Review

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Cefditoren and community-acquired lower respiratory tract infections

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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*.

RESUMEN

Cefditoren es una cefalosporina oral de tercera generación con buena actividad frente a los patógenos respiratorios, incluidos *S. pneumoniae* con sensibilidad disminuida y resistente a penicilina, y *H. influenzae* y *M. catarrhalis* productores de betalactamasas. Su actividad antibacteriana, medida por concentración mínima inhibitoria (CMI), es similar o superior a otros antibióticos habitualmente utilizados (penicilinas, cefalosporinas y fluoroquinolonas). El parámetro T>CMI por encima del 40% entre dosis consecutivas, que es el que mejor predice los resultados clínicos y microbiológicos, se logra con cefditoren para *S. pneumoniae* con CMI ≤0,5 μg/ml y ≤1 μg/ml con dosis de 200 mg y 400 mg, respectivamente, y en el 100% de los casos de *H. influenzae* y *M. catarrhalis*. Cefditoren produce una alta tasa de erradicación bacteriológica entre los principales patógenos causales de las infecciones del tracto respiratorio inferior (≈85% frente a *H. influenzae* y ≈90% frente a *S. pneumoniae*, incluidos los de sensibilidad intermedia y resistentes a penicilina). Es una opción muy apropiada para la terapia secuencial en caso de tratamiento con cefalosporinas de tercera generación intravenosa. Cefditoren está actualmente aprobado en España para el tratamiento de las infecciones del tracto respiratorio inferior del adulto y adolescente: exacerbación de la enfermedad pulmonar obstructiva crónica (EPOC) y neumonía comunitaria.

Palabras clave: Cefditoren, Infección respiratoria, *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 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[1,2].

Nowadays pneumonia is the first cause of mortality due to infectious diseases and the sixth cause of death in developed countries[3]. 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

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Table 1 **Resistance rates (%) in *S. pneumoniae* and *H. influenzae* following microbiological and PK/PD breakpoints[13]**

	S. pneumoniae		*H. influenzae*		
Antibiotic	CLSI	PK/PD	CLSI	PK/PD	Antibiotic
Penicillin	20.0	-	25.1	24.0	Ampicillin
Amoxicillin-clavulanate	4.4	7.8 (4.4)*	0.1	4 (0.1)*	Amoxicillin-clavulanate
Cefaclor	36.0	59.5	17.9	98.6	Cefaclor
Cefuroxime	25.6	32.6	0.0	27.2	Cefuroxime
Cefotaxime	0.4	3.3	0.0	97.8	Azithromycin
Erythromycin	34.5	35.2	27.7	98.8	Clarithromycin
Azithromycin	34.5	39.8	0.0	0.0	Ciprofloxacin
Ciprofloxacin	4.6	22.2			

*For amoxicillin-clavulanate 2000/125 mg (sustained-release). CLSI: breakpoints established by the Clinical and Laboratory Standards Institute; PK/PD: pharmacokinetic/pharmacodynamic breakpoints.

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 *Chlamydophila 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 was 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[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 (≈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 (cefaclor 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 AUC_{24h}/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. Due to this, new compounds as cefditoren are welcome. Among the desired characteristics for new antimicrobials stand above others a spectrum covering isolates resistant to previous compounds, a higher in vitro activity and pharmacodynamic

values implying high probability of bacterial eradication and subsequent cure.

CEFDITOREN 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)[27] (table 2). This higher in vitro activity of cefditoren was also found against pneumococci non-susceptible to penicillin, amoxicillin, cefuroxime and erythromycin[28-30], and is related with the structural conformational change produced by cefditoren in the structure of its target (PBP2x) that is different than the one produced by other cephalosporins[31]. The intrinsic activity of cefditoren against *H. influenzae* is similar to the one of cefotaxime (MIC_{90} ≤0.03 µg/ml) and higher to that of levofloxacin (MIC_{90} ≤0.06 µg/ml), cefpodoxime (MIC_{90} ≤0.12 µg/ml), amoxicillin-clavulanate (MIC_{90} =1 µg/ml), cefuroxime (MIC_{90} =2 µg/ml), amoxicillin (MIC_{90} =8 µg/ml) and macrolides (MIC_{90} =4 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 betalactams [cefotaxime and cefpodoxime (MIC_{90} =0.5 µg/ml), cefuroxime (MIC_{90} =2 µg/ml) and amoxicillin (MIC_{90} =8 µg/ml)][32].

