

# The role of cefditoren in the treatment of lower community-acquired respiratory tract infections (LRTIs): from bacterial eradication to reduced lung inflammation and epithelial damage

F. DI MARCO, F. BRAIDO<sup>1</sup>, P. SANTUS<sup>2</sup>, N. SCICHILONE<sup>3</sup>, F. BLASI<sup>4</sup>

Department of Health Sciences, Respiratory Unit, San Paolo Hospital, University of Milan, Italy

<sup>1</sup>Respiratory and Allergology Unit, Department of Internal Medicine (DiMI), IRCCS Azienda Ospedaliera Universitaria San Martino, Genoa, Italy

<sup>2</sup>Department of Health Sciences, University of Milan, IRCCS Pulmonary Rehabilitation Fondazione Salvatore Maugeri, Milan, Italy

<sup>3</sup>Biomedical Department of Specialist and Internal Medicine (Di.Bi.M.I.S.), Respiratory Unit, University of Palermo, Italy

<sup>4</sup>Department of Pathophysiology and Transplantation, University of Milan, IRCCS Fondazione Ca Granda, Milan, Italy

*Fabiano Di Marco and Fulvio Braido contributed equally to this article*

**Abstract. – OBJECTIVES:** Lower respiratory tract infections (LRTIs), including pneumonia and acute exacerbations of Chronic Obstructive Pulmonary Disease (COPD), are among the most common diagnoses in both outpatient and inpatient settings. Due to the burden of LRTIs healthcare providers must adopt practices focused on improving outcomes with the aim to reduce treatment failure and antibiotic resistances. Moreover, the role of acute and chronic infection in the pathogenesis of COPD has received considerable attention, since chronic infection can contribute to airways inflammation and COPD progression. This review discusses the role of cefditoren for the treatment of LRTIs, compared with the definition of “appropriate” of the WHO as “the cost-effective use of antimicrobials which maximizes clinical therapeutic effect while minimizing both drug-related toxicity and the development of antimicrobial resistance”.

**RESULTS AND CONCLUSIONS:** Cefditoren appears to meet the definition of “appropriate” for the treatment of LRTIs. In fact, this molecule shows an adequate pharmacokinetic profile without the need for any adjustment also in aged patients with mild renal impairment or mild-to-moderate hepatic dysfunction. The low drug-drug interaction potential of cefditoren can be an advantage also in poly-treated patients. The antimicrobial spectrum of cefditoren includes both Gram+ and Gram- bacteria, with high activity against *Streptococcus pneumoniae*, including drug-resistant strains, *Haemophilus influenzae* and *Moraxella catarrhalis*. Last, recent findings suggested that cefditoren can be a valid alternative to levofloxacin in outpatients with acute ex-

acerbation of COPD; in this setting a treatment with cefditoren showed to be associated with a significant reduction of some key inflammatory markers involved in epithelial damage, including KL-6 and IL-6.

*Key Words:*

Cefditoren, Community acquired pneumonia, Acute exacerbation of chronic obstructive pulmonary disease, Cephalosporin.

## Introduction

Lower respiratory tract infections (LRTIs), including pneumonia and acute exacerbations of chronic obstructive pulmonary disease (COPD), are one of the most common diagnoses in both outpatient and inpatient settings, represent the most common reason for seeking medical attention, and are the most frequent indication for antibiotic use<sup>1</sup>.

Due to the burden of LRTIs on morbidity and mortality, healthcare providers must adopt practices aimed at improving outcomes, including a careful use of antibiotics, in order to reduce treatment failure and the onset of antibiotic resistances. Moreover, the role of acute and chronic infections in the pathogenesis of COPD has recently received considerable attention, with the potential benefit of decreasing inflammatory biomarkers in acute exacerbation of COPD.

This review is aimed at underlying the appropriate use of antimicrobials, as defined by the World Health Organization (WHO) as “the cost-effective use of antimicrobials which maximizes clinical therapeutic effect while minimizing both drug-related toxicity and the development of antimicrobial resistance”<sup>2</sup>; furthermore, this article updates published data on cefditoren, from microbiology to clinical efficacy/safety, and discusses its role in the control of bronchial inflammation in patients with COPD exacerbation<sup>3</sup>.

### ***The Burden of Acute Exacerbation of COPD and Community Acquired Pneumonia (CAP)***

LRTIs represent one of the leading infectious causes of death worldwide and account for substantial use of healthcare resources<sup>4,5</sup>. Welte et al<sup>6</sup> have recently published a review on the available evidence which concerns clinical and economic burden of CAP among adults in Europe. The annual incidence of CAP is around 1.7 cases per 1000 population with a clear age-related increase. The estimated incidence of CAP in Italy ranges from 0.8/1000/year in patients younger than 64 years to 4.8 in those older than 64 years. When looking at the relationship between patient’s mortality and presence of comorbidity, COPD and other lung diseases deserve a relevant role, with CAP being more common in individuals who smoke cigarettes and/or have COPD<sup>7</sup>.

The European Respiratory Society and The Lung Health Foundation estimated a European overall cost due to pneumonia to be as high as 10.1 billion euro: 5.5 related to hospitalization, 0.2 to drugs, 4.1 to indirect cost and outpatients care. From an hospital perspective, the major determinant of costs were the length of hospital stay and admissions to the intensive care unit, whereas costs for staff were the major contributors to direct costs<sup>8</sup>. Interestingly, a retrospective study<sup>9</sup> showed that a shorter length of hospital stay did not show an increased readmission rate and post discharge mortality, while mortality was significantly higher in patients who were not treated according to current guidelines recommendations<sup>10,11</sup>.

COPD is one of the most important causes of morbidity and mortality overall the world with a prevalence expected to increase rapidly in the near future<sup>12</sup>. Patients with COPD typically experience acute exacerbation, which may result in hospitalization. The exact definition of acute exacerbation of COPD is an acute worsening of the

patient’s condition from the stable state, which is sustained and may warrant the patients to seek for additional treatment<sup>13</sup>. Among patients with severe COPD admitted in hospital for an acute exacerbation of the disease, the in-hospital mortality rate is 10%, rises to 30% in the following two months and reaches 49% at 2 years<sup>5</sup>. Most exacerbations are associated with bronchial infection<sup>14-16</sup>, a condition that have negative impact on the quality of life of COPD patients if they are frequent.

It has been estimated that exacerbations of chronic bronchitis are caused in 50-80% of cases by bacterial infections which can respond to antibiotic therapy<sup>3</sup>. Some Authors<sup>17</sup> have demonstrated that bacterial infection is present in 48.2% of patients with moderate-severe stable COPD, and this figure rises to 69.9% during exacerbations, when the bacterial concentration in the airways rises. Patients with a history of frequent exacerbations show an increase of inflammation in the upper airways, and bacterial concentration represents a major causal factor for this inflammatory state<sup>18</sup>. Chronic bacterial inflammation can, therefore, contribute to inflammation in COPD patients and to the progression of disease, as it acts as a direct inflammatory stimulus<sup>18</sup>. The reduction of the serum concentration of systemic markers of inflammation (e.g. IL-6, IL-8, CRP, TNF-alfa) is correlated with an improvement of symptoms, clinical conditions and pulmonary function after exacerbations<sup>3,19</sup>. The association between neutrophil inflammation, purulent exudate and bacterial exacerbations is well-established and represents a strong rationale for the use of antibiotic therapy during COPD exacerbations<sup>20</sup>.

COPD is a disease that brings significant economic and social costs for drugs, diagnostic procedures, disease follow-up, out-patients management, emergency ward, and hospitalizations, with approximately 80% of the total costs related to exacerbation management<sup>21,22</sup>.

These data illustrate the importance of a correct antibiotic management of both acute exacerbation of COPD and CAP, conditions which are associated with a significant economic and social burden, mainly in case of failure of the therapy that requires hospitalization.

