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Comparative In Vitro Activities of Amoxicillin-Clavulanic Acid and Imipenem against Anaerobic Bacteria Isolated from Community Hospitals

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The susceptibilities of recent clinical isolates of anaerobic bacteria from two community hospitals were determined. Thirty percent of pigmented *Bacteroides* species and bile-sensitive, nonpigmented *Bacteroides* species produced penicillinase and were resistant to amoxicillin. Cefoxitin and clindamycin showed good activity against most strains, with the exception of rare isolates of the *Bacteroides fragilis* group and some strains of *Clostridium* species. While amoxicillin was not active against *B. fragilis* and other members of the *B. fragilis* group, amoxicillin-clavulanic acid was very active against almost all of these organisms. Imipenem was the most potent agent against all strains tested.

The increasing incidence of resistance in a variety of anaerobic bacteria to available antimicrobial agents has been noted elsewhere (3, 6, 12). *Bacteroides* strains, other than of the *B. fragilis* group, resistant to penicillin and strains of the *B. fragilis* group resistant to cefoxitin and clindamycin have been noted (6, 12). Penicillin resistance of species other than *B. fragilis* has also been correlated with clinical therapeutic failure (4).

Data on the in vitro activities of newer beta-lactam antimicrobial agents against anaerobic bacteria have come from large university and research centers (1, 2, 6, 9). Since there is clustering of resistance and regional differences in resistance patterns, it is difficult to extrapolate published data to those clinical situations encountered at community hospitals. Most community hospital clinical microbiology laboratories do not perform susceptibility studies on anaerobic bacteria. Community hospitals often have patient populations and antibiotic usage patterns different from those of university and research centers.

To determine the relevance and potential utility of these agents to the community setting, we compared the activities of amoxicillin-clavulanic acid and imipenem with amoxicillin, cefoxitin, piperacillin, moxalactam, and clindamycin against anaerobic bacteria isolated from patients in community hospitals.

The 204 strains of anaerobic bacteria studied (Table 1) were recent clinical isolates from two primary-care community hospitals (Santa Monica Hospital Medical Center and St. John's Hospital Health Center, Santa Monica, Calif.). All isolates were identified by standard criteria (7, 11). Standard powders were kindly supplied as follows: cefoxitin and imipenem from Merck Sharp & Dohme, West Point, Pa.; clindamycin from The Upjohn Co., Kalamazoo, Mich.; moxalactam from Eli Lilly & Co., Indianapolis, Ind.; and amoxicillin and amoxicillin-potassium clavulanate from Beecham Laboratories, Bristol, Tenn. All antibiotics were tested against 204 strains of anaerobic bacteria, except imipenem, which was tested against 121 strains.

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The susceptibilities of isolates were determined by an agar dilution method (11). Before being tested, the isolates were grown overnight in thioglycolate 135C medium supplemented with vitamin K_1, hemin, and a marble chip (CalScott, Carson, Calif.). Occasional fastidious strains required additional supplementation with Fildes enrichment (Difco Laboratories, Detroit, Mich.) or formate-fumurate solution (11). The turbidity of growth was adjusted to one-half McFarland standard no. 1 with brucella broth that had been steamed for 10 min on the day of use. Antimicrobial agent solutions were prepared on the day of study and were incorporated into brucella agar supplemented with vitamin K_1, hemin, and 5% laked sheep blood to yield final concentrations of 256 to 0.06 μg/ml. The plates were inoculated with a Steers replicator (Craft Machine Inc., Chester, Pa.). Control plates containing no antibiotic were inoculated before and after each set of antibiotic-containing plates was inoculated. All plates were incubated for 48 h in GasPak jars (BBL Microbiology Systems, Cockeysville, Md.) or Anapak jars (Scott Laboratories, Inc., Fiskeville, R.I.) at 37°C. The MIC was defined as the lowest concentration of antimicrobial agent that allowed no growth, a barely visible haze, or one discrete colony. *Bacteroides thetaiotaomicron* ATCC 29741 and *B. fragilis* ATCC 25285 were included as controls in each test.

