Drug resistance in community-acquired respiratory tract infections: role for an emerging antibacterial

Lorenzo Aguilar1, María-José Giménez1, José Barberán2

1Microbiology Department, School of Medicine, University Complutense, Madrid; 2Infectious Diseases Department, Hospital Central de la Defensa Gomez Ulla, Madrid, Spain

Abstract: The nasopharynx is the ecological niche where evolution towards resistance occurs in respiratory tract isolates. Dynamics of different bacterial populations in antibiotic-free multibacterial niches are the baseline that antibiotic treatments can alter by shifting the competitive balance in favor of resistant populations. For this reason, antibiotic resistance is increasingly being considered to be an ecological problem. Traditionally, resistance has implied the need for development of new antibiotics for which basic efficacy and safety data are required prior to licensing. Antibiotic development is mainly focused on demonstrating clinical efficacy and setting susceptibility breakpoints for efficacy prediction. However, additional information on pharmacodynamic data predicting absence of selection of resistance and of resistant subpopulations, and specific surveillance on resistance to core antibiotics (to detect emerging resistances and its link with antibiotic consumption in the community) are valuable data in defining the role of a new antibiotic, not only from the perspective of its therapeutic potential but also from the ecologic perspective (countering resistances to core antibiotics in the community). The documented information on cefditoren gleaned from published studies in recent years is an example of the role for an emerging oral antibacterial facing current antibiotic resistance in community-acquired respiratory tract infections.

Keywords: respiratory tract infection, antibiotic resistance, cefditoren, community

Nasopharyngeal colonization and prevalent isolates

Mucosal surfaces are simultaneously colonized by multiple species, with an intricate balance in the nasopharynx between Streptococcus pneumoniae, Streptococcus pyogenes, Haemophilus influenzae, and other nasopharyngeal flora. These bacterial species share three characteristics, ie, they colonize the nasopharynx of humans as their exclusive host, are exogenously transmitted to colonize the nasopharynx of new hosts, and are common etiological agents (most prevalent isolates) of bacterial community-acquired respiratory tract infections when they endogenously migrate to different ecosystems or when changes within their natural ecosystem occur. Thus the upper respiratory tract, with its commensal flora, acts both as a colonization defense mechanism and as a primary bacterial source for respiratory tract infections, S. pyogenes being the etiologic agent of tonsillitis, and S. pneumoniae and H. influenzae being the causative agents of otitis media, sinusitis, and lower respiratory tract infections, ie, acute exacerbation of chronic bronchitis (AECB) and pneumonia.

Carriage of these common respiratory isolates depends on multiple factors, such as active or passive smoking, crowding, age, bacterial fitness, specific vaccination, and
bacterial interference in antibiotic-free niches.\textsuperscript{1,3} Approximately 80% of healthy individuals carry \textit{H. influenzae},\textsuperscript{4} with multiple strains in 50% positive samples and a high turnover of strains.\textsuperscript{2,5} In the case of \textit{S. pneumoniae}, carriage ranges from 10% to 40% in an age-dependent manner,\textsuperscript{6} with lower percentages of multiple strains in the same sample\textsuperscript{7} and a duration of nasopharyngeal carriage depending on age, seasonality, resistance to penicillin, serotype, and simultaneous carriage by other family members.\textsuperscript{8,9} \textit{S. pyogenes} frequently colonizes the nasopharynx of asymptomatic persons, with carriage rates of 15%–20% in school children (crowding favors interpersonal spread), but this is considerably lower in adults.\textsuperscript{10}

**Bacterial evolution towards resistance in respiratory tract isolates**

The nasopharynx is the ecological niche where evolution towards resistance occurs in respiratory tract isolates. The evolution of antibiotic resistance involves two processes, ie, emergence and spread.\textsuperscript{11,12} Resistance to \(\beta\)-lactams and macrolides is mostly due to acquisition of exogenous resistance genes, and has been described in \textit{S. pneumoniae} and \textit{H. influenzae} (in both cases, resistance to both \(\beta\)-lactams and to macrolides) and in \textit{S. pyogenes} (resistance to macrolides).\textsuperscript{13–16} with \textit{de novo} resistance occurring rarely within a given host in a susceptible bacterial population.\textsuperscript{13} In contrast, resistance to fluoroquinolones in \textit{S. pneumoniae} arises within a given host due to point mutations.\textsuperscript{13}

Evolution is based on production of variation, management of variation, and natural selection of variants.\textsuperscript{17} Dynamics of different bacterial populations in antibiotic-free niches are the baseline that antibiotic treatments can alter\textsuperscript{18,19} by shifting the competitive balance in favor of resistant populations. For this reason, antibiotic resistance is increasingly regarded as an ecological problem. Once resistance has emerged, physiologic concentrations of different antibiotic antibiotics may select resistant strains by eradicating the susceptible ones (thus unmasking resistant populations),\textsuperscript{19} or by selecting intrastrain-resistant subpopulations.\textsuperscript{20} Because multiple individuals harbor multiple bacterial populations exhibiting different degrees of antibiotic resistance at the community level, the prevalence of resistance is directly related to antibiotic consumption in the community.\textsuperscript{21}

