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Antimicrobial Activity of Cefditoren Tested Against *H. influenzae* and *M. catarrhalis* Causing Community-Acquired Respiratory Tract Infections (USA; 2004-2006)

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ABSTRACT

Background: Cefditoren (CDN) is a third-generation, beta-lactamase (BL)-stable orally administered cephalosporin (OAC) used in outpatient practice for respiratory tract infections (RTI). Given the widespread use of OAC, we evaluated the activity of CDN and other class agents to further characterize their spectrum against contemporary *H. influenzae* (HI) and *M. catarrhalis* (MCAT) strains.

Methods: 215 recent (2004-2006) HI isolates recovered from RTI in USA patients were used to screen CDN activity and included 100 BL-positive (BLP), 105 BL-negative (BLN) and 10 unusual BLN, ampicillin-resistant (BLNAR) strains. 101 MCAT isolates were also tested and included 90 that were BLP. All were susceptibility (S) tested by CLSI M7-A7 methods against CDN and eight other oral agents. Breakpoints for CDN were those of the US-FDA; all others were as specified by CLSI (M100-S17 and M45-A).

Results: CDN was the most potent agent tested against HI ($MIC_{50/90}$, ≤0.008/0.03 µg/ml) and was 32-, 64- and 512-fold more potent that CDR, CXM and CPR, respectively (see Table). All OAC except CPR (82% S) retained near-complete coverage (>99% S) of BLP HI strains. AMC and AZM also provided similar coverage to BLP strains, but were 64- and 128-fold less active than CDN. CDN was also more active against BLNAR strains (MIC_{50}, 0.03 µg/ml; 80% S) than other beta-lactams although AZM and CLM provided complete coverage (100% S) of these rare strains. All MCAT were readily inhibited by the OAC (exception, CPR; 9% with MIC results at >2 µg/ml), AMC, AZM and CLM.

	All HI[a]		BL-negative[b]		BL-positive[b]	
Agent	$MIC_{50/90}$	%S	$MIC_{50/90}$	%S	$MIC_{50/90}$	%S
Cefditoren (CDN)	≤0.008/0.03	99	≤0.008/0.015	100	≤0.008/0.015	100
Ampicillin (AM)	2/>8	49	≤0.25/1	100	>8/>8	0
Amox/clav (AMC)	0.5/2	98	0.25/2	100	0.5/1	99
Cefdinir (CDR)	0.25/1	93	0.25/1	93	0.25/0.5	99
Cefprozil (CPR)	4/16	82	2/16	88	4/>16	82
Cefuroxime (CXM)	0.5/4	95	0.5/4	95	0.5/2	99
Azithromycin (AZM)	1/2	>99	1/2	>99	1/2	100
Clarithromycin (CLM)	4/8	92	4/16	89	4/8	93

a. Includes 10 BLNAR strains.
b. Beta-lactamase-negative and -positive isolates, respectively.

INTRODUCTION

Cefditoren is a potent orally administered cephalosporin that is indicated for use against community-acquired respiratory infections and uncomplicated skin and skin structure infections. Included among the indications for the use of cefditoren against respiratory tract infections are acute bacterial exacerbation of chronic bronchitis, community-acquired pneumoniae, pharyngitis and tonsillitis. The most common causes of these community-acquired respiratory infections are *Streptococcus pneumoniae*, *S. pyogenes*, *Haemophilus influenzae* and *Moraxella catarrhalis*. These bacterial pathogens are responsible for a considerable number of physician office visits each year. Current clinical practice favors the use of orally-administered ß-lactams, including cephalosporins, as well as macrolides and some fluoroquinolones. These antimicrobial agents are generally well tolerated and can be utilized to eradicate most infections associated with the common bacterial causes of community-acquired respiratory tract infections (RTI).

