In vitro Activity of Cefditoren against Middle Ear Fluid Isolates from Costa Rican Children with Otitis Media

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Key Words

Otitis media · *Streptococcus pneumoniae* · Antibiotic resistance · Cefditoren

Abstract

Otitis media (OM) is one of the most common infections in children, *Streptococcus pneumoniae* and nontypable *Haemophilus influenzae* being the two most common pathogens isolated in the middle ear fluid (MEF) of children with OM. Cefditoren is a third-generation cephalosporin with broad-spectrum antibacterial activity, including activity against those pathogens commonly causing OM, with enhanced stability against common β -lactamases. The main objective of this study was to evaluate the in vitro activity of cefditoren against pathogens collected from the MEF of Costa Rican children with OM between 2006 and 2011. A total of 715 samples were analyzed. Among the 89 *S. pneumoniae* strains that were penicillin-nonsusceptible, only 7% were cefditoren-resistant according to Spanish Regulatory Agency criteria; among the *H. influenza* and *M. catarrhalis* isolates obtained, 100 and 90% of the isolates, respectively, were cefditoren-susceptible. MIC_{50/90} against the 207 PCV-13 *S. pneumoniae* serotyped strains and the 79 serotypes not covered by PCV-13 for cefditoren were 0.03/1 and 0.03/0.12 mg/l, respectively. For both amoxicillin-susceptible and resistant *H. influenzae* strains, the MIC range against cefditoren was from ≤ 0.015 to 0.06 mg/l as well. In conclusion, the con-

firmation of the wide spectrum of activity of cefditoren and its intrinsic strength against resistant strains allows us to suggest that cefditoren might be included as one of the best choices among antibiotics that are widely used in empiric therapy for OM in pediatric patients. © 2015 S. Karger AG, Basel

Introduction

Otitis media (OM) is one of the most common infections in children [1]. More than 80% of children will develop at least one OM episode before 3 years of age and around 40% will have six or more episodes by the age of 7 years [2].

In Costa Rica, since 1992 *Streptococcus pneumoniae* and nontypable *Haemophilus influenzae* have been the two most common pathogens isolated in the middle ear fluid (MEF) of children with OM [1, 3, 4]. The widespread use, early in children, of conjugate vaccines against *S. pneumoniae* has changed the MEF microbiology among children with OM; it has resulted in a proportional increase in the number of episodes caused by nontypable *H.*

At the time of study conduction Dr. Adriano Arguedas was the Director of the Instituto de Atención Pediátrica, however, currently he is a Pfizer Inc. employee.

influenzae and in a change of *S. pneumoniae* serotypes causing OM with a reduction in the seven serotypes included in the seven-valent conjugated pneumococcal vaccine (PCV-7) [5]. Following the introduction of PCV-7, a proportional increase in the number of nontypable *H. influenzae* isolated from the MEF of children was observed [6]. During the 80s, the most common mechanism of *H. influenzae* antimicrobial resistance was β -lactamase production; however, in the past years an increasing number of β -lactamase-negative ampicillin-resistant isolates have represented a therapeutic challenge [7, 8]. *Moraxella catarrhalis* and group A β -hemolytic streptococci (*Streptococcus pyogenes*) represent two other OM causative pathogens [4]. *M. catarrhalis* is, in the majority of cases, a β -lactamase-producing pathogen. Antimicrobial agents are widely used for the treatment of OM, particularly in younger children (≤ 24 months of age) or in complicated cases such as children that do not respond to an initial symptomatic treatment, children with recurrent OM or children with perforated OM or with systemic manifestations [5]. Concerns regarding the inappropriate use of antibiotics and its association with an increased number of antimicrobial-resistant MEF pathogens have been raised in recent years [6]; however, recent placebo control clinical trials have shown that in this specific younger population (≤ 24 months of age), the use of antimicrobials is associated with a faster clinical improvement and less failures and relapses compared with the use of symptomatic treatment without antimicrobials [7, 8].

