Antibiotic susceptibility of respiratory pathogens recently isolated in Italy: focus on ceftidoren

Journal of Chemotherapy Vol. 22 - n. 3 (153-159) - 2010

Antibiotic Susceptibility of Respiratory Pathogens Recently Isolated in Italy: Focus on Cefditoren

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Summary

The aim of this study was to evaluate the *in vitro* antibiotic susceptibility of respiratory pathogens recently isolated in Italy to commonly used antibiotics including cefditoren. Six clinical microbiological laboratories collected, between January and September 2009, a total of 2,510 respiratory pathogens from subjects with community-acquired respiratory tract infections (CARTI). Cefditoren, out of all the beta-lactams studied, had the lowest MIC_{90} against 965 strains of *Streptococcus pneumoniae* examined, followed by cefotaxime and ceftriaxone (2% resistance in penicillin-resistant *S. pneumoniae* (PRSP)). Against 470 *Haemophilus influenzae*, independently of their production of beta-lactamases or ampicillin resistance, cefditoren was the oral cephalosporin with the best *in vitro* activity, comparable to that of the injectable cephalosporins and levofloxacin. Higher MIC_{90}s were found for the macrolides (4 - 16 mg/L) and cefaclor (4 - 32 mg/L). As was foreseeable, *Streptococcus pyogenes* (225 strains) was uniformly sensitive to all the beta-lactam antibiotics, but the elevated MIC_{90} values reduced (<75%) susceptibility of this pathogen to macrolides. Beta-lactamase-negative *Moraxella catarrhalis* (100 strains) had reduced susceptibility only to the macrolides, while the 250 beta-lactamase-producing strains also had reduced susceptibility to cefuroxime. Levofloxacin showed the lowest MIC_{50}/MIC_{90} values in the producing strains, whereas cefditoren, cefotaxime and ceftriaxone in the non-producers. As regards the Enterobacteriaceae, cefditoren and levofloxacin had the lowest MIC_{90}s against *Klebsiella pneumoniae*. Cefditoren and the third-generation injectable cephalosporins had the lowest MIC_{90}s against *Escherichia coli* (100% susceptibility) while levofloxacin was less active (86% susceptibility).

In conclusion, cefditoren's wide spectrum and high intrinsic activity, as well as its capacity to overcome most of the resistance that has become consolidated in some classes of antibiotics widely used as empiric therapy for CARTI, allows us to suggest that cefditoren might be included in the European guidelines as one of the first-choice antibiotics in the treatment of CARTI.

***Key words*: Cefditoren, respiratory pathogens, susceptibility patterns, epidemiological study.**

INTRODUCTION

Acute community-acquired respiratory tract infections (CARTI), one of the principal causes of morbidity and mortality in the world,[1] are the primary cause of antibiotic use. Antimicrobial therapy of respiratory tract infections is generally empiric, both due to the severity of the disease (community-acquired pneumonia, CAP) that requires early therapy, and due to the difficulty of establishing a microbial etiology, as in the polymicrobial forms of acute or chronic otitis media, and in acute exacerbations during chronic bronchitis and sinusitis.[2]

While the community-acquired infectious etiology has not really changed over time, antibiotic resistance complicates treatment which then leads to therapeutic failure, relapse, prolonged symptoms and hospital stay, as well as increasing costs.

Since the 1980s there has been decreased sensitivity among all the respiratory pathogens to various antimicrobial drugs. The production of beta-lactamases occurs more frequently in *Haemophilus influenzae* and *Moraxella catarrhalis,* but *Streptococcus pneumoniae* can be resistant to beta-lactams and macrolides too.[3,4,5,6] The resistance to third-generation cephalosporins, with or without concomitant resistance to penicillin, is particularly alarming.[7]

Since the development of bacterial resistance to antibiotics is a worldwide and multifactorial phenomenon, the mechanisms and lack of sensitivity can vary among countries as well as regions of the same country.[2]

To establish correct empiric therapy, reduce the development of resistance and evaluate the potential use of new eradication strategies, it is necessary to have up-to-date data on the frequency of resistance in different geographic areas as well as on the activity of new antimicrobial drugs that are available to physicians.

