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Bacteremia Due to *Bacteroides fragilis* Group: Distribution of Species, β-Lactamase Production, and Antimicrobial Susceptibility Patterns

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A retrospective analysis of susceptibility data on 542 blood isolates of the *Bacteroides fragilis* group tested from 1987 to 1999 by the same NCCLS-recommended broth microdilution method throughout is presented. Metronidazole, β-lactam–β-lactamase inhibitor combinations, carbapenems, and trovafloxacin were the most active agents (susceptibility of ≥93%). Among the cephalosporin-cephamycins, the order of activity was cefoxitin > ceftizoxime > cefotetan = cefotaxime = cefmetazole > ceftriaxone. All isolates were resistant to penicillin G, and 22% were resistant to clindamycin. The susceptibility rates to piperacillin-tazobactam, imipenem, and meropenem were affected least among isolates resistant to cefoxitin or clindamycin. Except for piperacillin-tazobactam, imipenem, and meropenem, the *B. fragilis* species was more susceptible than were the non-*B. fragilis* species. These data underscore the importance of susceptibility testing of the *B. fragilis* group and can serve as a guide in the choice of empirical antimicrobial therapy.

The *Bacteroides fragilis* group comprises the most important anaerobic pathogens in human infections. These pathogens are often associated with polymicrobial infections such as intra-abdominal, obstetric-gynecologic, diabetic foot, and skin and skin structure infections. The virulence of these pathogens contributes to the spread of the infection, abscess formation, and the production of an antiphagocytic polysaccharide capsule (6).

Documented increases in antimicrobial resistance to β-lactams and clindamycin have been reported (5, 28). β-Lactam resistance is mediated predominantly by production of β-lactamase enzymes among both gram-negative and -positive bacilli, as well as *Acidaminococcus* (6, 14, 22). The incidence of β-lactamase production among the *B. fragilis* group has been reported to be ≥95% of isolates (6). These enzymes have been characterized primarily as cephalosporinases; however, penicillinases and carbapenemases have also been reported (8, 17, 18, 22, 23, 27, 30).

Anaerobic bacteremia is an infrequent infection; however, it can result in a high mortality rate. Two previous studies (9, 10) of *Bacteroides* bacteremia determined that the mortality rate varied according to the species isolated. Bacteremia due to *B. fragilis* had associated mortality rates of 24 and 31%, respectively, whereas the mortality rate for *B. distasonis* was 50% and that for *B. thetaiotaomicron* was as high as 100%. More recently Redondo et al. (25) compared a group of patients with *B. fragilis* group bacteremia to a demographically matched-pair group of patients without bacteremia. The mortality rate was significantly higher in the bacteremic group (28% versus 8.7%, $P = 0.002$) and had a mortality risk ratio of 4.9. Moreover, patients with bacteremia remained in the hospital 16 days longer. These authors also reported that the most common source of bacteremia was associated with bowel surgery or disease. Montravers et al. (19) studied 100 patients who developed postoperative peritonitis due to aerobes and anaerobes and compared their clinical outcome to the appropriateness of their antimicrobial therapy based on in vitro susceptibility data. Patients who were infected with resistant isolates had a significantly higher mortality rate than those infected with susceptible isolates (45% versus 16%, $P < 0.05$). These authors concluded that the choice of initial empirical therapy directly affected the clinical outcome and that the subsequent change of antibiotic therapy based on culture results did not affect clinical outcome when the initial therapy was judged as inadequate. In a similar study recently reported by Nguyen et al. (21), a multicenter, observational study of 128 patients with *Bacteriodes* bacteremia compared the clinical outcome of these patients with the in vitro susceptibility of their blood isolates. The mortality rate of patients who received appropriate therapy (susceptible in vitro) was 16% compared to patients who received inappropriate therapy (resistant in vitro), whose mortality rate was 45% ($P = 0.04$). Microbiological persistence was higher with inactive versus active therapy (42% versus 12%, $P = 0.06$). That study concluded that in vitro susceptibility results reliably predicted the clinical outcome of the patients with a specificity of 97% and positive predictive value of 82%.