**Antibiotic consumption as the driver of resistance: a global problem**

Infection, mainly of the respiratory tract,\textsuperscript{22,23} is the most frequent reason for seeking medical attendance in the community. Around 85%–90% of antibiotic consumption occurs in the community, and 80% of this consumption is for the treatment of respiratory tract infections.\textsuperscript{24} Antimicrobial consumption has been associated with resistance selection.\textsuperscript{25} Consumption of \(\beta\)-lactams and macrolides has been associated with penicillin/erythromycin resistance in \textit{S. pneumoniae}, both temporally\textsuperscript{25} and geographically,\textsuperscript{26} with high correlations between penicillin/erythromycin resistance and consumption of long half-life macrolides and second-generation oral cephalosporins.\textsuperscript{25,26} Associations between ampicillin/amoxicillin resistance in \textit{H. influenzae} and \textit{Moraxella catarrhalis} and consumption of aminopenicillins (with or without clavulanic acid),\textsuperscript{27,28} as well as the association between erythromycin resistance in \textit{S. pyogenes} and consumption of long half-life macrolides, have also been described.\textsuperscript{29,30}

Because antibiotic consumption in the community has been associated with resistance prevalence, in geographic locations with high antibiotic consumption, eg, Spain, associations between the resistance rates found in different bacterial species of respiratory tract isolates could be expected. In Spain, penicillin resistance in \textit{S. pneumoniae} has been significantly associated with erythromycin resistance (due to the co-resistance selection phenomenon),\textsuperscript{31,32} and with ampicillin resistance in \textit{H. influenzae} (due to the phenomenon of coselection of resistance). In addition, geographically, erythromycin resistance in \textit{S. pyogenes} was significantly related to penicillin and/or erythromycin resistance in \textit{S. pneumoniae} and to ampicillin resistance in \textit{H. influenzae}.\textsuperscript{13} Considering these associations, in Spain, as in other countries, resistance should be considered as a global problem with regard to respiratory isolates in the community.

**Current resistances in respiratory isolates in the community**

**\textit{Streptococcus pneumoniae}**

Penicillin/erythromycin nonsusceptibility in \textit{S. pneumoniae} is mainly clustered in a reduced number of serotypes. In invasive isolates, the increase in the prevalence of antibiotic nonsusceptibility and of certain serotypes that occurred in the 1980s and 1990s related to antibiotic consumption reversed in the 2000s when the seven-valent conjugate pneumococcal vaccine (PCV7) (including serotypes most associated with penicillin/erythromycin nonsusceptibility) was introduced for childhood immunization.\textsuperscript{33,34} The introduction of PCV7 produced not only a dramatic reduction in the incidence of invasive pneumococcal disease, but also a marked decrease in PCV7 serotypes which consequently affected penicillin and erythromycin nonsusceptibility in invasive isolates.\textsuperscript{34,35}
With respect to noninvasive isolates in Spain, surveillance including high number of isolates has shown that nonsusceptibility to penicillin was 45%–50% from 1998 to 2002, with full oral penicillin resistance rates of approximately 20%.31,36 Amoxicillin nonsusceptibility remained around 10% in this period but, among full penicillin-resistant isolates, this rate increased to around 40%.31,36 These penicillin-resistant isolates exhibited nearly 100% resistance to oral second-generation cephalosporins, eg, cefaclor or cefuroxime, and 55% resistance to macrolides.31 In a worldwide surveillance (1999–2004) of isolates from community-acquired infections in patients ≥65 years (including a high number of noninvasive isolates), penicillin nonsusceptibility was approximately 22% in Eastern Europe and North America, and up to about 60% in Far East.37

The emergence of amoxicillin resistance within pre-existing penicillin-resistant clones has also been related to macrolide and ciprofloxacin resistance,31,36,38 with reports of spread of troublesome clones with MIC values of amoxicillin higher than those of penicillin,39 mainly the four Spanish multiresistant ones (Spain23F-1, Spain6B-2, Spain9V-3, and Spain14-5).31

Erythromycin resistance in pneumococci has remained relatively stable in Spain, with rates of around 35% between 1996 and 2002 in surveillances including high numbers of noninvasive isolates.31,36,40 The main resistant phenotype is MLSb (approximately 90%), with M-efflux representing approximately 10%,31 thus erythromycin resistance also implies clarithromycin and azithromycin resistance. Similar resistance rates are found in the US (30.0%–35.3%), with an increase in highly resistant strains in recent years, and a decrease in M-efflux-mediated resistant strains.31

In the same surveillance, ciprofloxacin resistance (MIC ≥ 4 μg/mL) was around 5%–7%,31,37 but >85% of these isolates were susceptible to levofloxacin and moxifloxacin. From these data it is deduced that rates of nonsusceptibility to respiratory fluoroquinolones (levofloxacin and moxifloxacin) are not >1%.36 Worldwide, a 2.2% nonsusceptibility rate has been reported for levofloxacin.37

Multiple resistance, defined as full resistance to two or more of the six classes of antibacterials represented by penicillin, erythromycin, cefuroxime, tetracyclines, trimethoprim-sulfamethoxazole, and levofloxacin, has been reported in S. pneumoniae, with rates as high as 19.1% in North America, 27.7% in Western Europe, and 80.4% in the Far East.37

**Streptococcus pyogenes**

*S. pyogenes* is highly susceptible to all β-lactams. Prevalence of resistance to erythromycin was 37% in 2001–2002 in Spain,31 with the M-efflux phenotype being the most prevalent (86%), and with 14% of strains from the MLSb phenotype showing constitutive resistance.31 Since both mechanisms imply resistance to 14- and 15-membered macrolides, erythromycin resistance implies resistance to azithromycin and clarithromycin.42

