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Potency and Spectrum Re-Evaluation of Cefdinir Tested Against Pathogens Causing Skin and Soft Tissue Infections: A Sample of North American Isolates

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ABSTRACT

Background: Cefdinir is a widely used orally administered cephalosporin for community-acquired (CA) respiratory tract infections and (SSTI). Oral agents are infrequently tested *in vitro* against isolated SSTI pathogens due to their use in the CA environment, and this study investigates the contemporary activity of cefdinir against recent clinical/indicated species.

Methods: More than 400 isolates from CA-SSTI were tested from medical centers in North America (NA) including: 243 oxacillin-susceptible (OS) *S. aureus* (SA), 21 OS-coagulase-negative staphylococci (CoNS), 57 *S. pyogenes* (SPYO), 28 *S. agalactiae* (SAGA), 25 viridans group streptococci (VGS), 21 *Klebsiella* spp. (KSP) and 21 *E. coli*. All susceptibility (S) tests were performed using NCCLS reference broth microdilution methods comparing >35 antimicrobial agents. The applied S/resistant (R) breakpoints for cefdinir were ≤1/≥4 mg/L. All QC results were within acceptable NCCLS ranges.

Results: The cefdinir $MIC_{50/90}$ in mg/L/% S for the seven principal CA-SSTI pathogens are: OSSA (0.5/0.5/100%), OS-CoNS (0.06/0.12/100%), SPYO (≤0.03/≤0.03/100%), SAGA (≤0.03/0.06/100%), VGS (0.25/2/88%), KSP (0.12/1/95%) and *E. coli* (0.25/0.5/95%). Other pathogens commonly observed in nosocomial SSTI (*P. aeruginosa*, enterococci, unusual *Enterobacteriaceae*) were generally not cefdinir-S, but rarely isolated in CA-SSTI. Only 0.5% of all 416 recent CA-SSTI pathogens were R to cefdinir (MIC, ≥4 mg/L), all among the sampled Gram-negative species. Cefdinir (all MICs, ≤0.06 mg/L) was 2-fold more potent than cefprozil or cefpodoxime versus β-streptococci, but equally active (MIC_{50}, 0.25 mg/L) against VGS. Cefdinir was the most active oral cephalosporin when tested against OSSA (MIC_{90}, 0.5 mg/L); 2- to 8-fold more potent. Against *E. coli* and KSP, cefdinir was comparable or superior to each tested oral β-lactam, but was inactive versus the single ESBL-producing isolate observed in this collection.

Conclusion: All sampled/indicated commonly encountered CA-SSTI associated bacteria were inhibited by cefdinir, a spectrum and potency comparable or superior to other orally administered β-lactams. The continued cefdinir application for uncomplicated SSTI pathogens appears to be validated using contemporary clinical strains from NA.

BACKGROUND

Skin and soft tissue infection (SSTI) represents one of the most common community-acquired infections in all age groups. The term SSTI includes a broad range of infections. Some SSTI can be mild, such as most cases of impetigo, folliculitis, furuncles and carbuncles; while others can be more severe, like erysipelas and cellulitis. In addition, some types of SSTI, such as gangrenous cellulitis and necrotizing fasciitis, have a very high morbidity and mortality rates. Occasionally, a very mild case of SSTI can rapidly become a severe and life-threatening infection, especially when inappropriate initial empiric therapy is implemented.

Oral β-lactams are one of the most widely prescribed classes of antimicrobial agents for uncomplicated SSTI. Their broad spectrum of activity, clinical efficacy, and safety profile make them ideal for the treatment of several community-acquired (CA) infections. In addition, some compounds possess optimal pharmacokinetic properties (allowing once or twice daily dosing) and very low side effects, which increase compliance and, consequently, clinical efficacy.

In this study we evaluated the *in vitro* activity of cefdinir, a newer cephalosporin, and selected oral antimicrobial agents tested against recent clinical strains isolated from CA-SSTI infections in North America.

MATERIALS AND METHODS

Bacterial Strains

A total of 416 strains from CA-SSTI were collected from 34 medical centers located in the United States (353 isolates) and five centers located in Canada (63 isolates). The vast majority of isolates (83%), including all *S. aureus*, *E. coli* and *Klebsiella* spp., were collected in 2002. The rest of isolates were collected between 1997 and 2000. Because bacterial isolates were taken from non-sterile body sites, the participant medical centers were directed to collect only isolates that were clinically relevant and considered responsible for the infection. All isolates were identified at the participating institution by routine methodologies in use at each laboratory. Upon receipt at the coordinating center (JMI Laboratories, North Liberty, IA), isolates were subcultured in blood agar to ensure viability and purity. Confirmation of species identification was performed with Vitek (bioMerieux, Hazelwood, MO) or conventional methods, as required.