Cefditoren is a third-generation cephalosporin with broad-spectrum antibacterial activity, including activity against those pathogens commonly causing OM, with enhanced stability against many common β -lactamases [9, 10]. Cefditoren has been approved in various Asian countries, such as Japan, Europe and the US for the treatment of adults and adolescents (patients >12 years of age) with acute exacerbations of chronic bronchitis, community-acquired pneumonia, streptococcal pharyngitis/tonsillitis, uncomplicated skin and skin structure infections and acute maxillary sinusitis, showing strong bacterial activity among the antibiotics tested [10, 11].

Data from two in vitro studies have shown that for penicillin-susceptible *S. pneumoniae* cefditoren activity (minimum inhibitory concentration required to inhibit 90% of the isolates, MIC₉₀: 0.015 mg/l, $n = 336$ isolates; MIC₉₀: 0.03 mg/l, $n = 153$ isolates) is similar to that of ampicillin and amoxicillin/clavulanic acid. However, in two different studies cefditoren activity against penicillin-resistant isolates ($n = 56$ isolates and 48 isolates, respectively) was two times higher than the activity of all the

β -lactam agents tested, including amoxicillin with or without clavulanic acid [12, 13].

In another in vitro study, cefditoren MIC₉₀ obtained from various sites (respiratory, skin and soft tissue infection) of *S. pneumoniae* ($n = 877$ isolates), *H. influenzae* ($n = 1,213$ isolates), *M. catarrhalis* (142 isolates) and *S. pyogenes* ($n = 590$ isolates) were 0.5, <0.03 , 0.25 and ≤ 0.03 mg/l, respectively [14].

Although the in vitro data of cefditoren against pathogens that commonly produce respiratory tract infections is adequate [15] and various clinical trials suggest that cefditoren has good clinical and presumed bacteriological efficacy in the treatment of patients with various respiratory tract infections such as OM, cefditoren MEF penetration is unknown at the present time and further clinical trials evaluating this aspect and its clinical and microbiological efficacy are warranted [14, 15].

The main objective of this study was to evaluate the in vitro activity of cefditoren against MEF pathogens collected from the MEF of Costa Rican children with OM.

Materials and Methods

Study Population

As part of various clinical trials of antimicrobial drug efficacy for OM conducted between 2006 and 2011, a total of 1,415 isolates obtained from MEF in Costa Rican children with OM were analyzed.

Participants with the following findings were included in the current analysis: purulent otorrhea of <24 h duration, at least one otoscopic sign of middle ear effusion, decreased or absent tympanic membrane mobility, and at least one indication of acute inflammation. Participants were excluded from the analysis if the tympanic membrane was perforated for ≥ 48 h, if tympanic tubes were present, and if congenital craniofacial abnormalities or any known immunodeficiency were noted.

The data was also analyzed based on the vaccination history with PCV-7, PCV-10 and PCV-13. In order to be considered fully vaccinated, a child ≤ 12 months had to have received 2 or more vaccine doses of one of the indicated vaccines and for those children >12 months, a participant was considered fully vaccinated if he/she had received at least one vaccine dose.

All the study protocols were approved by an Institutional Review Board and informed consent was obtained from the parents or legal guardian of each study participant before enrollment.

MEF Sampling and Microbiology

Diagnostic tympanocentesis was performed according to our standard procedures [1].

MEF samples were inoculated onto regular blood agar, chocolate agar, MacConkey agar and mannitol salt agar for incubation at 37°C in 5% CO₂ environment for 18–72 h. If growth was present, *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, and *S. pyogenes* identification was performed by our standard procedures [3]. All *H. influenzae* and *M. catarrhalis* were tested for β -lactamase production with the chromogenic nitrocefin test.

Antimicrobial Susceptibility

Susceptibility testing for penicillin G, ampicillin, amoxicillin/clavulanate, amoxicillin, cefaclor, cefprozil, cefuroxime, cefixime, cefdinir, cefditoren, ceftriaxone, erythromycin, clarithromycin, azithromycin, and levofloxacin was performed by microdilution method, in accordance with Clinical and Laboratory Standards Institute (CLSI) recommendations [16]. Testing was performed at the Pharmaceutical Research Center, Meiji Seika Pharma Co., Ltd. (Yokohama, Japan).