In the last few years, *S. pyogenes* isolates showing low-level resistance to fluoroquinolones have been reported,43-45 with infrequent high-level resistance to date. However, due to the high prevalence of isolates harboring parC mutation, in the near future the frequency of high-level resistance may increase because only one new mutation in gyrA is required.46 In Spain, there has been a marked increase in the number of isolates with low-level resistance, and isolates showing high-level resistance have also been detected.47

**Haemophilus influenzae**

The basic problem of resistance in this species is defined by ampicillin as the resistance marker. According to successive surveillance studies carried out from 1996 to 2002, approximately 25% of *H. influenzae* isolates are resistant to ampicillin in Spain.31,48,49 Up to 80% of these ampicillin-resistant isolates produce β-lactamases (TEM-1, TEM-2, and with lower frequency ROB-1) that are inhibited by clavulanic acid. The remaining 20% ampicillin-resistant isolates (5% of all *H. influenzae* isolates in Spain) are resistant to ampicillin due to mutations in the *fisI* gene that cause alterations in the amino acid sequences of penicillin-binding protein 3 (PBP3).50 This resistance genotype defines BLNAR (β-lactamase negative ampicillin-resistant) strains and since alterations in PBP3 preclude the adequate binding of ampicillin and amoxicillin, BLNAR strains are also resistant to amoxicillin–clavulanic acid, ampicillin–sulbactam, cefaclor, and cefuroxime.31

Both mechanisms of resistance, ie, β-lactamase production and mutations in the *fisI* gene, are present in BLPACR (β-lactamase positive amoxicillin–clavulanic acid resistant) strains. Among Spanish isolates, according to data from different studies, there is an increasing prevalence of BLNAR (from 10% in 1997–1998 to approximately 30% in 2004–2005) and to a lesser extent BLPACR phenotypes,52,53 in relation to β-lactam consumption over time, mainly amoxicillin with or without clavulanic acid.51

**Efficacy prediction for commonly used antibiotics**

While “microbiologic breakpoints” detect wild-type bacterial populations that do not harbor any acquired or selected resistance to the antibacterial examined,
“pharmacokinetic/pharmacodynamic (PK/PD) breakpoints” have been associated with microbial killing as an endpoint to predict bacterial eradication and clinical outcome. By relating pharmacokinetic variables and susceptibility data (ie, antibiotic drug exposure relative to in vitro MIC), PK/PD breakpoints indicate the highest MIC value that produces the adequate value for the relevant PK/PD parameter.

In the case of *S. pneumoniae* and *H. influenzae*, and β-lactams or macrolides, the time (expressed as the percentage of the dosing interval) that antibiotic concentrations exceed the value of MIC (T > MIC) is the parameter predicting efficacy, with a cutoff value of 40%, but in the case of fluoroquinolones, the parameter is the relationship between the area under the serum concentration-time curve (AUC) and the MIC (AUC/MIC), with a cutoff value of 30.

In a multicenter surveillance study in Spain, similar susceptibility rates were found for *S. pneumoniae* by applying the breakpoints defined by the Clinical Laboratory Standards Institute (CLSI) and PK/PD breakpoints for amoxicillin (approximately 92%), cefuroxime–axetil (about 67%), erythromycin and azithromycin (about 64%), but not for cefaclor (61.7% versus 40.5%).

For *H. influenzae*, the use of CLSI or PK/PD breakpoints does not influence susceptibility rates of ciprofloxacin (100%), ampicillin (about 75%) or amoxicillin–clavulanic acid (about 97%), but changes the rates of susceptibility to cefuroxime–axetil (from 100% to 72.8%) and cefaclor (from 82.1% to 1.4%), with lower rates when applying PK/PD breakpoints. In the case of macrolides, differences are clearly evident, with reductions in susceptibility rates to clarithromycin and azithromycin from 72% 100%, respectively, by applying CLSI breakpoints, to 2.2% and 1.2%, respectively, by applying PK/PD breakpoints.

**Management strategies to overcome resistance**

Under circumstances of a global problem of resistance among prevalent isolates in community respiratory pathogens, there is a need for strategies countering resistance, ie, selection of coresistance within the same species and coselection of resistances between species. One possible strategy is based on increasing oral doses for the treatment of respiratory tract infections in the community that, although not adequate for macrolides (high-level resistance), has been used in the case of amoxicillin–clavulanic acid, with the development of new formulations adequate to minimize amoxicillin resistance in *S. pneumoniae*, but inadequate to counter BLNAR and BLPACR diffusion among *H. influenzae*. Another possible strategy is the development of new antibiotics with adequate pharmacokinetics and high in vitro activity against community prevalent isolates, achieving values of pharmacodynamic parameters predicting bacterial eradication. The need for new antibiotics in the community is mainly defined by antimicrobial activity against the prevalent resistance phenotypes rather than the activity against phenotypes susceptible to antibiotics previously used in the community. For this reason new antibiotics for the treatment of respiratory tract infections should demonstrate in vitro activity against *S. pneumoniae* not susceptible to previous antibiotics (with specific phenotypes of resistance and clones) and *H. influenzae* nonsusceptible to ampicillin (BLNAR, BLPACR).