Susceptibility Testing

Antimicrobial susceptibility testing was performed using broth microdilution methods as described by the National Committee for Clinical Laboratory Standards [NCCLS, 2003]. Antimicrobial agents were obtained from their respective manufacturers as reagent grade powder. Quality control measures were utilized by testing *Streptococcus pneumoniae* ATCC 49619, *Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212, *Escherichia coli* ATCC 25922, and *Pseudomonas aeruginosa* ATCC 27853. Breakpoint interpretive criteria used were those established by the NCCLS [2004]. Isolates of *Klebsiella pneumoniae* and *E. coli* with an increased minimum inhibitory concentration (MIC; ≥2 mg/L) for ceftazidime or ceftriaxone or cefotaxime or aztreonam were considered as possible extended-spectrum β-lactamase (ESBL)-producing phenotypes [NCCLS, 2004]. The ESBL phenotype strains were confirmed by using Etest ESBL strips (AB BIODISK, Solna, Sweden) that contain 4 mg/L of clavulanate.

COMMENTS

- Cefdinir was the most potent oral cephalosporin tested against oxacillin-susceptible *S. aureus* (OSSA), with MIC_{50} and MIC_{90} of 0.5 mg/L. Cefdinir was four-fold more potent than cefuroxime (MIC_{50}, 2 mg/L) and eight-fold more potent than cefpodoxime or cefaclor (MIC_{50}, 4 mg/L). Only one isolate (0.4%) had a cefdinir MIC higher than the susceptible breakpoint of ≤1 mg/L.
- As shown in previous studies, cefpodoxime showed marginal activity against OSSA strains (MIC_{50}, 4 mg/L). Only 43.6% of strains were considered susceptible and 55.6% of strains showed intermediate-resistance (MIC, 4 mg/L) to cefpodoxime. Resistance to erythromycin (MIC_{50}, 0.25 mg/L) was also relatively high (21.4%) among OSSA strains.
- Cefdinir was four- to eight-fold more potent than the other oral cephalosporins evaluated against CoNS (MIC_{50}, 0.06 mg/L). All CoNS isolates were susceptible to oral cephalosporins and amoxicillin/clavulanate; however, resistance rates were relatively high for erythromycin (38.1%) and trimethoprim/sulfamethoxazole (9.5%).
- Both group A (*S. pyogenes*) and group B (*S. agalactiae*) β-haemolytic streptococci were very susceptible to cefdinir (MIC_{90}, ≤0.03 and 0.06 mg/L, respectively) and to the other oral cephalosporins tested. However, resistance to erythromycin varied from 10.6% for *S. pyogenes* to 32.1% for *S. agalactiae*.
- Although no breakpoints has been established by the NCCLS for oral cephalosporins, viridans group streptococcal strains showed low cefdinir MICs, with 88% of isolates being inhibited at ≤1 mg/L.
- Cefdinir and cefpodoxime were the most active oral cephalosporins tested against the *Enterobacteriaceae* strains isolated from CA-SSTI. Only the ESBL-producing strains (one *E. coli* and one *K. pneumoniae* isolate) were resistant to cefdinir.
- Cefdinir (MIC_{50}, 0.25 mg/L) was 16-fold more potent than cefuroxime (MIC_{50}, 4 mg/L) and eight-fold more potent than cefaclor and cefprozil (MIC_{50}, 2 mg/L) against *E. coli*. Resistance rates varied among the oral cephalosporins from 4.8% for cefdinir and cefpodoxime to 42.9% for cefuroxime.
- Cefdinir (MIC_{50}, 0.12 mg/L) was 32-fold more potent than cefuroxime (MIC_{50}, 4 mg/L) and 16-fold more potent than cefaclor and cefprozil (MIC_{50}, 2 mg/L) against *Klebsiella* spp. Resistance rates varied among the oral cephalosporins from 4.8% for cefdinir and cefpodoxime to 14.3% for cefuroxime.