The results of the study are summarized in Table 1. Isolates from both hospitals showed similar patterns of resistance. As expected, amoxicillin had poor activity against *B. fragilis* and other *B. fragilis* group strains. In addition, 30% of pigmented *Bacteroides* species and bile-sensitive nonpigmented *Bacteroides* species were resistant. *Fusobacterium mortiferum* strains were resistant to amoxicillin, but *Fusobacterium nucleatum* and *Fusobacterium necrophorum* were susceptible. However, the amoxicillin-clavulanic acid had good activity against almost all isolates, including *B. fragilis* and other *B. fragilis* group strains. Three stains of *Clostridium perfringens* had higher MICs with amoxicillin-clavulanic acid than with amoxicillin alone. Imipenem was the most active agent tested, with virtually no resistance encountered. Cefoxitin was active against *B. fragilis* and other *B. fragilis* group isolates, but there was a clustering of susceptibility at 16 and 32 μg/ml, respectively.

TABLE 1. Activities of amoxicillin-clavulanic acid and imipenem compared with other agents against anaerobic bacteria isolated from community hospitals

Organism	No. of strains	Antimicrobial agent	MIC[a] (μg/ml)		
			Range	MIC_{50}	MIC_{90}
B. fragilis	64	Amoxicillin	4->256	16	128
		Amoxicillin-clavulanic acid	0.5–64	0.5	2
		Cefoxitin	4–128	16	16
		Moxalactam	0.25–128	1	8
		Piperacillin	2->256	4	32
		Clindamycin	≤0.06->256	0.5	2
	18	Imipenem	0.06–1	≤0.06	0.25
B. fragilis group	33	Amoxicillin	0.5->256	32	256
		Amoxicillin-clavulanic acid	0.5–8	1	4
		Cefoxitin	4–128	32	32
		Moxalactam	1–128	16	64
		Piperacillin	2–256	32	64
		Clindamycin	0.25->256	2	4
	18	Imipenem	≤0.06–2	0.25	0.5
Bile-sensitive nonpigmented *Bacteroides* spp.	16	Amoxicillin	≤0.06–64	4	32
		Amoxicillin-clavulanic acid	≤0.06–2	0.5	1
		Cefoxitin	0.12–32	2	16
		Moxalactam	≤0.06–16	2	16
		Piperacillin	0.12–32	4	16
		Clindamycin	≤0.06–4	≤0.06	4
		Impenem	≤0.06–1	≤0.06	0.25
Pigmented *Bacteroides* spp.	10	Amoxicillin	≤0.06–128	0.5	16
		Amoxicillin-clavulanic acid	≤0.06–2	0.25	0.5
		Cefoxitin	≤0.06–16	0.5	4
		Moxalactam	≤0.06–256	4	16
		Piperacillin	≤0.08–128	1	8
		Clindamycin	≤0.06	≤0.06	≤0.06
		Imipenem	≤0.06–0.25	≤0.06	≤0.06
Fusobacterium spp.	8	Amoxicillin	≤0.06–16	0.5	16
		Amoxicillin-clavulanic acid	≤0.06–4	0.12	4
		Cefoxitin	≤0.06–4	0.06	4
		Moxalactam	≤0.06–16	0.5	16
		Piperacillin	≤0.06–0.5	0.06	0.5
		Clindamycin	≤0.06–0.25	0.06	0.25
		Imipenem	≤0.06–1	≤0.06	1
Anaerobic cocci	28	Amoxicillin	≤0.06–2	0.25	0.25
		Amoxicillin-clavulanic acid	≤0.06–4	0.12	0.25
		Cefoxitin	≤0.06–8	0.5	4
		Moxalactam	≤0.06–64	0.5	16
		Piperacillin	≤0.06–32	0.06	16
		Clindamycin	≤0.06–8	0.12	1
	18	Imipenem	≤0.06–0.5	≤0.06	0.25
C. perfringens	12	Amoxicillin	≤0.06–0.25	0.12	0.25
		Amoxicillin-clavulanic acid	≤0.06–1	0.12	1
		Cefoxitin	1–4	2	2
		Moxalactam	0.25–2	0.5	1
		Piperacillin	≤0.06–0.5	0.25	0.5
		Clindamycin	0.12–4	2	4
		Imipenem	≤0.06–0.25	≤0.06	0.12
Other *Clostridium* spp.	10	Amoxicillin	≤0.06->256	0.25	>256
		Amoxicillin-clavulanic acid	≤0.06–16	0.25	16
		Cefoxitin	0.12–128	64	128
		Moxalactam	0.5–256	8	256
		Piperacillin	≤0.06->256	0.5	1
		Clindamycin	≤0.06->256	0.5	256
		Imipenem	≤0.06–4	0.25	2
Propionibacterium spp.	12	Amoxicillin	≤0.06–0.5	0.12	0.5
		Amoxicillin-clavulanic acid	≤0.06–0.25	≤0.06	0.25
		Cefoxitin	0.12–4	0.5	2
		Moxalactam	≤0.06–8	0.5	4
		Piperacillin	0.12–2	0.5	2
		Clindamycin	≤0.06–0.5	≤0.06	0.25
		Imipenem			

