ANTIMICROBIAL SUSCEPTIBILITY STUDIES

A Five-Year Multicenter Study of the Susceptibility of the *Bacteroides fragilis* Group Isolates to Cephalosporins, Cephamins, Penicillins, Clindamycin, and Metronidazole in the United States

Kenneth E. Aldridge, Michael Gelfand,
L. Barth Reller, Leona W. Ayers,
Carl L. Pierson, Fritz Schoenknecht,
Richard C. Tilton, Jeanette Wilkins†,
Amy Henderberg, Denise D. Schiro,
Marlene Johnson, Aileen Janney, and
Charles V. Sanders

Over 2800 clinical strains of the Bacteroides fragilis group were collected during a 5-year period from ten geographically separate sites and tested for their susceptibility to various antimicrobial agents using a broth microdilution method. Among the cephalosporins, ceftizoxime was the most active (13% resistance) and importantly exhibited relatively equal activity against both B. fragilis species and non-B. fragilis species. Cefotaxime exhibited similar activity with an overall resistance rate of 18%. Both ceftriaxone and cefoperazone were appreciably less active cephalosporins especially against non-B. fragilis species. With regard to cephamycins, cefoxitin (MIC$_{90}$, 32 µg/ml) was more active than cefotetan (MIC$_{90}$, ≥256 µg/ml) and cefmetazole (MIC$_{90}$, 64 µg/ml). Non-B. fragilis species were highly resistant to cefotetan and cefmetazole. Imipenem was highly active against all strains with the exception of four strains of B. fragilis. Ampicillin–sulbactam, amoxicillin–clavulanate, piperacillin–tazobactam, and cefoperazone–sulbactam were all highly active with resistance rates <2%. No resistance was detected to metronidazole, whereas 14% of isolates were resistant to clindamycin. When compared with other studies, these findings underscore the wide variability in susceptibility patterns reported nationwide and the need to continue monitoring these patterns to aid in choosing the most active compounds for therapy.

INTRODUCTION

The importance of anaerobic bacteria in mixed aerobic–anaerobic infections is well established (Finegold and George, 1989). Members of the *Bacteroides fragilis* group are the most important and most frequently isolated anaerobes from human infections. Of the various species within the *B. fragilis* group, the *B. fragilis* species is the most commonly isolated and tends to be the most susceptible to a variety of antimicrobial agents, especially β-lactams (Aldridge et al., 1984; Tally et al., 1985). It must be emphasized, however, that members of the non-*B. fragilis* species (*B. distasonis, B. ovatus, B. thetaiotaomicron,* and *B. vulgatus*) can comprise from 35% to 45% of the clinical isolates of the *B. fragilis* group (Brook, 1988; Cuchural et al., 1988). Furthermore, strains of the non-*B. fragilis* species tend to be highly resistant to certain antibiotics, especially β-lactams (Aldridge et al., 1988; Aldridge and Sanders, 1987; Goldstein and Citron, 1988). We performed a 5-year, multicenter study of the in vitro susceptibility of clinical isolates of the *B. fragilis* group. This report details the results of that study from 1987 to 1991. Some of our results contrast with those of other recent multicenter studies.

MATERIALS AND METHODS

Organisms

Over a 5-year period, clinical isolates of the *B. fragilis* group were collected from ten medical centers within the United States and sent to a single reference laboratory (Louisiana State University in New Orleans) for susceptibility testing. A total of 2876 strains were tested, comprised of 1681 *B. fragilis*, 484 *B. thetaiotaomicron*, 329 *B. ovatus*, 181 *B. distasonis*, 165 *B. vulgatus*, 25 *B. uniformis*, 10 *B. caccae*, and 1 *B. eggerthi*. All isolates were identified by using selective media, biochemical profiles, and gas–liquid chromatography (Jousimies-Somer and Finegold, 1991; Holdeman et al., 1977; Summanen et al., 1993). The sources of these isolates included abscesses, tissue, blood, body fluids, wounds, gastrointestinal and respiratory specimens, and bone. Because of changes in the antimicrobial composition in the test panels during the 5 years, not all strains were tested against each antimicrobial agent.