### ***Antibiotic Therapy in the Resistance Era: the Need for New Molecules***

The onset of resistance to antibiotic therapy by pathogens of the upper airways represents an emerging issue. Data collected in 2011 by the

European Antimicrobial Resistance Surveillance Network (EARS-Net) show that in Italy, 5-10% of *Streptococcus pneumoniae* strains are resistant to penicillin, while 30% are resistant to macrolides<sup>23</sup>. In this scenario – which can be attributed, at least in part, to a sometimes inappropriate use of available antibiotics – it becomes interesting to evaluate the recent introduction of cefditoren, an oral, third-generation cephalosporin: the use of a new antibiotic for the therapy of respiratory infections can reduce treatment failures and contribute to prevent the spread of bacterial resistances<sup>3</sup>.

Cefditoren, an oral cephalosporin with a broad spectrum of activity against Gram-positive and Gram-negative bacterial species has structural components similar to those of first and third-generation cephalosporins. The group attached at the C-7 position of the cephem skeleton retains activity against Gram-negative microorganisms, whereas the group attached at the C-3 position, not present in other non-first-generation cephalosporins, affords activity against Gram-positive bacteria. Like other  $\beta$ -lactam agents, cefditoren inhibits the synthesis of cell walls by binding to penicillin-binding proteins: this binding results in the loss of cell wall integrity and a subsequent rapid cellular death. Alterations of amino acids in significant penicillin-binding pro-

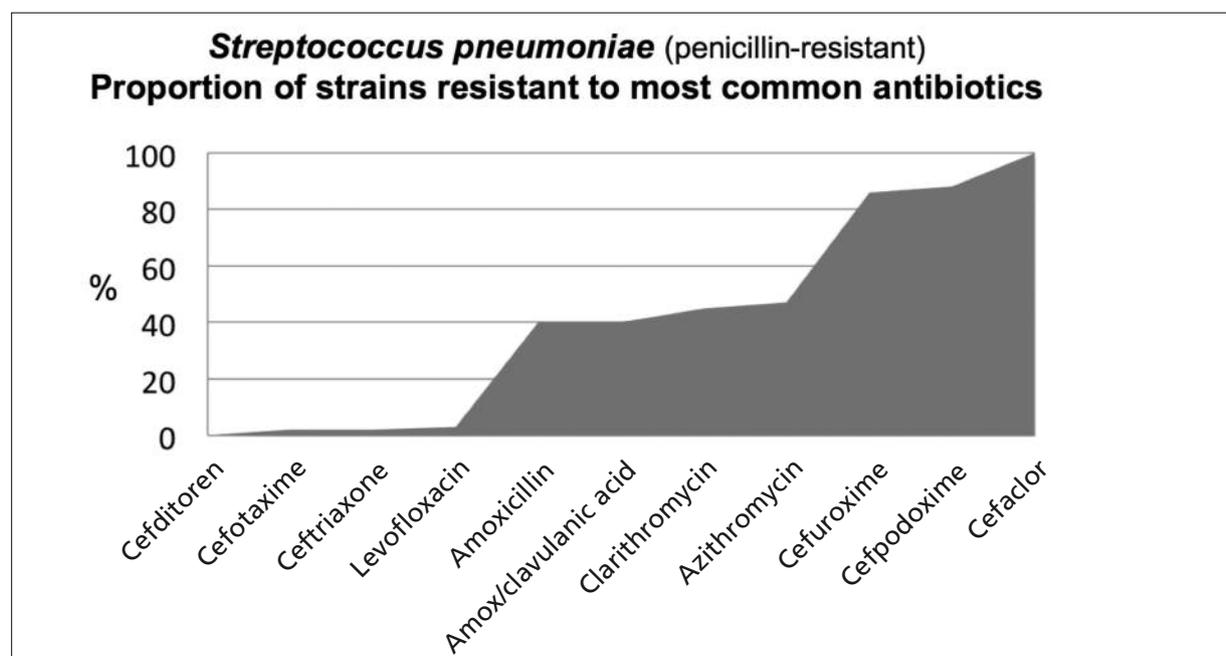
teins result in increased minimum inhibitory concentration (MIC) values for cefditoren and other  $\beta$ -lactam agents<sup>24,25</sup>.

Noteworthy, a recent epidemiological study, conducted in Italy, has documented the lack of resistance to cefditoren of penicillin-resistant strains of *Streptococcus pneumoniae*, differing from other cephalosporins, some macrolides and fluoroquinolones (Figure 1)<sup>26</sup>.

#### Pharmacokinetics of Cefditoren

Cefditoren is the active form of cefditoren pivoxil. After oral administration, the prodrug cefditoren pivoxil is rapidly and completely hydrolyzed by esterases as it passively diffuses through the intestinal membrane to form cefditoren and pivalate<sup>27</sup>. In fasting patients, the oral bioavailability of cefditoren pivoxil ranges from 15% to 20%, but when administered with high-fat meals, the mean maximum concentration ( $C_{max}$ ) and area under the concentration-time curve (AUC) values increases to 50% and 70%, respectively<sup>27</sup>.  $C_{max}$  and AUC values after administration of Cefditoren pivoxil 400 mg twice daily for 7 days are similar to those after a single dose, thus, indicating that accumulation of the drug does not occur.

Since  $\beta$ -lactam have a time-dependent efficacy, it is necessary to maximize the exposure of



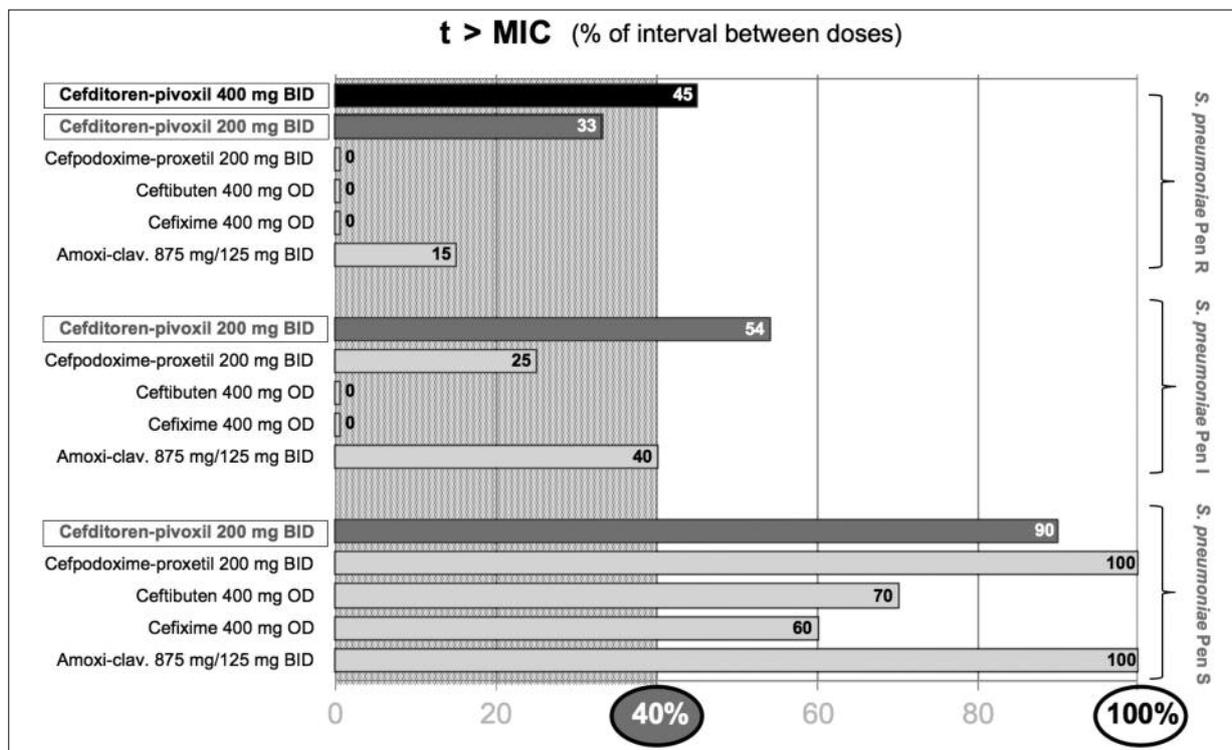
**Figure 1.** Bacterial resistance of penicillin-resistant *Streptococcus pneumoniae* strains in Italy against most commonly-used antibiotics used for the treatment of respiratory infections (modified from<sup>26</sup>).

bacteria to the molecule by increasing the time of serum concentrations over MIC ( $t > \text{MIC}$ ), expressed as percentage of the time interval between doses. Cephalosporins should have a  $t > \text{MIC}$  of 40% to exert a bacteriostatic effect, while higher  $t > \text{MIC}$  lead to a bactericidal effect. In adults, the recommended dose of cefditoren is 400 mg/day (Daily Defined Dose according to WHO), in two administrations of 200 mg every 12 hours, in order to increase  $t > \text{MIC}$ . At this dose, can exert activity also against sustained infections by *S. pneumoniae* strains with intermediate resistance to penicillin ( $\text{MIC}_{90} = 0.5 \text{ mg/L}$ ;  $t > \text{MIC} = 54.0\%$ ), and a doubling of daily dose increases  $t > \text{MIC}$  up to 44.1% (Figure 2)<sup>28,29</sup>.