Over the last few years, antibiotic resistance observed in pathogens responsible for CARTI has complicated the empiric choice of antibiotic therapy, leading to the necessity of using recent generation macrolides, cephalosporins, beta-lactam/beta-lactamase-inhibitor combinations, or fluoroquinolones.[8,9]

Despite the fact that all these drugs have different degrees of antimicrobial effectiveness, the new generation of oral cephalosporins offers better advantages, such as improved spectrum, rapid bactericidal activity, low rates of spontaneous mutation, extended post-antibiotic effect, and well-known safety profiles.[10-14]

The recent introduction in Italy of cefditoren pivoxil in 2008, a third-generation oral cephalosporin, active against both Gram-positive (*S. pneumoniae*, *Streptococcus pyogenes* and *Staphylococcus aureus,* MSSA), and Gram-negative (*H. influenzae*

 ISSN 1120-009X

and *M. catarrhalis*) bacteria,[10,12-13,15] and thus indicated in the treatment of acute pharyngotonsillitis, acute maxillary sinusitis, acute exacerbations of chronic bronchitis, and slight to moderate CAP, is of particular interest.[15-20]

Cefditoren's antimicrobial mechanism of action, common to all cephalosporins, consists in its inhibition of cell-wall synthesis thanks to its affinity for PBPs. However, its unique structure at the C-3 side chain of its cephem skeleton has been correlated with higher intrinsic activity against *S. pneumoniae*, both susceptible and resistant to penicillin (PSSP and PRSP).[21-22]

Administered orally, cefditoren pivoxil is absorbed in the gastrointestinal tract and then the active component cefditoren is hydrolyzed by plasmatic esterases.[23]

The good *in vitro* activity of cefditoren has been confirmed by numerous studies carried out over the last 10 years worldwide[24,25], and recently in more than 2,000 respiratory pathogens in Italy in 2008.[26]

The aim of this study was to evaluate the antibiotic susceptibility of respiratory pathogens recently isolated in Italy and to investigate their *in vitro* susceptibility to cedfditoren**.** Moreover, the results of a previous investigation[26] were analyzed for purposes of comparison.

MATERIALS AND METHODS

Participants

Six clinical microbiological laboratories uniformly distributed in Italy [Lombardy (420 strains), Piedmont (380 strains), Veneto (440 strains), The Marches (380 strains), Campania (440 strains) and Sicily (450 strains)] participated in this study. Each laboratory isolated bacterial strains from subjects with CARTI during the period January to September, 2009, and sent them to the coordinating center (Dept. of Microbiological Sciences, University of Catania).

Bacterial strains

A total of 2,510 respiratory pathogens were collected and identified: 965 strains of *S. pneumoniae* (of which 650 penicillin susceptible (PSSP), 215 intermediate (PISP), and 100 resistant (PRSP)), 470 strains of H. *influenzae,* of which 200 produce beta-lactamase and 20 beta-lactamase-negative ampicillin-resistant (BLNAR), 350 strains of *M. catarrhalis* of which 250 produce beta-lactamases, 225 strains of *S. pyogenes,* 300 strains of oxacillin-susceptible *S. aureus* (MSSA), 100 strains of *K. pneumoniae*, and 100 strains of *E. coli*.

S. pneumoniae strains were isolated from the lower respiratory tract (400), the upper respiratory tract (500), and blood (65).

H. influenzae and *M. catarrhalis* strains were isolated from the lower respiratory tract (85, 47) and from the upper respiratory tract (385, 303). *K. pneumoniae* and *E. coli* were isolated from the lower respiratory tract. The isolates were identified by means of Gram staining, growth on specific and selective media, colony morphology and biochemical tests (Biomerieux).

Antibiotics

Antimicrobial agents including oral cephalosporins (cefaclor, cefuroxime, cefixime, ceftibuten, cefpodoxime and cefditoren) and injectable cephalosporins (ceftriaxone and cefotaxime), penicillins (penicillin, amoxicillin, amoxi/clavulanate, ampicillin), macrolides (azithromycin and clarithromycin), and a fluoroquinolone (levofloxacin) were tested against the bacterial isolates. The drugs were purchased from Sigma Aldrich or obtained as a gift from their manufacturer.

Antibiotic susceptibility test

Susceptibility testing was performed by broth microdilution test, according to the guidelines of the Clinical Laboratory Standards Institute (CLSI) 2008 (M100-S18)[27] and 2006 (M45-A) for *M. catarrhalis*.[28]

As there are no approved CLSI breakpoints for cefditoren against *S. pneumoniae*, *H. influenzae*, *M. catarrhalis,* MSSA and *K. pneumoniae,* the breakpoints reported by Lee *et al.* (R ≥2 mg/L) were used.[29]

The following strains were used to evaluate quality control: *S. pneumoniae* ATCC 49619; *H. influenzae* ATCC 49247 and ATCC 49766; *S. aureus* ATCC 29213; *E. coli* ATCC 25922 and ATCC 35218.