We report here the results of a retrospective analysis of in vitro susceptibility of *B. fragilis* group blood isolates as a subset of >3,600 isolates tested from 1987 to 1999.

MATERIALS AND METHODS

Organisms. A total of 542 *B. fragilis* group isolates cultured from blood and representing isolates from 12 different medical centers throughout the United States were analyzed retrospectively for their susceptibility to various antimicrobial agents. Of this 542 isolate group, 233 isolates were included in a 1992 report (3) on the susceptibility of body fluid isolates, but the results were not detailed in that report except for the overall resistance rate to ceftizoxime (8%) and the lack of resistance to metronidazole and imipenem. We have, however, included those data in the present study. Due to the availability of various antimicrobial agents and formulary considerations during the testing period, not all antimicro-

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TABLE 1. Distribution of blood isolates of the *B. fragilis* group and β-lactamase production

Organism	No. of isolates (% of total)[a]	% β-Lactamase^{+}[b]
B. fragilis	339 (62.5)	98.5
B. thetaiotaomicron	95 (17.5)	100
B. ovatus	54 (10)	94.7
B. vulgatus	30 (5.5)	100
B. distasonis	17 (3.2)	75
B. uniformis	5 (0.9)	100
B. caccae	2 (0.4)	100

[a] The number in parenthesis indicates the percentage of the total *B. fragilis* group isolates.
[b] That is, the percentage of each species producing β-lactamase.

bial agents were tested against every isolate. Each clinical isolate was identified by using selective growth media, biochemical profiles, and gas-liquid chromatography (16, 29). The distribution of the various species of isolates is shown in Table 1. Production of β-lactamase was determined by using a nitrocephin test (Cefinase; BBL, Cockeysville, Md.).

Antimicrobial agents. Each of the following standard laboratory powders was provided by the manufacturer: penicillin G (Eli Lilly, Indianapolis, Ind.); clindamycin and cefmetazole (Pharmacia-Upjohn, Kalamazoo, Mich.); trovafloxacin, ampicillin, and sulbactam (Pfizer, Groton, Conn.); imipenem, ertapenem, and cefoxitin (Merck, West Point, Pa.); metronidazole (Searle, Skokie, Ill.); piperacillin and tazobactam (Wyeth-Ayerst, St. Davids, Pa.); meropenem and cefotetan (AstraZeneca, Wilmington, Del.); ticarcillin and clavulanate (Glaxo SmithKline, Philadelphia, Pa.); cefotaxime (Aventis, Bridgewater, N.J.); ceftriaxone (Roche, Nutley, N.J.); and ceftizoxime (Fujisawa, Deerfield, Ill.). All antimicrobial powders were stored at −20°C prior to use.

Susceptibility testing. MICs were determined by a broth microdilution method based on recommendations of the National Committee for Clinical Laboratory Standards (NCCLS) (20). Antimicrobial agents were prepared in serial twofold dilutions in anaerobe broth MIC (Difco) within a dilution range of 0.008 to 256 μg/ml. Ampicillin was combined with sulbactam in a 2:1 ratio, while serial twofold dilutions of piperacillin and ticarcillin were combined with tazobactam and clavulanate at constant concentrations of 4 and 2 μg/ml, respectively. Final test volumes of 100 μl were dispensed into microdilution wells. The inoculum of each isolate was prepared by suspending colonies from an anaerobic sheep blood agar plate incubated for 18 to 24 h in 5 ml of prereduced anaerobe broth MIC to a density equal to that of a no. 1 McFarland standard. The suspension was further diluted to give a final inoculum size of 10^5 CFU per well (10^6 CFU/ml). All plates were incubated at 35°C anaerobically for 48 h and then read with a mirror reader. The MIC was defined as the lowest concentration of each antimicrobial agent that inhibited the visible growth of the test isolate. With each susceptibility test run, quality control was performed with *B. fragilis* ATCC 25285, *B. thetaiotaomicron* ATCC 29741, and *Eubacterium lentum* ATCC 43055.