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TABLE 1—*Continued*

Organism	No. of strains	Antimicrobial agent	MIC[a] (μg/ml)		
			Range	MIC_{50}	MIC_{90}
Other nonsporeforming gram-positive rods	11	Amoxicillin	≤0.06–1	0.25	1
		Amoxicillin-clavulanic acid	≤0.06–1	0.25	0.5
		Cefoxitin	0.12–>256	8	128
		Moxalactam	0.25–256	32	128
		Piperacillin	0.25–16	1	4
		Clindamycin	≤0.06–4	0.25	4
		Imipenem	≤0.06–4	0.12	2

[a] By agar dilution method. MIC_{50}, MIC for 50% of strains tested; MIC_{90}, MIC for 90% of strains tested. Breakpoint values (micrograms per milliliter): amoxicillin, 8; amoxicillin-clavulanic acid, 8; cefoxitin, 32; moxalactam, 32; piperacillin, 128; clindamycin, 4; imipenem, 16.

No high-grade cefoxitin resistance was encountered. Clindamycin was active against most isolates, with occasional strains of the *B. fragilis* group displaying resistance. The activity of piperacillin was similar to that of ampicillin. Moxalactam had an intermediate level of activity.

Clavulanic acid inhibits the activity of many beta-lactamases, including those produced by *B. fragilis* (1, 9). Our study showed that amoxicillin-clavulanic acid was very active against most strains tested, including amoxicillin-resistant *Bacteroides* species, *B. fragilis*, and other *B. fragilis* group strains. Our community hospital isolates had a 30% resistance rate for non-*B. fragilis* group species. Our susceptibility results for other isolates are similar to the data reported by others (1, 9, 10) from university and research centers. Although clinical data on the therapy of infections involving anaerobic bacteria are sparse (5), our data suggest that amoxicillin-clavulanic acid may be useful as a single agent in the treatment of mixed infections.

Imipenem is a carbapenem antibiotic with a broad spectrum of activity and is coadministered with cilastatin, a renal dehydropeptidase I inhibitor. Our study showed it to exhibit potent activity against virtually all of the community anaerobic strains tested. This finding is in accord with other studies that noted imipenem to be more active than metronidazole, clindamycin, and chloramphenicol against the *B. fragilis* group (2, 8).

Of particular concern was the 30% rate of resistance to penicillin of the pigmented and nonpigmented, bile-sensitive *Bacteroides* species. The current policy of many community hospitals to limit susceptibility studies to *B. fragilis* group isolates should be reconsidered. As a minimum, testing for the presence of β-lactamase should be performed with these organisms.

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