The protocol of this study has been approved by the GIARIR (*Gruppo Italiano per lo studio delle Antibiotico Resistenze nelle Infezioni Respiratorie*) board.

RESULTS

This study included a total of 2,510 bacterial strains collected from community-acquired infections of the respiratory tract in the period between January and September, 2009, in Italy.

The results of the *in vitro* activity of cefditoren against seven respiratory pathogens are shown in *Tables 1-7*, while a comparison (MIC_{90}) with 14 other antimicrobial agents is summarized in *Table 8*.

S. pneumoniae strains (*Table 1*) are distributed in three phenotypic groups: susceptible, intermediate, and resistant, using, for penicillin, the breakpoints (CLSI 2008 - M100-S18) relative to parenteral administration against strains not responsible for meningitis. Cefditoren had the lowest MIC_{90} against *S. pneumoniae* of all the comparator drugs. According to the breakpoints suggested by Lee *et al.*,[29] cefditoren was the only antibiotic active against 100% of the strains examined, followed by the third-generation injectable cephalosporins (cefotaxime and ceftriaxone) (2% resistance in PRSP).

All antimicrobial agents examined demonstrated good activity against PSSP, with the exception of azithromycin and clarithromycin (15.4% of resistance); in terms of MIC values cefditoren showed excellent activity in comparison with the other beta-lactam antibiotics (cefixime and cefaclor: MIC_{50}/MIC_{90} less than 4-5 times).

Penicillin-intermediate (PISP) strains were resistant to cefaclor (74.4%) and cefuroxime (21.86%). Cefpodoxime showed 18.14% resistance, and levofloxacin 2.33%. Furthermore, 38.6% and 39.54% of strains were resistant to azithromycin and clarithromycin, respectively. Also in this case cefditoren showed the lowest MIC_{50}/MIC_{90} values.

Penicillin-resistant strains showed a high percentage of resistance against oral cephalosporins, i.e. cefaclor (100%), cefuroxime (86%), cefpdoxime (88%), amoxicillin with/without clavulanic acid (40%) and macrolides (45%-47%). Conversely, low resistance was observed to injectable cephalosporins (2%) and levofloxacin (3%).

Ampicillin-resistant beta-lactamase-positive *H. influenzae* strains (*Table 2*) showed 20% resistance to cefaclor and BLNAR 10% resistance to amoxicillin/clavulanate. Of the oral cephalosporins, cefditoren had the best *in vitro* activity, comparable to that of the injectable cephalosporins and levofloxacin. Higher levels of MIC_{90} were found for the macrolides (4 - 16 mg/L) and cefaclor (4 - 32 mg/L).

Beta-lactamase-negative *M. catarrhalis* (*Table 3*) showed reduced susceptibility to macrolides, while beta-lactamase-producing strains had reduced susceptibility to cefuroxime. Levofloxacin showed the lowest MIC_{50}/MIC_{90} values against beta-lactamase-producing strains, while cefditoren, cefotaxime and ceftriaxone against non-beta-lactamase-producers.

S. pyogenes (*Table 4*) was uniformly susceptible to all beta-

TABLE 1 - *In vitro activity of cefditoren and comparative antimicrobials agents against 965 isolates of S. pneumoniae grouped according to their penicillin susceptibility pattern.*