Data management. MICs were collated to determine the mode MIC, the MIC at which 50% of the isolates were inhibited (MIC_{50}), the MIC_{90}, and the percentage of isolates susceptible (%S) to each antimicrobial agent based on NCCLS recommendations (20) The statistical significance of differences in susceptibility rates for all pairwise comparisons was performed by using Pearson's chi-square test or the Fisher exact test. To control the familywise error rate for multiple comparisons, the *P* values were adjusted by the Bonferroni method. Statistical significance was achieved with a *P* value of ≤0.05 (12).

RESULTS AND DISCUSSION

The distribution of the 542 clinical isolates and β-lactamase production is shown in Table 1. *B. fragilis* isolates were the predominant species (62.5%), followed by *B. thetaiotaomicron* (17.5%), *B. ovatus* (10%), *B. vulgatus* (5.5%), and *B. distasonis* (3.2%). Only five and two isolates of *B. uniformis* and *B. caccae*, respectively, were isolated from blood. Nguyen et al. (21) recently reported a similar distribution of *B. fragilis* group blood isolates. That study showed essentially the same incidence of *B. fragilis*, *B. distasonis*, *B. thetaiotamicron*, and *B. vulgatus*, whereas we tested more *B. ovatus* and fewer *B. uniformis* and *B. caccae*. Overall, β-lactamase production for the *B. fragilis* group was 97.4%. Variation in β-lactamase production among the various species is shown in Table 1. Previous studies have reported a high rate of β-lactamase production among the *B. fragilis* group. In 1983 we found 87% of the *B. fragilis* group were cephalosporinase producers, whereas in 1988 and 2001 this rate was ≥97% (1, 2,7). Interestingly the *B. distasonis* isolates are often β-lactamase nonproducers but remain highly resistant to penicillin G or ampicillin (1, 13). Moreover, we previously reported (4) that of the *B. fragilis* group species, *B. distasonis* isolates were the most resistant to ampicillin-sulbactam, ticarcillin-clavulanate, and amoxicillin-clavulanate, whereas piperacillin-tazobactam was active against all of the same isolates.

The susceptibility results of the 542 blood isolates are shown in Table 2. Since the collection of the isolates ranged from 1987 to 1999 not all antimicrobials were tested against all isolates; therefore, the mix of various species tested for each antimicrobial agent varied. However, we feel these comparisons are valid since the reports that the empirical choice of antimicrobial therapy are important, regardless of the species, in the outcome of bacteremia and intra-abdominal infections involving the *B. fragilis* group (19, 21, 25).

Only metronidazole was active against all of the test isolates. All test isolates were resistant to penicillin G based on β-lactamase production or MICs. Both piperacillin and ticarcillin showed moderate activity with susceptibility rates (i.e., %S) of 77 and 63%, respectively. However, the piperacillin mode MIC was fourfold less than that of ticarcillin. Piperacillin-tazobactam, ticarcillin-clavulanate and ampicillin-sulbactam showed good activity (%S ≥ 96%) against the test isolates. Although no statistical differences were noted, more isolates were susceptible to piperacillin-tazobactam (%S = 99.1) than to ticarcillin-clavulanate (%S = 96%) and ampicillin-sulbactam (%S = 95%). Of 142 simultaneous comparisons of all three β-lactam–β-lactamase inhibitor combinations, 137 isolates were susceptible to all three agents. One *B. fragilis* isolate had an intermediate MIC for piperacillin-tazobactam but had resistant MICs for ticarcillin-clavulanate and ampicillin-sulbactam. Of the other four isolates (two *B. fragilis* and two *B. ovatus*), all were susceptible to piperacillin-tazobactam, three were intermediate, and one was susceptible to ticarcillin-clavulanate, and three were intermediate and one was resistant to ampicillin-sulbactam. The activity of the various cephalosporin-cephamycin agents varied widely. Cefoxitin was the most active of the group, with 83% of the isolates being susceptible, followed by ceftizoxime, with 78% being susceptible. Against the *B. fragilis* group overall, cefotaxime, cefotetan, and cefmetazole showed equal activity with susceptibility rates of 61 to 63%; however, distinct differences can be seen when analyzing individual species (see Table 3). Ceftriaxone had the poorest activity against the *B. fragilis* group, with only 49% of isolates being susceptible.