Table 1. Antimicrobial Activity of Cefdinir and Selected Antimicrobial Agents Against Isolates from Community-Acquired Skin and Soft Tissue Infections

Antimicrobial Agent/Organism	MIC (mg/L) 50%	90%	Range	% Susceptible[a]	% Resistant[a]
S. aureus (243)					
Cefdinir	0.5	0.5	≤0.03-2	99.6	0.0
Cefaclor	4	8	1-32	97.3	0.9
Cefprozil	1	2	0.25-4	100.0	0.0
Cefuroxime	2	4	0.12-4	100.0	0.0
Cefpodoxime	4	4	0.25->4	43.6	0.8
Amoxicillin/Clavulanate	1	2	0.25-8	99.6	0.4
Trimethoprim/Sulfamethoxazole	≤0.5	≤0.5	≤0.5->4	98.8	1.2
Erythromycin	0.25	>8	≤0.06->8	78.2	21.4
Coagulase-negative staphylococci (21)					
Cefdinir	0.06	0.12	≤0.03-0.25	100.0	0.0
Cefprozil	0.25	0.5	0.25-2	100.0	0.0
Cefuroxime	0.5	1	0.25-1	100.0	0.0
Cefpodoxime	0.5	2	0.5-2	100.0	0.0
Amoxicillin/Clavulanate	0.25	0.25	≤0.06-0.5	100.0	0.0
Trimethoprim/Sulfamethoxazole	≤0.5	4	≤0.5->4	81.0	9.5
Erythromycin	0.25	>8	0.12->8	61.9	38.1
Streptococcus pyogenes (57)					
Cefdinir	≤0.03	≤0.03	≤0.03	100.0	0.0
Cefprozil	≤0.12	≤0.12	≤0.12	100.0	0.0
Cefuroxime	≤0.06	≤0.06	≤0.06	100.0	0.0
Cefpodoxime	≤0.03	≤0.03	≤0.03	100.0	0.0
Amoxicillin/Clavulanate	≤0.06	≤0.06	≤0.06	100.0	0.0
Trimethoprim/Sulfamethoxazole	≤0.5	≤0.5	≤0.5-1	100.0	0.0
Erythromycin	≤0.06	1	≤0.06	87.7	10.6
S. agalactiae (28)					
Cefdinir	0.06	0.06	≤0.03-0.06	100.0	0.0
Cefprozil	≤0.12	0.25	≤0.12-0.25	100.0	0.0
Cefuroxime	≤0.06	≤0.06	≤0.06-0.12	100.0	0.0
Amoxicillin/Clavulanate	0.12	0.12	≤0.06-0.12	100.0	0.0
Trimethoprim/Sulfamethoxazole	≤0.5	≤0.5	≤0.5	100.0	0.0
Erythromycin	≤0.06	>8	≤0.06->8	67.9	32.1
viridans group streptococci (25)					
Cefdinir	0.25	2	0.06-2	–[b]	–
Cefprozil	0.5	2	≤0.12-8	–	–
Cefuroxime	0.25	2	≤0.06-4	–	–
Cefpodoxime	0.25	0.5	≤0.03->4	–	–
Amoxicillin/Clavulanate	0.12	0.25	≤0.06-0.5	–	–
Trimethoprim/Sulfamethoxazole	≤0.5	≤0.5	≤0.5-4	–	–
Erythromycin	≤0.06	0.5	≤0.06->8	76.0	8.0
Klebsiella spp. (21)					
Cefdinir	0.12	1	0.06->4	95.2	4.8
Cefaclor	2	4	1->32	90.5	9.5
Cefprozil	2	8	1->8	90.5	9.5
Cefuroxime	4	>8	1->8	66.7	14.3[c]
Cefpodoxime	0.12	1	0.06->4	95.2	4.8
Amoxicillin/Clavulanate	4	8	2->8	90.5	9.5[c]
Trimethoprim/Sulfamethoxazole	≤0.5	≤0.5	≤0.5->2	95.2	4.8
Escherichia coli (21)					
Cefdinir	0.25	0.5	0.12->4	95.2	4.8
Cefaclor	2	4	1->16	90.0	5.0
Cefprozil	2	4	1->16	90.5	9.5
Cefuroxime	4	8	2->8	57.1	42.9[c]
Cefpodoxime	0.25	0.5	0.25->4	95.2	4.8
Amoxicillin/Clavulanate	4	>8	2->8	85.7	14.3[c]
Trimethoprim/Sulfamethoxazole	≤0.5	>4	≤0.5->4	76.2	23.8

[a] The remaining percentage below 100% represents the proportion of strains in the intermediate category.
[b] No breakpoints have been established by the NCCLS.
[c] Includes resistant and intermediate.

CONCLUSIONS

- Cefdinir showed potency and spectrum comparable or superior to other orally administered cephalosporins against recent clinical isolates collected from CA-SSTI.
- The continued application of cefdinir for uncomplicated SSTI pathogens appears to be validated using contemporary clinical strains from North America.

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