Table 2 Susceptibility of *S. pneumoniae* and *H. influenzae* in terms of MIC_{90} (µg/ml)

Antibiotic	*S. pneumoniae*	*H. influenzae*
Cefditoren	0.5	≤0.03
Cefotaxime	1 (x 2)*	≤0.03
Levofloxacin	1 (x 2)*	≤0.06
Cefpodoxime	2 (x 4)*	≤0.12
Amoxicillin-clavulanate	2 (x 4)*	1
Amoxicillin	4 (x 8)*	8
Cefuroxime	8 (x 16)*	2
Erythromycin	≥16 (≥ x 32)*	4
Clarithromycin	≥256	8

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

MIC_{90}: Minimal inhibitory concentration for 90% isolates

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

	MIC_{90}		
	≤0.25	0.5	1
% isolates with MIC (ARISE study)	82.7%	11.3%	5.8%
% T>MIC (200 mg/12h)	>50%	37%	25%
% T>MIC (400 mg/12h)	>65%	55%	44%

Figure 1 **Percentage of T>minimal inhibitory concentration (MIC) for 200 and 400 mg/12h cefditoren in relation to MIC_{90} for *S. pneumoniae* strains included in the ARISE study[19,27,34,35]**

µg/ml after 400 mg dosing and 0.5 µg/ml after 200 mg dosing, the target T>MIC value of 40% is achieved for *S. pneumoniae* strains inhibited by ≤1 µg/ml and ≤0.5 µg/ml cefditoren concentrations, respectively[19,34,35] (figure 1). According to cefditoren MIC distribution for *S. pneumoniae* in the ARISE study, 94% of isolates fall within the therapeutic range for the 200 mg dose and 99% for the 400 mg dose[19,27,32]. With respect to *H. influenzae*, since the cefditoren MIC_{90} is ≤0.03 µg/ml, 100% of isolates are covered by the pharmacodynamic breakpoints above mentioned[19,32,34,35].

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[36-38]. Bacterial eradication should be the main goal in CAP treatment, while in AECB the goal should be the maximal reduction in 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[38-43].

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[44-49]. 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 betalactamase-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 betalactamase-positive strains). In 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 antibacterial therapy in the treatment of lower respiratory tract infections[49].

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)[49,50].

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)[51-53].

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[53]. 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[54].

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[55,56]. 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[57]. 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%[13,58]. Cefditoren is the best switch for intravenous third-generation cephalosporins (cefotaxime, ceftriaxone) due to its similar spectrum, higher

intrinsic activity and adequate T>MIC that is not provided by cefuroxime[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% *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