All three carbapenems were highly active. Imipenem was the most active, with an isolate susceptibility of 99.5%. Meropenem and ertapenem had equal activity (%S ≥ 94%). Ertapenem is a newly Food and Drug Administration-approved carbapenem with pharmacokinetics compatible with once-a-day dosing (15). The mode MICs of imipenem, however, were

TABLE 2. Comparison of in vitro susceptibility rates of blood isolates of the *B. fragilis* group

Antimicrobial agent	No. of isolates tested	MIC (μg/ml)				All isolates (%S)[a]	Cfx-I&R[b]		Clin-I&R[c]	
		Range	Mode	MIC_{50}	MIC_{90}		%S	%SΔ[d]	%S	%SΔ
Penicillin G	160	0.06–128	8	8	128	0	0	0	0	0
Piperacillin	384	0.12–256	2	8	128	77	46	−31	60	−17
Ticarcillin	137	0.12–256	16	32	128	63	21	−42	39	−24
Piperacillin-tazobactam	142	0.06–64	2	1	8	99.3	96	−3.3	96.1	−3.2
Ticarcillin-clavulanate	191	0.25–256	1	0.5	8	96	83	−13	86	−10
Ampicillin-sulbactam	382	0.03–128	1	1	8	93	81	−12	80	−13
Cefotaxime	384	0.06–256	4	8	64	62	32	−30	34	−28
Ceftriaxone	138	1–128	2	32	128	49	7	−42	7	−42
Cefoxitin	515	0.12–128	8	8	32	84	0		73	−11
Cefotetan	473	0.06–256	8	8	64	64	8	−56	26	−38
Cefmetazole	84	0.25–128	8	16	64	61	0	−61	35	−26
Ceftizoxime	358	0.06–256	4	4	64	78	67	−11	65	−13
Imipenem	378	0.015–32	0.03	0.12	1	99.5	97	−2.5	98	−1.5
Meropenem	127	0.015–32	0.12	0.5	0.5	98	94	−4	94	−4
Ertapenem	92	0.06–32	0.25	0.25	2	94	64	−30	86	−8
Trovafloxacin	156	0.03–16	0.25	0.25	2	96	86	−10	88	−8
Clindamycin	542	0.015–64	0.25	0.5	16	78	63	−15	0	
Metronidazole	542	0.06–8	1	1	2	100	100	0	100	0

[a] The following MIC values (μg/ml) were used as susceptibility breakpoints as recommended by the NCCLS (14): penicillin G, ≤0.5; piperacillin, ≤32; ticarcillin, ≤32; piperacillin-tazobactam, ≤32; ticarcillin-clavulanate, ≤32; ampicillin-sulbactam, ≤8; cefotaxime, ≤16; ceftriaxone, ≤16; cefoxitin, ≤16; cefotetan, ≤16; cefmetazole, ≤16; ceftizoxime, ≤16; imipenem, ≤4; meropenem, ≤4; trovafloxacin, ≤2; clindamycin, ≤2; and metronidazole, ≤8. Ertapenem susceptibility was ≤4 μg/ml, as recommended by the manufacturer. Test isolates with higher than stated susceptible MICs were considered "not susceptible" and were comprised of isolates with MICs interpreted as intermediate or fully resistant.

[b] Contains isolates with cefoxitin (Cfx) MICs of ≥32 μg/ml.

[c] Contains isolates with clindamycin (Clin) MICs of ≥4 μg/ml.

[d] Indicates the decrease in the percentage of isolates susceptible to isolates "not-susceptible" to cefoxitin or clindamycin.

four- and eightfold lower than those of meropenem and ertapenem, respectively. For one isolate of *B. fragilis*, the imipenem MIC was 8 μg/ml (intermediate) and had meropenem and ertapenem MICs of ≥32 μg/ml (resistant). Another isolate of *B. fragilis* was susceptible (MIC = 1 μg/ml) to imipenem but was resistant to meropenem and ertapenem (MICs of ≥32 μg/ml). Trovafloxacin was active against 96% of the isolates, whereas clindamycin was active against only 76% of the test isolates.