Antimicrobial drug	MIC (mg/L) Penicillin susceptible (n= 650)				Penicillin intermediate (n= 215)				Penicillin resistant (n= 100)			
	MIC_{50}	MIC_{90}	%I	%R	MIC_{50}	MIC_{90}	%I	%R	MIC_{50}	MIC_{90}	%I	%R
Cefditoren*	≤0.015	0.03	0	0	0.06	0.5	0	0	0.25	0.50	0	0
Cefaclor	0.5	1.0	0	0	8	≥64	5.6	74.4	≥64	≥64	0	100
Cefuroxime	0.03	0.12	0	0	1	8	26.05	21.9	4	32	14	86
Cefixime	0.25	0.50	NA	NA	2	8	NA	NA	32	32	NA	NA
Ceftibuten	0.03	0.25	NA	NA	1	4	NA	NA	32	32	NA	NA
Cefpodoxime	0.03	0.06	0	0	0.5	2	31.6	18.1	2	4	12	88
Cefotaxime	0.03	0.06	0	0	0.25	0.5	0	0	1	2	17	2
Ceftriaxone	0.03	0.06	0	0	0.25	0.5	0	0	1	2	16	2
Amoxicillin	0.03	0.12	0	0	0.5	1	0	0	4	8	45	40
Amoxicillin-clavulanate	0.03	0.12	0	0	0.5	1	0	0	4	8	45	40
Clarithromycin	0.25	≥64	4.6	15.4	0.25	≥64	3.25	39.5	0.5	≥64	6	45
Azithromycin	0,12	≥64	9.1	15.4	0.12	≥64	4.2	38.6	0.5	≥64	3	47
Levofloxacin	0.12	1	0	0	0.25	2	2.8	2.3	0.5	1	1	3

NA, not available. * Breakpoint as in Lee et al.[29]

TABLE 2 - *In vitro activity of cefditoren and comparative antimicrobial agents against 470 isolates of H. influenzae grouped according to their susceptibility to ampicillin (β-lactamase-negative or positive).*

Antimicrobial drug	MIC (mg/L) Ampicillin-susceptible β-lactamase negative (n= 250)				Ampicillin-resistant β-lactamase positive (n= 200)				Ampicillin-resistant β-lactamase negative (n=20)			
	MIC_{50}	MIC_{90}	%I	%R	MIC_{50}	MIC_{90}	%I	%R	MIC_{50}	MIC_{90}	%I	%R
Cefditoren*	≤0.015	0.03	0	0	≤ 0.015	0.03	0	0	≤ 0.015	0.03	0	0
Cefaclor	1	4	0	0	8	32	21	20	2	4	0	0
Cefuroxime	0.5	2	0	0	1	2	1	1	0.5	2	0	0
Cefixime	0.03	0.25	0	0	0.03	0.06	0	0	0.12	0.25	0	0
Ceftibuten	0.25	0.5	0	0	0.12	0.5	0	0	0.12	0.25	0	0
Cefpodoxime	0.12	0.25	0	0	0.12	0.5	0	0	0.12	0.25	0	0
Cefotaxime	≤0.015	≤0.015	0	0	≤0.015	≤0.015	0	0	≤ 0.015	0.03	0	0
Ceftriaxone	≤0.015	≤0.015	0	0	≤0.015	≤0.015	0	0	≤ 0.015	0.03	0	0
Ampicillin	0.25	1.0	0	0	≥64	≥64	0	100	4	8	0	100
Amoxi-clavulanate	0.12	2	0	0	0.5	2	0	0	2	4	0	10
Clarithromycin	1	4	0	0	4	8.0	2	1	8	16	25	0
Azithromycin	1	4	0	0	1.0	4	0	0	1	2	0	0
Levofloxacin	≤0.015	≤0.03	0	0	≤0.015	≤0.03	0	0	≤0.015	≤0.03	0	0

* Breakpoint as in Lee et al.[29]

lactams; the MIC_{50}/MIC_{90} values of cefditoren were comparable, with the exception of cefaclor (>4 times) and of ceftibuten (>3 times). The elevated MIC_{90} values found for azithromycin and clarithromycin confirm the reduced susceptibility of this pathogen to macrolides.

87% of methicillin-sensitive *S. aureus* (MSSA) (*Table 5*) were resistant to penicillin; 46% of the strains were also resistant to macrolides, while only 2.66% showed reduced susceptibility to levofloxacin. All the other tested antibiotics for which it was possible to obtain the MIC breakpoints were found to be active. According to the breakpoints suggested by Lee *et al*, cefditoren showed good activity with MIC_{50}/MIC_{90} similar to those of amoxicillin/clavulanate and levofloxacin and much higher than that of all other oral molecules of the same class.

As regards the Enterobacteriaceae, in particular *K. pneumoniae* (*Tables 6-7*), cefditoren and levofloxacin showed the lowest MIC_{90} values, even if, probably due to the presence of extended-spectrum beta-lactamase producing (ESBL) strains, bacteria resistant to all the antibiotics tested were detected. Both cefditoren and the injectable cephalosporins were totally active against *E. coli*, whereas levofloxacin had reduced activity (86% susceptible). Cefditoren was the most active antimicrobial agent, both in terms of MIC_{50} and MIC_{90} values.

