

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

Correspondence: Lorenzo Aguilar
Microbiology Department, School of Medicine, University Complutense, Avda. Complutense s/n, 28040 Madrid, Spain
Tel +34 913 941 505
Fax +34 913 941 511
Email laguilar@med.ucm.es

bacterial interference in antibiotic-free niches.^{1–3} Approximately 80% of healthy individuals carry *H. influenzae*,⁴ with multiple strains in 50% positive samples and a high turnover of strains.^{2,5} In the case of *S. pneumoniae*, carriage ranges from 10% to 40% in an age-dependent manner,⁶ with lower percentages of multiple strains in the same sample⁷ and a duration of nasopharyngeal carriage depending on age, seasonality, resistance to penicillin, serotype, and simultaneous carriage by other family members.^{8,9} *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.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.^{11,12} Resistance to β -lactams and macrolides is mostly due to acquisition of exogenous resistance genes, and has been described in *S. pneumoniae* and *H. influenzae* (in both cases, resistance to both β -lactams and to macrolides) and in *S. pyogenes* (resistance to macrolides),^{13–16} with *de novo* resistance occurring rarely within a given host in a susceptible bacterial population.¹³ In contrast, resistance to fluoroquinolones in *S. pneumoniae* arises within a given host due to point mutations.¹³

Evolution is based on production of variation, management of variation, and natural selection of variants.¹⁷ Dynamics of different bacterial populations in antibiotic-free niches are the baseline that antibiotic treatments can alter^{18,19} by shifting the competitive balance in favor of resistant populations. For this reason, antibiotic resistance is increasingly regarded as an ecologic problem. Once resistance has emerged, physiologic concentrations of different antibiotics may select resistant strains by eradicating the susceptible ones (thus unmasking resistant populations),¹⁹ or by selecting intrastrain-resistant subpopulations.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.²¹

Antibiotic consumption as the driver of resistance: a global problem

Infection, mainly of the respiratory tract,^{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.²⁴ Antibiotic consumption has been associated with resistance selection.²¹ Consumption of β -lactams and macrolides has been associated with penicillin/erythromycin resistance in *S. pneumoniae*, both temporally²⁵ and geographically,²⁶ with high correlations between penicillin/erythromycin resistance and consumption of long half-life macrolides and second-generation oral cephalosporins.^{25,26} Associations between ampicillin/amoxicillin resistance in *H. influenzae* and *Moraxella catarrhalis* and consumption of aminopenicillins (with or without clavulanic acid),^{27,28} as well as the association between erythromycin resistance in *S. pyogenes* and consumption of long half-life macrolides, have also been described.^{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 *S. pneumoniae* has been significantly associated with erythromycin resistance (due to the coresistance selection phenomenon),^{31,32} and with ampicillin resistance in *H. influenzae* (due to the phenomenon of coselection of resistance). In addition, geographically, erythromycin resistance in *S. pyogenes* was significantly related to penicillin and/or erythromycin resistance in *S. pneumoniae* and to ampicillin resistance in *H. influenzae*.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

Streptococcus pneumoniae

Penicillin/erythromycin nonsusceptibility in *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.^{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.^{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 (Spain^{23F}-1, Spain^{6B}-2, Spain^{9V}-3, and Spain¹⁴-5).

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 MLS_B (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.⁴¹

In the same surveillance, ciprofloxacin resistance (MIC ≥ 4 μ g/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 MLS_B 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 *ftsI* 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.⁵¹

Both mechanisms of resistance, ie, β -lactamase production and mutations in the *ftsI* 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.⁵³

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.^{54–56} 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%).³¹

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.³¹ 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.³¹