Table 2 also presents the changes in susceptibility rates to the various antimicrobial agents when subsets of isolates for which the MICs of cefoxitin or clindamycin are intermediate or fully resistant are compared to the entire test group. Except for penicillin or metronidazole, all of the remaining antimicrobial agents altered the susceptibility rates. Only piperacillin-tazobactam and imipenem were associated with decreases in susceptibility rates of <4% among both cefoxitin- and clindamycin-resistant isolates. Ticarcillin-clavulanate and ampicillin-

TABLE 3. Comparison of susceptibility rates of various species of the *B. fragilis* group isolated from blood

Antimicrobial agent	% S value(s)[a]						
	B. fragilis	*B. thetaiotaomicron*	*B. distasonis*	*B. ovatus*	*B. vulgatus*	*B. uniformis*	*B. caccae*
Penicillin G	0	0	0	0	0	0	4, 32*
Piperacillin	80	76	64	74	45	32, 32, 32*	NT
Ticarcillin	69	68	16, 256	39	44	256	NT
Piperacillin-tazobactam	99.1	100	100	100	100	0.12, 0.25*	0.5, 2*
Ticarcillin-clavulanate	99.2	100	1, 32, 128, 128	77	100	8*	NT
Ampicillin-sulbactam	95	98	77	84	88	1, 2, 2, 2*	1, 16*
Cefotaxime	74	39	36	46	50	32, 64, 64*	NT
Ceftriaxone	69	8	17	11	0	NT	NT
Cefoxitin	90	70	53	88	69	1, 2, 16, 64*	4, 32*
Cefotetan	87	19	21	26	50	64, 128*	NT
Cefmetazole	85	6	33	20	8, 16*	128*	NT
Ceftizoxime	81	76	64	81	56	32, 32*	NT
Imipenem	99.2	100	100	100	100	100	0.03, 0.25*
Meropenem	96	100	100	100	100	0.06, 0.12, 0.25*	0.12, 2*
Ertapenem	94	100	60	88	100	0.06, 0.12*	0.25, 2*
Trovafloxacin	100	92	100	90	92	0.03, 0.5*	0.12, 2*
Clindamycin	89	63	53	48	73	60	16, 16*
Metronidazole	100	100	100	100	100	100	0.25, 0.5*

[a] *, when four or fewer isolates were tested, the individual MICs are listed. NT, not tested.

sulbactam were associated with susceptibility decreases of from 10 to 13%, whereas meropenem and ertapenem were associated with reductions in susceptibility of 4 to 30%. With cefoxitin-resistant isolates, the susceptibility rates associated with other cephalosporin-cephamycin agents were reduced from 11 to 61%, and with clindamycin-resistant isolates the decreases in susceptibility rates ranged from 11 to 42%. Susceptibility to clindamycin decreased 15% in cefoxitin-resistant isolates. The susceptibility rate associated with trovafloxacin decreased 10% with cefoxitin-resistant isolates and 8% with clindamycin-resistant isolates.

Table 3 indicates the susceptibility rates among the *B. fragilis* group species to the test antimicrobial agents. Overall, the *B. fragilis* species remains the most susceptible of the *B. fragilis* group. Only metronidazole was active against all of the species; however, Rotimi et al. (26) recently reported from Kuwait the isolation of metronidazole-resistant *B. fragilis*, *B. ovatus*, and *B. distasonis* strains from patients with abdominal infections who were clinical failures while being treated with metronidazole. For ticarcillin-clavulanate and ampicillin-sulbactam, isolates of *B. distasonis* and *B. ovatus* were the least susceptible (%S = 50 and 77%, respectively). With piperacillin-tazobactam, reduced susceptibility (intermediate) was noted for a single isolate of *B. fragilis.*