1. Huovinen P, Cars O. Control of antimicrobial resistance: time for action. The essentials of control are already well known. BMJ 1998;317:613-14.
2. McCaig LF, Hughes JM. Trends in antimicrobial drug prescribing among office-based physicians in the United States. JAMA 1995;273:214-9.
3. Bartlett JG, Dowell SF, Mandell LA, File TM Jr, Musher DM, Fine MJ. Practice guidelines for the management of community-acquired pneumonia in adults. Clin Infect Dis 2000;31:347-82.
4. Seemungal TA, Donaldson GC, Paul EA, Bestall JC, Jeffries DJ, Wedzicha JA et al. Effect of exacerbation on quality of life in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1998;157:1418–22.
5. Burrows B, Earle RH. Course and prognosis of chronic obstructive lung disease: a prospective study of 200 patients. N Engl J Med 1969;280:397–404.
6. Ballester F, Pérez-Hoyos S, Rivera ML, Merelles T, Tenías JM, Soriano JB et al. Patrones de frecuentación y factores asociados al ingreso en el hospital de las urgencias hospitalarias por asma y enfermedad pulmonar obstructiva crónica. Arch Bronconeumol 1999;35:20-6.
7. Aspa J, Rajas O, de Castro FR. Pneumococcal antimicrobial resistance: therapeutic strategy and management in community-acquired pneumonia. Expert Opin Pharmacother 2008;9:229-41.
8. García-Rodríguez JA, Muñoz JL. Etiología de la infección respiratoria. Med Clin Monogr (Barc) 2004;5:2-5.
9. Cunha BA. The atypical pneumonias: clinical diagnosis and importance. Clin Microbiol Infect 2006;12 (Supl. 3):12–24.
10. Bouza E, Rodríguez-Creisems M. ¿Son las quinolonas los fármacos de elección en la neumonía causada por microorganismos del género Legionella? Enferm Infect Dis Microbiol Clin 1999;17 (Supl. 1):19-23.
11. Ball P. Epidemiology and treatment of chronic bronchitis and its exacerbations. Chest 1995;108 (Supl. 2):43-52.
12. Sethi S. Infectious etiology of acute exacerbations of chronic bronchitis. Chest 2000;117:S380–5.
13. Pérez-Trallero E, García de la Fuente C, García Rey C, Baquero F, Aguilar L, Dal Ré R et al. Geographical and ecological analysis of resistance, coresistance, and coupled resistance to antimicrobials in respiratory pathogenic bacteria in Spain. Antimicrob Agents Chemother 2005; 49:1965-72.
14. Marco F, Garcia de Lomas J, Garcia-Rey C, Bouza E, Aguilar L, Fernández Mazarrasa C et al. Antimicrobial susceptibilities of 1,730 Haemophilus influenzae respiratory tract isolates in Spain in 1998–1999. Antimicrob Agents Chemother 2001;45:3226–28.
15. Aracil B, Gómez Garcés JL, Alós JI y Grupo de Estudio de Infección en Atención Primaria de la SEIMC. Sensitivity of Haemophilus influenzae isolates in Spain to 17 oral antibiotics [Article in Spanish]. Enferm Infecc Microbiol Clin 2003;21:131-6.
16. Cantón R, Morosini MI, Loza E, Gómez G. de la Pedrosa E. Infecciones comunitarias. Patrones de sensibilidad a los antimicrobianos utilizados por vía oral de los microorganismos más comunes. Rev Clin Esp 2008;208 (Supl. 3):3-11.
17. Jacobs MR. How can we predict bacterial eradication? Int J Infect Dis 2003;7 (Supl. 1):S13-20.
18. Soriano F. Importancia de los parámetros farmacocinéticos y farmacodinámicos en la elección del tratamiento antimicrobiano de la infección respiratoria. Med Clin Monogr (Barc) 2004;5:6-11.
19. Giménez MJ, Gómez-Lus ML, Valdés L, Aguilar L. Situación de la cefalosporina oral de tercera generación cefditoreno pivoxil en el tratamiento de la infección comunitaria del adulto. Rev Esp Quimioterap 2005;18:210-18.
20. Wellington K, Curran MP. Cefditoren pivoxil: a review of its use in the treatment of bacterial infections. Drugs 2004;64:2597-618.
21. Tratamiento antibiótico empírico inicial de la neumonía adquirida en la comunidad el paciente adulto inmunocompetente. Rev Esp Quimioter 2003;16:457-66.
22. Tercer documento de consenso sobre el uso de antimicrobianos en la agudización de la enfermedad pulmonar obstructiva crónica. Rev Esp Quimioter 2007;20:93-105.
23. Barberán J, Giménez MJ, Aguilar L, Prieto J. Evidencia científica y concepción global del tratamiento empírico de la infección de vías respiratorias bajas en la comunidad. Rev Esp Quimioter 2004;17:317-24.
24. Karlowsky JA, Critchley IA, Draghi DC, Jones ME, Thornsberry C, Sahm DF. Activity of cefditoren against beta-lactamase -positive and -negative Haemophilus influenzae and Moraxella catarrhalis. Diagn Microbiol Infect Dis 2002;42:53-8.
25. Lerma M, Cebrián L, Giménez MJ, Coronel P, Gimeno M, Aguilar L et al. B-lactam susceptibility of Escherichia coli isolates from urinary tract infections exhibiting different resistance phenotypes. Rev Esp Quimioter 2008;21:149-52.
26. Mattie H. Kinetics of antimicrobial action. Rev Infect Dis. 1981;3:19-27.
27. Soriano F, Granizo JJ, Fenoll A, Gracia M, Fernandez-Roblas R, Esteban J et al. Antimicrobial resistance among clinical isolates of Streptococcus pneumoniae isolated in four southern European countries (ARISE project) from adult patients: results from the cefditoren surveillance program. J Chemother 2003;15:107-12.
28. Pérez-Trallero E, Marimón JM, Ercibengoa M, Giménez MJ, Coronel P, Aguilar L. Antimicrobial susceptibilities of amoxycillin-nonsusceptible and susceptible isolates among penicillin-non-

