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Susceptibility of the *Bacteroides fragilis* Group in the United States: Analysis by Site of Isolation

GEORGE J. CUCHURAL, JR.,[1,2]* FRANCIS P. TALLY,[2]† NILDA V. JACOBUS,[2] KENNETH ALDRIDGE,[3] TIMOTHY CLEARY,[4] SYDNEY M. FINEGOLD,[5] GALE HILL,[6] PAUL IANNINI,[7] J. PAUL O'KEEFE,[8] CARL PIERSON,[9] DERRICK CROOK,[1]‡ TOM RUSSO,[1] AND DAVID HECHT[1]

Geographic Medicine/Infectious Disease Service, Department of Medicine,[1] and Clinical Microbiology, Department of Pathology,[2] Tufts-New England Medical Center Hospitals, Boston, Massachusetts 02111; Charity Hospital, Louisiana State University Medical Center, New Orleans, Louisiana 76112[3]; University of Miami/Jackson Memorial Medical Center, Miami, Florida 33136[4]; Wadsworth Veterans Administration Medical Center, Los Angeles, California 90073[5]; Duke University Medical Center, Durham, North Carolina 27710[6]; Danbury Hospital, Danbury, Connecticut 06810[7]; Loyola University Medical Center, Maywood, Illinois 60153[8]; and University of Michigan Medical Hospital, Ann Arbor, Michigan 48104[9]*

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An ongoing survey of the susceptibility of the *Bacteroides fragilis* group of bacteria was continued at New England Medical Center in 1984 and 1985. A total of 1,229 strains were obtained from eight centers in the United States. These results were compared with those for 1,847 isolates tested in 1981 through 1983. The most active β-lactam drugs were imipenem and ticarcillin-clavulanic acid (Timentin), which had a less than 1% resistance rate. No metronidazole- or chloramphenicol-resistant isolates were found during the 5 years of the study. Isolates obtained from blood, perinatal, and bone sites of infection were more resistant to a variety of antimicrobial agents. Susceptibility patterns of the members of the *B. fragilis* group varied at the eight hospitals and among species. These data indicate the need for determining the susceptibility patterns for the *B. fragilis* group of organisms at each hospital.

Members of the *Bacteroides fragilis* group of organisms are the most frequently recovered anaerobic bacterial pathogens of humans. They are usually cultured from infections involving inoculation of a sterile site by colonic flora as a result of contamination after abdominal surgery, ruptured appendicitis, bowel ischemia, infected decubitus ulcers, colonic cancer, endometritis, pelvic inflammatory disease, and abdominal trauma (4, 8). Less frequently, infections such as primary bacteremia, amnionitis, endocarditis, biliary tract sepsis, meningitis, and osteomyelitis may also occur (4). This report marks the fifth year of an ongoing survey of *B. fragilis* group susceptibilities in the United States (1, 10, 11). In previous analyses, we described instances of drug resistance at various clinical centers (1). We also documented a difference in resistance rates by species (1).

In this report, the in vitro activities of several new β-lactam drugs were tested. Species isolation rates were tabulated by body site, and resistance patterns of organisms isolated from particular sites are detailed. Analyses of rates of drug resistance and cross resistance were performed.

MATERIALS AND METHODS

Antimicrobial drugs. Standard powders were obtained as follows: ticarcillin-clavulanic acid (Timentin), Beecham Laboratories, Bristol, Tenn.; cefoxitin and imipenem, Merck Sharp & Dohme, Rahway, N.J.; moxalactam, Eli Lilly & Co., Indianapolis, Ind.; cefoperazone, Pfizer Inc., New York, N.Y.; cefotaxime, Hoechst-Roussel Pharmaceuticals Inc., Somerville, N.J.; piperacillin, Lederle Laboratories, Pearl River, N.Y.; clindamycin, The Upjohn Co., Kalamazoo, Mich.; metronidazole, Searle Laboratories, Chicago, Ill.; and tetracycline and chloramphenicol, Sigma Chemical Co., St. Louis, Mo.

Isolates. Nonduplicated clinical isolates of the *B. fragilis* group were collected by the eight centers making up the study group (1) and were sent to the Tufts anaerobe laboratory from January 1984 through December 1985. Species identification was performed by established methodology (5). The clinical site of isolation was recorded.

Susceptibility testing. Susceptibility testing was done by an agar dilution technique with the Steers replicator. The medium used was brain heart infusion broth and agar supplemented with vitamin K_1 and 5% laked sheep erythrocytes. Anaerobic chamber techniques were used as previously described (13). For ticarcillin-clavulanic acid testing, the clavulanic acid concentration was kept constant at 2 μg/ml, while the ticarcillin component was varied.

Data analysis. Data were stored, retrieved, and analyzed by Dbase II (Ashton-Tate, Culver City, Calif.), Lotus 1-2-3 (Lotus Development Corp., Cambridge, Mass.), and statistical programs written in BASIC developed for the IBM-PC computer (International Business Machines, Inc., Boca Raton, Fla.) or in a Multiplan spreadsheet (Micropro, San Rafael, Calif.) for the model 200 Tandy computer (Fort Worth, Tex.) by George Cuchural.