MIC50 was defined as the MIC of a given antimicrobial drug that inhibited growth of 50% of the isolates, and MIC90 was defined as the MIC of a given antimicrobial drug that inhibited growth of 90% of the isolates.

Multidrug-resistant (MDR) isolates were defined as those strains resistant to ≥ 3 of the following different antimicrobial classes: penicillin, cephalosporins, macrolides and quinolones.

Breakpoints used for the interpretation of susceptibility testing results for agents other than cefditoren were those defined in CLSI 2012 [16]. In the case of cefditoren there are two established breakpoints recommended, one recommendation established by the FDA (<http://www.fda.gov>) and another recommendation established by the Spanish Regulatory Agency (<http://www.aemps.es>) for Europe. In the case of the FDA, recommendation for *S. pneumoniae* susceptibility is defined as an MIC of ≤ 0.125 mg/l and as a resistance value of ≥ 0.50 mg/l. In the case of the values established by the Spanish Regulatory Agency for Europe a value of ≤ 0.5 mg/l is considered to indicate susceptibility and a value of ≥ 2.0 mg/l resistance. Data is presented for the two recommended breakpoints.

FDA-recommended breakpoints defined for *H. influenzae* are: susceptibility ≤ 0.125 mg/l, resistance ≥ 0.50 mg/l, and for *S. pyogenes* susceptibility is ≤ 0.125 mg/l, while no breakpoints were defined for *M. catarrhalis* [17]. Meanwhile, European approved Summary Product Characteristics recommended breakpoints for *H. influenzae*, *S. pyogenes* and *M. catarrhalis* are: susceptibility ≤ 0.5 mg/l, resistance ≥ 2.0 mg/l for all pathogens as well as for *S. pneumoniae* [18]. In this report, isolates susceptible to cefditoren for *H. influenzae*, *S. pyogenes* and *M. catarrhalis* are defined as those with the following MICs: ≤ 0.125 , ≤ 0.125 and ≤ 0.5 mg/l, respectively.

S. pneumoniae Serotyping

Isolates were stored at -70°C at the Centro de Investigaciones Médicas in Costa Rica using Micro Bank vials (Pro-Lab Diagnostics, Austin, Tex., USA) and then shipped on dry ice or on transport media at room temperature to the Research Laboratory of the Pediatric Infectious Diseases Unit at Soroka University Medical Center, Beer-Sheva, Israel. Serogrouping and serotyping of 275 (96%) *S. pneumoniae* isolates were performed in Beer-Sheva, Israel, by the Quellung reaction with antisera from Statens Serum Institute, Copenhagen, Denmark [19]. Serotyping of 11 (4%) *S. pneumoniae* strains was performed at the Pharmaceutical Research Center, Meiji Seika Pharma Co., Ltd. following the same methodology.

Results

Between January 2006 and December 2011, 1,415 MEF samples were obtained from 1,014 children with OM. Children's mean age was 26 months (range: 2–96 months)

and 447 (44%) children were less than 24 months old. Among the 1,014 children with OM, 329 (32.5%), 0 (0%), and 1 (0.1%) were fully vaccinated with PCV-7, PCV-10 and PCV-13, respectively. The remaining 684 (67.4%) children were not considered fully vaccinated with any of the conjugated vaccines according to the criteria established for this study.

Among all MEF samples collected, a positive MEF isolate for any of the four target pathogens (*S. pneumoniae*, *H. influenzae*, *M. catarrhalis* and *S. pyogenes*) was detected in 715 (50%) samples. Specific target pathogen distribution was as follows: 286 (40%) *S. pneumoniae* isolates, 292 (41%) *H. influenzae* isolates [285 (98%) isolates were nontypable strains], 101 (14%) *M. catarrhalis* isolates and 36 (5%) *S. pyogenes* isolates. Among the *H. influenzae* and *M. catarrhalis* isolates, β -lactamase production was observed in 82/292 (28%) and 100/101 (99%), respectively.