**Cefditoren for community-acquired respiratory tract infections**

*In vitro activity*

Cefditoren is an oral, third-generation aminothiazolyl cephalosporin with structural components similar to those of first- and third-generation cephalosporins. In general, cephalosporins differ from one another mainly in the two side chain components attached to the cephem scaffold. In cefditoren, the group attached at the C-7 position affords activity against first- and third-generation cephalosporins. In vitro studies carried out to explore the activity of cefditoren included not only a high number of strains isolated in the community but also a significant number of strains with troublesome resistance phenotypes/genotypes. Cefditoren exhibited potent intrinsic activity, inhibiting all penicillin-susceptible *S. pneumoniae* at concentrations of 0.12 µg/mL (MIC90 of ≤0.03 µg/mL). At concentrations of 0.5 µg/mL, cefditoren inhibited 92.6% of cefotaxime nonsusceptible pneumococci and >97% of strains nonsusceptible to the other antibiotics (penicillins, cephalosporins, macrolides, ketolides, and quinolones). With respect to Spanish multiresistant clones, cefditoren exhibited an MIC90 of ≤0.5 µg/mL against strains belonging to Spain14-5 (with susceptibility rates to amoxicillin–clavulanic acid of 4.2%, to macrolides of 66.7%, and to cefotaxime of 95.8%), Spain14-3 (with susceptibility rates to amoxicillin–clavulanic acid of 30%, to macrolides of 81.7%, and to cefotaxime of 85%), and Spain14-2 (with susceptibility rates to amoxicillin–clavulanic acid of 6.8%, to macrolides of 4.5%, and to cefotaxime of 81.8%). Against the most troublesome strains of the clone Spain14-5 (that exhibited susceptibility rates of 7.3%
to amoxicillin, 4.9% to macrolides, 57.3% to cefotaxime, and only 65.9% to levofloxacin, cefditoren MIC$_{50}$/MIC$_{90}$ values were 0.5/1 µg/mL, one dilution lower than values for cefotaxime.$^{60}$

Against *H. influenzae*, while amoxicillin–clavulanic acid and cefuroxime MIC$_{50}$/MIC$_{90}$ values increased from 0.5/1 µg/mL for amoxicillin-susceptible strains to 2/4 and 1/4 µg/mL, respectively, for BLNAR strains, and up to 4/8 and 4/16 µg/mL, respectively, for BLPACR strains, cefditoren exhibited similar intrinsic activity to that of cefotaxime against amoxicillin-susceptible, BLNAR and BLPACR strains with MIC$_{50}$/MIC$_{90}$ values of 0.03/0.06 µg/mL.$^{61,62}$ The excellent intrinsic activity of cefditoren against *H. influenzae* has recently been confirmed in a multicenter European study testing 665 clinical isolates, with MIC$_{50}$/MIC$_{90}$ for cefditoren of ≤0.06/≤0.06 µg/mL.$^{63}$

**Pharmacokinetics and pharmacodynamics**

In a Phase I study administering a single dose of 400 mg cefditoren–pivoxil with food to 10 healthy Caucasian male volunteers, Cmax was 3.7 ± 0.7 µg/mL, T$_{max}$ was 2 hours, AUC$_{0-4}$ was 12.5 ± 1.6 µg × h/mL, and the elimination half-life was 1.54 ± 0.20 hours.$^{64}$ In the theoretical pharmacodynamic assessment performed with these data, considering T > MIC as the relevant PK/PD parameter, the 400 mg bid regimen of cefditoren–pivoxil obtained a value of T > MIC for total drug of approximately 55% for MIC 0.5 µg/mL, 68% for MIC 0.25 µg/mL, 81% for MIC 0.12 µg/mL and 94% for MIC 0.06 µg/mL.$^{64}$

This pharmacodynamic analysis was performed considering the total drug. Cefditoren is a highly protein-bound antimicrobial with 88% protein binding.$^{37}$ It has been suggested that only the unbound fraction of an antimicrobial is active *in vitro*, but the reversibility of protein binding implies that limitation of activity may be far from absolute, even in highly protein-bound agents.$^{65}$ To explore the activity of cefditoren in the presence of human albumin, a one-compartmental *in vitro* dynamic model simulating the cefditoren 400 mg bid serum profile over 24 hours, using media consisting of 75% human serum and 25% broth with albumin at physiologic concentration (4.9 g/dL), was used.$^{66}$ Antibacterial activity was determined over time against *S. pneumoniae* exhibiting MICs of 0.25 and 0.5 µg/mL.$^{66}$ The cefditoren protein binding in the system was 87.1%, thus potentially interfering with cefditoren activity as in *in vivo* situations. Under these circumstances, at 24 hours, initial inoculum reductions for strains with MIC of 0.25 µg/mL was >99.9% (bactericidal activity), and ranged from 53% to 97% (an effect higher than simply bacteriostatic) for strains with MIC 0.5 µg/mL.$^{66}$

For extrapolation to humans, a Monte Carlo simulation, i.e., the method for determining the probability to achieve a specific value of a PK/PD index in the general population, was performed using cefditoren data from a Phase I study,$^{64}$ and considering both total and free (calculated using the rate of protein binding) concentrations of cefditoren.$^{67}$ Considering the target attainment of T > MIC ≥ 40% (as predictive of efficacy),$^{68,69}$ cefditoren covered (>90% probability to achieve this value of T > MIC) strains with MIC values of ≤0.5 µg/mL (total drug), and ≤0.12 µg/mL (free drug). When the bacteriostatic target attainment (33% T > MIC)$^{70}$ was considered, based on definitions of “susceptibility” by the FDA$^{71}$ and CLSI$^{51}$ as “pathogen likely inhibition by blood concentrations”, cefditoren had a >90% probability to achieve this bacteriostatic endpoint for MICs ≤0.5 µg/mL and ≤0.25 µg/mL for total and free drug, respectively.$^{67}$

