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Antimicrobial Activity, Spectrum, and Recommendations for Disk Diffusion Susceptibility Testing of Ceftibuten (7432-S; SCH 39720), a New Orally Administered Cephalosporin

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The antimicrobial activity and spectrum of ceftibuten (7432-S; SCH 39720) was determined on a wide variety of bacterial species selected for resistance to oral and parenteral beta-lactam antimicrobial agents. Ceftibuten was found to be the most active beta-lactam tested against members of the family *Enterobacteriaceae*, inhibiting 81.6% of strains at ≤8.0 μg/ml compared with 75.0 and 54.8% of strains inhibited by cefixime and cefuroxime, respectively. All strains of *Haemophilus influenzae* (MIC for 90% of strains [MIC_{90}], ≤0.06 μg/ml), *Branhamella catarrhalis* (MIC_{90}, 3.0 μg/ml), and pathogenic *Neisseria* spp. (MIC_{90}, ≤0.06 and 0.019 μg/ml) were susceptible to ceftibuten. Beta-hemolytic *Streptococcus* spp. (serogroups A, B, C, and G) were also inhibited by ceftibuten, but penicillin-resistant pneumococci were generally resistant to cefixime and ceftibuten. The activity and spectrum of ceftibuten seem most applicable to infections of the respiratory and urinary tract plus those infections caused by pathogenic *Neisseria* spp. Ceftibuten disks (30 μg) were evaluated and found to have an acceptable correlation ($r = 0.88$) with ceftibuten MICs. Preliminary zone size interpretive criteria for MIC breakpoints of ≤4.0 and ≤8.0 μg/ml were calculated.

Ceftibuten (7432-S; SCH 39720; Schering Corp.) is a recently described, orally administered cephalosporin having the structural formula 7β-[(*Z*)-2-(2-aminothiazol-4-yl)-4-carboxy-2-butenoylamino]-3-cephem-4-carboxylic acid (T. Yoshida, H. Hamashima, S. Matsuura, Y. Komatsu, and S. Kuwahara, Program Abstr. 26th Intersci. Conf. Antimicrob. Agents Chemother. abstr. no. 589, 1986). Preliminary human volunteer pharmacokinetic information indicates efficient absorption from the gastrointestinal tract, producing peak levels in serum of 11.6 μg/ml after a 200-mg dose (M. Nakashima, M. Iida, T. Yoshida, T. Kitagawa, T. Oguma, and H. Ishii, 26th ICAAC, abstr. no. 591, 1986). Ceftibuten exhibits protein binding of 67%, a half-life in serum of 1.5 to 2.1 h, and a urinary recovery of 67.5 to 75.2% at 24 h. Oral administration of ceftibuten does not require the ester formulation necessary for other investigational cephems such as cefuroxime axetil, cefetamet (Ro 15-8074), cefteram (Ro 19-5247 or T-2588), and CS-807 (1, 5, 6, 14, 15; S. Sugawara, M. Iwata, M. Tajima, T. Maguribuchi, H. Yanagisawa, H. Nakao, J. Kumazawa, and S. Kuwahara, 26th ICAAC, abstr. no. 592, 1986). Other newer oral cephems have unique structural characteristics that allow oral administration without ester prodrugs, e.g., cefixime and BMY-28100 (3, 4, 7, 8). All of these drugs possess comparable or superior pharmacokinetics and/or greater potency against some gram-negative organisms compared with currently available oral cephalosporins (2, 13).

In this study, we report the antimicrobial activity of ceftibuten tested against 690 selected bacterial strains. In addition, we evaluated the effects of inoculum density on ceftibuten MICs, determined the bactericidal activity, and evaluated the 30-μg disk for in vitro susceptibility testing.

MATERIALS AND METHODS

Antimicrobial agents. Ceftibuten (7432-S; SCH 39720) was obtained from the Schering Corp., Bloomfield, N.J. The reagent drugs used for comparison were supplied by their U.S. licensed distributors.