Interestingly, resistance to the carbapenems was found only among *B. fragilis* species isolates, whereas resistance to ertapenem varied from 6 to 40% among isolates of *B. fragilis*, *B. ovatus*, and *B. distasonis*. The non-*B. fragilis* species varied widely in susceptibility rates to the cephalosporin-cephamycin agents (Table 3). Overall, cefoxitin remained the most active, with susceptibility rates ranging from 53 to 84% compared to cefotetan, with susceptibility rates ranging from 0 to 50%. Of the cephalosporins, ceftizoxime was the most active, with the exception of *B. uniformis* isolates, which were resistant to all cephalosporin-cephamycins except for cefoxitin. For cefotaxime, ceftriaxone, and cefmetazole, ≤50% of all isolates of the non-*B. fragilis* species were resistant to these agents. Patey et al. (24) studied 416 blood isolates of the *B. fragilis* group from patients in France over a 2-year period. These researchers obtained results similar to ours in that all species were highly susceptible (>98%) to metronidazole, β-lactam–β-lactamase inhibitors, and carbapenems. Compared to the *B. fragilis* species, the non-*B. fragilis* species showed reduced susceptibility to piperacillin (88%), clindamycin (86%), cefotetan (23%), and cefotaxime (69%), although these authors did not specify results for individual species. In the present study, only strains of *B. ovatus* and *B. vulgatus* were found to be resistant to trovafloxacin, whereas resistance to clindamycin occurred among all of the species, including the two isolates of *B. caccae*.

Table 4 summarizes the statistical relationships between all pairwise combinations of antimicrobial agents against the *B. fragilis* group isolates when susceptibility rates were compared. Metronidazole was statistically more active than all of the antimicrobial agents except for piperacillin-tazobactam, the carbapenems, and trovafloxacin. No statistical differences were found within the β-lactam–β-lactamase inhibitor group, but as a group they were statistically more active than the cephalosporin-cephamycins, piperacillin, ticarcillin, and clindamycin. Similarly, no statistical differences were noted among the carbapenem compounds compared to the β-lactam–β-lactamase

TABLE 4. *P* values for pairwise comparisons of susceptibility rates among the various antimicrobial agents

Antibiotic	*n*	%S	*P* values for pairwise %S comparisons[a]														
			PIP (384, 76.6)	TIC (137, 63)	TZP (142, 99.3)	TIM (191, 95.8)	SAM (382, 92.9)	CTX (384, 62)	CRO (138, 49.3)	FOX (515, 84.1)	CTT (473, 64.5)	CMZ (84, 61)	ZOX (358, 78)	IPM (378, 99.5)	MEM (127, 97.6)	ERT (92, 93.5)	TVA (156, 95.5)	CLI (542, 77.7)	MTR (542, 100)
PEN G	160	0	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
PIP	384	76.6	-	0.278	<0.001*	<0.001*	<0.001*	0.002*	<0.001*	0.704	0.019*	0.428	1.000	<0.001*	<0.001*	0.043*	<0.001*	1.000	<0.001*
TIC	137	63	-	-	<0.001*	<0.001*	<0.001*	1.000	1.000	<0.001*	1.000	1.000	0.093	<0.001*	<0.001*	<0.001*	<0.001*	0.052	<0.001*
TZP	142	99.3	-	-	-	1.000	0.610	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	1.000	1.000	1.000	1.000	<0.001*	1.000
TIM	191	95.8	-	-	-	-	1.000	<0.001*	<0.001*	0.005*	<0.001*	<0.001*	<0.001*	0.507	1.000	1.000	1.000	<0.001*	0.003*
SAM	382	92.9	-	-	-	-	-	<0.001*	<0.001*	0.009*	<0.001*	<0.001*	<0.001*	<0.001*	1.000	1.000	1.000	<0.001*	<0.001*
CTX	384	62	-	-	-	-	-	-	1.000	<0.001*	1.000	1.000	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
CRO	138	49.3	-	-	-	-	-	-	-	<0.001*	0.194	1.000	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
FOX	515	84.1	-	-	-	-	-	-	-	-	<0.001*	<0.001*	1.000	<0.001*	0.008*	1.000	0.034*	1.000	<0.001*
CTT	473	64.5	-	-	-	-	-	-	-	-	-	1.000	0.004*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*	<0.001*
CMZ	84	61	-	-	-	-	-	-	-	-	-	-	0.167	<0.001*	<0.001*	<0.001*	<0.001*	0.120	<0.001*
ZOX	358	78	-	-	-	-	-	-	-	-	-	-	-	<0.001*	<0.001*	0.104	<0.001*	1.000	<0.001*
IPM	378	99.5	-	-	-	-	-	-	-	-	-	-	-	-	1.000	0.149	0.515	<0.001*	1.000
MEM	127	97.6	-	-	-	-	-	-	-	-	-	-	-	-	-	1.000	1.000	<0.001*	1.000
ERT	92	93.5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1.000	0.071	0.001*
TVA	156	95.5	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	<0.001*	0.004*
CLI	542	77.7	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	<0.001*