**Cefditoren breakpoints**

Experimental data (*in vitro* susceptibility and PK/PD experimental data) and Monte Carlo extrapolations are valuable data for assessing potential breakpoints for cefditoren. Different values have been proposed or defined for cefditoren. While breakpoint values proposed by the FDA are ≤0.12 µg/mL for susceptibility and ≤0.5 µg/mL for resistance, some authors have suggested cefditoren susceptibility breakpoint values of ≤0.5 µg/mL or ≤1 µg/mL,$^{72-74}$ considering cefditoren MIC$_{90}$ values lower than the breakpoint values for parenteral third-generation cephalosporins and the pharmacokinetics of cefditoren. Although nowadays there are no established breakpoints defined by the CLSI or the European Committee on Antimicrobial Susceptibility Testing, experimental and Monte Carlo results are in accordance with the susceptibility breakpoint approved by the Spanish Agency during the registration procedure in Europe (susceptibility ≤0.5 µg/mL).$^{75}$ With this breakpoint value, 100% isolates of *H. influenzae* and *S. pyogenes* and 94% of *S. pneumoniae* are covered in Spain.$^{76}$

**Clinical data on cefditoren in community-acquired respiratory tract infections**

Upper respiratory tract infections

Data from all six clinical trials carried out during the clinical development of cefditoren in upper respiratory tract infections were combined in a pooled analysis.$^{77}$ With
respect to pharyngotonsillitis, no significant differences in clinical response were found between cefditoren and penicillin V, with success rates ranging from 89.4% to 95.3% when pooling data from the three comparative multicenter studies (two previously published)78,79 already performed.77 Eradication of S. pyogenes was higher with cefditoren at the end of therapy (90.4% versus 82.7%; P = 0.002) and at the end of follow-up (84.7% versus 76.7%; P = 0.008), although statistical significance (set at P < 0.001) was not reached.77

Similarly, in acute sinusitis, no differences in clinical response were found between cefditoren and comparators (cefuroxime or amoxicillin-clavulanic acid) both at the end of therapy (80.2% versus 84.8%) and at the end of follow-up (71.2% versus 77.4%) pooling data from the three studies (one previously published)80 performed during the clinical development of cefditoren.77

Lower respiratory tract infections
Seven studies were carried out in the clinical development of cefditoren for the treatment of lower respiratory tract infections, four studies in community-acquired pneumonia (CAP), and three studies in AECB. A pooled analysis of data was performed including a total of 4159 randomized patients.81 In CAP studies (two previously published),82,83 no significant differences were found in pooled clinical response rates between cefditoren and comparators (amoxicillin–clavulanic acid or cefpodoxime), with percentages of responders ranging from 89.2% to 91.8% at the end of therapy, and from 85.9% to 90.4% at the end of follow-up.

In AECB, pooled data from the three published studies84-86 showed clinical response rates ranging from 85.8% to 91.3% at the end of therapy, and from 81.2% to 83.3% at the end of follow-up, without significant differences between cefditoren and the comparators, ie, cefuroxime or clarithromycin.

CAP and AECB data were pooled to explore microbiologic outcomes.81 With respect to S. pneumoniae, there were no significant between-group differences in the rate of bacteriologic responders, with rates ranging from 88.5% to 92.0%. All penicillin nonsusceptible (MIC  $\geq$0.12 µg/mL) isolates of S. pneumoniae in the cefditoren 400 mg group (n = 20), 16 of 19 strains (84.2%) in the cefditoren 200 mg group, and 16 of 17 strains (94.1%) in the comparator group were eradicated or presumed to be eradicated.81 Among penicillin-resistant (MIC  $\geq$2 µg/mL) isolates, 17 of 18 (94.4%) isolates in both cefditoren arms were eradicated or presumed to be eradicated compared with 10 of 11 (90.9%) in the comparator group.81 No significant differences in microbiologic outcome with respect to H. influenzae were found between groups, with pooled response rates ranging from 82.7% to 86.6%.81

Safety profile
Safety data from all the 13 clinical trials carried out with cefditoren in the treatment of community-acquired respiratory tract infections were analyzed in a pooled analysis. The safety population was defined as all randomized patients with at least one dose intake, and consisted of 4592 patients for cefditoren. Cefditoren exhibited an adverse event profile similar to that of other antibiotics currently used in the treatment of community-acquired respiratory tract infections, with diarrhea being the most frequent adverse event (9.9%) followed by nausea (3.5%), abdominal pain (1.8%), and dyspepsia (1.1%).87 The rate of vaginosis reported in the female population was 3.9%.87