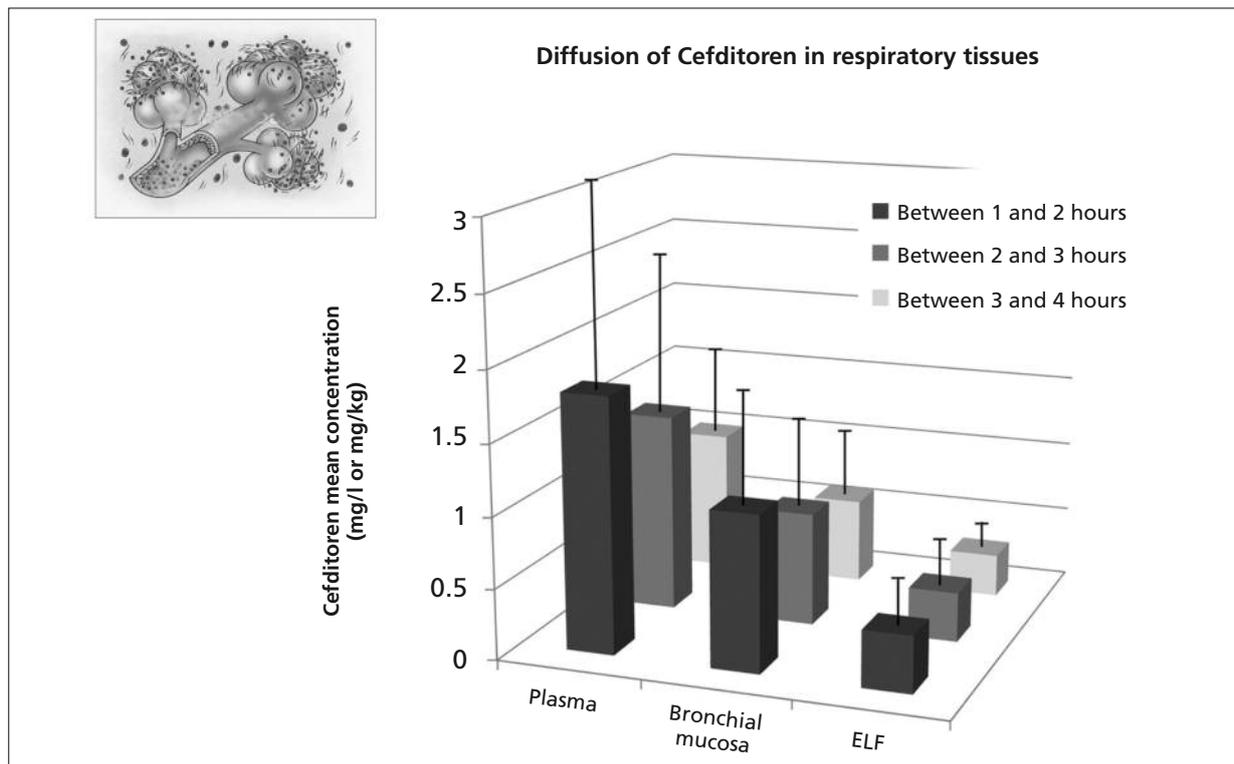
Cefditoren is widely distributed and penetrates into bronchial mucosa, and epithelial lining fluid. Between 1 and 4 hours after a single 400 mg dose of cefditoren pivoxil in patients undergoing fibre-optic bronchoscopy, mean cefditoren concentration in bronchial mucosa (0.56-1.04 mg/kg) and epithelial lining fluid (0.30-0.39 mg/L) were therapeutically relevant (tissue-to-plasma concentration ratios at 4 hours were 0.545 and 0.318, respectively) (Figure 3)<sup>27</sup>.

Both age and gender can affect the pharmacokinetics of cefditoren, but these variations are not considered clinically relevant; thus dose adjustment is not recommended. Only moderate (creatinine clearance between 30 and 50 mL/min), or severe (creatinine clearance lower than 30 mL/min) renal impairment significantly affect its clearance<sup>27</sup>; thus, dosage adjustment is recommended in patients with moderate or severe renal impairment. Mild-to-moderate hepatic dysfunction (Child-Pugh class A or B) does not clinically affect the plasma concentrations of cefditoren and, therefore, no dosage adjustments are required in these patients. In patients with severe hepatic impairment, the pharmacokinetic properties of cefditoren have not been studied<sup>27</sup>.

Cefditoren pivoxil presents an overall favorable drug interaction profile, with no evidence indicating that cefditoren pivoxil affects the pharmacokinetics of co-administered agents. However, H<sub>2</sub>-receptor antagonists and aluminium/magnesium-containing antacid suspension, or other drugs that increase gastric pH, such as proton pump inhibitors can reduce the C<sub>max</sub> and AUC of cefditoren and the concomitant administration of these drugs is not recommended<sup>27</sup>.



**Figure 2.**  $t > \text{MIC}$  of most commonly used oral  $\beta$ -lactams against *Streptococcus pneumoniae* strains (sensitive = Pen-S; intermediate sensitivity = Pen-I; resistant = Pen-R)<sup>28,29</sup>.



**Figure 3.** Diffusion of Cefditoren in respiratory tissues (modified from<sup>27</sup>). ELF: epithelial lining fluid.

The pharmacokinetics of cefditoren may provide some advantages in clinical practice. In fact, the twice-daily administration is more convenient when compared with amoxicillin, that requires three administrations/day, and is more appropriate from a microbiological point of view when compared with once daily administration of other oral cephalosporin that do not guarantee prolonged time with high plasma concentration. Moreover, the fact that no dose variation is needed in patients with mild renal impairment or mild to moderate hepatic disease, and the favorable drug interaction profile are to be taken into consideration, since many patients with respiratory infections present comorbidities.

#### **Antibacterial Activity of Cefditoren**

Cefditoren has a broad spectrum of activity against Gram-positive and Gram-negative bacteria, including common respiratory pathogens such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Streptococcus pyogenes*, *Klebsiella pneumoniae*, and methicillin-susceptible strains of *Staphylococcus aureus* (MSSA)<sup>28,30</sup>. The *in vitro* activity against respiratory pathogens frequently isolated in Italy, compared with other commonly used antibiotics, is shown in Table I<sup>26</sup>.

Cefditoren showed high intrinsic activity against penicillin-susceptible strains of *Streptococcus pneumoniae*, with a MIC<sub>90</sub> from  $\leq 0.03$  to  $0.06 \mu\text{g/mL}$ ; the MIC<sub>90</sub> values against penicillin-intermediate and penicillin-resistant isolates of *Streptococcus pneumoniae* ranged from  $0.25$  to  $0.5 \mu\text{g/mL}$ , and from  $0.5$  to  $1 \mu\text{g/mL}$ , respectively. It is noteworthy that MIC values of cefditoren against penicillin-intermediate and -resistant strains of *Streptococcus pneumoniae* were lower than those of amoxicillin, cefdinir, cefprozil, cefuroxime, cefixime, ceftibuten, cefpodoxime, erythromycin, clarithromycin, and azithromycin. MIC<sub>90</sub> values against penicillin non-susceptible isolates were one-dilution lower than that of cefotaxime<sup>26,31-38</sup>. Antibiotic resistance for *Streptococcus pneumoniae* depends on geographic location and time, antibiotic consumption, and the use of vaccines. Tempera et al<sup>26</sup> found that cefditoren was the only antibiotic with activity against 100% of the strains of *Streptococcus pneumoniae* examined, followed by the third-generation injectable cephalosporins (cefotaxime and ceftriaxone), that showed 2% of resistance against penicillin-resistant isolates.

