

# In Vitro Activity of Cefdinir Against Community-Acquired Bacterial Pathogens

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## Abstract

Three hundred and eighteen bacterial pathogens of community-acquired infections were evaluated for their susceptibilities to cephalexin, cefaclor, cefuroxime, cefetamet, cefixime, cefdinir, erythromycin, roxithromycin, gentamicin and ciprofloxacin. Oxacillin and penicillin were added to the study when *S. aureus* and *S. pneumoniae* were employed. These pathogens were isolated from blood, sputum, urine, stool and pus obtained from patients admitted to Siriraj Hospital or a nearby medical centre during 1994-1995. They were *E. coli*, *Klebsiella pneumoniae*, *Salmonella typhi*, *Salmonella* spp., *Shigella* spp., *S. aureus*, *S. saprophyticus*, *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* which comprised of 18.5, 15.4, 5.7, 12.6, 4.1, 16.7, 5.0, 6.6, 9.7 and 5.7 percent of total pathogens respectively. The MIC<sub>50</sub> and MIC<sub>90</sub> values for cefdinir against *S. aureus* and *S. saprophyticus* ranged 0.8-1.6 and 1.6-3.2 mg/l respectively and was as active as cefuroxime, erythromycin and roxithromycin but more active than cephalexin and cefaclor. The MIC<sub>50</sub> and MIC<sub>90</sub> of cefetamet and cefixime against *S. aureus* and *S. saprophyticus* ranged 12.5-50 and 25-50 mg/l or higher respectively. All cephalosporins were active against *S. pneumoniae* but cefuroxime and cefdinir were the most active and were comparable to erythromycin and roxithromycin. For all gram-negative bacteria, ciprofloxacin is the most active drug with its MIC<sub>90</sub> of less than 1 mg/l. Cefixime, cefetamet, cefdinir and gentamicin exhibited comparable activities against these gram-negative bacteria and all were inferior to ciprofloxacin with regards to the MIC values. Cephalexin, cefaclor and cefuroxime were the least active drugs against gram-negative bacteria in this study. We concluded that cefdinir was active against various common community-acquired bacterial pathogens. (*J Infect Dis Antimicrob Agents* 1996;13:1-5.)

## INTRODUCTION

Oral beta-lactams and macrolides are widely used to treat various community-acquired infections of respiratory tract, urinary tract, skin and soft tissue and alimentary tract. Among beta-lactams, cephalosporins exhibit broader antibacterial activity than penicillins due to its relative intrinsic resistance to beta-lactamases and hence

gains wider activity against *S. aureus* and various gram-negative bacteria. Macrolides are active against gram-positive bacteria, mycoplasma and chlamydia but activity against gram-negative bacteria is limited. Hence cephalosporins are frequently employed to treat bacterial infections in various organs. The so-call third-generation cephalosporins have perhaps widest clinical application though newer generations are being introduced to market.

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However, for cephalosporins to retain their spectrums of clinical applicability for therapy of community-acquired infection, the drug must be active against gram-positive as well as gram-negative bacteria.

Oral third-generation cephalosporins are being released and recommended as empiric or "switch" therapies for patients whose clinical status have stabilized and infections are brought under control by parenteral drug. Cefdinir is one of the newly released oral third-generation cephalosporins in Thai market. The compound claimed to be active against gram-positive as well as gram-negative bacteria. This study was designed to examine the *in vitro* antimicrobial spectrum of the new compound compared to other cephalosporins, gentamicin and ciprofloxacin against a wide selection of community-acquired bacterial isolates.

## MATERIALS AND METHODS

The bacterial microorganisms used in the study were clinical isolates recovered from blood, sputum, urine, stool or pus obtained from patients with community-acquired infections during 1994 to 1995. They were either hospitalized at Siriraj Hospital or sought medication at Yothin Medical Clinic which serves as a primary health care. The isolates were stored at  $-70^{\circ}\text{C}$  until used.

Antimicrobial susceptibility was determined by an agar dilution technique as recommended by the National Committee for Clinical Laboratory Standards (1) and reference strains (*E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853 and *S. aureus* ATCC 29213) were included in the test whenever appropriate. Inocula were prepared from overnight cultures and were diluted to yield  $1 \times 10^5$  CFU per spot when applied by multiple replicating inoculator device on the surface of agar plates containing serial concentrations of antimicrobial agents. For all organisms, Mueller-Hinton agar (BBL Microbiology Systems, Cockeysville, Md.) was used. For *S. pneumoniae*, *H. influenzae* and *M. catarrhalis*, 5 percent sheep blood and 1 percent IsoVital X (BBL Microbiology Systems, Cockeysville, Md.) were added to the agar. The plates were incubated for 18 hours at  $35^{\circ}\text{C}$  with room air or with 5 percent  $\text{CO}_2$  supplementation for *S. pneumoniae* and *H. influenzae*. The MIC was defined as the lowest drug concentration which completely prevented visible growth of bacteria.