TABLE 3 - *In vitro activity of cefditoren and comparative antimicrobial agents against 350 M. catarrhalis grouped according to their β-lactamase production. (CLSI 2006 M45-A) NA, not available.*

Antimicrobial drug	β-lactamase negative (n=100)				β-lactamase positive (n=250)			
	MIC_{50}	MIC_{90}	% I	% R	MIC_{50}	MIC_{90}	% I	% R
Cefditoren*	≤ 0.015	≤ 0.015	0	0	0.12	0.25	0	0
Cefaclor	0.5	1	0	0	1	4	0	0
Cefuroxime	0.25	0.5	0	0	1	8	14	2.8
Cefixime	0.03	0.25	NA	NA	0.25	1	NA	NA
Ceftibuten	0.06	0.25	NA	NA	0.25	0.5	NA	NA
Cefpodoxime	0.25	0.5	NA	NA	0.25	0.5	NA	NA
Cefotaxime	≤ 0.015	≤ 0.015	0	0	0.25	1	0	0
Ceftriaxone	≤ 0.015	≤ 0.015	0	0	0.25	1	0	0
Ampicillin	0.12	0.25	NA	NA	2	8	NA	NA
Amoxi-clavulanate	0.03	0.06	0	0	0.25	1	0	0
Clarithromycin	1	2	5	0	1	4	14	0
Azithromycin	0.5	2	10	0	1	4	12	0
Levofloxacin	0.03	0.06	0	0	≤ 0.015	0.03	0	0

* Breakpoint as in Lee et al.[29]

TABLE 4 - *In vitro activity of cefditoren and comparative antimicrobial agents against 225 S. pyogenes.*

Antimicrobial drug	MIC (mg/L)			
	MIC_{50}	MIC_{90}	%I	%R
Cefditoren	0.03	0.03	NA	NA
Cefaclor	0.5	1	NA	NA
Cefixime	0.06	0.12	NA	NA
Cefuroxime	0.03	0.12	NA	NA
Ceftibuten	0.25	0.5	NA	NA
Cefpodoxime	0.06	0.12	NA	NA
Cefotaxime	0.03	0.06	0	0
Ceftriaxone	0.03	0.06	0	0
Penicillin	0.03	0.06	0	0
Amoxicillin	0.06	0.06	NA	NA
Clarithromycin	0.25	≥64	1.8	23.5
Azithromycin	0.25	≥64	1.3	24
Levofloxacin	0.25	0.5	0	0

NA, not available.

TABLE 5 - *In vitro activity of cefditoren and comparative antimicrobial agents against 300 methicillin-susceptible S. aureus.*

Antimicrobial drug	MIC (mg/L)			
	MIC_{50}	MIC_{90}	% I	%R
Cefditoren*	0.25	0.5	0	0
Cefaclor	2	8	0	0
Cefuroxime	1	2	0	0
Cefixime	16	16	NA	NA
Ceftibuten	32	≥64	NA	NA
Cefpodoxime	0.5	4	23	0
Cefotaxime	2	4	0	0
Ceftriaxone	4	4	0	0
Penicillin	1	32	0	87
Amoxi-clavulanate	0.25	1	0	0
Clarithromycin	0.5	32	0	46
Azithromycin	0.5	32	0	46
Levofloxacin	0.25	0.25	2.66	0

NA, not available. * Breakpoint as in Lee et al.[29]

TABLE 6 - *In vitro activity of cefditoren and comparative antimicrobial agents against 100 K. pneumoniae.*

Antimicrobial drug	MIC (mg/L)			
	MIC_{50}	MIC_{90}	% I	%R
Cefditoren*	0.25	2	0	22
Cefaclor	4	32	0	29
Cefuroxime	4	≥64	2	40
Cefixime	0.12	32	6	28
Ceftibuten	0.12	32	NA	NA
Cefpodoxime	0.25	32	0	30
Cefotaxime	0.12	≥64	0	29
Ceftriaxone	0.25	≥64	0	18
Amoxi-clavulanate	4	16	5	8
Levofloxacin	0.06	1	0	6

NA, not available. *Breakpoint as in Lee et al.[29]

TABLE 7 - *In vitro activity of cefditoren and comparative antimicrobial agents against 100 E. coli.*

Antimicrobial drug	MIC (mg/L)			
	MIC_{50}	MIC_{90}	% I	%R
Cefditoren	0.03	0.5	NA	NA
Cefaclor	2	≥64	8	21
Cefuroxime	4	16	30	5
Cefixime	0.25	4	9	15
Ceftibuten	0.25	16	NA	NA
Cefpodoxime	0.5	16	6	20
Cefotaxime	0.06	2	0	0
Ceftriaxone	0.06	2	0	0
Amoxi-clavulanate	4	32	9	20
Levofloxacin	0.12	8	2	12

NA, not available.