Overall, cefditoren has demonstrated a high intrinsic activity against *Haemophilus influen-*

**Table I.** *In vitro* activity of cefditoren against some respiratory pathogens: comparison of MIC<sub>90</sub> with other antimicrobial agents commonly used) (modified from<sup>26</sup>).

		PRSP	Hiβ <sup>+</sup>	Mcβ <sup>+</sup>	S. pyo	MSSA	KI pn
Oral cephalosporins	Cefditoren	0.5	0.03	≤ 0.015	0.05	0.5	2
	Cefaclor	≥ 64	4	1	1	8	32
	Cefuroxime	32	2	0.5	0.12	2	≥ 64
	Cefixime	32	0.25	0.25	0.12	16	32
	Ceftibuten	32	0.5	0.25	0.5	≥ 64	32
	Cefpodoxime	4	0.25	0.5	0.12	4	32
i.v. cephalosporins	Cefotaxime	2	≤ 0.015	≤ 0.015	0.06	4	≥ 64
	Ceftriaxone	2	≤ 0.015	≤ 0.015	0.06	4	≥ 64
Penicillin	Amoxi/Clav acid	8	2	0.06		1	16
Macrolides	Clarithromycin	≥ 64	4	≤ 0.015	≥ 64	32	
	Azithromycin	≥ 64	4	≤ 0.015	≥ 64	32	
Fluoroquinolones	Levofloxacin	1	0.03	0.06	0.03	0.5	1

Data are expressed as MIC<sub>90</sub> values (mg/L). PRSP: penicillin-resistant *S. pneumoniae*; Hiβ<sup>+</sup>: *H. influenzae* β-lactamase positive; Mcβ<sup>+</sup>: *M. catarrhalis* β-lactamase positive; S pyo: *S. pyogenes*; MSSA: methicillin-susceptible *S. aureus*; KI pn: *K. pneumoniae*; amoxi-clav: amoxicillin-clavulanate.

*zae* and *Streptococcus pyogenes*, with an MIC<sub>90</sub> ≤ 0.06 µg/mL in the studies performed<sup>26,31,33,38-45</sup>. For *Haemophilus influenzae*, β-lactams resistance is defined by using ampicillin as a marker of resistance, with most ampicillin-resistant isolates that produce β-lactamase (TEM-1, TEM-2, and ROB-1). Another way to develop resistance against ampicillin is the mutation in the *FTSL* gene that causes an alteration in the amino acid sequences of penicillin-binding protein 3 (PBP3). The *Haemophilus influenzae* phenotypes that show mutations in the *FTSL* gene can be identified as β-lactamase negative ampicillin resistant (BLNAR) or β-lactamase positive amoxicillin/clavulanic acid resistant (BLPACR) in case of the concomitant presence the β-lactamase production other than the *FTSL* gene mutation.

In the study of Tempera et al<sup>26</sup>, cefditoren was the oral cephalosporin with the highest *in vitro* activity against *Haemophilus influenzae*,

independently of their production of beta-lactamases or their ampicillin resistance. The activity was comparable to that of the injectable cephalosporins and levofloxacin, whereas the highest MIC<sub>90</sub> were found for macrolides (MIC<sub>90</sub> values between 4 and 16 mg/L), and cefaclor (MIC<sub>90</sub> values between 4 and 32 mg/L).

In general, *Streptococcus pyogenes* is to be considered as highly susceptible to penicillin, since strains with MIC > 0.12 µg/mL have not been identified to date. By contrast, resistance to erythromycin is widely reported; moreover, since both the mechanisms of resistance found (M-eflux and MLS<sub>B</sub>) imply resistance to 14- and 15-membered macrolides, erythromycin resistance implies resistance to azithromycin and clarithromycin<sup>46</sup>. As previously stated, cefditoren showed high intrinsic activity against *Streptococcus pyogenes*; in the study of Tempera et al<sup>26</sup>, all the 225 strains of *Streptococcus pyogenes* were sensitive to cefditoren.

With respect to penicillin-nonsusceptible (MIC > 0.12 µg/mL) strains of *Streptococcus pneumoniae*, cefditoren was associated with a response rate of 92.3%. When only penicillin-resistant (MIC > 2 µg/mL) strains were considered, the overall response rate was 94.4%<sup>47</sup>.

### Clinical Efficacy of Cefditoren in the Treatment of Lower Community-Acquired Respiratory Tract Infections

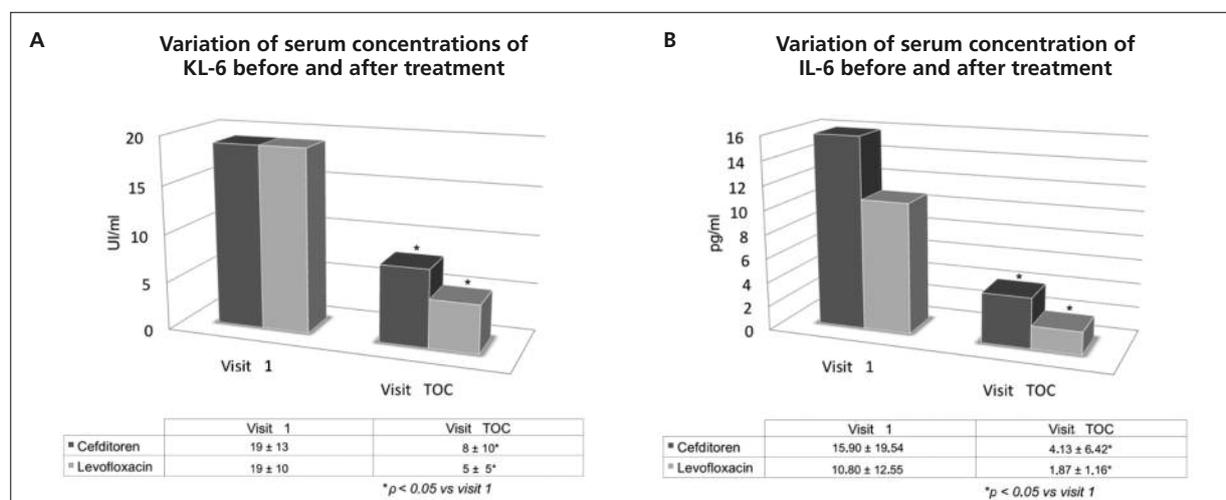
Clinical studies conducted to date have documented the efficacy of cefditoren in the treatment of LRTIs, such as exacerbations of chronic bronchitis and mild-to-moderate CAP.