Antimicrobial Susceptibility

The antibacterial activities of the various agents evaluated are depicted in table 1. The cumulative MICs of cefditoren, amoxicillin/clavulanate, cefdinir and ceftriaxone against the *S. pneumoniae* strains according to penicillin-susceptible, penicillin-intermediate and penicillin-resistant characteristics are presented in figure 1. All 197 penicillin-susceptible strains were susceptible to cefditoren, and the shift of range of cefditoren was not as large as that of the competitors such as cefdinir or amoxicillin/clavulanate. Among the 89 *S. pneumoniae* strains that were penicillin-nonsusceptible, 49 (55%) strains were cefditoren-resistant according to the FDA recommended criteria while only 6 (7%) strains were also cefditoren-resistant according to the Spanish Regulatory Agency criteria.

MIC50/90 against the 207 PCV-13 serotyped strains and the 79 serotypes not covered by PCV-13 for penicillin were 0.03/2 and 0.03/0.25 mg/l, respectively, and those for cefditoren were 0.03/1 and 0.03/0.12 mg/l, respectively. Those against azithromycin showed the same MIC50/90 value of 0.12/32 mg/l.

Multidrug Resistance

Among the 286 *S. pneumoniae* strains a total of 53 (18.5%) were considered MDR. The most common MDR serotypes were ST 19F (17 strains), ST 19A (10 strains), ST 6A (8 strains), ST 6B (6 strains), ST 23F (2 strains), and non-PCV 13 strains (10 strains). The prevalence of MDR strains was particularly high in serotype 19A strains (10/13, 76.9%) compared with other serotypes: ST 19F (17/68, 25.0%); ST 6A (8/15, 53.3%); ST 6B (6/19, 31.6%);

Table 1. Antimicrobial activities against MEF pathogens obtained from MEF of Costa Rican children with OM between 2006 and 2011

Organisms	Antimicrobial	MIC, mg/l			Percentages of resistance	
		range	50%	90%	susceptible	resistant
<i>S. pneumoniae</i> (n = 286)						
	penicillin	≤0.015–8.0	0.03	2.0	69	14.7
	ampicillin	≤0.015–16	0.03	4.0	70.6	29.4
	amoxicillin/clavulanate	≤0.015–8.0	0.03	2.0	96.5	2.5
	amoxicillin	≤0.015–8.0	0.03	2.0	96.6	2.5
	cefaclor	0.12–>32	1.0	>32	66.1	22
	cefprozil	0.03–16	0.25	16	82.9	16.8
	cefuroxime	≤0.015–32	0.06	8.0	81.8	17.1
	cefixime	0.12–>32	0.5	32	45.1	22.4
	cefdinir	≤0.015–32	0.12	8.0	80.5	16.4
	cefditoren	≤0.015–4.0	0.03	1.0	79.4 ^a 88.5 ^b	17.1 ^a 2.1 ^b
	ceftriaxone	≤0.015–4.0	0.03	1.0	95.1	14
	erythromycin	≤0.015–>32	0.06	>32	76.9	23.1
	clarithromycin	≤0.015–>32	0.06	>32	72	27
	azithromycin	≤0.015–>32	0.12	32	77	22.4
	levofloxacin	0.25–2.0	1.0	1.0	100	0
<i>H. influenzae</i> (n = 292)						
	penicillin	0.06–>32	0.25	>32	100	0
	ampicillin	0.06–>32	0.25	32	81.5	6.1
	amoxicillin/clavulanate	0.12–4.0	0.5	2.0	100	0
	amoxicillin	0.12–>32	0.5	32	100	0
	cefaclor	0.5–16	2.0	8.0	96.6	3.1
	cefprozil	0.5–16	2.0	8.0	–	–
	cefuroxime	0.12–8.0	1.0	2.0	–	–
	cefixime	≤0.015–0.25	0.03	0.06	–	–
	cefdinir	0.06–2.0	0.25	0.5	–	–
	cefditoren	≤0.015–0.06	≤0.015	0.03	100	0
	ceftriaxone	≤0.015–0.03	≤0.015	≤0.015	100	0
	erythromycin	0.12–16	4.0	8.0	–	–
	clarithromycin	0.12–8.0	4.0	8.0	–	–
	azithromycin	0.12–2.0	1.0	1.0	100	0
	levofloxacin	≤0.015–0.03	≤0.015	0.03	100	0
<i>M. catarrhalis</i> (n = 100)						
	penicillin	0.5–32	16	32		
	ampicillin	0.25–32	4.0	8.0		
	amoxicillin/clavulanate	0.03–0.5	0.25	0.25		
	amoxicillin	0.25–16	4.0	8.0		
	cefaclor	0.5–2.0	1.0	2.0		
	cefprozil	1.0–4.0	2.0	4.0		
	cefuroxime	0.5–4.0	2.0	2.0		
	cefixime	0.03–0.5	0.25	0.5		
	cefdinir	0.12–0.5	0.25	0.25		
	cefditoren	≤0.015–1.0	0.5	0.5		
	ceftriaxone	≤0.015–1.0	0.5	1.0		
	erythromycin	0.06–0.5	0.25	0.25		
	clarithromycin	0.03–0.25	0.12	0.12		
	azithromycin	0.03–0.06	0.03	0.06		
	levofloxacin	0.03–1.0	0.06	0.06		