This study determined the potency and activity of cefditoren compared to other orally administered antimicrobial agents tested against a contemporary collection of *H. influenzae* and *M. catarrhalis*. Currently, ß-lactamase production among these two species has remained fairly stable over the past decade. In the United States (USA), ß-lactamase production in *H. influenzae* and *M. catarrhalis* is approximately 30 and 90%, respectively. The collection utilized in this study consisted of a large percentage of ß-lactamase-producing *H. influenzae* and isolates that are ß-lactamase-negative and ampicillin-resistant, which are not commonly isolated in the USA. The collection of *M. catarrhalis* isolates was distributed according to current ß-lactamase production rates for this species.

MATERIALS AND METHODS

Organisms studied: A collection of recent clinical isolates from patients diagnosed with community-acquired respiratory tract infections in the USA were selected for testing the potency of cefditoren and other orally administered antimicrobial agents. Bacterial strains included 215 isolates of *H. influenzae*, consisting of 105 ß-lactamase-negative, 100 ß-lactamase-positive and 10 ß-lactamase-negative, ampicillin-resistant strains (BLNAR; MIC, ≥2 µg/ml). In addition, 101 isolates of *M. catarrhalis* were selected and included 90 ß-lactamase-positive and 11 ß-lactamase-negative strains. Isolates were identified locally by the contributing medical centers and confirmed by the central reference laboratory using colony and growth characteristics, as well as confirmatory biochemical tests. All isolates were tested for ß-lactamase production using the nitrocefin disk test (Remel, Lenexa, KS).

Susceptibility testing methods: Susceptibility to cefditoren and other orally administered ß-lactams and macrolides was determined using the CLSI broth microdilution method (M7-A7; 2006). *H. influenzae* isolates were tested using Haemophilus Test Media (HTM) and *M. catarrhalis* isolates were tested using cation-adjusted Mueller-Hinton broth. Complete inhibition of growth was determined to be the MIC for all tested agents and susceptibility percentages were based upon the recommended breakpoint criteria by the CLSI (M100-S17; 2007). Susceptibility to cefditoren was determined using the USA Food and Drug Administration's approved criteria for testing *Haemophilus* spp., when tested in HTM and using broth microdilution methods, only. These recommendations are as follows: susceptible (≤0.12 µg/ml), intermediate (0.25 µg/ml) and resistant (≥0.5 µg/ml). Susceptibility breakpoint criteria for testing *M. catarrhalis* are those found in the CLSI M45-A guideline (2007).

Quality control (QC) strains were tested concurrently during each day of testing and included American Type Culture Collection (ATCC) isolates. All QC values were within the published range for *Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *H. influenzae* ATCC 49247 and ATCC 49766 (CLSI M100-S17; 2007).

RESULTS

- The potency of cefditoren was equivalent (MIC_{90}; 0.015 µg/ml) among the wild-type ß-lactamase-negative and the ß-lactamase-positive population of *H. influenzae* (Table 1). All strains were susceptible to cefditoren using established USA-FDA breakpoint criteria; and cefditoren had a marked potency advantage (≥64-fold) compared to the other tested agents.

Table 1. Activity of cefditoren and seven orally administered antimicrobial agents tested against recently collected clinical isolates (215) of *H. influenzae*.

	MIC (µg/ml)		
Organism/Antimicrobial agent (No.)	MIC_{50}	MIC_{90}	% Susceptible[a]
H. influenzae			
All (215)			
Cefditoren	≤0.008	0.03	99.1
Ampicillin	2	>8	48.8
Amoxacillin/clavulanate	0.5	2	98.1
Cefdinir	0.25	1	93.0
Cefprozil	4	16	82.3
Cefuroxime	0.5	4	94.9
Azithromycin	1	2	99.5
Clarithromycin	4	8	91.6
ß-lactamase-negative (105)			
Cefditoren	≤0.008	0.015	100.0
Ampicillin	≤0.25	1	100.0
Amoxacillin/clavulanate	0.25	2	100.0
Cefdinir	0.25	1	93.3
Cefprozil	2	16	87.6
Cefuroxime	0.5	4	95.2
Azithromycin	1	2	99.1
Clarithromycin	4	16	89.5
ß-lactamase-positive (100)			
Cefditoren	≤0.008	0.015	100.0
Ampicillin	>8	>8	0.0
Amoxacillin/clavulanate	0.5	1	99.0
Cefdinir	0.25	0.5	99.0
Cefprozil	4	>16	82.0
Cefuroxime	0.5	2	99.0
Azithromycin	1	2	100.0
Clarithromycin	4	8	93.0
BLNAR (10)[b]			
Cefditoren	0.03	0.25	80.0
Ampicillin	2	8	0.0
Amoxacillin/clavulanate	4	8	70.0
Cefdinir	2	4	30.0
Cefprozil	16	>16	30.0
Cefuroxime	4	16	50.0
Azithromycin	1	2	100.0
Clarithromycin	8	8	100.0