The most recent study<sup>3</sup> enrolled 40 outpatients with mild to moderate acute exacerbation of COPD and investigated the effect of cefditoren (200 mg twice daily for 5 days) and the comparator (levofloxacin 500 mg od for 7 days) on serum inflammatory biomarkers, further to clinical efficacy and microbiological eradication. Interestingly, the Authors found that the use of cefditoren is associated with a significant reduction of IL-6 and KL-6, two mediators of lung inflammation and epithelial damage. KL-6 decreased both in the overall study population (from 19±11 UI/mL to 6±8 UI/mL,  $p = 0.000$ ) and in the cefditoren (from 19±13 UI/mL to 8±10 UI/mL,  $p = 0.006$ ) and levofloxacin (from 19±10 UI/mL to 5±5 UI/mL,  $p = 0.000$ ) arms. Similarly, IL-6 decreased both in the overall study population (from 13.35±16.41 pg/mL to 3.0±4.7 pg/mL,  $p = 0.000$ ) and in the cefditoren (from 15.90±19.54 pg/mL to 4.13±6.42 pg/mL,  $p = 0.015$ ) and levofloxacin (from 10.80±12.55 pg/mL to 1.87±1.16 pg/mL,  $p =$

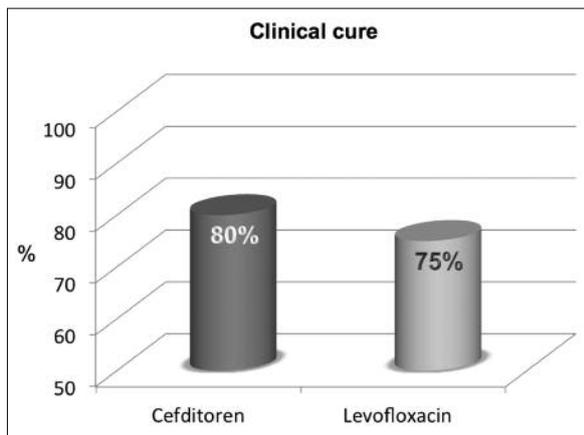
0.003) arms (Figure 4). At the end of treatment (test-of-cure, 6-9 days after drug initiation), the clinical success rate in the overall study population was 78%; the clinical cure rate was 80% in the cefditoren arm and 75% in the levofloxacin arm (Figure 5). Globally, bacteriological eradication at test-of-cure was obtained in 85% of the overall study population. Both treatments were well tolerated. Thus, Authors concluded that cefditoren represents a valid option in the treatment of severe cases of acute exacerbation of COPD in the outpatient care setting<sup>3</sup>. This work also confirms the conclusion of a previous probability model (therapeutic outcomes model) analysis of Canut et al<sup>48</sup>, aimed at predicting the likelihood of clinical success with particular antimicrobial agents in the treatment of patients with acute exacerbation of COPD. According to this model, fluoroquinolones (levofloxacin, ciprofloxacin and moxifloxacin), cefditoren and amoxicillin/clavulanate are the most appropriate antibiotics for the treatment of patients with acute exacerbation of COPD, in terms of predicted clinical efficacy, with wide differences from other antibiotics commonly used in the treatment of these patients, such as clarithromycin and azithromycin<sup>48</sup>.

### The Benefit of Decreasing Inflammatory Biomarkers in Acute Exacerbation of COPD

In COPD patients, the innate lung defense is disrupted as a result of exposure to smoke and other environmental irritants, with the presence of two distinct infection cycles (i.e. acute and chronic; Figure 6) that could contribute to progressive loss of lung function, leading to the par-



**Figure 4.** Levels of KL6 (A) and IL6 (B) with cefditoren and levofloxacin, at visit 1 and test of cure<sup>3</sup>. \* $p < 0.05$  versus visit (modified from<sup>27</sup>).



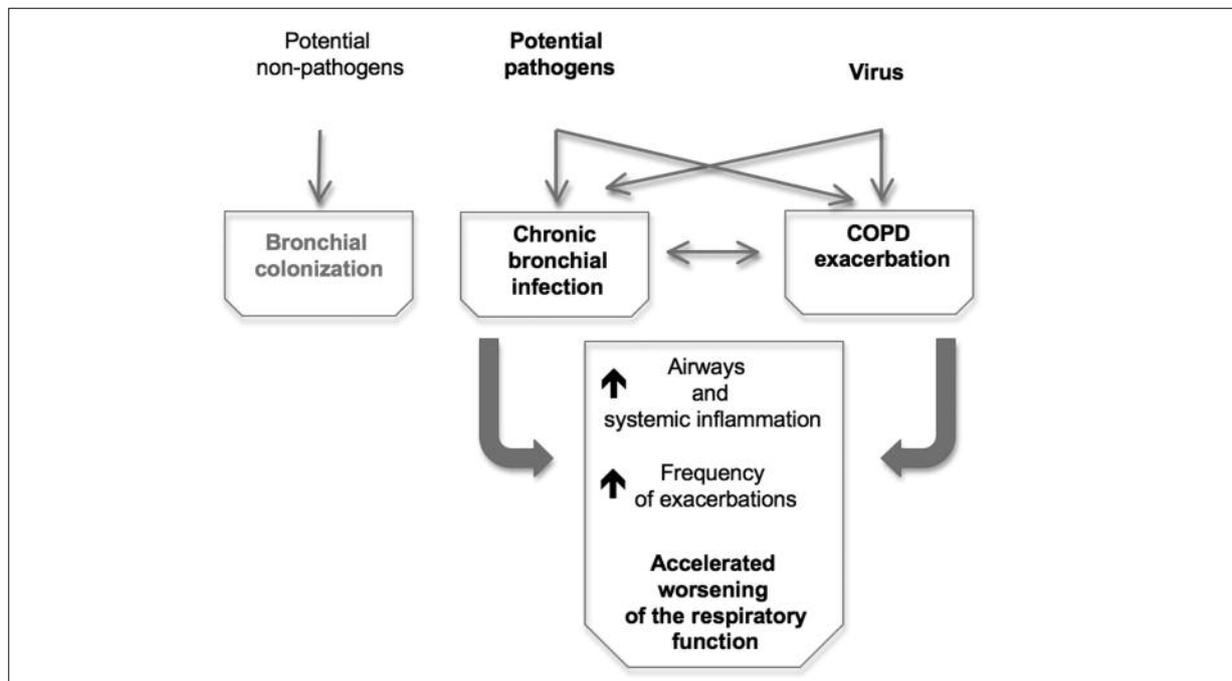
**Figure 5.** Clinical cure in patients with COPD exacerbation treated with cefditoren (200 mg twice daily for 5 days) or levofloxacin (500 mg once daily for 7 days) (modified from<sup>27</sup>).

adigm of “infection as a comorbidity of COPD”<sup>18</sup>. Chronic microbial infection can contribute to inflammation in COPD as a direct inflammatory stimulus or indirectly by altering the host response to tobacco smoke, with COPD progression significantly affected by the vicious circle between infection and inflammation<sup>18</sup>.

Thus, in COPD high level of inflammatory biomarkers, such as for IL-6 and fibrinogen, are present also when patients are in stable condition,

with a further increase during exacerbation. The increase of inflammatory biomarkers have been shown to be associated with impaired functional capacity, reduced daily physical activity, and decreased health status<sup>49</sup>. Notably, two recent reports in COPD patients demonstrated that high levels of IL6, but not other biomarkers such as tumor necrosis factor alpha or IL-8, are predictors of increased mortality and poor clinical outcomes<sup>50,51</sup>. Last, KL-6, a biomarker currently largely used for management of interstitial lung disease, is increased in the lung, induced sputum and plasma of aged smoking patients, and has been used to assess the presence of fibrosis in the lungs of patients with combined pulmonary fibrosis and emphysema<sup>52,53</sup>. Bacterial load itself is an important determinant of airway inflammation, with increasing concentrations associated with greater intensity of neutrophilic airway inflammation<sup>14</sup>.

Blasi et al<sup>3</sup> showed that cefditoren in acute exacerbation of COPD is effective in decreasing inflammatory biomarkers, such as KL-6, and IL-6, an effect which is probably related to its antibacterial efficacy. The demonstration of a significant reduction of inflammatory biomarkers after an appropriate antimicrobial treatment appears clinically significant, especially in a disease characterized by a high level of local and systemic inflammation such as COPD.



**Figure 6.** A modification in bacterial strains and/or an increase in bacterial load can enhance inflammation in the airways and elicit COPD exacerbations (modified from<sup>18</sup>).

### **Tolerability Considerations**

Safety data from the trials carried out in adults during the clinical development of cefditoren for the treatment of community-acquired respiratory infections showed that the tolerability profile of cefditoren and comparators are similar<sup>54</sup>.

The tolerability profile of cefditoren pivoxil, administered either at a dose of 200 or 400 mg twice daily for up to 14 days has been assessed in about 6000 patients enrolled in controlled clinical trials. The molecule was overall well-tolerated: in the wide majority of cases, adverse effects were of mild-to-moderate severity and spontaneously resolved. No deaths or permanent disabilities were correlated with cefditoren pivoxil. The treatment was interrupted for adverse reactions in 2.6% of patients only<sup>54</sup>.