Table 1. (continued)

Organisms	Antimicrobial	MIC, mg/l			Percentages of resistance	
		range	50%	90%	susceptible	resistant
<i>S. pyogenes</i> (n = 36)						
	penicillin	≤0.015	≤0.015	≤0.015	100	0
	ampicillin	≤0.015–0.03	≤0.015	0.03	–	–
	amoxicillin/clavulanate	≤0.015–0.03	≤0.015	≤0.015	100	0
	amoxicillin	≤0.015–0.03	≤0.015	≤0.015	–	–
	cefaclor	0.12–0.5	0.25	0.25	100	0
	cefprozil	≤0.015–0.06	0.03	0.03	–	–
	cefuroxime	≤0.015–0.03	≤0.015	≤0.015	–	–
	cefixime	0.06–0.25	0.12	0.12	–	–
	cefdinir	≤0.015–0.03	≤0.015	≤0.015	–	–
	Cefditoren	≤0.015	≤0.015	≤0.015	100	0
	ceftriaxone	≤0.015–0.06	0.03	0.06	100	0
	erythromycin	0.03–4.0	0.06	0.12	–	–
	clarithromycin	0.03–2.0	0.03	0.06	–	–
	azithromycin	0.06–4.0	0.12	0.25	100	0
	levofloxacin	0.25–2.0	0.5	1.0	99.7	0.3

N = Number of isolates.

^a *S. pneumoniae* cefditoren susceptibility applying the FDA breakpoints.

^b *S. pneumoniae* cefditoren susceptibility applying the Spanish Regulatory Agency standard breakpoints.

Fig. 1. Cumulative distribution of MICs (mg/l) against *S. pneumoniae* (n = 286) isolates obtained from MEF of Costa Rican children with OM between 2006 and 2011. FDA-BP = Breakpoint of cefditoren recommended by FDA; SRA-BP = breakpoint of cefdi-

toren recommended by the Spanish Regulatory Agency for Europe. **a** Penicillin-susceptible *S. pneumoniae* (n = 197). **b** Penicillin-intermediate *S. pneumoniae* (n = 47). **c** Penicillin-resistant *S. pneumoniae* (n = 42).