Organisms tested. The bacterial strains were clinical isolates selected from the stock culture collections of the Clinical Microbiology Institute and the Centers for Disease Control. Many of the gram-negative isolates were resistant to beta-lactam antimicrobial agents, particularly the oral drugs such as amoxicillin (17% susceptible) and some parenteral cephalosporins, namely, cefoperazone and cefotaxime (50 to 74% susceptible). These 690 strains were distributed as follows: 59 *Staphylococcus aureus* (10 oxacillin resistant), 30 coagulase-negative *Staphylococcus* spp. (8 oxacillin resistant), 60 beta-hemolytic streptococci, 10 *Streptococcus bovis*, 30 *Streptococcus pneumoniae* (11 penicillin resistant), 33 *Enterococcus* spp. (3 species), 10 *Listeria monocytogenes*, 228 members of the family *Enterobacteriaceae* (13 species), 15 *Acinetobacter* spp., 55 *Pseudomonas aeruginosa*, 28 other *Pseudomonas* spp., 20 *Branhamella catarrhalis* (17 beta-lactamase producers), 42 *Haemophilus influenzae* (20 ampicillin resistant), 19 *Neisseria meningitidis*, and 50 *N. gonorrhoeae* (26 β-lactamase positive). An additional group of organisms was tested that produced well-characterized β-lactamases of both the plasmid- and chromosome-mediated types. The recommended quality control organisms were tested daily to ensure comparable and valid results in both participating laboratories. The quality control modes for all comparison drugs were within limits recommended by the National Committee for Clinical Laboratory Standards (NCCLS) (11).

Antimicrobial susceptibility testing. All MICs were determined by standardized reference broth microdilution methods (11) described by the NCCLS. The inoculum was 5×10^5 CFU/ml, and all endpoints were read at 16 to 20 h. For fastidious organisms such as *H. influenzae*, pneumococci, and beta-hemolytic streptococci, medium supplements specified in the NCCLS standard M7-A (11) were used. *N. gonorrhoeae* strains were tested by the agar dilution procedure on proteose peptone agar no. 3 supplemented with 1%

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TABLE 1. Antimicrobial activity of ceftibuten compared with activities of five orally administered drugs tested against 228 members of the *Enterobacteriaceae*[a]

Organism (no. tested)	Antimicrobial agent	MIC (μg/ml)			% Susceptible[b]
		50%	90%	Range	
Citrobacter diversus (10)	Ceftibuten	≤0.06	≤0.06	≤0.06–0.5	100.0
	Cefixime	≤0.06	0.12	≤0.06–0.5	100.0
	Cefaclor	0.5	1.0	0.5–4.0	100.0
	Cefuroxime	4.0	4.0	4.0–8.0	100.0
	Amox-clav[c]	2.0	2.0	1.0–16	90.0
	Amoxicillin	>16	>16	>16	0.0
Citrobacter freundii (10)	Ceftibuten	>32	>32	1.0–>32	10.0
	Cefixime	>32	>32	1.0–>32	10.0
	Cefuroxime	>32	>32	4.0–>32	10.0
	Amoxicillin	>16	>16	16–>16	0.0
	Amox-clav	>16	>16	16–>16	0.0
	Cefaclor	>32	>32	>32	0.0
Enterobacter aerogenes (20)	Ceftibuten	0.5	>32	0.12–>32	60.0
	Cefuroxime	8.0	>32	2.0–>32	50.0
	Cefixime	2.0	>32	0.25–>32	40.0
	Amoxicillin	>16	>16	16–>16	0.0
	Amox-clav	>16	>16	16–>16	0.0
	Cefaclor	>32	>32	16–>32	0.0
Enterobacter agglomerans (10)	Ceftibuten	0.12	8.0	≤0.06–>32	90.0
	Cefixime	0.12	8.0	≤0.06–>32	60.0
	Amox-clav	2.0	>16	1.0–>16	50.0
	Cefuroxime	8.0	>32	2.0–>32	50.0
	Cefaclor	4.0	>32	0.25–>32	50.0
	Amoxicillin	>16	>16	16–>16	0.0
Enterobacter cloacae (22)	Ceftibuten	>32	>32	≤0.06–>32	45.5
	Cefuroxime	>32	>32	1.0–>32	36.4
	Cefixime	>32	>32	≤0.06–>32	31.8
	Cefaclor	>32	>32	4.0–>32	9.1
	Amoxicillin	>16	>16	4.0–>16	4.5
	Amox-clav	>16	>16	4.0–>16	4.5
Escherichia coli (35)	Ceftibuten	0.12	0.25	≤0.06–>32	97.1
	Cefixime	0.25	0.5	0.12–>32	94.3
	Cefaclor	2.0	16	0.5–>32	85.7
	Cefuroxime	4.0	16	2.0–>32	85.7
	Amox-clav	8.0	16	2.0–>16	71.4
	Amoxicillin	>16	>16	2.0–>16	42.9
Klebsiella pneumoniae (23)	Ceftibuten	≤0.06	0.25	≤0.06–8.0	100.0
	Cefixime	≤0.06	0.25	≤0.06–16	95.7
	Cefuroxime	4.0	16	1.0–>32	78.3
	Cefaclor	1.0	>32	0.5–>32	73.9
	Amox-clav	2.0	>16	1.0–>16	73.9
	Amoxicillin	>16	>16	>16	0.0
Morganella morganii (10)	Ceftibuten	0.12	8.0	≤0.06–16	90.0
	Cefixime	2.0	32	0.25–>32	40.0
	Cefuroxime	32	>32	16–>32	0.0
	Amoxicillin	>16	>16	>16	0.0
	Amox-clav	>16	>16	>16	0.0
	Cefaclor	>32	>32	>32	0.0
Proteus mirabilis (20)	Cefixime	≤0.06	≤0.06	≤0.06	100.0
	Ceftibuten	≤0.06	≤0.06	≤0.06–0.12	100.0
	Cefuroxime	1.0	1.0	0.5–4.0	100.0
	Amoxicillin	1.0	2.0	0.5–2.0	100.0
	Amox-clav	1.0	2.0	0.5–2.0	100.0
	Cefaclor	2.0	2.0	0.5–4.0	100.0
Proteus vulgaris (10)	Ceftibuten	≤0.06	≤0.06	≤0.06	100.0
	Cefixime	≤0.06	≤0.06	≤0.06	100.0
	Amox-clav	8.0	16	4.0–16	80.0