TABLE 8 - *In vitro activity of cefditoren against 7 respiratory pathogens: comparison (MIC_{90}) with other 14 antimicrobial agents.*

Antimicrobial drug	MIC_{90} (mg/L)										
	PSSP* (650)	**PISP* (215)**	**PRSP* (100)**	***H.i.* β+* (250)**	***H.i.* β-* (200)**	***M.c.*β-* (100)**	***M.c.*β+* (250)**	***S.pyo** (225)**	**MSSA* (300)**	***Kl.pn.** (100)**	***E.coli** (100)**
Cefditoren*	0.03	0.5	0.5	0.03	0.03	≤0.015	0.25	0.03	0.5	2	0.5
Cefaclor	1.0	≥64	≥64	4	32	1	4	1	8	32	≥64
Cefuroxime	0.12	8	32	2	2	0.5	8	0.12	2	≥64	16
Cefixime	0.50	8	32	0.25	0.06	0.25	1	0.12	16	32	4
Ceftibuten	0.25	4	32	0.5	0.5	0.25	0.5	0.5	≥64	32	16
Cefpodoxime	0.06	2	4	0.25	0.5	0.5	0.5	0.12	4	32	16
Cefotaxime	0.06	0.5	2	≤0.015	≤0.015	≤0.015	1	0.06	4	≥64	2
Ceftriaxone	0.06	0.5	2	≤0.015	≤0.015	≤0.015	1	0.06	4	≥64	2
Penicillin								0.06	32		
Ampicllin				1	≥64	0.25	8				
Amoxicillin	0.12	1.0	8					0.06			
Amoxicillin-clavulanate	0.12	1.0	8	2	2	0.06	1		1	16	32
Clarithromycin	≥64	≥64	≥64	4	8.0	2	4	≥64	32		
Azithromycin	≥64	≥64	≥64	4	4	2	4	≥64	32		
Levofloxacin	1.0	2.0	1.0	0.03	0.03	0.06	0.03	0.5	0.25	1	8

*Abbreviations: penicillin-susceptible *S. pneumoniae*, penicillin-intermediate *S. pneumoniae*, penicillin-resistant *S. pneumoniae*, *H. influenzae* β-lactamase positive, *H. influenzae* β-lactamase negative, *M. cattarhalis* β-lactamase negative, *M. cattarhalis* β-lactamase positive, *S. pyogenes,* methicillin-susceptible *S. aureus*, *K. pneumoniae, E. coli*.

DISCUSSION

The therapy for community-acquired respiratory tract infections (CARTI) is usually empiric, based on knowledge of the most probable etiology, and on updated antibiotic susceptibility profiles. Antibiotic resistance in respiratory pathogens, especially in *S. pneumoniae*, is increasing against important and intensively used classes of antibiotics in Italy as well as other countries, with the logical consequence of decreased clinical efficacy and increased complications due to incomplete microbiological eradication.

While epidemiological monitoring of the sensitivity profiles of *S. pneumoniae, H. influenzae* and *M. catarrhalis, (*but also in *S. pyogenes, K. pneumoniae,* MSSA and *E. coli)* is undoubtedly useful for selecting therapy, the use of new antibiotics with greater intrinsic efficacy which are able to overcome most emerging resistance, could be the winning strategy in CARTI. The data obtained from surveillance studies are necessary, both for a correct use of antibiotics and to prevent the spread of antibiotic resistance.

One of the greatest problems in evaluating antibiotic activity *in vitro* is the lack or nonconformity of the MIC breakpoints. In the first case, it is difficult to prescribe therapy, and to determine the correct dose, and in the second case it is difficult to compare the various antibiotics based on their MIC values. The nonconformity of the MIC breakpoints, moreover, makes it impossible to correctly describe the category of activity of a drug, i.e. susceptibility or resistance.

