**ABSTRACT**

Cefditoren is a third-generation oral cephalosporin with good activity against respiratory tract pathogens, including penicillin-intermediate and -resistant strains of *S. pneumoniae*, and betalactamase producing strains of *H. influenzae* and *M. catarrhalis*. Its antibacterial activity, measured by minimum inhibitory concentration (MIC), is similar or superior to that of many other commonly used antibiotics (penicillins, cephalosporins and fluoroquinolones). Considering the target attainment of T>MIC of ≥40%, a reliable predictor of clinical and microbiologic outcomes, cefditoren covers strains of *S. pneumoniae* with MIC values ≤0.5 μg/mL and ≤1 μg/mL in the case of doses of 200 mg and 400 mg, respectively, and all strains of *H. influenzae*. Cefditoren has been associated with high rates of bacteriologic response among the main causative pathogens in lower respiratory tract infection (= 85% against *H. influenzae* and =90% against *S. pneumoniae*, including penicillin-intermediate and penicillin-resistant strains). It is a reliable option for switch therapy in case of treatment with third-generation intravenous cephalosporin. Cefditoren is currently approved in Spain for the treatment of adults and adolescents with acute exacerbations of chronic bronchitis (AECB) and community-acquired pneumonia (CAP), two of the lower respiratory tract infections most commonly encountered in clinical practice.

**Key words: Cefditoren, Respiratory tract infections, Haemophilus influenzae, Streptococcus pneumoniae.**

**RELEVANCE AND CURRENT SITUATION OF LOWER RESPIRATORY TRACT INFECTIONS**

Community-acquired lower respiratory tract infections, represented by pneumonia and acute exacerbations of chronic bronchitis (AECB), are a first order sanitary problem in developed countries due to their incidence, mortality, morbidity and the subsequent antibiotic consumption. Up to 80% of antibiotic consumption in the community is for the treatment of respiratory infections. This figure acquires higher relevance if we take into account that 80-90% of all antibiotic consumption occurs in the community.

Nowadays pneumonia is the first cause of mortality due to infectious diseases and the sixth cause of death in developed countries. AECB presents high morbidity, decreases the quality of life of patients with chronic obstructive pulmonary disease (COPD), and represents the principal cause of death in these...
patients and a frequent cause of consultation in hospital emergency departments, although with seasonality variations\(^4\)\(^-\)\(^6\).

*Streptococcus pneumoniae* remains the main aetiological agent of community-acquired pneumonia (CAP)\(^7\), being responsible for approx. 50% of cases. The importance of other aetiological agents depends on the age of the patients. *Haemophilus influenzae* causes around 10% cases\(^8\). The prevalence of *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* acquires relevance in CAP not requiring hospitalisation, but with great geographical variations\(^9\). Out of epidemic outbreaks, *Legionella pneumophila* represents only 1-5% of all CAP cases\(^10\).

With respect to AECB, *H. influenzae*, *S. pneumoniae* and *Moraxella catarrhalis* are present in more than 70% cases (\(H.\) *influenzae* in 30-35%, *S. pneumoniae* in 20% and *M. catarrhalis* in 15%)\(^11,12\).

Several surveillance studies have analysed over time susceptibility of respiratory pathogens in Spain. In the larger study most recently published, resistance prevalence in *S. pneumoniae* was: 20% to penicillin, more than 30% to macrolides and over 25% to second generation cephalosporins. Non-susceptibility to quinolones and amoxicillin-clavulanic acid was lower than 5% and only 0.4% to cefotaxime\(^13\) (table 1). With respect to *H. influenzae* and *M. catarrhalis*, production of betalactamases is found in 20-30% (TEM-1, TEM-2, and ROB-1) and 99% (BRO-1, BRO-2 and BRO-3) strains, respectively, implying resistance to ampicillin and amoxicillin-clavulanate\(^13-16\). In *H. influenzae* this mechanism of resistance also implies resistance to other oral betalactams commonly used in the treatment of community-acquired respiratory tract infections as cefaclor (\(\approx\)18%)\(^13\) (table 1). In this microorganism, non-betalactamase-mediated resistance to penicillin is due to alterations in PBP3 (protein binding penicillin 3), a resistance mechanism present in the so-called BLNAR (betalactamase negative ampicillin resistant) isolates, with lower prevalence in Spain (1.2-12%) and compromising susceptibility to amoxicillin-clavulanic acid and second generation cephalosporins (cefclor and cefuroxime-axetil)\(^13-16\). Resistance to clarithromycin in *H. influenzae* was approximately 27%\(^13\) (table 1).