$\beta$ -lactams and fluoroquinolones represent the more effective drugs for the treatment of patients with exacerbations of COPD. However, in mild COPD without comorbidities, oral cephalosporins should be considered as first-line treatments, while the use of fluoroquinolones should be reserved for more severe exacerbations. In fact, fluoroquinolones, one of the most common alternatives to  $\beta$ -lactams for the treatment of respiratory infections, are generally well-tolerated but can be associated with adverse drug reactions – potentially severe – which include central nervous system toxicity, phototoxicity, cardiotoxicity, arthropathy, and tendon toxicity, especially in patients with predisposing factors, such as diabetes and heart disease<sup>55</sup>. These data have been confirmed in the analysis of four regional pharmacovigilance databases in Italy<sup>56,57</sup>. Moreover, because of physiological changes in renal function and the high number of expected comorbidities, some special considerations are needed in elderly patients treated with fluoroquinolones<sup>57,58</sup>.

### **Conclusions**

The appropriate use of antimicrobials is defined by the World Health Organization as “the cost-effective use of antimicrobials which maximizes clinical and therapeutic effect while minimizing both drug-related toxicity and the development of antimicrobial resistance”<sup>2</sup>, mainly in an era characterized by a limited number of new antibiotics in the pipeline. In this context, cefditoren appears to meet the definition of “appropriate” for the treatment of LRTIs. In fact, it shows an adequate pharmacokinetics, with a clinical relevant concen-

tration both in bronchial mucosa and in epithelial lining fluid after oral administration. Since dosage adjustment is not needed in aged patients even if in presence of mild renal impairment or mild to moderate hepatic dysfunction, cefditoren can be used in the majority of cases. In patients with many comorbidities, like most COPD patients, the low drug-interaction of cefditoren can be a relevant advantage in the clinical practice. The antimicrobial activity of cefditoren answers to the request of new antibiotics aiming at treating community respiratory infections, due to its activity against both *Streptococcus pneumoniae* and *Haemophilus influenzae*, the most prevalent isolates.

Cefditoren is more expensive than many other  $\beta$ -lactams and quinolones, including levofloxacin, at least in Italy, and so far, to the best of our knowledge, a formal study aimed at evaluating the cost effectiveness of this antibiotic for the treatment of LTRIs compared with other ones has not yet been carried out. However, it must be noted that pharmacoeconomic studies showed that the cost of the antibiotic itself, although important, does not play a critical role in the healthcare cost savings for the treatment of respiratory infections, including CAP and acute exacerbation of COPD. On the contrary, the choice of antibiotic should be based on spectrum of activity, efficacy, dosage regimen and appropriateness for the infectious episode and each single patient<sup>55</sup>. In fact, the cost of the initial antibiotic accounts for 18% only of the total cost in outpatients, and can be further reduced to 10% in patients who require hospitalization<sup>59</sup>. It is noteworthy that in case of therapeutic failure, a significant increase of the costs is expected, not only for CAP but also for acute exacerbation of COPD, as demonstrated by Miravittles et al<sup>60</sup>.

Acute exacerbations of COPD and CAP are usually treated with oral antibiotics since they are more easily administered and accepted on the part of the patients. In this field, cefditoren, thanks to its good pharmacokinetic and pharmacodynamic profile, may be not only the first choice, but also the logical option for sequential therapy after treatment with parenteral cephalosporins, such as ceftriaxone or cefotaxime. Finally, recent data have shown that cefditoren represents a valid alternative to levofloxacin in the treatment of mild-to-moderately severe cases of acute exacerbation of COPD in the outpatients setting, with a significant reduction of key mediators of lung inflammation and epithelial damage, factors probably involved in the progression of the disease.

### Financial support

This review was supported by an unrestricted grant from Zambon (Italy).

### Conflict of Interest

Fabiano Di Marco has received financial support for research from Novartis, Pfizer and Boehringer Ingelheim. He has received honoraria for lectures at national meetings from Chiesi Farmaceutici, Novartis, Zambon, AstraZeneca, Glaxo Smith Kline, Menarini, Almiral, Guidotti, and Malesci. He is consultant in the field of educational programs for Novartis. The author states that no funding sources influenced the preparation of the current manuscript in its parts: collection, interpretation and presentation of data. Pierachille Santus has received financial support for research and for congress attendance from Pfizer, Boehringer Ingelheim, Novartis, Chiesi Farmaceutici, Glaxo Smith Kline, Menarini, AirLiquide. He has received honoraria for lectures at national meetings from Chiesi Farmaceutici, Novartis, Zambon, AstraZeneca. He has served as consultant for Zambon, Astra Zeneca, Novartis, Chiesi. The author states that no funding sources influenced the preparation of the current manuscript in its parts: collection, interpretation and presentation of data. Fulvio Braido has received financial support for research and for congress attendance from Astra Zeneca, GSK, Novartis, Menarini, Chiesi, Boehringer, Pfizer, MSD. He has received honoraria for lectures at national meetings from Astra Zeneca, GSK, Novartis, Menarini, Chiesi, Zambon, Abbott, Boehringer, Pfizer, MSD. The author states that no funding sources influenced the preparation of the current manuscript in its parts: collection, interpretation and presentation of data. Nicola Scichilone has received financial support for research and for congress attendance from Boehringer Ingelheim, Novartis, Chiesi Farmaceutici, Glaxo Smith Kline, Menarini. He has received honoraria for lectures at national meetings from Chiesi Farmaceutici, Novartis, Zambon, Has served as consultant for Zambon, Astra Zeneca, Mundipharma, Novartis, Chiesi. The author states that no funding sources influenced the preparation of the current manuscript in its parts: collection, interpretation and presentation of data. Francesco Blasi has received financial support for research from Pfizer, Novartis, Chiesi, Zambon. He has received honoraria for lectures at national meetings from Almiral, Chiesi, Glaxo Smith Kline, Menarini, Guidotti-Malesci, Novartis, Zambon, AstraZeneca. He has served as consultant for Novartis, Chiesi, Pfizer, AstraZeneca. The author states that no funding sources influenced the preparation of the current manuscript in its parts: collection, interpretation and presentation of data.

### References

- 1) MIZGERD JP. Acute lower respiratory tract infection. *N Engl J Med* 2008; 358: 716-727.
- 2) World Health Organization DoCD, Containment SaRWGSf, Organization; oARGWH, [http://www.who.int/csr/resources/publications/Af\\_drugresist/en/EGlobal\\_Strat.pdf](http://www.who.int/csr/resources/publications/Af_drugresist/en/EGlobal_Strat.pdf). Accessed December 2013.
- 3) BLASI F, TARSIA P, MANTERO M, MORLACCHI LC, PIFFER F. Cefditoren versus levofloxacin in patients with exacerbations of chronic bronchitis: serum inflammatory biomarkers, clinical efficacy, and microbiological eradication. *Ther Clin Risk Manag* 2013; 9: 55-64.
- 4) GUEST JF, MORRIS A. Community-acquired pneumonia: the annual cost to the National Health Service in the UK. *Eur Respir J* 1997; 10: 1530-1534.
- 5) WOODHEAD M. Community-acquired pneumonia: severity of illness evaluation. *Infect Dis Clin North Am* 2004; 18: 791-807; viii.
- 6) WELTE T, TORRES A, NATHWANI D. Clinical and economic burden of community-acquired pneumonia among adults in Europe. *Thorax* 2012; 67: 71-79.
- 7) EWIG S, BIRKNER N, STRAUSS R, SCHAEFER E, PAULETZKI J, BISCHOFF H, SCHRAEDER P, WELTE T, HOEFFKEN G. New perspectives on community-acquired pneumonia in 388 406 patients. Results from a nationwide mandatory performance measurement programme in healthcare quality. *Thorax* 2009; 64: 1062-1069.
- 8) BAUER TT, WELTE T, ERNEN C, SCHLOSSER BM, THATE-WASCHKE I, DE ZEEUW J, SCHULTZE-WERNINGHAUS G. Cost analyses of community-acquired pneumonia from the hospital perspective. *Chest* 2005; 128: 2238-2246.
- 9) CABRE M, BOLIVAR I, PERA G, PALLARES R. Factors influencing length of hospital stay in community-acquired pneumonia: a study in 27 community hospitals. *Epidemiol Infect* 2004; 132: 821-829.
- 10) DAMBRAVA PG, TORRES A, VALLES X, MENSA J, MARCOS MA, PENARROJA G, CAMPS M, ESTRUCH R, SÁNCHEZ M, MENÉNDEZ R, NIEDERMAN MS. Adherence to guidelines' empirical antibiotic recommendations and community-acquired pneumonia outcome. *Eur Respir J* 2008; 32: 892-901.
- 11) MENENDEZ R, FERRANDO D, VALLES JM, VALLTERRA J. Influence of deviation from guidelines on the outcome of community-acquired pneumonia. *Chest* 2002; 122: 612-617.
- 12) LOPEZ AD, SHIBUYA K, RAO C, MATHERS CD, HANSELL AL, HELD LS, SCHMID V, BUIST S. Chronic obstructive pulmonary disease: current burden and future projections. *Eur Respir J* 2006; 27: 397-412.
- 13) BURGE S, WEDZICHA JA. COPD exacerbations: definitions and classifications. *Eur Respir J Suppl* 2003; 41: 46s-53s.
- 14) SETHI S, MUSCARELLA K, EVANS N, KLINGMAN KL, GRANT BJ, MURPHY TF. Airway inflammation and etiology of acute exacerbations of chronic bronchitis. *Chest* 2000; 118: 1557-1565.
- 15) WHITE AJ, GOMPERTZ S, BAYLEY DL, HILL SL, O'BRIEN C, UNSAL I, STOCKLEY RA. Resolution of bronchial inflammation is related to bacterial eradication following treatment of exacerbations of chronic bronchitis. *Thorax* 2003; 58: 680-685.
- 16) WHITE AJ, GOMPERTZ S, STOCKLEY RA. Chronic obstructive pulmonary disease . 6: The aetiology of exacerbations of chronic obstructive pulmonary disease. *Thorax* 2003; 58: 73-80.