Conclusions
There is increasingly evidence confirming that bacterial eradication should be the primary goal of antibiotic therapy because eradication is the main determinant of both therapeutic outcome and prevention of resistance. In the most prevalent bacterial isolates from community-acquired respiratory tract infections, that are responsible for 80% of consumption of antibiotics in the community, there is a global problem of resistance. This means that geographic correlations of resistances are consistently found between different antibiotics in one species and in different species, due to the selection of coresistance and coselection of resistance by antibiotic pressure. Resistance has traditionally implied the development of new antibiotics for which basic efficacy and safety data are required prior to licensing. However, during the clinical development of a new compound, apart from collecting data on safety and tolerance, there is a need to explore the adequacy of pharmacodynamic parameters in predicting eradication (bacteriologic response) and subsequent clinical efficacy to establish breakpoints. Since evolution of bacteria towards resistance is a dynamic process, several issues should also be addressed after the introduction of a new antibiotic to the market. These issues will establish differences between the new compound and older antibiotics, and are mainly focused on the pharmacodynamic data needed to predict selection of resistance and of resistant subpopulations in multibacterial niches (simulating the nasopharynx as the specific site for emergence of resistance in respiratory tract isolates), followed in the postmarketing phase by...
specific surveillance on resistance to core antibiotics to detect emerging resistances and any link with antibiotic consumption in the community. This will define the role of the new antibiotic, not only from the perspective of its therapeutic potential, but also from the ecologic perspective, ie, countering resistances to core antibiotics in the community. The introduction of new antibiotics with documented adequate PK/PD and ecologic potentials might impact antibiotic policies, ie, decreased use of antibiotics with high resistance selection potential.

The documented information on cephalotin gathered from published studies in recent years, including those showing its ecologic potential in multibacterial niches, is an example of the role for an emerging oral antibacterial facing the current antibiotic resistances in community-acquired respiratory tract infections.

Disclosures
LA and MJG have received travel grants from Tedec-Meiji Farma SA, Madrid, Spain for Congress presentation of results of research carried out at the Microbiology Department, School of Medicine, University, Complutense, Madrid, Spain.

References
1. Brook I, Gober AE. Recovery of potential pathogens and interfering bacteria in the nasopharynx of otitis media-prone children and their smoking and nonsmoking parents. Arch Otolaryngol Head Neck Surg. 2005;131:509–512.
2. Sá-Leão R, Nunes S, Brito-Avô A, et al. High rates of transmission of colonization by Streptococcus pneumoniae and Haemophilus influenzae within a day care center revealed in a longitudinal study. J Clin Microbiol. 2008;46:225–234.
3. Hammitt LL, Bruden DL, Butler JC, et al. Indirect effect of conjugate vaccine on adult carriage of Streptococcus pneumoniae: An explanation of trends in invasive pneumococcal disease. J Infect Dis. 2006;193:1487–1494.
4. Murthy TF. Haemophilus influenzae. In: Mandell GL, Bennett JE, Dolin R, editors. Principles and Practice of Infectious Diseases. 6th ed. Philadelphia, PA: Elsevier Churchill Livingstone; 2005.
5. Smith-Vaughan HC, Leach AJ, Shelby-James TM, Kemp K, Kemp DJ, Mathews JD. Carriage of multiple ribotypes of non-encapsulated Haemophilus influenzae in aboriginal infants with otitis media. Epidemiol Infect. 1996;116:177–183.
6. Musher DM. Streptococcus pneumoniae. In: Mandell GL, Bennett JE, Dolin R, editors. Principles and Practice of Infectious Diseases. 6th ed. Philadelphia, PA: Elsevier Churchill Livingstone; 2005.
7. Sá-Leão R, Tomasz A, Santos Sanches I, de Lancastre H. Pilot study of the genetic diversity of the pneumococcal nasopharyngeal flora among children attending day care centers. J Clin Microbiol. 2002;40:3577–3585.
8. Melegaro A, Choi Y, Pehboy R, Gay N. Pneumococcal carriage in United Kingdom families: Estimating serotype-specific transmission parameters from longitudinal data. Am J Epidemiol. 2007;166:228–235.
9. Ekáhl K, Ahlinder I, Hansson HB, et al. Duration of nasopharyngeal carriage of penicillin-resistant Streptococcus pneumoniae: Experiences from the South Swedish Pneumococcal Intervention Project. Clin Infect Dis. 1997;25:1113–1117.
10. Bisno AL, Stevens DL. Streptococcus pyogenes. In: Mandell GL, Bennett JE, Dolin R, editors. Principles and Practice of Infectious Diseases. 6th ed. Philadelphia, PA: Elsevier Churchill Livingstone; 2005.
11. Cafini F, Aguilar L, Sevillano D, et al. Decrease in bacterial load versus resistance selection of pneumococcal subpopulations by β-lactam physiological concentrations over time: An in vitro pharmacodynamic simulation. Microbiol Drug Res. 2008;14:13–21.
12. Sevillano D, Aguilar L, Alou L, et al. Effects of antimicrobials on the competitive growth of Streptococcus pneumoniae: A pharmacodynamic in vitro model approach to selection of resistant populations. J Antimicrob Chemother. 2006;58:794–801.
13. Baquero F. Modularization and evolvability in antibiotic resistance. In: Baquero F, Nombela C, Cassell GH, Gutierrez-Fuentes JA, editors. Evolutionary Biology of Bacterial and Fungal Pathogens. Washington, DC: ASM Press; 2008.
14. Courvalin P. Antimicrobial drug resistance: Prediction is very difficult, especially about the future. Emerg Infect Dis. 2005;11:1503–1506.
15. Smith DL, Laxminarayan R. Human interventions on the evolution of host-bacterium interactions. In: Baquero F, Nombela C, Cassell GH, Gutierrez-Fuentes JA, editors. Evolutionary Biology of Bacterial and Fungal Pathogens. Washington, DC: ASM Press; 2008.
16. Knudsen JD, Odenholt I, Erlandsdottir H, et al. Selection of resistant Streptococcus pneumoniae during penicillin treatment in vitro and in three animal models. Antimicrob Agents Chemother. 2003;47:2499–2506.
17. Campos J, Aracil B, Garcia-Cobos S, Oteo J. Evolution of Haemophilus influenzae and Haemophilus infections. In: Baquero F, Nombela C, Cassell GH, Gutierrez-Fuentes JA, editors. Evolutionary Biology of Bacterial and Fungal Pathogens. Washington, DC: ASM Press; 2008.
18. Takahata S, Kato Y, Sanbongi Y, Maebashi K, Ida T. Comparison of the efficacy of oral (beta)-lactams in selection of Haemophilus influenzae transformants with mutated fts I genes. Antimicrob Agents Chemother. 2008;52:1880–1883.
19. Jönsson M, Swedberg G. Macrolide resistance can be transferred by conjugation from viridans streptococci to Streptococcus pyogenes. Int J Antimicrob Agents. 2006;28:101–103.
20. Alou L, Gimenez MJ, Sevillano D, et al. A pharmacodynamic approach to antimicrobial activity in serum and epithelial lining fluid against in vivo-selected Streptococcus pneumoniae mutants and association with clinical failure in pneumonia. J Antimicrob Chemother. 2006;58:349–358.
21. Garcia-Rey C, Fenoll A, Aguilar L, Casal J. Effect of social and climatological factors on antimicrobial use and Streptococcus pneumoniae resistance in different provinces in Spain. J Antimicrob Chemother. 2004;54:465–471.
22. Llor C. Considerations for antibiotic prescription in primary care. Med Clin Monogr (Barc). 2004;5(3):52–57.
23. Mogyorós C. Challenges of managed care organisations in treating respiratory tract infections in an age of antibiotic resistance. Am J Manag Care. 2001;7(Suppl 6):163–169.
24. Huovinen P, Cars O. Control of antimicrobial resistance: Time for action. The essentials of control are already well known. BMJ. 1998;317:613–614.
25. Granizo JJ, Aguilar L, Casal J, Garcia-Rey C, Dal-Ré R, Baquero F. Streptococcus pneumoniae resistance to erythromycin and penicillin in relation to macrolide and beta-lactam consumption in Spain (1979–1997). J Antimicrob Chemother. 2000;46:767–773.
26. Garcia-Rey C, Aguilar L, Baquero F, Casal J, Dal-Ré R. Importance of local variations in antibiotic consumption and geographical differences of erythromycin and penicillin resistance in Streptococcus pneumoniae. J Clin Microbiol. 2002;40:159–164.
27. Gómez J, Ruiz-Gómez J, Hernández-Cardona JL, Nuñez ML, Canetares M, Valdés M. Antibiotic resistance patterns of Streptococcus pneumoniae, Haemophilus influenzae and Moraxella catarhalis: A prospective study in Murcia, Spain, 1983–1992. Chemotherapy. 1994;40:299–303.
43. Albertí S, Cortés G, García-Rey C, et al.