susceptible Streptococcus pneumoniae. Clin Microbiol Infect 2007;13:937-40.
29. Fenoll A, Aguilar L, Robledo O, Gimenez MJ, Tarragó D, Granizo JJ et al. Influence of the -lactam resistance phenotype on the cefuroxime versus cefditoren susceptibility of Streptococcus pneumoniae and Haemophilus influenzae recovered from children with acute otitis media. Journal of Antimicrobial Chemotherapy 2007;60:323–7.
30. Fenoll A, Giménez MJ, Robledo O, Aguilar L, Tarragó D, Granizo JJ et al. In vitro activity of oral cephalosporins against pediatric isolates of Streptococcus pneumoniae non-susceptible to penicillin, amoxicillin or erythromycin. J Chemother 2008;20:175-9.
31. Yamada M, Watanabe T, Miyara T, Baba N, Saito J, Takeuchi Y et al. Crystal structure of cefditoren complexed with Streptococcus pneumoniae penicillin-binding protein 2X: structural basis for its high antimicrobial activity. Antimicrob Agents Chemother 2007;51:3902-7.
32. Soriano F, Granizo JJ, Coronel P, Gimeno M, Rodenas E, Gracia M et al. Antimicrobial susceptibility of Haemophilus influenzae, Haemophilus parainfluenzae and Moraxella catarrhalis isolated from adult patients with respiratory tract infections in four southern European countries. The ARISE project. Int J Antimicrob Agents 2004;23:296-9.
33. Li JT, Hou F, Lu H, Li TY, Li H. Phase I clinical trial of cefditoren pivoxil (ME 1207): Pharmacokinetics in healthy volunteers. Drugs Exp Clin Res 1997;23:145-50.
34. Eiros Bouza JM, Valdés Verelst L, Bachiller Luque MR. Contribución de la farmacodinamia en la elección antimicrobiano para las exacerbaciones de la EPOC. Rev Esp Quimioter 2006;19:220-30.
35. Sádaba B, Azanza JR, Quetglas EG, Campanero MA, Honorato J, Coronel P, Gimeno M. Pharmacokinetic/pharmacodynamic serum and urine profile of cefditoren following single-dose and multiple twice- and thrice-daily regimens in healthy volunteers: a phase I study. Rev Esp Quimioter 2007;20:51-60.
36. Ball P, Baquero F, Cars O, File T, Garau J, Klugman K et al. Consensus Group on Resistance and Prescribing in Respiratory Tract Infection. Antibiotic therapy of community respiratory tract infections: strategies for optimal outcomes and minimized resistance emergence. J Antimicrob Chemother 2002;49:31-40.
37. Dagan R, Klugman KP, Craig WA, Baquero F. Evidence to support the rationale that bacterial eradication in respiratory tract infection is an important aim of antimicrobial therapy. J Antimicrob Chemother 2001;47:129-40.
38. Clark CL, Nagai K, Dewasse BE, Pankuch GA, Ednie LM, Jacobs MR et al. Activity of cefditoren against respiratory pathogens. J Antimicrob Chemother 2002;50:33-41.
39. Sethi S, Murphy TF. Bacterial infection in chronic obstructive pulmonary disease in 2000: a state-of-the-art review. Clin Microbiol Rev 2001;14:336-63.
40. Chodosh S. Clinical significance of the infection-free interval in the management of acute bacterial exacerbations of chronic bronchitis. Chest 2005;127:2231-6.
41. Wilkinson TM, Patel IS, Wilks M, Donalson GC, Weidzcha JA. Airway bacterial load and FEV1 decline in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2003;167:1090-5.
42. Miravitlles M. Exacerbations of chronic obstructive pulmonary disease: when are bacteria important? Eur Resp J 2002;20 (Supl. 36): 9-19.
43. Donaldson GC, Seemungal TA, Bhowmik A, Wedzicha JA. Relationship between exacerbation frequency and lung function decline in chronic obstructive pulmonary disease. Thorax 2002;57:847-52.