Antimicrobial Agents

Laboratory standard powders of each of the following agents were provided by the manufacturer: cefoperazone, ampicillin, and sulbactam (Roerig Pharmaceuticals, New York City, NY, USA); ceftizoxime (Fujisawa Pharmaceuticals, Deerfield, IL, USA); amoxicillin and clavulanate (SmithKline Beecham Pharmaceuticals, Philadelphia, PA, USA); cefoxitin and imipenem (Merck Sharp and Dohme, West Point, PA, USA); cefotetan (Stuart Pharmaceuticals, Wilmington, DE, USA); piperacillin and tazobactam (Lederle Laboratories, Wayne, NJ, USA); cefotaxime (Hoechst-Roussel Pharmaceuticals, Somerville, NJ, USA); mezlocillin (Miles Pharmaceuticals, West Haven, CT, USA); ceftriaxone (Roche Laboratories, Nutley, NJ, USA); clindamycin (Upjohn, Kalamazoo, MI, USA); and metronidazole (G.D. Searle, Chicago, IL, USA). All standard powders were stored desiccated at −20°C until use.

Antimicrobial Susceptibility Testing

Each strain was tested by a broth microdilution method as recommended by the National Committee for Clinical Laboratory Standards (NCCLS, 1988). Serial twofold dilutions of each antimicrobial agent (or combination) were prepared using anaerobe broth MIC (Difco) within a dilution scheme of 0.01 to 256 μg/ml. When combining ampicillin or cefoperazone with sulbactam, or amoxicillin with clavulanate, a 2:1 ratio was used. Piperacillin was combined with tazobactam in an 8:1 ratio or a constant tazobactam concentration of 4 μg/ml. The inoculum of each strain was prepared by inoculating 3–5 colonies into 5 ml of pre-reduced anaerobe broth MIC and incubating for 3–6 h anaerobically at 35°C. The broth culture was then adjusted to a density equal to a no. 1 McFarland nephelometer standard and further diluted to give a final inoculum size of 1 × 10^5 colony forming units per well (1 × 10^6 CFU/ ml). All plates were incubated for 48 h at 35°C anaerobically and then read. The MIC (minimum inhibitory concentration) was defined as the lowest concentration of each antimicrobial agent (or combination) that inhibited the visible growth of the test isolate. If trailing end points were observed, the antimicrobial concentration where the most significant reduction of growth was observed was chosen as the MIC. With each susceptibility run, quality assurance was performed with *B. fragilis* American Type Culture Collection (ATCC) 25285, *B. thetaiotaomicron* ATCC 29741, and *Eubacterium lentum* ATCC 43055.

β-Lactamase Assay

Production of β-lactamase was detected by using a nitrocephin test (Cefinase; BBL, Cockeysville, MD, USA).

RESULTS

Table 1 compares the in vitro activity of the various antimicrobial agents against the *B. fragilis* group. Ceftizoxime was the most active cephalosporin with

TABLE 1 Comparison of in vitro Activity of Various Antimicrobials Against the *Bacteroides fragilis* Group

Antimicrobial	No. of Strains Tested	Range[a]	Mode MIC	MIC_{50}	MIC_{90}	% Resistant[b]
Ceftizoxime	2869	0.03–≥256[a]	2	4	64	13
Cefotaxime	2868	0.06–≥256	4	8	≥256	18
Cefoperazone	2734	0.06–≥256	16	32	≥256	34
Ceftriaxone	1085	0.25–≥256	2	8	≥256	34
Cefoxitin	2868	0.06–≥256	8	16	32	6
Cefotetan	2869	0.06–≥256	8	8	≥256	27
Cefmetazole	742	0.06–≥256	8	16	64	20
Piperacillin	2869	0.12–≥256	2	8	128	12
Mezlocillin	1743	0.5–≥256	8	8	128	12
Imipenem	2371	0.01–32	0.03	0.12	0.25	0.1
Ampicillin–sulbactam	2391	0.03–≥256	1	1	4	1
Amoxicillin–clavulanate	1649	0.06–64	0.5	0.5	2	1.4
Cefoperazone–sulbactam	2390	0.01–≥256	2	4	16	0.7
Piperacillin–tazobactam	1649	0.06–≥256	1	2	16	0.2
Clindamycin	2869	0.01–≥256	0.5	0.5	8	14
Metronidazole	2869	0.01–16	1	1	2	0