Table 2. MIC values among MDR *S. pneumoniae* vaccine type strains isolated from the MEF of Costa Rican children with OM between 2006 and 2011 (n = 53)

	PCV-13 serotypes (n = 43)									Nonvaccine serotypes (n = 10) ^b		
	serotype 19A (n = 10)			serotype 19F (n = 17)			other serotypes (n = 16) ^a			range	MIC90	geom.
	range	MIC90	geom.	range	MIC90	geom.	range	MIC90	geom.			
Penicillin	0.12–4	4	1.3	0.12–8	8	0.68	0.12–2	2	0.31	0.12–2	0.5	0.35
Ampicillin	0.25–16	16	4.0	0.12–16	16	1.3	0.25–4	4	0.57	0.06–4	4	0.30
Amoxicillin/clavulanate	0.12–8	8	2.0	0.12–8	8	0.58	0.12–4	1	0.23	0.03–2	1	0.15
Amoxicillin	0.12–8	8	1.9	0.12–8	8	0.58	0.12–4	1	0.23	0.03–2	1	0.15
Cefaclor	2–>32	>32	30	1–>32	>32	11	2–>32	>32	5.7	1–>32	16	3.0
Cefprozil	0.5–16	16	6.5	0.25–16	16	2.9	0.5–16	16	1.5	0.12–16	8	0.70
Cefuroxime	0.5–16	16	5.3	0.12–32	32	1.9	0.25–8	4	0.74	0.5–8	4	1.1
Cefixime	4–>32	32	20	0.5–>32	>32	5.5	0.5–32	16	3.0	2–16	8	4.3
Cefdinir	0.5–16	16	4.0	0.25–32	32	2.0	0.25–8	4	0.81	0.12–4	1	0.43
Cefditoren	0.25–1	1	0.66	0.03–4	4	0.34	0.06–1	0.5	0.14	0.12–0.5	0.5	0.20
Ceftriaxone	0.25–1	1	0.76	0.06–4	4	0.47	0.06–1	1	0.23	0.12–1	0.5	0.25
Erythromycin	>32	>32	>32	2–>32	>32	8.3	2–>32	>32	13	2–>32	>32	32
Clarithromycin	>32	>32	>32	0.5–>32	>32	4.3	1–>32	>32	9.1	1–>32	>32	30
Azithromycin	32	32	32	2–32	32	7.4	2–32	32	9.1	1–32	32	17
Levofloxacin	0.5–1	1	0.93	0.5–1	1	0.88	0.5–1	1	0.81	0.5–1	1	0.93

geom. = Geometric mean.

^a ST 6A [8], 6B [6], 23F [2].

^b ST 19B [1], 6C [1], 35B [1], 15A [4], 15C [1], 11F [2].

ST 23F (2/10, 20.0%), and non-PCV 13 strains (10/79, 12.7%).

Among the MDR strains, 81% (43/53) were PCV-13 serotypes, 47% (25/53) were PCV-10 strains and 47% (25/53) were PCV-7 strains (table 2).

H. influenzae β -Lactamase-Negative Susceptibility

Among β -lactamase-negative *H. influenzae* isolates, 6 (2.1%) low- β -lactamase-negative ampicillin-resistant (L-BLNAR) strains (amoxicillin MIC = 2 mg/l) were found. Cefditoren MIC against L-BLNAR strains were ≤ 0.015 mg/l for 2 strains and 0.03 for 4 strains.

The activity of cefditoren amoxicillin/clavulanate, cefdinir, ceftriaxone and levofloxacin against amoxicillin-susceptible (amoxicillin MIC ≤ 1 mg/l) and amoxicillin-resistant (MIC ≥ 2 mg/l) *H. influenzae* strains according to clinical breakpoints of the European Committee on Antimicrobial Susceptibility Testing (<http://www.eucast.org>) criteria is described in figure 2, to compare amoxicillin with or without clavulanic acid (no amoxicillin criteria in CLSI for *H. influenzae* are defined). For both amoxicillin-susceptible and resistant strains, the MIC range against cefditoren was from ≤ 0.015 to 0.06 mg/l as well, while the MIC of amoxicillin/clavulanate and cefdinir showed much reduction of susceptibility.

Discussion

OM is globally known to be the most common cause of vaccine-preventable disease in children less than 5 years of age [3] and many oral antimicrobials have been successfully used for its treatment. Also it is known that the four most common pathogens that cause OM in this population are *S. pneumoniae*, *H. influenzae*, *M. catarrhalis* and *S. pyogenes*; therefore the ideal agent must be active against these four pathogens and, preferably, be stable in the presence of β -lactamase [20].