41. Jenkins SG, Farrell DJ. Increase in pneumococcus macrolide resistance, and susceptible isolates among penicillin-non-susceptible Streptococcus pneumoniae isolates in Spain from 1979 to 2007. J Clin Microbiol. 2009;47:1012–1020.

42. Pérez-Trallero E, Marimón JM, Ercibengoa M, Giménez MJ, Coronel P, et al. Antimicrobial susceptibility of 1,730 Haemophilus influenzae respiratory tract isolates in Spain in 1998–1999. Antimicrob Agents Chemother. 2001;45:3334–3340.

45. Malhotra-Kumar S, Van Heirstraeten L, Lammens C, Chapelle S, Goossens H. Emergence of high-level fluoroquinolone resistance in emm6 Streptococcus pyogenes and in vitro resistance selection with ciprofloxacin, levofloxacin and moxifloxacin. J Antimicrob Chemother. 2009;63:886–894.

46. García-Rodriguez JA, Baquero F, García de Lomas J, Aguilar L. Antimicrobial susceptibility of 1,422 Haemophilus influenzae isolates from respiratory tract infections in Spain. Results of a 1-year (1996–97) multicenter surveillance study. Spanish Surveillance Group for Respiratory Pathogens. Infection. 1999;27:265–267.

Montes M, Tamayo E, Orden B, Larruskain J, Perez-Trailero E. Prevalence and clonal characterization of Streptococcus pyogenes clinical isolates with reduced fluoroquinolone susceptibility in Spain. Antimicrob Agents Chemother. 2010;54:93–97.

48. Garcia-Rodriguez JA, Baquero F, Garcia de Lomas J, Aguilar L. Antimicrobial susceptibility of 1,113 Streptococcus pneumoniae isolates from patients with respiratory tract infections in Spain: Results of a 1-year (1996–1997) multicenter surveillance study. The Spanish Surveillance Group for Respiratory Pathogens. Antimicrob Agents Chemother. 1999;43:357–359.

49. Jenkins SG, Farrell DJ. Increase in pneumococcus macrolide resistance, and susceptible isolates among penicillin-non-susceptible Streptococcus pneumoniae. Clin Microbiol Infect. 2007;13:937–940.