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TABLE 1—*Continued*

Organism (no. tested)	Antimicrobial agent	MIC (μg/ml)			% Susceptible[b]
		50%	90%	Range	
	Amoxicillin	>16	>16	>16	0.0
	Cefaclor	>32	>32	>32	0.0
	Cefuroxime	>32	>32	>32	0.0
Providencia rettgeri (10)	Ceftibuten	≤0.06	≤0.06	≤0.06	100.0
	Cefixime	≤0.06	≤0.06	≤0.06–0.5	100.0
	Cefuroxime	0.5	8.0	0.12–32	90.0
	Amoxicillin	16	>16	4.0–>16	30.0
	Amox-clav	16	>16	4.0–>16	20.0
	Cefaclor	32	>32	0.5–>32	10.0
Providencia stuartii (19)	Ceftibuten	≤0.06	≤0.06	≤0.06–0.12	100.0
	Cefixime	≤0.06	0.5	≤0.06–>32	100.0
	Cefuroxime	2.0	32	0.5–>32	73.7
	Amoxicillin	>16	>16	1.0–>16	10.5
	Amox-clav	>16	>16	1.0–>16	10.5
	Cefaclor	>32	>32	0.25–>32	10.5
Serratia marcescens (29)	Ceftibuten	0.5	32	≤0.06–32	69.0
	Cefixime	0.5	>32	0.12–>32	62.1
	Amoxicillin	>16	>16	8.0–>16	3.4
	Amox-clav	>16	>16	16–>16	0.0
	Cefuroxime	>32	>32	16–>32	0.0
	Cefaclor	>32	>32	32–>32	0.0

[a] MIC_{50}s and MIC_{90}s by antimicrobial agent are listed in rank order of potency (Schmidt, Antimicrob. Newsl. 4:1–8, 1987).
[b] Susceptible breakpoints as defined by the NCCLS, standard M7-A (11): ≤8.0 μg/ml for ceftibuten or as proposed in publications (3).
[c] Amox-clav, Amoxicillin (2 parts)-clavulanic acid (1 part). Only the MIC of the amoxicillin component of the combination is listed.

hemin and 1% Kellogg supplement. All incubation was in ambient air except for the *N. gonorrhoeae* and *S. pneumoniae* strains, which required 5% CO_2 for necessary growth.