In previous studies, cefditoren has been active against common pediatric pathogens, was stable in the presence of β -lactamase isolates and achieved appropriate middle ear concentrations [11, 12]. In our study, cefditoren activity against the target pathogens was similar to the comparative agents.

For the *S. pneumoniae* strains, cefditoren activity (using both recommended breakpoints) was similar to the comparative agents of the cephalosporin family commonly used for the treatment of OM, but it was more active than penicillin, erythromycin and clarithromycin. For the penicillin-nonsusceptible *S. pneumoniae* strains, cefditoren showed very good activity, with only 7% of the strains being also cefditoren-resis-

Fig. 2. Cumulative distribution of MICs (mg/l) against amoxicillin-susceptible and resistant *H. influenzae* (n = 292) isolates obtained from MEF of Costa Rican children with OM between 2006

and 2011. FDA-BP = Breakpoint of cefditoren recommended by FDA. **a** Amoxicillin-susceptible *H. influenzae* (n = 227). **b** Amoxicillin-resistant *H. influenzae* (n = 65).

tant according to the Spanish Regulatory Agency criteria.

Cefditoren was found to be the drug with the lowest MIC values against MDR strains. Serotype 19A is one of the common MDR serotypes; 76.9% of its isolates were resistant to ≥ 3 different antimicrobial families, which shows the importance of an increasing vaccination coverage. The MIC₉₀ of cefditoren against the MDR 19A serotypes was 1.0 mg/l, suggesting that the activity of cefditoren against these problematic serotypes may be limited and should be evaluated if double-tympanocentesis clinical trials are conducted. Likewise, the MIC₉₀ values for cefditoren were basically lower in value than the other reagents tested, mainly the ones in the cephalosporin family.

Among the MDR serotypes, the MIC₉₀ values for cefditoren of the non-PCV-13 vaccine type and the PCV-13 vaccine type *S. pneumoniae* isolates were 0.12 and 1 mg/l, respectively, which was relatively low com-

pared to the other reagents. With the increasing prevalence of MDR serotypes of *S. pneumoniae* and the limited number of serotypes accounting for most infections with drug-resistant strains these days, usage of antimicrobials with intrinsic activity such as cefditoren should be evaluated.

Cefditoren has also maintained the same level of intrinsic strength against *H. influenzae* independently of the production of β -lactamases or ampicillin resistance and L-BLNAR phenotype. The production of β -lactamase by *H. influenzae* and *M. catarrhalis* did not influence the activity of cefditoren and *S. pyogenes* was susceptible to all β -lactams studied with a low resistance rate to macrolides.

In conclusion, the confirmation of the wide spectrum of activity of cefditoren and its intrinsic strength against resistant strains allows us to suggest that cefditoren might be one of the best choices among antibiotics that are widely used in empiric therapy for OM in pediatric patients.

References

- Arguedas A, Loaiza C, Perez A, Vargas F, Herrera M, Rodriguez G, Gutierrez A, Mohs E: Microbiology of acute otitis media in Costa Rican children. *Pediatr Infect Dis J* 1998;17: 680–689.
- Vergison A, Dagan R, Arguedas A, Bonhoeffer J, Cohen R, Dhooge I, Hoberman A, Liese J, Marchisio P, Palmu AA, Ray GT, Sanders EA, Simões EA, Uhari M, van Eldere J, Pelton SI: Otitis media and its consequences: beyond the earache. *Lancet Infect Dis* 2010;10:195–203.
- Arguedas A, Dagan R, Soley C, Loaiza C, Knudsen K, Porat N, Perez A, Brilla E, Herrera ML: Microbiology of otitis media in Costa Rican children, 1999 through 2001. *Pediatr Infect Dis J* 2003;22:1063–1068.
- Aguilar L, Alvarado O, Soley C, Abdelnour A, Dagan R, Arguedas A: Microbiology of the middle ear fluid in Costa Rican children between 2002 and 2007. *Int J Pediatr Otorhinolaryngol* 2009;73:1407–1411.
- Sanders S, Glasziou P, Del Mar C, Rovers M: Antibiotics for acute otitis media in children (review). *Cochrane Database Syst Rev* 2009;2: 1–43.
- Tähtinen PA, Laine MK, Huovinen P, Jalava J, Ruuskanen O, Ruohola A: A placebo-controlled trial of antimicrobial treatment for acute otitis media. *N Engl J Med* 2011;364:116–126.