When instead of microbiological breakpoints defined by the Clinical and Laboratory Standards Institute (CLSI), to categorise an isolate as resistant, we use the value of the pharmacodynamic parameter that best predicts bacterial eradication (\(T>\)minimal inhibitory concentration (MIC) for betalactams, erythromycin and clarithromycin, and \(\text{AUC}_{24\text{h}}/\text{MIC}\) for quinolones and azithromycin) resistance rates are higher\(^17-19\). In *S. pneumoniae* resistance rates are 4% to sustained-release amoxicillin-clavulanate, 8% to amoxicillin-clavulanate and levofloxacin, 33% to cefuroxime-axetil, 35-40% to macrolides and 60% to cefaclor. In *H. influenzae* resistance rates are 4% to amoxicillin-clavulanate, 24% to ampicillin, 27% to cefuroxime-axetil, 98% to azithromycin and cefaclor, and 99% to clarithromycin\(^13,18,19\) (table 1), showing great differences in resistance rates by using pharmacodynamic versus microbiological criteria. According to pharmacodynamic criteria, only amoxicillin-clavulanate and quinolones remain useful.

In last years therapeutic options for the treatment of respiratory tract infections have been reduced due to bacterial resistances limiting the use of some antibiotics (penicillins, second generation cephalosporins and macrolides) and the withdrawal of other compounds due to toxicity problems, as occurred with some fluoroquinolones and telithromycin. Nowadays, amoxicillin-clavulanate or a fluoroquinolone (levofloxacin or moxifloxacin) are the only adequate empirical oral treatments.

| Table 1 | Resistance rates (%) in *S. pneumoniae* and *H. influenzae* following microbiological and PK/PD breakpoints\(^13\) |
| --- | --- | --- |
| Antibiotic | CLSI | PK/PD |
| Penicillin | 20.0 | - |
| Amoxicillin-clavulanate | 4.4 | 7.8 (4.4)* |
| Cefaclor | 36.0 | 59.5 |
| Cefuroxime | 25.6 | 32.6 |
| Cefotaxime | 0.4 | 3.3 |
| Erythromycin | 34.5 | 35.2 |
| Azithromycin | 34.5 | 39.8 |
| Ciprofloxacin | 4.6 | 22.2 |


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\(\text{AUC}_{24\text{h}}/\text{MIC}\): area under the concentration-time curve over 24 hours divided byMIC.
values implying high probability of bacterial eradication and subsequent cure.

**CEFIDITOREN IN LOWER RESPIRATORY TRACT INFECTIONS**

Cefditoren-pivoxil is a new oral third-generation cephalosporin with adequate microbiological, pharmacokinetic/pharmacodynamic (PK/PD), efficacy and safety profiles for the treatment of community-acquired lower respiratory tract infections\[^{20}\].

**Microbiology**

In most cases, the antimicrobial treatment of lower respiratory tract infections is empirical, both at hospital level (microbiological studies are not indicated except in severe cases or nonresponding patients) and at community level (due to the lack of microbiology facilities)\[^{21,22}\]. Therefore the election of antibiotic treatments is based on the most frequent aetiological agents causing each lower respiratory infection and on local susceptibility patterns. Other factors to be considered are safety, drug interactions, dosing, treatment compliance, costs, etc. The microbiological spectrum of cefditoren covers, with the exception of atypical bacterial, all bacterial respiratory pathogens in the community, including penicillin- and drug-resistant pneumococci, betalactamase-producing *M. catarrhalis* and *H. influenzae*, BLNAR *H. influenzae* isolates and also enterobacteria present in some patients with comorbidities\[^{23-25}\].