Tests with the investigator-prepared 30-μg ceftibuten disks were performed by NCCLS methods (10). A 30-μg cefuroxime disk (BBL Microbiology Systems, Cockeysville, Md.) was also tested as a methods control. All control zone diameters were within limits published by the NCCLS (10).

Statistical analyses comparing the zones of inhibition and MICs were performed, using the method of least squares, and error rates were calculated (9). An effort was made to minimize false-susceptible disk diffusion result error to ≤1.0%, false-resistant error to ≤5.0%, and minor interpretive errors to a total of ≤10.0%. MIC susceptible breakpoints of ≤4.0 and ≤8.0 μg/ml were used for ceftibuten based on preliminary pharmacokinetic data and our previous experience with similar oral cephalosporins (3, 6, 13; Nakashima et al., 26th ICAAC).

In all tables with comparative data, the antimicrobial agents were ranked by using the highest number of isolates inhibited at a clinically susceptible drug concentration and then further classified by the MICs for 50 and 90% of the strains (MIC_{50} and MIC_{90}, respectively), using the methods published by Schmidt (L. H. Schmidt., Antimicrob. Newsl. 4:1–8, 1987).

Bactericidal and inoculum effect tests. The bactericidal activity (MBC) of ceftibuten and the effects of inoculum concentrations on its MICs were studied by testing organisms with known resistance mechanisms in broth microdilution trays. The MBC was determined by subculturing duplicate 10-μl samples from each well showing no visible growth to a drug-free blood agar plate. The initial inocula were determined by colony counts to be 1.1×10^5 to 7.4×10^5 CFU/ml. The MBC was defined as the lowest concentration displaying colony counts specific for a ≥99.9% kill, using the rejection criteria published by Pearson et al. (12). The inoculum effect studies for the ceftibuten MICs were evaluated following the delivery of 10^4, 5×10^5, and 10^7 CFU/ml to broth microdilution wells.

RESULTS AND DISCUSSION

Activity against members of the *Enterobacteriaceae*. Ceftibuten had excellent inhibitory activity against the 13 species of enteric bacilli shown in Table 1. These strains were selected to be highly resistant to older beta-lactams and some newer parenteral cephalosporins such as cefoperazone. Only for *Citrobacter freundii* and *Enterobacter cloacae* were resistant-range ceftibuten MIC_{50}s seen. In addition, the ceftibuten MIC_{90}s were >8.0 μg/ml for both *E. aerogenes* and *Serratia marcescens*. This level of antimicrobial activity was equal, and in most cases superior, to that of the most active of the other beta-lactams used for comparison, cefixime. Ceftibuten inhibited 81.6% of these enteric bacilli at ≤8.0 μg/ml compared with 75.0 and 54.8% for the two next best cephalosporins, cefixime (≤1.0 μg/ml) and cefuroxime (≤8.0 μg/ml), respectively.

Activity against *Branhamella*, *Haemophilus*, and *Neisseria* spp. and streptococci. Table 2 summarizes the in vitro activities of ceftibuten, five other beta-lactams, and erythromycin against four genera of bacteria. Ceftibuten possesses excellent inhibitory activity against *H. influenzae* and pathogenic *Neisseria* spp. strains (MICs, ≤0.06 μg/ml). For organisms producing a β-lactamase among these species, ceftibuten MICs were not higher than those for organisms without a detectable enzyme. Cefaclor was markedly affected by the *H. influenzae* β-lactamase, exhibiting a MIC_{50} difference of nearly 16 μg/ml for enzyme-producing strains compared with 0.5 μg/ml for β-lactamase-negative strains. Erythromycin was the least active drug tested.

