125 mg amoxicillin/clavulanic acid 3 times daily, and 400 mg cefditoren twice daily using individual and mixed inocula (proportions 1:1:1:1) of 1 *S. pyogenes* isolate, 1 penicillin-resistant *S. pneumoniae*, 1  $\beta$ -lactamase positive *H. influenzae*, and 1 BLPACR *H. influenzae* isolate.<sup>66</sup> At 24 hours amoxicillin was able to eradicate *S. pyogenes* in simulations carried out with the individual *S. pyogenes* inoculum but failed to do so in simulations with the mixed inocula where *S. pyogenes* was protected by  $\beta$ -lactamases produced by the *H. influenzae* isolates.<sup>66</sup> In contrast *S. pyogenes* was eradicated by cefditoren, both in individual and mixed simulations where both strains of *H. influenzae* were also eradicated.<sup>66</sup>

One of the AECB studies included in the pooled analysis of lower respiratory tract infections<sup>62</sup> exploring the relationship of bacteriological and clinical responses has been individually published.<sup>67</sup> In this study, including 541 patients, inclusion criteria, baseline characteristics of patients (age and pre-study smoking history), and the required symptoms of exacerbation (Anthonisen I and II) ensured inclusion of patients with underlying chronic bronchitis, and increased the chance of the bacterial origin of the exacerbation. Improvement/efficacy was more evident in signs linked to the presence of bacteria, such as rales, ronchi, and the volume and purulence of the sputum (which decreased from about 80% patients in the pre-treatment visit to about 10% patients at day 30) than in signs linked to chronic structural damage such as dyspnea which decreased from only about 99% in the pre-treatment visit to 75% patients at day 30.<sup>67</sup> Globally, per-pathogen bacterial response related well to clinical success: 83.5% isolates (out of 164 baseline isolates) from patients

resulting in clinical response were eradicated or presumably eradicated in contrast to only 3% isolates (out of 33 baseline isolates) from patients resulting in clinical failure.<sup>67</sup>

## Safety data from clinical trials performed during the clinical development of cefditoren

Safety data from all the 13 clinical trials carried out during the clinical development of cefditoren for the treatment of community-acquired respiratory infections were analyzed in a pooled analysis.<sup>68</sup> Safety population was defined as all randomized patients with at least 1 dose intake, and comprised 4592 patients for cefditoren.<sup>68</sup> Cefditoren exhibited an adverse event profile similar to that of previous antibiotics currently used in the treatment of community-acquired respiratory tract infections, diarrhea being the most frequent adverse event (9.9%) followed by vaginosis (3.9% among female population), nausea (3.5%), abdominal pain (1.8%), and dyspepsia (1.1%).<sup>68</sup>

## Conclusions

The pharmaceutical industry has decreased its efforts to develop new antimicrobials, and the lack of a robust pipeline of new compounds has been suggested.<sup>69</sup> In this situation, the fact that the main ecological effect of antimicrobials is promoting the emergence of resistance<sup>70</sup> (a risk associated with the imprudent use of available drugs) implies that clinicians may have limited options within the current armamentarium. Since the use of agents to which pathogens are resistant contributes to increased morbidity, mortality, and associated expenses,<sup>71</sup> the rational use of antibiotics can help to stop or minimize the emergence, spread, and diversification of antibiotic resistance.

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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