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.⁵⁷ 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 Gram-negative microorganisms, whereas the one attached at the C-3 position affords activity against Gram-positive bacteria (not seen in other non-first-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 $\mu\text{g/mL}$ (MIC_{90} of $\leq 0.03 \mu\text{g/mL}$).⁵⁸ At concentrations of 0.5 $\mu\text{g/mL}$, cefditoren inhibited 92.6% of cefotaxime nonsusceptible pneumococci and $>97\%$ of strains nonsusceptible to the other antibiotics (penicillins, cephalosporins, macrolides, ketolides, and quinolones).⁵⁹ With respect to Spanish multiresistant clones, cefditoren exhibited an MIC_{90} of $\leq 0.5 \mu\text{g/mL}$ against strains belonging to Spain^{23F}-1 (with susceptibility rates to amoxicillin–clavulanic acid of 4.2%, to macrolides of 66.7%, and to cefotaxime of 95.8%), Spain^{9V}-3 (with susceptibility rates to amoxicillin–clavulanic acid of 30%, to macrolides of 81.7%, and to cefotaxime of 85%), and Spain^{6B}-2 (with susceptibility rates to amoxicillin–clavulanic acid of 6.8%, to macrolides of 4.5%, and to cefotaxime of 81.8%).⁶⁰ 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), ceftidoren MIC₅₀/MIC₉₀ values were 0.5/1 µg/mL, one dilution lower than values for cefotaxime.⁶⁰

Against *H. influenzae*, while amoxicillin–clavulanic acid and cefuroxime MIC₅₀/MIC₉₀ values increased from 0.5/1 µg/mL for ampicillin-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, ceftidoren exhibited similar intrinsic activity to that of cefotaxime against ampicillin-susceptible, BLNAR and BLPACR strains with MIC₅₀/MIC₉₀ values of 0.03/0.06 µg/mL.^{61,62} The excellent intrinsic activity of ceftidoren against *H. influenzae* has recently been confirmed in a multicenter European study testing 665 clinical isolates, with MIC₅₀/MIC₉₀ for ceftidoren of ≤0.06/≤0.06 µg/mL.⁶³

Pharmacokinetics and pharmacodynamics

In a Phase I study administering a single dose of 400 mg ceftidoren–pivoxil with food to 10 healthy Caucasian male volunteers, C_{max} was 3.7 ± 0.7 µg/mL, T_{max} was 2 hours, AUC_{0–∞} was 12.5 ± 1.6 µg × hour/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 ceftidoren–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. Ceftidoren is a highly protein-bound antimicrobial with 88% protein binding.⁵⁷ 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 ceftidoren in the presence of human albumin, a one-compartmental *in vitro* dynamic model simulating the ceftidoren 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 ceftidoren protein binding in the system was 87.1%, thus potentially interfering with ceftidoren 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, ie, the method for determining the probability to achieve a specific value of a PK/PD index in the general population, was performed using ceftidoren data from a Phase I study,⁶⁴ and considering both total and free (calculated using the rate of protein binding) concentrations of ceftidoren.⁶⁷ Considering the target attainment of T > MIC ≥ 40% (as predictive of efficacy),^{68,69} ceftidoren 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 FDA⁷¹ and CLSI⁵¹ as “pathogen likely inhibition by blood concentrations”, ceftidoren 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

Ceftidoren breakpoints

Experimental data (*in vitro* susceptibility and PK/PD experimental data) and Monte Carlo extrapolations are valuable data for assessing potential breakpoints for ceftidoren. Different values have been proposed or defined for ceftidoren. 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 ceftidoren susceptibility breakpoint values of ≤0.5 µg/mL or ≤1 µg/mL,^{72–74} considering ceftidoren MIC₉₀ values lower than the breakpoint values for parenteral third-generation cephalosporins and the pharmacokinetics of ceftidoren. 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 ceftidoren in community-acquired respiratory tract infections

Upper respiratory tract infections

Data from all six clinical trials carried out during the clinical development of ceftidoren 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 studies^{84–86} 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 ($\text{MIC} \geq 0.12 \mu\text{g/mL}$) 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 ($\text{MIC} \geq 2 \mu\text{g/mL}$) 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.⁸⁷ 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.⁸⁸ 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 cefditoren gathered from published studies in recent years, including those showing its ecologic potential in multibacterial niches,^{11,89} is an example of the role for an emerging oral antibacterial facing the current antibiotic resistances in community-acquired respiratory tract infections.

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