- 17) WEDZICHA JA, SEEMUNGAL TRA. COPD exacerbations: defining their cause and prevention. *Lancet* 2007; 370: 786-796.
- 18) SETHI S. Infection as a comorbidity of COPD. *Eur Respir J* 2010; 35: 1209-1215.
- 19) SETHI S, MAHLER DA, MARCUS P, OWEN CA, YAWN B, RENNARD S. Inflammation in COPD: implications for management *Am J Med* 2012; 125: 1162-1170.
- 20) MATKOVIC Z, MIRAVITLLES M. Chronic bronchial infection in COPD. Is there an infective phenotype? *Resp Med* 2013; 107: 10-22.
- 21) ANDERSSON F, BORG S, JANSSON SA, JONSSON AC, ERICSSON A, PRUTZ C, RÖNMARK E, LUNDBÄCK B. The costs of exacerbations in chronic obstructive pulmonary disease (COPD). *Respir Med* 2002; 96: 700-708.
- 22) SULLIVAN SD, RAMSEY SD, LEE TA. The economic burden of COPD. *Chest* 2000; 117: 5S-9S.
- 23) EUROPEAN CENTRE FOR DISEASE PREVENTION AND CONTROL. Antimicrobial resistance surveillance in Europe 2011. Annual Report of the European Antimicrobial Resistance Surveillance Network (EARS-Net). Stockholm: ECDC; 2012.
- 24) NAGAI K, DAVIES TA, JACOBS MR, APPELBAUM PC. Effects of amino acid alterations in penicillin-binding proteins (PBPs) 1a, 2b, and 2x on PBP affinities of penicillin, ampicillin, amoxicillin, cefditoren, cefuroxime, cefprozil, and cefaclor in 18 clinical isolates of penicillin-susceptible, -intermediate, and -resistant pneumococci. *Antimicrob Agents Chemother* 2002; 46: 1273-1280.
- 25) YAMADA M, WATANABE T, MIYARA T, BABA N, SAITO J, Takeuchi Y, Ohsawa F. Crystal structure of cefditoren complexed with *Streptococcus pneumoniae* penicillin-binding protein 2X: structural basis for its high antimicrobial activity. *Antimicrob Agents Chemother* 2007; 51: 3902-3907.
- 26) TEMPERA G, FURNERI PM, CARLONE NA, COCUZZA C, RIGOLI R, MUSUMECI R, PILLONI AP, PRENNA M, TUFANO MA, TULLIO V, VITALI LA, NICOLETTI G. Antibiotic susceptibility of respiratory pathogens recently isolated in Italy: focus on cefditoren. *J Chemother* 2010; 22: 153-159.
- 27) WELLINGTON K, CURRAN MP. Cefditoren pivoxil: a review of its use in the treatment of bacterial infections. *Drugs* 2004; 64: 2597-2618.
- 28) CLARK CL, NAGAI K, DEWASSE BE, PANKUCH GA, EDNIE LM, JACOBS MR, APPELBAUM PC. Activity of cefditoren against respiratory pathogens. *J Antimicrob Chemother* 2002; 50: 33-41.
- 29) BLASI F, CONCIA E, MAZZEI T, MORETTI AM, NICOLETTI G, NOVELLI A, TEMPERA G; GIARIR. Role of the oral Beta-lactams in the treatment of exacerbations of chronic bronchitis: critical analysis and therapeutics recommendations. *J Chemother* 2010; 22 Suppl 1: 3-4.
- 30) LEE MY, KO KS, OH WS, PARK S, LEE JY, BAEK JY, SUH JY, PECK KR, LEE NY, SONG JH. *In vitro* activity of cefditoren: antimicrobial efficacy against major respiratory pathogens from Asian countries. *Int J Antimicrob Agents* 2006; 28: 14-18.
- 31) BIEDENBACH DJ, JONES RN. Update of cefditoren activity tested against community-acquired pathogens associated with infections of the respiratory tract and skin and skin structures, including recent pharmacodynamic considerations. *Diagn Microbiol Infect Dis* 2009; 64: 202-212.
- 32) FENOLL A, AGUILAR L, ROBLEDO O, GIMENEZ MJ, TARRAGO D, GRANIZO JJ, GIMENO M, CORONEL P. Influence of the beta-lactam resistance phenotype on the cefuroxime versus cefditoren susceptibility of *Streptococcus pneumoniae* and *Haemophilus influenzae* recovered from children with acute otitis media. *J Antimicrob Chemother* 2007; 60: 323-327.
- 33) FENOLL A, GIMENEZ MJ, ROBLEDO O, AGUILAR L, TARRAGO D, GRANIZO JJ, GIMENO M, CORONEL P. *In vitro* activity of oral cephalosporins against pediatric isolates of *Streptococcus pneumoniae* non-susceptible to penicillin, amoxicillin or erythromycin. *J Chemother* 2008; 20: 175-179.
- 34) FENOLL A, GIMENEZ MJ, ROBLEDO O, AGUILAR L, TARRAGO D, GRANIZO JJ, MARTÍN-HERRERO JE. Influence of penicillin/amoxicillin non-susceptibility on the activity of third-generation cephalosporins against *Streptococcus pneumoniae*. *Eur J Clin Microbiol Infect Dis* 2008; 27: 75-80.
- 35) FENOLL A, GIMENEZ MJ, ROBLEDO O, CORONEL P, GIMENO M, CASAL J, AGUILAR L. Activity of cefditoren against clinical isolates of *Streptococcus pneumoniae* showing non-susceptibility to penicillins, cephalosporins, macrolides, ketolides or quinolones. *Int J Antimicrob Agents* 2007; 29: 224-226.
- 36) FRITSCHER TR, BIEDENBACH DJ, JONES RN. Update of the activity of cefditoren and comparator oral beta-lactam agents tested against community-acquired *Streptococcus pneumoniae* isolates (USA, 2004-2006). *J Chemother* 2008; 20: 170-174.
- 37) SERAL C, SUAREZ L, RUBIO-CALVO C, GOMEZ-LUS R, GIMENO M, CORONEL P, DURÁN E, BECERRIL R, OCA M, CASTILLO FJ. *In vitro* activity of cefditoren and other antimicrobial agents against 288 *Streptococcus pneumoniae* and 220 *Haemophilus influenzae* clinical strains isolated in Zaragoza, Spain. *Diagn Microbiol Infect Dis* 2008; 62: 210-215.
- 38) STEFANI S, MEZZATESTA ML, FADDA G, MATTINA R, PALU G, ROSSANO F, TUFANO MA, SCHITO GC, NICOLETTI G. Antibacterial activity of cefditoren against major community-acquired respiratory pathogens recently isolated in Italy. *J Chemother* 2008; 20: 561-569.
- 39) BIEDENBACH DJ, JONES RN, FRITSCHER TR. Antimicrobial activity of cefditoren tested against contemporary (2004-2006) isolates of *Haemophilus influenzae* and *Moraxella catarrhalis* responsible for community-acquired respiratory tract infections in the United States. *Diagn Microbiol Infect Dis* 2008; 61: 240-244.
- 40) GARCIA-DE-LOMAS J, LERMA M, CEBRIAN L, JUAN-BANON JL, CORONEL P, GIMENEZ MJ, AGUILAR L. Influence of *Haemophilus influenzae* beta-lactamase production and/or *ftsI* gene mutations on *in vitro* activity of and susceptibility rates to aminopenicillins and second- and third-generation cephalosporins. *Int J Antimicrob Agents* 2007; 30: 190-192.