[a] *P* values are derived from Fisher's exact test or Pearson's chi-square test, adjusted for multiple comparisons with the Bonferroni correction. The asterisks indicate values that were statistically significant at an alpha level of 0.05. Antibiotics: PEN G, penicillin G; PIP, piperacillin; TIC, ticarcillin; TZP, piperacillin-tazobactam; TIM, ticarcillin-clavulanate; SAM, ampicillin-sulbactam; TAX, cefotaxime; CRO, ceftriaxone; FOX, cefoxitin; CTT, cefotetan; CMZ, cefmetazole; ZOX, ceftizoxime; IPM, imipenem; MEM, meropenem; ERT, ertapenem; TVA, trovafloxacin; CLI, clindamycin; MTR, metronidazole. Parenthetic values indicate the following: *n*, %S.

inhibitor agents and trovafloxacin; however, significance was achieved with few exceptions between carbapenems and cephalosporin-cephamycins, piperacillin, ticarcillin, and clindamycin. Various degrees of significance were also achieved among isolated comparisons, particularly among the cephalosporin-cephamycin agents (Table 4).

Many in vitro susceptibility studies have included *B. fragilis* group isolates, but few of these studies have selected out blood isolates for discussion. In 1974 Chow and Guze (10) detailed the clinical and demographic factors from 112 patients with *Bacteroidaceae* bacteremia.These authors found that, of 36 isolates of the *B. fragilis* group, 97, 94, 47, and 36% were susceptible to chloramphenicol, clindamycin, lincomycin, and tetracycline, respectively, by using higher breakpoints than are currently recommended by the NCCLS (14). Although no β-lactamase results were reported, 25% of the isolates were susceptible to penicillin at ≤5 μg/ml, whereas 75% (21 of 28) were susceptible to erythromycin at 2.5 μg/ml. By comparison, this report indicates that for blood isolates susceptibility to clindamycin has fallen to 76% and for cefoxitin it fell to 83%, whereas metronidazole remained active against all *B. fragilis* group isolates. Cuchural et al. (11) reported that, in a susceptibility study of *B. fragilis* group isolates done in 1984 and 1985, blood isolates had a resistance rate to cefoxitin of 10.7% at a breakpoint of ≤16 μg/ml, which is lower than the 16% we found in our analysis with the same breakpoint. This finding may be related to the test isolate population of Cuchural et al., 71.4% of which were *B. fragilis* species isolates compared to the 62.5% *B. fragilis* isolates in our study, which traditionally tend to be more susceptible to a variety of antimicrobial agents than other species. Moreover, these authors reported a susceptibility rate to clindamycin of 90% compared to our finding of 78%, which is probably due to their use of a higher breakpoint (4 μg/ml). In a similar report from that laboratory (28) comparing the susceptibilities of the *B. fragilis* group from 1995 and 1996 from all sources, the resistances to cefoxitin were 8 and 5%, respectively, whereas the resistance rate to clindamycin was 16% for both years. By comparison, in the latter study the percentage of *B. fragilis* species tested decreased to 53.4%. It should be pointed out that in both of their studies the authors chose to include intermediate MICs for both agents in the susceptible category, whereas we included them in the resistant category.

The present analysis, to our knowledge the largest yet reported, indicates that blood isolates collected from several geographical areas in the United States over a 12-year period have shown decreased susceptibility to certain antimicrobial agents, such as clindamycin, but remain susceptible to numerous other agents. Such data are important in the choice of empirical therapy of infections involving the *B. fragilis* group, particularly for bacteremia due to these organisms, which has been shown to be an independent risk factor for mortality (21, 25). Moreover, these data did not demonstrate any metronidazole-resistant *B. fragilis* group isolates as reported in Kuwait nor high resistance rates to imipenem as reported in Japan. However, we must remain vigilant through additional studies such as this to detect any future significant changes in antimicrobial resistance.

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