- 7 Sato Y, Toyonaga Y, Hanaki H, Nonoyama M, Oishi T, Sunakawa K: Nationwide survey of the development of drug-resistant pathogens in the pediatric field: drug sensitivity of *Streptococcus pneumoniae* in Japan. *J Infect Chemother* 2009;15:396–401.
- 8 Hoberman A, Paradise JL, Rockette HE, Shaikh N, Wald ER, Kearney DH, Colborn DK, Kurs-Lasky M, Bhatnagar S, Haralam MA, Zoffel LM, Jenkins C, Pope MA, Balentine TL, Barbadora KA: Treatment of acute otitis media in children under 2 years of age. *N Engl J Med* 2011;364:105–115.
- 9 Cefditoren pivoxil: a guide to its use in the treatment of bacterial infections of the respiratory tract or skin and skin structures. *Drugs Ther Perspect* 2008;24:5–8.
- 10 Fenoll A, Aguilar L, Robledo O, Giménez MJ, Tarragó D, Granizo JJ, Gimeno M, Coronel P: Influence of the beta-lactam resistance phenotype on the cefuroxime versus cefditoren susceptibility of *Streptococcus pneumoniae* and *Haemophilus influenzae* recovered from children with acute otitis media. *J Antimicrob Chemother* 2007;60:323–327.
- 11 Kang JH, Lee SY, Kim JH, Hur JK, Lee KY: In vitro antimicrobial activity of cefditoren and other oral antibiotics against *Streptococcus pneumoniae*, isolated from children with community acquired respiratory tract infections. *Jpn J Antibiot* 2010;63:11–17.
- 12 Jones RN, Biedenbach DJ, Croco MA, Barrett MS: In vitro evaluation of a novel orally administered cephalosporin (Cefditoren) tested against 1249 recent clinical isolates of *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pneumoniae*. *Diagn Microbiol Infect Dis* 1998;31:573–578.
- 13 Fuchs PC, Barry AL, Brown SD: Susceptibility of *Streptococcus pneumoniae* and *Haemophilus influenzae* to cefditoren, and provisional interpretive criteria. *Diagn Microbiol Infect Dis* 2000;37:265–269.
- 14 Wellington K, Curran MP: Cefditoren pivoxil: a review of its use in the treatment of bacterial infections. *Drugs* 2004;64:2597–2618.
- 15 Hernández-Martín J, Romá E, Salavert M, Doménech L, Poveda JL: Cefditoren pivoxil: a new oral cephalosporin for skin, soft tissue and respiratory tract infections (in Spanish). *Rev Esp Quimioterap* 2006;19:231–246.
- 16 Clinical and Laboratory Standards Institute: Performance Standards for Antimicrobial Susceptibility Testing. Twenty-Third Informational Supplement. CLSI Document M100-S23 (ISBN 1–56238–865–7).
- 17 Cornerstone Therapeutics Inc: Spectracef: Summary of Product Characteristics. 2011. <http://www.crtx.com/docs/spectracef.pdf>.
- 18 Head of Medicine Agencies: Meiact: Summary of Product Characteristics. 2012. http://mri.medagencies.org/download/ES_H_0133_002_FinalPI.pdf.
- 19 Austrian R: The quellung reaction, a neglected microbiologic technique. *Mt Sinai J Med* 1976;43:699–709.
- 20 Arguedas A, Arrieta A, Stutman H, Akaniro J, Marks M: In-vitro activity of cefprozil (BMY 28100) and loracarbef (LY 163892) against pathogens obtained from middle ear fluid. *J Antimicrob Chemother* 1991;27:311–318.