Cefaclor, cefuroxime, cephalixin, ciprofloxacin, erythromycin, gentamicin and penicillin were purchased

from Sigma Chemical Company, St. Louis, Mo.. Cefdinir, cefixime were generous gifts of Parke-Davis Pharmaceutical Research, Ann Arbor, Michigan, U.S.A. Cefetamet was also gift of F. Hoffman-La Roche Ltd., Basle and roxithromycin of Hoechst Roussel Pharmaceuticals, Inc., Somerville, N.J., U.S.A.

## RESULTS

A total of three hundred and eighteen bacterial pathogens of community-acquired infections were evaluated for their susceptibilities to the antimicrobials. *E. coli*, *Klebsiella pneumoniae*, *Salmonella* spp., *Shigella* spp., *S. aureus*, *S. saprophyticus*, *S. pneumoniae*, *H. influenzae* and *M. catarrhalis* comprised of 18.5, 15.4, 5.7, 12.6, 4, 16.7, 5.0, 6.6, 9.7 and 5.7 percent of total isolates respectively. The MIC<sub>50</sub> and MIC<sub>90</sub> values for cefdinir against *S. aureus* and *S. saprophyticus* ranged 0.8-1.6 and 1.6-3.2 mg/l respectively and was as active as cefuroxime, erythromycin and roxithromycin but more active than cephalixin and cefaclor. The MIC<sub>50</sub> and MIC<sub>90</sub> values of cefetamet and cefixime for *S. aureus* and *S. saprophyticus* ranged 12.5-50 and 25-50 mg/l or higher and thus several folds less active than cefdinir against these organisms. All cephalosporins were active against *S. pneumoniae* but cefuroxime and cefdinir were the most active drugs and were comparable to erythromycin and roxithromycin. For *H. influenzae* and *M. catarrhalis*, cefdinir inhibited all 31 and 18 strains tested at concentrations of 0.4 mg/l or less while cefetamet and cefixime inhibited at similar or slightly higher concentrations. However, for all gram-negative bacteria, ciprofloxacin was the most active drug with its MIC<sub>90</sub> values of less than 1 mg/l. Cefdinir, cefetamet, cefixime and gentamicin exhibited comparable activities against *E. coli*, klebsiella, salmonella and shigella and were more active than cephalixin, cefaclor and cefuroxime. The details of *in vitro* activities of the antimicrobials against all clinical isolates were shown in Table 1.

## DISCUSSION

In the present study, the *in vitro* activities of cefdinir was similar to those observed in other country (2) with the exception of gram-positive bacteria and *Klebsiella pneumoniae*. The ranges of MIC<sub>90</sub> of cefdinir for *S. pneumoniae* and *S. aureus* were  $<0.06$ -0.5 and 0.03-1 mg/l respectively in previous report (2) which

Table 1. Comparative *in vitro* activity of cefdinir.