TABLE 2. Ceftibuten comparative antimicrobial activity against *B. catarrhalis*, *H. influenzae*, pathogenic *Neisseria* spp., and streptococci (201 strains)[a]

Organism (no. tested)	Antimicrobial agent	MIC (μg/ml)			% Susceptible[b]
		50%	90%	Range	
Branhamella catarrhalis (20)[c]	Cefixime	≤0.06	0.25	≤0.06–0.25	100.0
	Amox-clav[d]	≤0.06	0.25	≤0.06–0.25	100.0
	Erythromycin	0.25	1.0	0.12–0.5	100.0
	Ceftibuten	0.25	4.0	≤0.06–4.0	100.0
	Cefaclor	0.5	1.0	0.25–2.0	100.0
	Cefuroxime	0.5	2.0	≤0.06–2.0	100.0
Haemophilus influenzae					
Ampicillin resistant (20)	Ceftibuten	≤0.06	≤0.06	≤0.06	100.0
	Cefixime	≤0.06	≤0.06	≤0.06–0.5	100.0
	Cefuroxime	0.25	0.5	0.12–1.0	100.0
	Amox-clav	0.5	1.0	0.25–4.0	100.0
	Cefaclor	16	>32	2.0–>32	40.0
	Erythromycin	8.0	16	8.0–16	0.0
Ampicillin susceptible (22)	Ceftibuten	≤0.06	≤0.06	≤0.06	100.0
	Cefixime	≤0.06	≤0.06	≤0.06	100.0
	Amox-clav	0.12	0.25	0.12–0.25	100.0
	Cefuroxime	0.25	0.5	0.12–0.5	100.0
	Cefaclor	0.5	1.0	0.25–1.0	100.0
	Erythromycin	8.0	16	0.25–16	13.6
Neisseria meningitidis (19)	Ceftibuten	≤0.06	≤0.06	≤0.06	100.0
	Cefixime	≤0.06	≤0.06	≤0.06	100.0
	Cefuroxime	≤0.06	≤0.06	≤0.06	100.0
	Amox-clav	≤0.06	0.12	≤0.06–0.12	100.0
	Cefaclor	≤0.06	0.12	≤0.06–0.12	100.0
	Amoxicillin	≤0.06	0.25	≤0.06–0.25	100.0
	Erythromycin	1.0	8.0	0.5–8.0	73.7
Neisseria gonorrhoeae					
β-Lactamase positive (26)	Ceftibuten	0.004	0.03	0.004–0.03	100.0
β-Lactamase negative (24)	Ceftibuten	0.008	0.03	≤0.002–0.12	100.0
Beta-hemolytic streptococci					
Serogroup A (20)	Amox-clav	≤0.06	≤0.06	≤0.06	100.0
	Cefaclor	≤0.06	≤0.06	≤0.06	100.0
	Cefuroxime	≤0.06	≤0.06	≤0.06	100.0
	Amoxicillin	≤0.06	0.12	≤0.06–0.12	100.0
	Cefixime	≤0.06	0.12	≤0.06–0.12	100.0
	Ceftibuten	0.5	0.5	0.25–1.0	100.0
	Erythromycin	0.12	>32	≤0.06–>32	75.0
Serogroup C (10)	Amoxicillin	≤0.06	≤0.06	≤0.06	100.0
	Amox-clav	≤0.06	≤0.06	≤0.06	100.0
	Cefaclor	≤0.06	≤0.06	≤0.06–0.12	100.0
	Cefuroxime	≤0.06	≤0.06	≤0.06–0.12	100.0
	Cefixime	≤0.06	0.12	≤0.06–0.25	100.0
	Ceftibuten	0.5	1.0	0.25–1.0	100.0
	Erythromycin	0.12	4.0	≤0.06–8.0	80.0
Serogroup G (10)	Amox-clav	≤0.06	≤0.06	≤0.06	100.0
	Cefuroxime	≤0.06	≤0.06	≤0.06	100.0
	Amoxicillin	≤0.06	≤0.06	≤0.06–0.12	100.0
	Cefaclor	≤0.06	≤0.06	≤0.06–0.12	100.0
	Cefixime	0.12	0.12	≤0.06–0.25	100.0
	Ceftibuten	1.0	1.0	0.25–2.0	100.0
	Erythromycin	0.25	8.0	0.12–>32	50.0
Streptococcus pneumoniae					
Penicillin susceptible (19)	Amox-clav	≤0.06	≤0.06	≤0.06–0.25	100.0
	Cefuroxime	≤0.06	≤0.06	≤0.06–0.25	100.0
	Cefixime	0.25	0.25	≤0.06–0.5	100.0
	Cefaclor	0.5	0.5	0.12–0.5	100.0
	Ceftibuten	4.0	8.0	2.0–8.0	100.0