The in vitro activity is one of the most important factors in antibiotic election, since it shows good correlation with clinical efficacy\[^{26}\]. The in vitro activity is assessed by the minimal antibiotic concentration needed to inhibit 90% isolates (MIC\[^{90}\]) and is used as a measure of antibiotic potency. In the ARISE (Antimicrobial Resistant Isolates in Southern European Countries) study, *S. pneumoniae* and *H. influenzae* isolates collected in Spain were inhibited by concentrations of cefditoren lower than those of the other antibiotics tested (cefditoren MIC\[^{90}\] = 0.5 µg/ml for *S. pneumoniae* and ≤0.03 µg/ml for *H. influenzae*). For *S. pneumoniae* the intrinsic activity of cefditoren was two-times higher than that of levofloxacin and cefotaxime (MIC\[^{90}\] = 1 µg/ml), four-times higher than that of cefpodoxime and amoxicillin-clavulanate (MIC\[^{90}\] = 2 µg/ml), eight-times higher than that of amoxicillin (MIC\[^{90}\] = 4 µg/ml), 16-times higher than that of cefuroxime (MIC\[^{90}\] = 8 µg/ml), and more than 32-times higher than that of macrolides (MIC\[^{90}\] ≥16 µg/ml)\[^{32}\] (table 2). Lastly, its activity against *M. catarrhalis* (MIC\[^{90}\] = 0.25 µg/ml) is somehow lower than that of levofloxacin (MIC\[^{90}\] ≤0.06 µg/ml), similar to that of macrolides (MIC\[^{90}\] 0.12 -0.25 µg/ml) and amoxicillin-clavulanate (MIC\[^{90}\] =0.25 µg/ml), and higher to that of other betalactamams (cefotaxime and cefpodoxime (MIC\[^{90}\] =0.5 µg/ml), cefuroxime (MIC\[^{90}\] =2 µg/ml) and amoxicillin (MIC\[^{90}\] =8 µg/ml)\[^{22}\].

**Pharmacokinetics/Pharmacodynamics**

Following oral administration, cefditoren-pivoxil is absorbed through passive diffusion and hydrolized by estearases to the active compound, cefditoren. Under fasting conditions, bioavailability of cefditoren is 15-20%, but this bioavailability increases when administered with a high fat meal, thus increasing the maximal concentration in serum (Cmax) and the area under the concentration-time curve in serum (AUC) by 50% and 70%, respectively. The volume of distribution is 9.3 l and the protein binding is 88%. The Cmax value is 2.8 µg/ml after 200 mg administration and 4.6 µg/ml after 400 mg administration. With this last dose, concentrations in bronchial mucosa are 0.6-1 µg/g. As most betalactams, cefditoren is mainly eliminated unchanged by excretion into urine, with an elimination half-life of 1.5h\[^{20,33}\].

To assess the pharmacodynamic potential of an antibiotic against target bacteria, the relation between the in vitro activity and pharmacokinetics is determined. From the pharmacodynamic perspective, concentrations of cefditoren reached in serum after dosing (200-400 mg/12h) provide values of T>MIC of at least 40% of the dosing interval. Since the serum concentration of cefditoren is maintained along 6h (50% dosing interval) over 1

### Table 2

Susceptibility of *S. pneumoniae* and *H. influenzae* in terms of MIC\[^{90}\] (µg/ml)

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th><em>S. pneumoniae</em></th>
<th><em>H. influenzae</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefditoren</td>
<td>0.5</td>
<td>≤0.03</td>
</tr>
<tr>
<td>Cefotaxime</td>
<td>1 (x 2)*</td>
<td>≤0.03</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>1 (x 2)*</td>
<td>≤0.06</td>
</tr>
<tr>
<td>Cefpodoxime</td>
<td>2 (x 4)*</td>
<td>≤0.12</td>
</tr>
<tr>
<td>Amoxicillin-clavulanate</td>
<td>2 (x 4)*</td>
<td>1</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>4 (x 8)*</td>
<td>8</td>
</tr>
<tr>
<td>Cefuroxime</td>
<td>8 (x 16)*</td>
<td>2</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>≥16 (x 32)*</td>
<td>4</td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>≥256</td>
<td>8</td>
</tr>
</tbody>
</table>

*No. of times that cefditoren activity was higher than the activity of the referred antibiotic

MIC\[^{90}\] : Minimal inhibitory concentration for 90% isolates
The adequate PK/PD profile of cefditoren, subsequent to its high intrinsic activity against *S. pneumoniae* and *H. influenzae*, increases the probability of bacterial eradication that is the primary objective of the treatment of respiratory tract infections because of its correlation with therapeutic outcome and prevention of resistances, thus offering a potential ecological benefit. Bacterial eradication should be the main goal in CAP treatment, while in AECB the goal should be the maximal reduction of bacterial load driving to resolution of the exacerbation, increase in the time free of symptoms between exacerbations, decrease in bronchial damage and bacterial variability, and a lower risk for emergence and spread of resistances.