44. Alvarez-Sala JL, Kardos P, Martinez-Beltran J, Coronel P, Aguilar L and the Cefditoren AECB Working Group. Clinical and bacteriological efficacy in treatment of acute exacerbations of chronic bronchitis with cefditoren-pivoxil versus cefuroxime-axetil. Antimicrob Agents Chemother 2006;50:1762-7.
45. van Zyl L, le RouxJG, LaFata JA, Volk RS, Palo WA, Flamm R et al. Cefditoren pivoxil versus cefpodoxime proxetil for community acquired pneumonia: Results of a multicenter, prospective, randomized, double-blind study. Clin Ther 2002;24:1840-53.
46. Fogarty CM, Cyganowski M, Palo WA, Hom RC, Craig WA. A comparison of cefditoren pivoxil and amoxicillin/clavulanate in the treatment of community-acquired pneumonia: A multicenter, prospective, randomized, investigator-blinded, parallel group study. Clin Ther 2002;24:1854-70.
47. Ramirez JA, Tucker RM, Bettis RB. Treating acute exacerbations of chronic bronchitis. J Res Dis 2001;22(Supl. 8):75-80.
48. Henry DC, Poling TL, Bettis RB. A double-blind, randomized study of cefditoren vs cefuroxime for AECB. J Respir Dis 2001;22(Supl. 8):69-74.
49. Granizo JJ, Giménez MJ, Barberán J, Coronel P, Gimeno M, Aguilar L. The efficacy of cefditoren pivoxil in the treatment of lower respiratory tract infections, with a focus on the per-pathogen bacteriologic response in infections caused by Streptococcus pneumoniae and Haemophilus influenzae: A pooled analysis of seven clinical trials. Clin Ther 2006;28:2061-9.
50. Granizo J, Aguilar L, Giménez M, Coronel P, Gimeno M, Prieto J. Safety profile of cefditoren: A pooled analysis of data from clinical trials in community-acquired respiratory tract infections. Rev Esp Quimioter 2009;22:57-61.
51. Halm EA, Fine MJ, Marrie TJ, Coley CM, Kapoor WN, Obrosky DS et al. Time to clinical stability in patients hospitalized with community-acquired pneumonia. Implications for practice guidelines. JAMA 1998;279:1452-7.
52. Siegel RE, Halpern NA, Almenoff PL, Lee A, Cashin R, Greene JA. A prospective randomized study of inpatient iv. antibiotics for community-acquired pneumonia. The optimal duration of therapy. Chest 1996;110:965-71.
53. Reyes Calzada S, Martínez Tomás R, Menéndez Villanueva R. Pacientes Hospitalizados con infección del tracto respiratorio inferior: ventajas del tratamiento secuencial. Med Clin Monogr (Barc) 2006;7:30-5.
54. Niederman MS, Mandell LA, Anzueto A, Bass JB, Broughton WA, Campbell GD, et al. Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. Am J Respir Crit Care Med 2001;163:1730–54.
55. Carratalá J, Navas E, San Juan R, Soliano F, Rodríguez V. Guía de Recomendaciones en la Terapia Secuencial Antibiótica (TSA). En: Aguado JM, Fortún J. Guías Clínicas SEIMC 2006. www.seimc.org.

56. Sevinç F, Prins JM, Koopmans RP, Langendijk PN, Dankert J, Speelman P. Early switch from intravenous to oral antibiotics: Guidelines and implementation in a teaching hospital. J Antimicrob Chemother 1999;43:601-6.
57. Odenholt I, Cars O. Pharmacodynamics of moxifloxacin and levofloxacin against Streptococcus pneumoniae, Staphylococcus aureus, Klebsiella pneumoniae and Escherichia coli: simulation of human plasma concentrations after intravenous dosage in an in vitro kinetic model. J Antimicrob Chemother 2006;58: 960–5.
58. Candel González FJ. ¿Cuál es el tratamiento más adecuado como continuación de las cefalosporinas parenterales? Emergencias 2006;18:207-14.