50. Matic V, Bozdogan B, Jacobs MR, Ubukata K, Appelbaum PC. Contribution of beta-lactamase and PBP amino acid substitutions to amoxicillin/clavulanic acid resistance in beta-lactamase-positive, amoxicillin/clavulanic-resistant Haemophilus influenzae. J Antimicrob Chemother. 2003;52:1015–1021.

51. Clinical and Laboratory Standards Institute. Performance standards for antimicrobial susceptibility testing; nineteenth informational supplement. CLSI document M100-S19. Wayne, PA: Clinical and Laboratory Standards Institute; 2009.

52. Jansen WT, Verel A, Beitsma M, Verhoef J, Milatovic D. Longitudinal European surveillance study of antibiotic resistance of Haemophilus influenzae. J Antimicrob Chemother. 2006;58:873–877.

53. García-Cobos S, Campos J, Lázaro E, et al. Ampicillin-resistant non-beta-lactamase-producing Haemophilus influenzae in Spain: Recent emergence of clinical isolates with increased resistance to cefotaxime and cefixime. Antimicrob Agents Chemother. 2007;51:2564–2573.

54. MacGowan AP. Elements of design: The knowledge on which we build. Clin Microbiol Infect. 2004;10 Suppl 2:6–11.

55. Druzano GL. Antimicrobial pharmacodynamics: Critical interactions of ‘bug and drug’. Nat Rev Microbiol. 2004;2:288–300.

56. Turnidge JD, Paterson DL. Setting and revising antibacterial susceptibility breakpoints. Clin Microbiol Rev. 2007;20:391–408.

57. Wellington K, Curran MP. Cefditoren pivoxil: A review of its use in the treatment of bacterial infections. Drugs. 2004;64:2597–2618.

58. Fenoll A, Giménez MJ, Robledo O, et al. 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.

59. Fenoll A, Giménez MJ, Robledo O, et al. 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.

60. Pérez-Trailero E, Marínón JM, Ercibengoa M, Giménez MJ, Coronel P, Aguilar L. Antimicrobial susceptibilities of amoxicillin-non-susceptible and susceptible isolates among penicillin-non-susceptible Streptococcus pneumoniae. Clin Microbiol Infect. 2009;25:267–270.
63. Gracia M, Díaz C, Coronel P, et al. 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.

64. Sádaba B, Azanza JR, Quetglas EG, et al. 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.

65. Moellerig RC, Eliopoulos GM. Principles of anti-infective therapy. In: Mandell GL, Bennett JE, Dolin R, editors. *Principles and Practice of Infectious Diseases*. 6th ed. Philadelphia, PA: Elsevier Churchill Livingstone; 2005.

66. Sevillano D, Aguilar L, Alou L, et al. High protein binding and cidal activity against penicillin-resistant *S. pneumoniae*: A cefditoren in vitro pharmacodynamic simulation. *PLoS One*. 2008;3(7):e2717.

67. Granizo JJ, Sádaba B, Honorato J, et al. Monte Carlo simulation describing the pharmacodynamic profile of cefditoren in plasma from healthy volunteers. *Int J Antimicrob Agents*. 2008;31:396–398.

68. Craig WA. Pharmacokinetic/pharmacodynamic parameters: Rationale for antibacterial dosing of mice and men. *Clin Infect Dis*. 1998;26:1–10.

69. Heffelfinger JD, Dowell SF, Jorgensen JH, et al. Management of community-acquired pneumonia in the era of pneumococcal resistance: A report from the Drug-Resistant *Streptococcus pneumoniae* Therapeutic Working Group. *Arch Intern Med*. 2000;160:1399–1408.

70. Lodise TP, Kinzig-Schippers M, Drusano GL, et al. Use of population pharmacokinetic modeling and Monte Carlo simulation to describe the pharmacodynamic profile of cefditoren in plasma and epithelial lining fluid. *Antimicrob Agents Chemother*. 2008;52:1945–1951.

71. US Food and Drug Administration. www.fda.gov

72. Karlowsky JA, Jones ME, Draghi DC, Critchley IA, Thornberry C, Sahn DF. In vitro susceptibility of recent clinical isolates of pneumococci to the investigational cephalexin cefditoren. *Diagn Microbiol Infect Dis*. 2002;42:59–64.

73. Johnson DM, Biedenbach DJ, Beach ML, Pfaffer MA, Jones RN. Antimicrobial activity and *in vitro* susceptibility test development for cefditoren against *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus* species. *Diagn Microbiol Infect Dis*. 2000;37:99–105.

74. Jones RN, Biedenbach DJ, Croco MA, Barrett MS. In vitro evaluation of a novel orally administered cephalexin (Cefditoren) tested against 1249 recent clinical isolates of *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae*. *Diagn Microbiol Infect Dis*. 1998;31:573–578.

75. Agencia Española de Medicamentos y Productos Sanitarios. Available at: https://sinaem4.agemed.es/consaem/fichasTecnicas.do?metodo=detalleForm. Accessed on Apr 29, 2010.

76. Giménez MJ, Gómez-Lus ML, Valdés L, Aguilar L. The role of third-generation oral cephalexin cefditoren pivoxil in the treatment of community-acquired infection in adults. *Rev Esp Quimioter*. 2005;18:210–216.

77. Granizo JJ, Giménez MJ, Barberán J, Coronel P, Gimeno M, Aguilar L. Efficacy of cefditoren in the treatment of upper respiratory tract infections: A pooled analysis of six clinical trials. *Rev Esp Quimioter*. 2008;21:14–21.