[a]Results in μg/ml.
[b]Based on NCCLS (1992) or manufacturer recommendations, the following MICs (μg/ml) were used as the resistant cutoff values: ≥8, clindamycin and amoxicillin–clavulanate; ≥16, imipenem; ≥32, metronidazole and ampicillin–sulbactam; ≥64, ceftizoxime, cefotaxime, cefoperazone, ceftriaxone, cefoxitin, cefotetan, cefmetazole, and cefoperazone–sulbactam; and ≥128, mezlocillin, piperacillin, and piperacillin–tazobactam.

only 13% of the isolates being resistant and was followed by cefotaxime, cefoperazone, and ceftriaxone with resistance rates of 18%, 34%, and 34%, respectively. Among the cephamycins, resistance to cefoxitin was 6% compared with 27% and 20% to cefotetan and cefmetazole, respectively. Imipenem was the most active β-lactam agent tested, with an MIC_{90} of 0.25 μg/ml and a resistance rate of 0.1%. Both piperacillin and mezlocillin showed comparable activity, with a 12% resistance rate for each. The addition of a β-lactamase inhibitor to selected β-lactams appreciably enhanced the activity of the latter compounds. A comparison of MIC_{90} of the β-lactam–β-lactamase inhibitor combinations indicated that amoxicillin–clavulanate was only slightly more active than ampicillin–sulbactam but eightfold more active than cefoperazone–sulbactam and piperacillin–tazobactam. Resistance rates to the combinations were low, with piperacillin–tazobactam having the lowest resistant rate (0.2%). Resistance to clindamycin among the *B. fragilis* group was 14%, whereas no metronidazole resistance was detected.

Table 2 compares the resistance rates of the *B. fragilis* group by test year. In general, increases in

resistance over the 5 years were noted for the cephalosporins and cephamycins. Among the cephalosporins, cefoperazone resistance increased the most from 28% in 1987 to 41% in 1991. Both ceftizoxime and cefotaxime had a 5% variation in resistance rates during the testing years while ceftriaxone resistance remained in the low to middle 30 percentages during the same period. Among cephamycins, cefotetan showed a variation in resistance rates from 22% to 31%. Cefmetazole was tested only during 1989 and the resistance rate was 20% among those isolates. Cefoxitin resistance remained <10% for each test year. Resistance rates to piperacillin and mezlocillin were similar for all years tested, but overall piperacillin resistance increased slightly more among the isolates than did resistance to mezlocillin. For imipenem and the β-lactam–β-lactamase inhibitor combinations, no consistent increase in resistance rates were observed. However, the resistance rates to clindamycin increased almost fourfold (5%–18%) during the 5-year period.

Table 3 compares the resistance rates of the various species of the *B. fragilis* group to the test antimicrobials. Among the cephalosporins, ceftizoxime was the most active against the various species. In

TABLE 2 Comparison of Resistance Rates (%) of
the *Bacteroides fragilis* Group by
Test Years

Antimicrobial	Test Year				
	1987	1988	1989	1990	1991
Ceftizoxime	11	10	12	15	15
Cefotaxime	15	16	18	20	19
Cefoperazone	28	35	27	38	41
Ceftriaxone	32	35	ND[a]	36	ND
Cefoxitin	8	5	5	6	8
Cefotetan	22	27	23	28	31
Cefmetazole	ND	ND	20	ND	ND
Piperacillin	7	11	10	16	13
Mezlocillin	11	10	ND	16	11
Imipenem	0.1	0.2	0.2	ND	0
Ampicillin–sulbactam	ND	0.6	1.1	1.4	0.8
Amoxicillin–clavulanate	ND	1.8	ND	0.8	1.5
Cefoperazone–sulbactam	ND	1	2.7	5.8	1.2
Piperacillin–tazobactam	ND	0	ND	0.4	0.2
Clindamycin	5	11	13	19	18
Metronidazole	0	0	0	0	0

[a]Not done.