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TABLE 2—*Continued*

Organism (no. tested)	Antimicrobial agent	MIC (μg/ml)			% Susceptible[b]
		50%	90%	Range	
Penicillin resistant (11)[e]	Cefuroxime	0.5	2.0	0.12–4.0	100.0
	Amox-clav	≤0.06	1.0	≤0.06–1.0	81.8
	Cefaclor	0.5	16	0.25–32	81.8
	Cefixime	4.0	16	1.0–16	18.2
	Ceftibuten	>32	>32	8.0–>32	9.1

[a] See footnote *a*, Table 1.
[b] See footnote *b*, Table 1.
[c] Seventeen strains were resistant to penicillins by β-lactamase tests.
[d] See footnote *c*, Table 1.
[e] Penicillin resistance was defined as a MIC of ≥0.12 μg/ml or a screening oxacillin zone diameter of ≤19 mm (11). Two high-grade penicillin-resistant strains were tested (MIC, >1.0 μg/ml).

The *B. catarrhalis* isolates were generally resistant to amoxicillin by a β-lactamase mechanism. However, all tested beta-lactams and erythromycin were effective in vitro at clinically achievable concentrations. Cefixime, amoxicillin-clavulanic acid, and erythromycin were more active than ceftibuten.

The beta-hemolytic streptococci were inhibited by all tested beta-lactams. Several strains in each serogroup showed a high-grade resistance to erythromycin. The *S. pneumoniae* strains demonstrated a reduced susceptibility to the oral cephalosporins, correlating with their penicillin susceptibility (16). Ceftibuten was the least active beta-lactam against the penicillin-resistant pneumococci. Cefixime was also relatively inactive against these isolates: the MIC_{90} was 16 μg/ml, with only 18.2% susceptible.

Activity against other organisms. Several bacterial species were refractory to ceftibuten inhibition. These organisms include *Acinetobacter anitratus, Pseudomonas* spp. (six species groups), *Staphylococcus* spp., *Streptococcus agalactiae*, serogroup D streptococci, *Enterococcus* spp., and *L. monocytogenes*. The MIC_{90}s for all of these strains were >16 μg/ml. Only strains of *Pseudomonas acidovorans* among all tested pseudomonads were inhibited by ceftibuten (MIC range, 0.25 to 0.5 μg/ml for three isolates).

Activity against β-lactamase-producing strains. The activities of ceftibuten, cefixime, and cefaclor are compared in Table 3 against 17 strains producing known β-lactamase types. Ceftibuten and the other oral cephems appear stable to all plasmid-mediated enzymes, with MICs generally remaining below 8.0 μg/ml. The MICs of ceftibuten were lowest for all test strains. The enteric bacilli with chromosomally mediated enzymes (types I and IV) were resistant to cefaclor but remained susceptible to ceftibuten and cefixime.

TABLE 3. Antimicrobial activity of ceftibuten and two other oral cephalosporins tested against 17 gram-negative strains producing well-characterized types of β-lactamase

Organism	Enzyme type	MIC (μg/ml)		
		Ceftibuten	Cefixime	Cefaclor
Enterobacter cloacae	I (P99)	>32	>32	>32
Escherichia coli	I	8.0	16	32
	III (TEM-1)	0.25	0.5	4.0
	III (TEM-2)	0.12	0.12	32
	V (OXA-1)	0.25	1.0	2.0
	V (OXA-2)	0.5	0.5	2.0
	V (OXA-3)	0.25	0.5	1.0
	V (SHV-1)	0.25	0.5	1.0
	V (HMS-1)	0.25	0.5	8.0
Klebsiella oxytoca	IV (K1)	≤0.06	0.25	>32
	IV (K14)	≤0.06	0.25	>32
Serratia marcescens	I	≤0.06	0.12	>32
Pseudomonas aeruginosa	I	>32	>32	>32
	V (CARB-1)	>32	>32	>32
	V (CARB-2)	>32	>32	>32
	V (CARB-4)	>32	>32	>32
	V (OXA-4)	>32	>32	>32

