Evaluation of Cefditoren and Comparator Oral ß-lactam Agents Tested Against Recent Community-Acquired *S. pneumoniae* (USA; 2004-2006)

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ABSTRACT

Background: Orally administered cephalosporins (OAC) remain among the dominantly prescribed agents for respiratory tract infections (RTI), even with rising penicillin resistance (PEN-R) among *S. pneumoniae* (SPN). Among them, cefditoren (CDN) possesses broad-spectrum activity against the common RTI pathogens, but has been rarely tested in vitro to directly confirm sustained potency and spectrum. We report on the activity of CDN and other class agents against contemporary USA strains of SPN, including PEN-intermediate (I) and -R subsets.

Methods: 359 recent (2004-2006) SPN isolates recovered from RTI in USA patients were used to screen CDN activity and included 234 PEN-susceptible (S), 43 PEN-I and 82 PEN-R strains. All were S tested by CLSI M7-A7 methods against CDN and seven other oral agents. Breakpoints for CDN were those of the USA-FDA; all others were as specified by CLSI (M100-S17).

Results: Overall, CDN was the most potent OAC tested against SPN (MIC_{50}, 0.015 vs. 0.03 to 0.12 µg/ml) and was two-fold more potent than CXM and four- and eight-fold more potent than CDR and CPR, respectively (see Table). While no R was detected among the tested OAC in PEN-S strains, R was noted among PEN-I strains and varied from only 7% for CDN to 21, 31 and 35% for CXM, CPR and CDR, respectively. Among other tested agents, amoxicillin/clavulanate provided the widest overall coverage for PEN-I (100% S) and -R (28% S) isolates although CDN remained as the most potent oral agent ($MIC_{50/90}$, 0.12/0.25 and 0.5/µg/ml, respectively). Overall, 37 and 22% of isolates were resistant to ERY and CC, respectively.

	All SPN			PEN-S			PEN-I			PEN-R		
Agent	MIC_{50}[a]	MIC_{90}	%R	MIC_{50}	MIC_{90}	%R	MIC_{50}	MIC_{90}	%R	MIC_{50}	MIC_{90}	%R
Cefditoren (CDN)	0.015	0.5	22	≤0.008	0.03	0	0.12	0.25	7	0.5	1	94
Cefdinir (CDR)	0.06	8	27	0.06	0.12	0	0.5	4	35	8	16	100
Cefprozil (CPR)	0.12	>16	25	0.12	0.25	0	1	8	31	>16	>16	100
Cefuroxime (CXM)	0.03	8	25	0.03	0.12	0	0.5	4	21	8	16	99
Erythromycin (ERY)	≤0.12	>4	37	≤0.12	2	11	>4	>4	79	>4	>4	89
Clindamycin (CC)	≤0.12	>4	22	≤0.12	≤0.12	2	≤0.12	>4	33	>4	>4	84

a. MIC values in µg/ml.

Conclusions: CDN continues to demonstrate a spectrum and potency against SPN that surpasses that of other OAC and displays less resistance than other commonly used class agents.

INTRODUCTION

Orally administered cephalosporins remain among the dominantly prescribed agents for respiratory tract infections (RTI), even with rising penicillin resistance among *Streptococcus pneumoniae*. Among these agents commonly utilized by physicians who treat community-acquired RTI, cefditoren possesses a broad-spectrum of activity which includes *S. pneumoniae*, the leading cause of this type of infection, as well as Gram-negative fastidious pathogens which include *Haemophilus influenzae* and *Moraxella catarrhalis*. However, cefditoren has been rarely tested in vitro to directly confirm sustained potency and spectrum against contemporary RTI isolates.

After oral administration, cefditoren pivoxil is hydrolyzed by esterases to an active form upon absorption from the gastrointestinal tract. Indications include treatment of numerous types of RTI as well as uncomplicated skin and skin-structure infections. Currently, cefditoren is approved for use against *Haemophilus* spp., *S. pneumoniae*, *Staphylococcus aureus* and *Streptococcus pyogenes* associated with these indications. We report here on the in vitro activity of cefditoren and five other class agents against contemporary strains of *S. pneumoniae* collected from medical centers located in the United States (USA), including penicillin-intermediate and -resistant subsets.