RESULTS

The most active β-lactam drugs were imipenem and ticarcillin-clavulanic acid (Table 1). Only one strain of *B. dista-*

* Corresponding author.
† Present address: Infectious Disease and Molecular Biology Research, Lederle Laboratories, Pearl River, NY 10965.
‡ Present address: Public Health Laboratory, John Radcliffe Hospital, Headington, Oxford, England.

TABLE 1. Antimicrobial agents against the *B. fragilis* group

Drug	No. of isolates	MIC (μg/ml)				% Resistant[a]	Breakpoint drug concn (μg/ml)
		50%	90%	Range			
				Low	High		
Imipenem[b]	679	0.5	1	<0.125	8	0.2	4
						0.2	8
Ticarcillin-clavulanic acid	554	0.5	4	<0.25	>128	0.2	64
						0.2	128
Cefoxitin	669	8	16	0.5	>128	5.0	16
						2.0	32
Piperacillin	682	8	128	0.5	>128	11.0	64
						7.0	128
Moxalactam	681	2	32	<0.25	>128	15.0	16
						9.0	32
Cefotetan	524	8	64	1	>256	26.0	16
						14.0	32
Ceftizoxime	673	16	128	<0.25	>128	37.0	16
						22.0	32
Cefotaxime	678	16	>128	0.5	>128	41.0	16
						23.0	32
Cefoperazone	683	32	>128	0.5	>128	54.0	16
						30.0	32
Ceftazadime	674	32	>128	2	>128	68.0	16
						48.0	32
Clindamycin	678	0.25	2	<0.125	>256	5.0	4
						5.0	8
Chloramphenicol	675	4	8	0.5	8	0.0	8
						0.0	16
Metronidazole	673	0.5	1	<0.25	4	0.0	8
						0.0	16

[a] Isolates were classified as resistant when the MIC was greater than the breakpoint concentration.
[b] Data from 1985 isolates only.

sonis was resistant to both drugs. Cefoxitin, piperacillin, and moxalactam were the next most active drugs. They showed good activity with low resistance rates of 5, 11, and 15%, respectively. Ceftizoxime and cefotetan were less active and had resistance rates of 37 and 26%, respectively. Similarly, cefotaxime, cefoperazone, and ceftazidime showed less activity with resistance rates of 41, 54, and 68%, respectively. Only imipenem, ticarcillin-clavulanic acid, cefoxitin, and moxalactam had MICs for 90% of strains tested (MIC_{90}s) less than or equal to 32 μg/ml.

The overall susceptibility of the nine drugs studied since 1981 is shown in Table 2. Piperacillin and cefoxitin were the most active β-lactam drugs tested in 1984; the resistance rate was 12%, which dropped somewhat for cefoxitin to 5% in 1985. The survey cefoxitin resistance rate peaked in 1983 and was 4% lower in 1984 and 11% lower in 1985. The resistance rate to moxalactam (12%) increased 3% from 1983 to 1984 and remained the same in 1985. Piperacillin resistance rates have been relatively stable over the 5 years, varying only by 5% during that period. The high resistance rates for cefotaxime and cefoperazone were again noted in 1984 and 1985. Cefotaxime resistance rates fell, while cefoperazone resistance remained stable. Clindamycin resistance fluctuated, ranging from 3 to 9%, and declining from 9% in 1984 to 5% in 1985. For the 5-year period, there were no isolates resistant to metronidazole or chloramphenicol within the *B. fragilis* group. A high level of resistance to tetracycline continued to be observed in 1984, which was the last year for testing.

Variability in the resistance rates reported from the eight centers was again noted in 1984 and 1985 (Table 3). The high cefoxitin resistance rate of 30% observed at the New England Medical Center in 1982 decreased to 13% in 1983 and is now 10%. The cefoxitin resistance rate decreased in six of the seven other hospitals in 1985, which accounted for the overall nationwide decrease. In 1985, cefoxitin showed relatively uniform activity at the various centers. The lowest cefoxitin resistance rate was 2% at Loyola University, while the highest was 10% at Tufts University. The lowest piperacillin resistance rate was 8% at Tufts University, while the highest was 20% at the University of Michigan. Also, in 1985, cefotetan displayed a higher rate of variability among centers, with a low rate of 15% at the University of Miami/Jackson Memorial Medical Center and a high rate of 36% at the University of Michigan. Because of the very low rates of resistance to imipenem and ticarcillin-clavulanic acid, no clustering of resistance could be detected.

The susceptibility of the various species within the *B. fragilis* group revealed no changes from the pattern reported in 1981 through 1983 (Table 4) (1). Among the various

TABLE 2. Resistance rates of *B. fragilis* group

Yr	No. of isolates	% Resistant[a] to:						
		FOX	PIP	MOX	CTX	CPZ	CLN	TET
1981	755	8	12	22	54	57	6	63
1982	531	10	7	12	48	54	3	59
1983	555	16	8	12	42	54	7	67
1984	551	12	12	15	39	54	9	63
1985	669	5	11	15	41	54	5	

[a] Resistance breakpoints at lower breakpoints of Table 1. No resistance was found to chloramphenicol or metronidazole. Abbrevations: FOX, cefoxitin; PIP, piperacillin; MOX, moxalactam; CTX, cefotaxime; CPZ, cefoperazone; CLN, clindamycin; TET, tetracycline.