- 41) GRACIA M, DIAZ C, CORONEL P, GIMENO M, GARCIA-RODAS R, DEL PRADO G, HUELVES L, RUIZ V, NAVES PL, PONTE MC, GRANIZO JJ, SORIANO F. Antimicrobial susceptibility of *Haemophilus influenzae* and *Moraxella catarrhalis* isolates in eight Central, East and Baltic European countries in 2005-06: results of the Cefditoren Surveillance Study. *J Antimicrob Chemother* 2008; 61: 1180-1181.
- 42) GRACIA M, DIAZ C, CORONEL P, GIMENO M, GARCIA-RODAS R, RODRIGUEZ-CERRATO V, DEL PRADO G, HUELVES L, RUIZ V, NAVES PF, PONTE MC, GRANIZO JJ, SORIANO F. Antimicrobial susceptibility of *Streptococcus pyogenes* in Central, Eastern, and Baltic European Countries, 2005 to 2006: the cefditoren surveillance program. *Diagn Microbiol Infect Dis* 2009; 64: 52-56.
- 43) HARIMAYA A, YOKOTA S, SATO K, HIMI T, FUJII N. Remarkably high prevalence of *fts I* gene mutations in *Haemophilus influenzae* isolates from upper respiratory tract infections in children of the Sapporo district, Japan. *J Infect Chemother* 2008; 14: 223-227.
- 44) PEREZ-TRALLERO E, MARTIN-HERRERO JE, MAZON A, GARCIA-DELA FUENTE C, ROBLES P, IRIARTE V, DAL-RÉ R, GARCIA-DE-LOMAS J; SPANISH SURVEILLANCE GROUP FOR RESPIRATORY PATHOGENS. Antimicrobial resistance among respiratory pathogens in Spain: latest data and changes over 11 years (1996-1997 to 2006-2007). *Antimicrob Agents Chemother* 2010; 54: 2953-2959.
- 45) SEVILLANO D, GIMENEZ MJ, CERCENADO E, CAFINI F, GENE A, ALOU L, MARCO F, MARTÍNEZ-MARTÍNEZ L, CORONEL P, AGUILAR L. Genotypic versus phenotypic characterization, with respect to beta-lactam susceptibility, of *Haemophilus influenzae* isolates exhibiting decreased susceptibility to beta-lactam resistance markers. *Antimicrob Agents Chemother* 2009; 53: 267-270.
- 46) PRIETO J, CALVO A, GOMEZ-LUS ML. Antimicrobial resistance: a class effect? *J Antimicrob Chemother* 2002; 50 Suppl S2: 7-12.
- 47) GRANIZO JJ, GIMENEZ MJ, BARBERAN 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: 2061-2069.
- 48) CANUT A, MARTIN-HERRERO JE, LABORA A, MAORTUA H. What are the most appropriate antibiotics for the treatment of acute exacerbation of chronic obstructive pulmonary disease? A therapeutic outcomes model. *J Antimicrob Chemother* 2007; 60: 605-612.
- 49) YANBAEVA DG, DENTENER MA, SPRUIT MA, HOUWING-DUISTERMAAT JJ, KOTZ D, PASSOS VL, WOUTERS EF. IL6 and CRP haplotypes are associated with COPD risk and systemic inflammation: a case-control study. *BMC Med Genet* 2009; 10: 23.
- 50) AGUSTI A, EDWARDS LD, RENNARD SI, MACNEE W, TAL-SINGER R, MILLER BE, VESTBO J, LOMAS DA, CALVERLEY PM, WOUTERS E, CRIM C, YATES JC, SILVERMAN EK, COXSON HO, BAKKE P, MAYER RJ, CELLI B; EVALUATION OF COPD LONGITUDINALLY TO IDENTIFY PREDICTIVE SURROGATE ENDPOINTS (ECLIPSE) INVESTIGATORS. Persistent systemic inflammation is associated with poor clinical outcomes in COPD: a novel phenotype. *PLoS One* 2012; 7: e37483.
- 51) CELLI BR, LOCANTORE N, YATES J, TAL-SINGER R, MILLER BE, BAKKE P, CALVERLEY P, COXSON H, CRIM C, EDWARDS LD, LOMAS DA, DUVOIX A, MACNEE W, RENNARD S, SILVERMAN E, VESTBO J, WOUTERS E, AGUSTÍ A; ECLIPSE INVESTIGATORS. Inflammatory biomarkers improve clinical prediction of mortality in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2012; 185: 1065-1072.
- 52) CHIBA S, OHTA H, ABE K, HISATA S, OHKOUCHI S, HOSHIKAWA Y, KONDO T, EBINA M. The Diagnostic Value of the Interstitial Biomarkers KL-6 and SP-D for the Degree of Fibrosis in Combined Pulmonary Fibrosis and Emphysema. *Pulm Med* 2012; 2012: 492960.
- 53) ISHIKAWA N, MAZUR W, TOLJAMO T, VUOPALA K, RONTY M, HORIMASU Y, KOHNO N, KINNULA VL. Ageing and long-term smoking affects KL-6 levels in the lung, induced sputum and plasma. *BMC Pulm Med* 2011; 11: 22.
- 54) GRANIZO JJ, AGUILAR L, GIMENEZ MJ, 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.
- 55) PUGI A, LONGO L, BARTOLONI A, ROSSOLINI GM, MUGELLI A, VANNACCI A, LAPI F. Cardiovascular and metabolic safety profiles of the fluoroquinolones. *Expert Opin Drug Saf* 2012; 11: 53-69.
- 56) LAPI F, TUCCORI M, MOTOLA D, PUGI A, VIETRI M, MONTANARO N, VACCHERI A, LEONI O, COCCI A, LEONE R, CONFORTI A, MORETTI U, SESSA E, MAZZAGLIA G, MUGELLI A, MAZZEI T, VANNACCI A. Safety profile of the fluoroquinolones: analysis of adverse drug reactions in relation to prescription data using four regional pharmacovigilance databases in Italy. *Drug Saf* 2010; 33: 789-799.
- 57) LODE H. Safety and tolerability of commonly prescribed oral antibiotics for the treatment of respiratory tract infections. *Am J Med* 2010; 123: S26-S38.
- 58) STAHLMANN R, LODE H. Safety considerations of fluoroquinolones in the elderly: an update. *Drugs Aging* 2010; 27: 193-209.
- 59) MONTE SV, PAOLINI NM, SLAZAK EM, SCHENTAG JJ, PALADINO JA. Costs of treating lower respiratory tract infections. *Am J Manag Care* 2008; 14: 190-196.
- 60) MIRAVITLLES M, MURIO C, GUERRERO T, GISBERT R. Pharmacoeconomic evaluation of acute exacerbations of chronic bronchitis and COPD. *Chest* 2002; 121: 1449-1455.