contrast, resistance rates to cefoperazone and ceftriaxone were very high among the non-*B. fragilis* species. Among the cephamycins, resistance rates to cefotetan and cefmetazole were high among *B. thetaiotaomicron*, *B. ovatus*, and *B. distasonis*. Cefoxitin was the most active cephamycin, but increased resistance was noted among the non-*B. fragilis* species compared with the *B. fragilis* species. Resistance rates to piperacillin and mezlocillin were similar among the various species; however, resistance rates were higher among non-*B. fragilis* species. Only a few strains of *B. fragilis* exhibited resistance to imipenem. Resistance to all β-lactam/β-lactamase inhibitor combinations was noted, but the highest rates were noted among *B. distasonis* and *B. ovatus*. Strains of non-*B. fragilis* species were appreciably more resistant to clindamycin than were *B. fragilis* strains.

DISCUSSION

The resistance rates of the *B. fragilis* group to various antimicrobial agents have been reported to be both species and geographically dependent (Aldridge et al., 1984; Aldridge et al., 1988; Tally et al., 1985). The

predominant mechanism of resistance to β-lactams among the *B. fragilis* group is β-lactamase production (Nord et al., 1985). Although the most common β-lactamases from these isolates are characterized as cephalosporinases, some *B. fragilis* group strains elaborate β-lactamases capable of destroying antimicrobials considered β-lactamase stable such as cefoxitin, imipenem, and piperacillin (Cuchural et al., 1983; Sato et al., 1982). Moreover, β-lactamase-mediated cefoxitin resistance among strains of the *B. fragilis* group has been shown to be transferable (Cuchural et al., 1986a).

Results of the present study confirm that there are significant differences in the activity of certain antimicrobial agents against *B. fragilis* group isolates. Among the single agents tested, metronidazole and imipenem were the most active. Among the cephalosporin compounds, ceftizoxime was more active than cefotaxime, cefoperazone, and ceftriaxone, while among cephamycins, cefoxitin was more active than cefotetan and cefmetazole. Piperacillin, mezlocillin, and clindamycin had comparable resistance rates. With the exception of imipenem, the non-*B. fragilis* species were significantly more resistant to the β-lactam antimicrobials alone (no β-lactamase inhibitor) than were strains of the *B. fragilis* species; a similar pattern was seen with clindamycin.

Prevention of β-lactam degradation by addition of a β-lactamase inhibitor has proven to be very effective. The addition of sulbactam, clavulanate, or tazobactam significantly reduced the resistance rates to the accompanying β-lactams and potentiated the activity of the antimicrobials by reducing the mode MICs and MIC90 up to 32-fold and 64-fold, respectively. One strain of *B. fragilis* resistant to all of the β-lactam–β-lactamase inhibitor combinations except piperacillin–tazobactam was also resistant to all other β-lactams tested. This strain probably produces the metallo-containing β-lactamase enzyme that has been shown to destroy all penicillins and cephalosporins (Cuchural et al., 1986b).

A comparison of our data with the recent US reports by Cuchural et al. (1988 and 1990) shows similarities and differences. Overall, the two reports correlated well with regard to resistance rates to imipenem, cefoxitin, piperacillin, cefoperazone, and clindamycin. However, reported resistance rates of 22%, 23%, and 14% to ceftizoxime, cefotaxime, and cefotetan, respectively, differed from our results showing resistance rates of 13%, 18%, and 27% to the same antimicrobials. Furthermore, the ceftizoxime MIC90 in our study was 64 μg/ml compared with ≥128 μg/ml in their study. Our ceftizoxime data are in contrast to theirs and, from a comparison of our in vitro data, we can conclude that ceftizoxime has good coverage against *B. fragilis* group isolates with

TABLE 3 Comparison of Resistance Rates (%) of the Various Species of the *Bacteroides fragilis* Group to the Antimicrobials