### Clinical efficacy and safety

Seven prospective studies have been performed with cefditoren in the treatment of lower respiratory tract infections: six comparative, double-blind and randomised studies, and one non-comparative study. Four were CAP studies and three AECB studies, including a total of 4,159 patients. No significant differences in clinical and bacteriological responses were found between the two cefditoren regimens or between cefditoren and comparators, both in CAP and AECB studies.

In the per-pathogen analysis no significant differences were found in the microbiological response for *S. pneumoniae* (penicillin-susceptible, intermediate or resistant), *H. influenzae* and *M. catarrhalis* (both including beta-lactamase-positive strains). It should be highlighted the high rates of bacteriological response obtained: 90% for *S. pneumoniae* (including penicillin-susceptible, intermediate-susceptible and resistant strains), and 85% for *H. influenzae* (including beta-lactamase-positive strains).

Infections caused by penicillin-susceptible or penicillin-intermediate *S. pneumoniae*, the microbiological response was 92.3% (36 out of 39), and the three failures corresponded to the 200 mg cefditoren treatment arm. In those caused by penicillin-resistant *S. pneumoniae*, the microbiological response was 94.4% (17 out of 18). This pooled analysis, despite its limitations (differences in study design, definitions of CAP and AECB, exclusion criteria and resistance prevalences between study sites), offers an analysis of microbiological response, the main goal of antibiotic therapy in the treatment of lower respiratory tract infections.

With respect to safety, reported adverse events were: 24.4% for 200 mg cefditoren, 26.7% for 400 mg cefditoren and 25.9% for comparators, being gastrointestinal adverse events the most frequent (14.2%, 19.5% and 16.9%, respectively). A sequential therapy with cefditoren

### Sequential therapy with cefditoren

Sequential therapy, the switch from intravenous to oral treatment, reduces length of hospitalisation, risk of nosocomial infections and hospital expenses, improving the quality of life of the patient. Sequential therapy has demonstrated to be safe and free of risks in patients showing clinical stability (oral tolerance, absence of fever, tachypnea, tachycardia and no alterations in other hemodynamic parameters, mental status and oxygen saturation).

Prior to the switch to oral treatment, the results of microbiological tests, the antimicrobial spectrum of the oral antibiotic, the severity of the infection and the presence of bacteremia should be considered. Some scientific societies recommend a minimal duration of intravenous treatment of 2-4 days and to only discharge the patient, switching to oral therapy, 24h after the clinical stability is reached.

Adequate oral antibiotics for sequential therapy are those with an spectrum and intrinsic activity similar to that of the previous intravenous antibiotic, and a pharmacodynamic profile providing the adequate PK/PD value predicting bacterial eradication and subsequent cure. If the initial intravenous therapy has been efficacious, the best option is to continue with the same drug as oral formulation, although this is not always possible. With fluoroquinolones (levofloxacin, moxifloxacin) sequential therapy is easily performed due to the high bioavailability of these drugs, making bioequivalent intravenous and oral formulations. Oral amoxicillin/clavulanate is the natural switch for its intravenous formulation, although against target *S. pneumoniae* only the 875/125 mg/8h and the 2000/125 mg/12h regimens provide T>MIC of >40%.

Cefditoren is the best switch for intravenous third-generation cephalosporins (cefotaxime, ceftriaxone) due to its similar spectrum, higher bioavailability. Cefditoren should be used as a switch in infections caused by beta-lactamase-producing *H. influenzae* and *S. pneumoniae*.
intrinsic activity and adequate T>MIC that is not provided by cefuroxime\textsuperscript{13,19,27,32,58}.

Conclusions

Cefditoren is considered a first election antibiotic in the empirical treatment of respiratory infections for which election of adequate treatments was, up to now, limited to amoxicillin/clavulanate and fluoroquinolones, and no new antibiotics are expected in the following years. The in vitro antibacterial activity of cefditoren, equal or higher than that of other oral antibiotics, and the high probability of eradication based on obtained T>MIC values of at least 40\%, assures in Spain its activity against 100\% \textit{H. influenzae} isolates, and nearly 100\% pneumococci with MIC ≤1 µg/ml with the 400mg/12h regimen, and 94\% pneumococci with MIC ≤0.5 µg/ml with the 200mg/12h regimen.

REFERENCES