Bactericidal activity and effects of inoculum concentration on MICs. Table 4 summarizes the results of MBC tests and the effects of three inoculum densities on ceftibuten MICs. The ceftibuten MBCs were rarely >1 $\log_2$ dilution greater than the MIC. Ceftibuten MICs at an inoculum concentration of 10^4 CFU/ml were approximately twofold lower than at the commonly used MIC inoculum of 5×10^5 CFU/ml. At an inoculum of 10^7 CFU/ml, several strains exhibited a MIC increase of ≥fourfold including isolates having type IV and

TABLE 4. MBCs and inoculum effects on ceftibuten, using inocula of 10^4, 5×10^5, and 10^7 CFU/ml

Organism	MIC (μg/ml) with 10^4 CFU/ml	5×10 CFU/ml		MIC (μg/ml) with 10^7 CFU/ml
		MIC (μg/ml)	MBC (μg/ml)	
Escherichia coli				
ATCC 25922[a]	0.25	0.25	0.5	0.25
OXA-2	0.25	0.5	0.5	1.0
TEM-1	0.25	0.25	0.25	>32
Enterobacter cloacae				
P99	>32	>32	>32	>32
63[a]	0.5	1.0	2.0	1.0
76[a]	0.25	0.5	1.0	1.0
341-82[a]	0.25	0.5	1.0	1.0
Klebsiella oxytoca				
35[a]	≤0.06	≤0.06	≤0.06	8.0
K1	≤0.06	≤0.06	0.12	0.25
K14	≤0.06	≤0.06	0.5	0.25
Branhamella catarrhalis				
β-Lactamase positive	4.0	4.0	4.0	16
β-Lactamase negative	0.12	0.12	0.25	0.25
Haemophilus influenzae				
β-Lactamase positive	≤0.06	≤0.06	0.25	0.12
β-Lactamase negative	≤0.06	≤0.06	0.12	≤0.06
Streptococcus pneumoniae, penicillin susceptible	4.0	4.0	4.0	8.0

[a] Wild-type clinical or quality control isolate without unusual resistance for its respective species.

TABLE 5. Regression analysis, suggested interpretive criteria, and error rates comparing ceftibuten MICs with zones of inhibition around a 30-μg disk[a]

MIC (μg/ml) for:		Zone (mm)		% Interpretive error[b]		
Susceptibility	Resistance	Susceptibility	Resistance	Very major	Major	Minor
≤8.0	≥32	≥18	≤14	0.3	0.7	5.6
		≥17[c]	≤13[c]	0.3	0.2	4.7
		≥16[c]	≤12	0.3	0.2	6.1
≤4.0	≥16	≥19[c]	≤15[c]	0.3	0.0	4.9
		≥18	≤14	0.3	0.0	7.3
		≥17	≤13	0.3	0.0	8.8

[a] Regression formula is $y = 18.0 - 0.39x$, where y = MIC as the $\log_2 + 9$ and x = zone diameter in millimeters. Regression formula for the MIC used as the dependent variable: $y = 41.0 - 2.0x$. The correlation coefficient was 0.88.
[b] Very major, False-susceptibility result by the disk diffusion test; major, false-resistance disk diffusion results; minor, intermediate by one of the test methods.
[c] Zone criteria calculated from the regression formula.

TEM β-lactamases. In addition to the strains listed in Table 4, five strains each of *Staphylococcus aureus* and *P. aeruginosa* were tested. False-susceptible ceftibuten MICs were not observed among those two species when the lower inoculum concentration was used.