Antimicrobial	*Bacteroides*					
	fragilis	*thetaiotao-micron*	*ovatus*	*distasonis*	*vulgatus*	Other[a]
Ceftizoxime	11	16	15	17	8	11
Cefotaxime	16	23	23	20	11	21
Cefoperazone	25	51	57	31	25	12
Ceftriaxone	19	72	58	46	31	31
Cefoxitin	4	9	12	12	9	15
Cefotetan	8	51	67	53	20	29
Cefmetazole	0	0	0	0	0	33
Piperacillin	9	13	16	17	18	9
Mezlocillin	11	11	14	19	16	8
Imipenem	0.2	0	0	0	0	0
Ampicillin–sulbactam	0.7	0.5	1.4	5	0	0
Amoxicillin–clavulanate	1.0	1.6	2.5	4.3	0	0
Cefoperazone–sulbactam	1.8	2.7	3.1	0.7	1.4	0
Piperacillin–tazobactam	0.1	0.4	0.4	0	0	0
Clindamycin	8	20	26	22	18	13
Metronidazole	0	0	0	0	0	0

[a]Contains 25 *B. uniformis*, 10 *B. caccae*, and 1 *B. eggerthii*.

activity comparable to that of clindamycin. A clinical study by Bennion et al. (1992) in patients with perforated or gangrenous appendicitis with peritonitis reported that ceftizoxime exhibited good antianaerobic coverage. These differences in in vitro results are probably related to differences in susceptibility testing methodologies (Aldridge and Sanders, 1987; Aldridge et al., 1990).

Other US investigators have reported the high level of activity with β-lactam–β-lactamase inhibitor combinations with results similar to ours. Barry et al. (1986) reported that sulbactam reduced the MIC_{90} of ampicillin and cefoperazone from ≥ 16 μg/ml to 2 μg/ml and from 128 μg/ml to 16 μg/ml, respectively. Wexler et al. (1985) showed an MIC_{90} reduction from ≥ 256 μg/ml to 8 μg/ml when sulbactam was added to ampicillin. Clavulanate has been reported to increase the activity of amoxicillin 16-fold (Barry et al., 1986). Appelbaum et al. (1986) have also shown a significant increase in the activity of piperacillin in the presence of tazobactam (YTR 830). In our study, ampicillin–sulbactam and amoxicillin–clavulanate appeared to be slightly more active (MICs) than the other β-lactam–β-lactamase inhibitor combinations; however, no appreciable differences in resistance rates were noted. Currently the

approach of protecting β-lactams with β-lactamase inhibitors appears to remain highly effective.

Phillips et al. (1992) reported on an in vitro survey of the susceptibility of *B. fragilis* group by using broth microdilution testing of isolates from 15 European and Scandinavian countries. Their results were similar to ours with regard to amoxicillin–clavulanate, cefoxitin, cefotetan, imipenem, and metronidazole. Similarly we found imipenem resistance among *B. fragilis* strains. Notable differences for overall results were that mezlocillin resistance was 12% in our study versus 6% in theirs, and clindamycin resistance was higher in our study (14% versus 9%). Our higher rates of clindamycin resistance more closely agree with reports from Spain and France (Dubreuil et al., 1992; Reig et al., 1984; Garcia-Rodriquez and Garcia-Sanchez, 1985). In Japan, a report by Watanabe et al. (1992) described susceptibility patterns of *B. fragilis* and *B. thetaiotaomicron* strains. Resistance to imipenem was found among both groups of isolates, with resistance rates of 1.6% and 3.4%, respectively. They also reported good activity for ceftizoxime and cefoperazone–sulbactam similar to ours. For the two test groups, they reported clindamycin resistances of 24% and 27.5%, respectively. Moreover, their piperacillin re-

sistance rate among *B. thetaiotaomicron* was 26.8% compared with our 13%. Fortunately no metronidazole resistance was noted.

This study has shown that a variety of susceptibility patterns can be observed among strains of the *B. fragilis* group. Currently metronidazole, imipenem, and the β-lactam–β-lactamase inhibitor combinations are the most active. Good activity was also seen for mezlocillin, piperacillin, ceftizoxime, cefoxitin, and clindamycin. Because of reports of resistance to metronidazole, imipenem, and other antimicrobials among anaerobes (Breuil et al., 1989;

Brogan et al., 1989; LaMothe et al., 1986), additional in vitro studies to monitor changes in susceptibility patterns are warranted not only in the United States but elsewhere.

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