a. Percent susceptible calculated using CLSI recommended breakpoints (M100-S17; 2007) or those of the US-FDA (cefditoren).
b. ß-lactamase-negative, ampicillin-resistant.

- Reduced potency and activity was noted among the BLNAR *H. influenzae* isolates for all tested ß-lactam agents. However, cefditoren (MIC_{90}; 0.25 µg/ml) retained a higher potency (≥16-fold) compared to cefdinir (MIC_{90}; 4 µg/ml) > amoxicillin/clavulanate (MIC_{90}; 8 µg/ml) > cefuroxime (MIC_{90}; 16 µg/ml) > cefprozil (MIC_{90}; >16 µg/ml).

- The *M. catarrhalis* isolates showed that ß-lactamase producing strains compromised the activity of all ß-lactams (Table 2). MIC_{90} values for the orally administered cephalosporins ranged from ≤0.008 µg/ml (cefditoren) to 0.5 µg/ml among the ß-lactamase-negative isolates and 0.12 – 2 µg/ml for ß-lactamase-positive isolates.

- All isolates of *M. catarrhalis* were susceptible to the orally administered antimicrobial agents tested in this study.

Table 2. Activity of cefditoren and seven orally administered antimicrobial agents tested against 101 isolates of recently collected clinical isolates of *M. catarrhalis*.

	MIC (µg/ml)		
Organism/Antimicrobial agent (No.)	MIC_{50}	MIC_{90}	% Susceptible[a]
M. catarrhalis			
All (101)			
Cefditoren	0.12	0.25	-
Ampicillin	2	4	-
Amoxacillin/clavulanate	0.12	0.12	100.0
Cefdinir	0.12	0.12	-
Cefprozil	1	2	-
Cefuroxime	1	2	100.0
Azithromycin	0.03	0.06	100.0
Clarithromycin	0.12	0.12	100.0
ß-lactamase-negative (11)			
Cefditoren	≤0.008	≤0.008	-
Ampicillin	≤0.25	≤0.25	-
Amoxacillin/clavulanate	≤0.015	≤0.015	100.0
Cefdinir	0.06	0.06	-
Cefprozil	0.25	0.5	-
Cefuroxime	0.25	0.5	100.0
Azithromycin	0.03	0.03	100.0
Clarithromycin	≤0.06	0.12	100.0
ß-lactamase-positive (90)			
Cefditoren	0.12	0.5	-
Ampicillin	2	4	-
Amoxacillin/clavulanate	0.12	0.12	100.0
Cefdinir	0.12	0.12	-
Cefprozil	1	2	-
Cefuroxime	1	2	100.0
Azithromycin	0.03	0.06	100.0
Clarithromycin	0.12	0.12	100.0

a. Percent susceptible calculated using CLSI recommended breakpoints (M45-A; 2007).

CONCLUSIONS

- Cefditoren is a highly potent cephalosporin when tested against *H. influenzae* and *M. catarrhalis* isolates recently collected from patients diagnosed with community-acquired respiratory infections in the USA.
- Although many of the commonly prescribed orally administered antimicrobial agents have good activity against *H. influenzae*, the overall susceptibility percentages to cefditoren were greater compared to the other cephalosporins tested.
- According to the data generated in this study, the activity of the cephalosporin class of antimicrobial agents would be compromised if BLNAR isolates of *H. influenzae* were to become more prevalent within the USA.

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