A problem of the last few years has been the emergence of strains of penicillin-resistant *S. pneumoniae*. This phenomenon has diminished the intrinsic activity of many beta-lactams, and necessitated the use of new molecules such as macrolides and fluoroquinolones. In the past, macrolides provided an alternative therapy for patients allergic to beta-lactams, however, they have become continuously less active due to the increased diffusion of resistant strains over the years. Quinolones, even if they are not advisable in pediatric patients, represent a valid alternative to beta-lactams both in the presence of ESBL-producing strains and in the presence of beta-lactam- and macrolide-resistant strains.

Our results are in agreement with the most recent international literature and confirm that cefditoren is the most active beta-lactam *in vitro* against the respiratory pathogen *S. pneumoniae*.[11-13,14-20,24-26,30-33] The values of MIC_{50} and MIC_{90} found in the present study are, after one year of commercialization of cefditoren in Italy, almost one dilution lower than those reported in the multicenter study in Italy in 2008.[26]

S. pneumoniae susceptibilities to oral cephalosporins have been extremely variable in Europe over the last 3 years. For example, in Spain, the susceptibility of PRSP to cefpodoxime varied from 92% in 2006[30] to 64.2% (amoxicillin-sensitive strains) or 87.7% (amoxicillin-resistant strains) in 2007[31] and to 97.5% in 2008.[32] Susceptibility in Italy was 58% in 2008,[26] and in this study 88%. A possible explanation for this disagreement could come from a recent report by Sader[14]: the activity of cefpodoxime against PISP and PRSP is significantly reduced. When analyzing the literature of the last 10 years in light of the MIC breakpoints of the CLSI 2008, it can be seen that the MIC_{90s} are almost the same, while the categories are different. The same pattern was also found for cefuroxime.[26,30,14] It should be noted that cefixime and ceftibuten are inactive against PISP and PRSP. Even in the absence of breakpoints, it is obvious that the high levels of MIC_{90} (8.4 mg/L for PISP and 32 mg/L for PRSP) make these oral cephalosporins, on the basis of pharmacokinetic and pharmacodynamic considerations[23], ineffective from a clinical point of view.

Monitoring has shown that there is a trend of an increase in resistance to levofloxacin in both PSSP and PRSP. We found lower resistance in levofloxacin than that described by Seral,[34] but higher than that reported by Biedenbach *et al.,*[25] Stefani *et al.,*[26] and Blasi *et al*.[35]; the phenomenon of a constant increase in resistance to levofloxacin has been well documented by Jones *et al*.[36,37] Our results obtained with the macrolides indicate that *S. pneumoniae* is highly resistant to these molecules, independently of penicillin resistance, making them unacceptable for empiric therapy.

S. pyogenes was susceptible to all beta-lactams studied. Cefditoren showed the highest intrinsic activity. The resistance to macrolides is similar to that reported in Italy over the last few years[44-46] and is lower than that reported in a previous study.[26]

The production of beta-lactamases by *H. influenzae* and *M. catarrhalis* did not influence the activity of cefditoren nor the other beta-lactamase-resistant cephalosporins. The activity of the antibiotics studied against *H. influenzae* and BLNAR strains is similar worldwide and in Europe.[26,33,38-43] Cefditoren's activity is comparable to that of the injectable cephalosporins tested and to levofloxacin, while it is higher than that of all the oral beta-lactams.[25-26,38-43] Cefditoren has maintained the same level of intrinsic strength against *H. influenzae* shown in the previous study[26], independently of the production of beta-lactamases or ampicillin resistance. It should be noted that the increase in resistance to cefaclor compared with the study of 2008[26] confirms the data of Johnson *et al*.,[41] and of more recent observations.[42,43]

Our results on the activity of the antibiotics tested against *M. catarrhalis* are in agreement with the literature data.[11-13,25-26,29,38,40-43] There has been an increase in MIC values among beta-lactamase-positive and -negative strains for all the beta-lactams. In agreement with the breakpoints suggested for cefditoren, *M. catarrhalis* should be considered susceptible.

The activity of cefditoren against MSSA is almost the same as that of amoxicillin clavulanate and is higher than all the other beta-lactams while being less than that of levofloxacin.

In conclusion, the confirmation of the wide spectrum of activity of cefditoren and its elevated intrinsic strength, its PK/PD parameters,[23] as well as its capacity to overcome much of the resistance that has become consolidated in some classes of antibiotics that are widely used in empiric therapy for CARTI, allows us to suggest that cefditoren might be included in the European guidelines among the "first choice antibiotics" for treatment of community-acquired respiratory tract infections.

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