Disk diffusion tests with the ceftibuten disk. Table 5 and Fig. 1 contain the test results comparing ceftibuten MICs and 30-μg-disk zone diameters. The regression formula ($y = 41.0 - 2.0\,x$)-calculated zone size criteria for the ≤8.0-μg/ml MIC breakpoint were ≥17 mm for susceptibility and ≤13 mm for resistance. The corresponding zone size criteria for the ≤4.0-μg/ml breakpoint were 2 mm larger, i.e., ≥19 and ≤15 mm. The lowest total error rate (6.2%) also favors the calculated zone breakpoints for both possible susceptibility breakpoint MICs (9). Only 8.0% of the ceftibuten MICs (Fig. 1) were observed within the MIC range of 1.0 to 8.0 μg/ml. This finding will minimize potential interpretive errors applying MIC breakpoint criteria through this MIC range and ensures a reliable guideline with low rates of discrepancies regardless of the final pharmacokinetic-directed MIC breakpoint.

Our studies confirm the preliminary reports that ceftibuten has very potent antimicrobial activity against nearly all species of the *Enterobacteriaceae*, *H. influenzae*, *N. meningitidis*, *N. gonorrhoeae*, *B. catarrhalis*, penicillin-susceptible pneumococci, and beta-hemolytic streptococci (Yoshida et al., 26th ICAAC). This spectrum of activity appears most similar to those of cefixime, cefetamet, and cefteram among the oral cephalosporins investigated (3, 6, 7, 15). Some other newer oral cephems have significant antistaphylococcal activity but lack the potency of ceftibuten against the gram-negative enteric and fastidious bacilli (1, 5, 8).

Studies comparing the dilution and disk diffusion test results for ceftibuten demonstrated that the 30-μg disks performed very well. As more human pharmacokinetic data become available, the choice between a ≤4.0 and a ≤8.0-μg/ml susceptibility MIC breakpoint can be made. Interpretive zone diameter criteria were selected and resulted in a very acceptable absolute interpretive agreement of 93.4 to 94.8%. False-susceptible disk diffusion results were quite rare, i.e., 0.3% regardless of MIC breakpoint concentration.

This new cephalosporin seems most applicable as therapy for urinary tract infections caused by the *Enterobacteriaceae*; for respiratory infections caused by *Haemophilus*

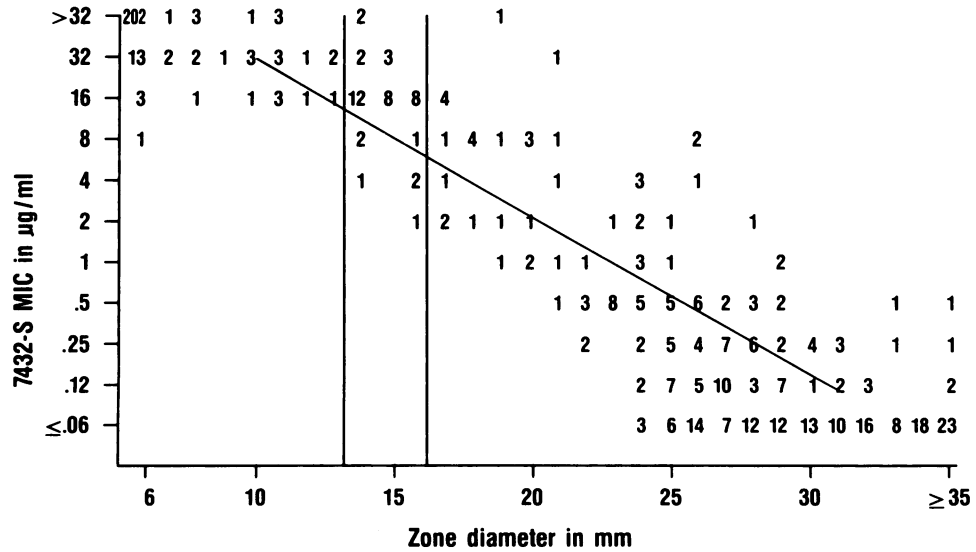

FIG. 1. Scattergram comparing ceftibuten (7432-S) MICs with zones of inhibition surrounding the investigator-prepared 30-μg disks. Nearly 600 bacterial strains were tested, and preliminary zone recommendations having the lowest interpretive error are shown for the ≤8.0-μg/ml susceptibility MIC (solid vertical lines). The drawn regression line is for the MIC interval of 0.12 to 32 μg/ml ($y = 18.0 - 0.39x$).

spp., *Branhamella* spp., pneumococci, and beta-hemolytic streptococci; and for gonococcal genital infections.

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