Organism (no. of strains)	Agent	MIC (mg/l)		
		Range	50%	90%
<i>S. aureus</i> (53)	Cefdinir	0.2-3.1	1.6	3.1
	Cephalexin	1.6-12.5	6.2	6.2
	Cefuroxime	0.8-6.2	1.6	3.1
	Cefaclor	0.8-6.2	1.6	3.1
	Cefixime	6.2-50	25	25
	Cefetamet	0.2-≥25	12.5	≥25
	Erythromycin	0.4-25	0.4	0.8
	Roxithromycin	1.6-25	1.6	6.2
	Ciprofloxacin	0.05-0.8	0.4	0.8
	Gentamicin	0.05-3.1	0.8	3.1
<i>S. saprophyticus</i> (16)	Oxacillin	0.2-0.8	0.4	0.4
	Cefdinir	0.4-3.1	0.8	1.6
	Cephalexin	1.6-6.2	3.1	6.2
	Cefuroxime	0.8-3.1	1.6	3.1
	Cefaclor	0.4-3.1	1.6	1.6
	Cefixime	12.5-50	50	50
	Cefetamet	0.2-≥25	12.5	≥25
	Erythromycin	0.2-≥25	0.4	≥25
	Roxithromycin	0.4-≥25	1.6	≥25
	Ciprofloxacin	0.2-0.8	0.4	0.8
<i>S. pneumoniae</i> (21)	Gentamicin	0.05-3.1	0.2	3.1
	Oxacillin	0.4-0.8	0.8	0.8
	Penicillin	≤0.01-0.8	≤0.01	0.4
	Cefdinir	≤0.01-6.2	0.025	1.6
	Cephalexin	0.05-6.2	1.6	6.2
	Cefuroxime	≤0.01-3.1	0.025	1.6
	Cefaclor	0.05-6.2	0.4	3.1
	Cefixime	0.05-12.5	0.1	6.2
	Cefetamet	0.05-6.2	0.2	6.2
	Erythromycin	≤0.01-6.2	0.05	3.1
<i>H. influenzae</i> (31)	Roxithromycin	≤0.01-6.2	0.1	3.1
	Ciprofloxacin	0.05-≥12.5	0.8	3.1
	Gentamicin	≤0.01-12.5	6.2	12.5
	Oxacillin	0.05-≥12.5	3.1	≥12.5
	Cefdinir	≤0.01-0.4	0.4	0.4
	Cephalexin	0.4-12.5	3.1	6.2
	Cefuroxime	0.2-1.6	1.6	1.6
	Cefaclor	0.2-6.2	3.1	6.2
	Cefixime	0.1-3.1	0.8	1.6
	Cefetamet	0.1-0.4	0.1	0.2
<i>E. coli</i> (59)	Erythromycin	0.8-6.2	1.6	3.1
	Roxithromycin	3.1-25	6.2	12.5
	Ciprofloxacin	≤0.01	≤0.01	≤0.01
	Gentamicin	0.4-0.8	0.8	0.8
	Cefdinir	0.1-12.5	0.4	0.8
	Cephalexin	3.1-100	6.2	25
	Cefuroxime	0.8-50	3.1	12.5
	Cefaclor	0.8-≥100	3.1	12.5
	Cefixime	0.1-25	0.4	0.8
	Cefetamet	0.1-12.5	0.4	1.6

Table 1. (continued 1) Comparative *in vitro* activity of cefdinir.

Organism (no. of strains)	Agent	MIC (mg/l)		
		Range	50%	90%
<i>K. pneumoniae</i> (49)	Cefdinir	≤0.01-50	0.4	12.5
	Cephalexin	0.8-100	6.2	100
	Cefuroxime	0.8-100	3.1	50
	Cefaclor	0.8-≥100	6.2	≥100
	Cefixime	0.025-≥100	0.2	100
	Cefetamet	0.1-12.5	0.2	3.1
	Erythromycin	25-≥100	100	≥100
	Roxithromycin	100-≥100	≥100	≥100
	Ciprofloxacin	0.025-≥12.5	0.05	0.8
	Gentamicin	0.4-≥100	1.6	≥100
<i>M. catarrhalis</i> (18)	Cefdinir	≤0.01-0.2	0.05	0.2
	Cephalexin	0.4-3.1	3.1	3.1
	Cefuroxime	≤0.01-1.6	0.4	1.6
	Cefaclor	0.1-0.8	0.4	0.8
	Cefixime	≤0.01-0.4	0.1	0.2
	Cefetamet	0.1-0.8	0.4	0.8
	Erythromycin	0.1-0.4	0.1	0.2
	Roxithromycin	0.1-0.4	0.2	0.4
	Ciprofloxacin	≤0.01-0.2	≤0.01	≤0.01
	Gentamicin	0.4-12.5	0.4	0.8
<i>Salmonella</i> spp. (58)	Cefdinir	0.2-50	0.2	0.4
	Cephalexin	6.2-≥100	6.2	12.5
	Cefuroxime	3.1-100	6.2	12.5
	Cefaclor	1.6-≥100	3.1	6.2
	Cefixime	0.1-100	0.2	0.4
	Cefetamet	0.2-12.5	0.8	1.6
	Erythromycin	50-≥100	100	≥100
	Roxithromycin	25-≥100	100	≥100
	Ciprofloxacin	≥0.01-0.4	0.05	0.2
	Gentamicin	0.8-≥100	0.5	25
<i>Shigella</i> spp. (13)	Cefdinir	0.2-1.6	0.2	0.4
	Cephalexin	6.2-≥100	6.2	12.5
	Cefuroxime	1.6-6.2	3.1	6.2
	Cefaclor	1.6-≥100	3.1	6.2
	Cefixime	0.4-0.8	0.4	0.4
	Cefetamet	0.2-0.4	0.2	0.2
	Erythromycin	25-≥100	25	≥100
	Roxithromycin	50-≥100	100	≥100
	Ciprofloxacin	≤0.01-0.4	0.025	0.4
	Gentamicin	0.8-1.6	1.6	1.6