MATERIALS AND METHODS

Organisms studied: This study utilized a collection of 359 recent clinical isolates of *S. pneumoniae* from patients in the USA that were diagnosed with community-acquired respiratory tract infections. Among the tested strains, 234 isolates were susceptible to penicillin and the remaining strains had intermediate (43 strains) or resistant (82 strains) penicillin MIC values. Isolates were identified by local medical centers (21 sites) geographically distributed throughout the USA and referred to a central laboratory for identification confirmation and reference antimicrobial susceptibility testing. Pneumococcal isolates received at the central laboratory were examined for typical colony formation on blood agar plates, confirmation of alpha-type hemolysis and all were tested for bile solubility and optochin susceptibility.

Susceptibility testing methods: Isolates were susceptibility tested against cefditoren, cefdinir, cefprozil, cefuroxime, erythromycin and clindamycin using the Clinical and Laboratory Standards Institute (CLSI) reference broth microdilution methods (M7-A7; 2006). Strains were tested in Mueller-Hinton broth which was supplemented with 2-5% lysed horse blood. MIC values were determined as the complete inhibition of growth after incubation at 35°C in ambient air for 24 hours for all tested antimicrobial agents. Susceptibility breakpoints utilized were those of the USA-Food and Drug Administration for cefditoren (see package insert) and CLSI (M100-S17, 2007) for all comparator agents. Quality control (QC) strain *S. pneumoniae* ATCC 49619 was tested concurrently to confirm that proper test conditions were utilized. All values for this QC strain were accurately within the range established by the CLSI (M100-S17; 2007).

RESULTS

- Among orally administered cephalosporins, cefditoren was the most active agent tested against penicillin-susceptible *S. pneumoniae* (MIC_{90}, 0.03 µg/ml), being four-fold more potent than cefuroxime and cefdinir, and eight-fold more potent than cefprozil (see Table 1).
- Based upon current breakpoints, cefditoren provided complete coverage (100.0% susceptibility rate) of penicillin-susceptible *S. pneumoniae*.
- Among the tested macrolide and lincosamide agents, clindamycin provided the broadest coverage against all tested strains (78% susceptible) compared to erythromycin (63% susceptible).
- Cefditoren remained as the most active agent against penicillin-intermediate and-resistant *S. pneumoniae*. However, nearly all penicillin-resistant isolates were also resistant to the orally administered cephalosporins as well as resistant (75 to 89%) to MLS_B agents.

Table 1. Activity of cefditoren and seven orally administered antimicrobial agents tested against 359 isolates of recently collected clinical isolates of *S. pneumoniae*.

	MIC (µg/ml)		
Organism/Antimicrobial agent (No.)	MIC_{50}	MIC_{90}	% Resistant[a]
S. pneumoniae			
All (359)			
Cefditoren	0.015	0.5	22.3
Cefdinir	0.06	8	27.0
Cefprozil	0.12	>16	25.4
Cefuroxime	0.03	8	25.1
Erythromycin	≤0.12	>4	36.8
Clindamycin	≤0.12	>4	22.3
Penicillin-susceptible (234)			
Cefditoren	≤0.008	0.03	0.0
Cefdinir	0.06	0.12	0.0
Cefprozil	0.12	0.25	0.0
Cefuroxime	0.03	0.12	0.0
Erythromycin	≤0.12	2	10.7
Clindamycin	≤0.12	≤0.12	2.1
Penicillin-intermediate (43)			
Cefditoren	0.12	0.25	7.0
Cefdinir	0.5	4	34.9
Cefprozil	1	8	20.9
Cefuroxime	0.5	4	20.9
Erythromycin	>4	>4	79.1
Clindamycin	≤0.12	>4	32.6
Penicillin-resistant (82)			
Cefditoren	0.5	1	93.9
Cefdinir	8	16	100.0
Cefprozil	>16	>16	100.0
Cefuroxime	8	16	98.8
Erythromycin	>4	>4	89.0
Clindamycin	>4	>4	74.4

a. Percent resistant calculated using CLSI recommended breakpoints (M100-S17; 2007), or the USA-FDA breakpoints for cefditoren (≤0.12 µg/ml susceptible, 0.25 µg/ml intermediate, and ≥0.5 µg/ml resistant).

CONCLUSIONS

- Overall, cefditoren was the most active orally administered cephalosporin tested against *S. pneumoniae*; and 37 and 22% of isolates were resistant to erythromycin and clindamycin, respectively.
- While no resistance was detected among the tested orally administered cephalosporins in penicillin-susceptible strains, resistance to these agents was noted among penicillin-intermediate and -resistant strains.
- Cefditoren continues to demonstrate a spectrum and potency against *S. pneumoniae* that surpasses that of other orally administered cephalosporins and displays less resistance in vitro than other commonly used class agents.

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