are approximately three-fold lower than those obtained from our study. The discrepancy is obviously explained by different strains tested and in Thailand, antimicrobials have been overused and easily accessed by any people. Our study revealed the MIC90 value of 12.5 mg/l for *Klebsiella pneumoniae* which was highest among the isolates tested. It was ten-fold higher than previously reported in other country (2) but was five-fold lower than a study in Thailand (3). Perhaps, not all klebsiella in our study were truly community-acquired since many strains were isolated from immuno-compromised patients

who were frequently hospitalised and had been treated with antimicrobials. The contaminated strains will raise the MIC value since they are more resistant to various antimicrobial than the community-acquired strain (4). In addition, its ability to produce extended beta-lactamases and multi-resistance property are well recognised (5). A study at Siriraj Hospital revealed 37 percent of *Klebsiella pneumoniae* produced extended beta-lactamases which probably were TEM- and SHV-related and also plasmid-mediated (6). Consequently, the MIC<sub>90</sub> was raised beyond therapeutic level. For other gram-negative bacteria, cefdinir is very active against *H. influenzae* and *M. catarrhalis* and inhibited growth at concentrations of 0.2-0.4 mg/l. Ninety percent of *E. coli*, *Shigella* spp. and *Salmonella* spp. were also inhibited at concentration below 1 mg/l. The *in vitro* activity of cefetamet reported five years ago (7) against *E. coli*, salmonella, klebsiella and *S. aureus* compared with those of cefetamet from our study showed almost identical values of MIC<sub>50</sub> and MIC<sub>90</sub> though the MICs of *S. aureus* was slightly higher in previous study. Ciprofloxacin had the highest *in vitro* activity against gram-negative bacteria tested. *Streptococcus pyogenes* was not included in our study due to its extreme susceptibility to cefdinir (2) and other beta-lactams. In brief, cefdinir were active against gram-positive bacteria including *S. aureus* and *S. saprophyticus* for which cefetamet and cefixime lack significant activity. Against gram-negative pathogens, cefdinir was also active and was superior to cephalixin, cefaclor and cefuroxime. Its activity is equivalent to cefuroxime and macrolides against gram-positive organisms and to cefixime and cefetamet against gram-negative organisms.

Further clinical trial should be performed to illustrate the effectiveness of cefdinir in respiratory tract, urinary tract, skin and soft tissue infections before it can be recommended for empiric or "switch" therapy. Because of its low MIC levels against most respiratory tract pathogens which is easily achievable in serum, together with its beta-lactamase stability which may help prevent treatment failure due to penicillinase-producing co-pathogens, cefdinir may play important role in therapy of respiratory tract infection. Its safety profile in children which exceeds those of quinolones would booster its use in children to avoid organ damage due to bacterial infection and possible adverse reaction of other drugs. We did not find resistant pneumococci in our limited strains though as high as 9.7 and 21.5 percent of *S. pneumoniae* and *H. influenzae* were reported from

this country to be completely resistant to penicillin and ampicillin respectively (8). However, the sites of isolation are different. Both bacteria were isolated from nasopharynx of patients who had acute upper respiratory tract infection or pneumonia and hence they may colonize rather than be the cause of infection. In our study, they were recovered from blood and sputum specimens and thus, represented true pathogens. However, we believe that pathogenic pneumococci is increasingly resistance to beta-lactams (9) and the situation should alert physicians to rational use of antimicrobials since the cost of antimicrobial treatment for resistant pneumococci is very expensive (10). At present, even decreased activity of erythromycin against *Streptococcus pyogenes* was reported (11) probably due to overuse of the drug.

Cefdinir should be considered to use in community-acquired urinary tract infection since it is active against *E. coli*, some strains of *Klebsiella pneumoniae*, proteus (2), and *S. saprophyticus* which are dominant pathogens of community-acquired urinary tract infection. Skin and soft tissue infection due to single pathogen namely *S. aureus* and *S. pyogenes* should also respond to cefdinir therapy if indicated. For shigellosis, co-trimoxazole is no longer the drug of choice due to its resistance rate approaching 80-95 percent since 1991 (12). Resistance rates of salmonella to co-trimoxazole and ampicillin varied from 0-74 and 0-65 percent respectively (13). However, most of them were almost 100 percent susceptible to third-generation cephalosporins with the exception of *Salmonella ohio* which was seldom isolated and relatively resistant to most antimicrobials used to treat salmonellosis. Cefdinir, though is *in vitro* active against salmonella and shigella, may not be clinically effective since failure of cefixime in shigellosis was reported despite its good *in vitro* activity against shigella (14).

In conclusion, cefdinir deserves further clinical trial to reveal its effectiveness as well as safety profiles in Thai patients.

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