TABLE 3. Resistance rates of the *B. fragilis* group by referral center

Center	Yr	No. of isolates	% Resistance for the following antimicrobial agent[a]:										
			IMP[b]	TIM[b]	FOX	PIP	MOX	CTT[b]	ZOX[b]	CTX	CPZ	TAZ[b]	CLN
Danbury	1981	47			17	9	23			53	60		0
	1982	37			5	8	8			54	54		3
	1983	60			15	3	12			37	45		3
	1984	40			5	5	3			24	61		8
	1985	53	0	0	4	9	13	29	38	43	57	58	0
Duke	1981	136			7	14	24			58	62		5
	1982	73			10	5	14			56	60		0
	1983	89			16	9	9			47	56		7
	1984	115			11	12	22			48	60		8
	1985	198	0	0	3	7	14	23	35	44	58	67	6
Jackson	1981	86			5	17	23			62	62		13
	1982	48			8	10	14			46	62		4
	1983	140			17	7	10			44	59		5
	1984	129			11	7	12			34	54		6
	1985	88	0	0	9	9	18	15	40	31	42	56	9
Louisiana State University	1981	89			11	12	19			58	53		9
	1982	46			0	4	15			52	59		0
	1983	26			23	8	15			50	58		8
	1984	10			10	10	20			40	40		10
	1985	53	0	0	6	13	19	28	51	56	66	62	2
Loyola	1981	100			5	5	12			43	58		5
	1982	48			8	4	6			37	44		0
	1983	77			16	6	8			35	52		8
	1984	8			0	13	13			43	43		13
	1985	59	2	2	2	10	15	29	31	42	54	71	10
University of Michigan	1981	96			6	16	27			63	51		8
	1982	60			6	8	11			47	56		4
	1983	52			19	11	16			57	61		9
	1984	44			19	23	25			47	63		10
	1985	112	0	0	6	20	21	36	44	49	65	82	5
Tufts	1981	67			14	13	23			51	52		0
	1982	68			30	11	24			59	60		8
	1983	32			13	8	15			21	38		4
	1984	68			16	16	11			38	49		7
	1985	40	0	0	10	8	13	19	34	30	48	72	0
Wadsworth	1981	67			7	22	19			43	42		10
	1982	68			7	7	4			41	46		3
	1983	32			6	16	19			25	44		17
	1984	68			10	7	16			37	52		7
	1985	77	0	0	5	12	10	25	26	26	39	71	1

[a] Percent resistant at lower breakpoints of Table 1. Chloramphenicol and metronidazole are not included in this table, because no resistant isolates were found. Abbreviations: IMP, imipenem; TIM, ticarcillin-clavulanic acid; FOX, cefoxitin; PIP, piperacillin; MOX, moxalactam; CTT, cefotetan; ZOX, ceftizoxime; CTX, cefotaxime; CPZ, cefoperazone; TAZ, ceftazidime; CLN, clindamycin; TET, tetracycline.

[b] Imipenem, ticarcillin-clavulanic acid, cefotetan, ceftizoxime, and ceftazidime were tested in 1985 only.

TABLE 4. Resistance rates of *B. fragilis* group

Species	No. of isolates[a]	% Resistant to the following antimicrobial agent[b]:											
		IMP	TIM	FOX	PIP	MOX	CTT	ZOX	CTX	CPZ	TAZ	CLN	TET
All species	1,229	0.2	0.2	8.9	12.3	15.3	26.0	39.0	41.0	56.3	68.0	6.4	63.0
B. distasonis	53	3.0	3.0	37.7	18.9	73.4	77.0	26.0	35.8	54.5	97.0	5.8	40.0
B. fragilis	779	0.0	0.0	3.9	9.4	6.3	8.0	38.0	35.8	49.9	54.0	4.9	67.0
B. ovatus	107	0.0	0.0	20.0	8.8	24.5	83.0	22.0	39.7	56.6	98.0	6.5	77.0
B. thetaiotaomicron	208	0.0	0.0	21.1	12.8	21.7	59.0	50.0	65.7	65.3	99.0	9.7	53.0
B. vulgatus	70	0.0	0.0	4.4	20.9	17.6	25.0	16.0	29.8	46.7	62.0	14.8	75.0

[a] Data are combined from years 1984 and 1985.

[b] Abbreviations and resistance breakpoints as in Tables 2 and 3. Drugs tested only in 1985: ticarcillin-clavulanic acid, cefotetan, imipenem, ceftazidime, and ceftizoxime have approximately one-half the number of strains tested.

TABLE 5. Distribution of *B. fragilis* group species by site of isolation

Site of isolation	No. of isolates	% of total				
		B. distasonis	*B. fragilis*	*B. ovatus*	*B. thetaiotaomicron*	*B. vulgatus*
All isolates	1,229	4.3	63.3	8.8	17.1	5.8
Intra-abdominal	408	6.4	56.6	11.6	19.5	5.0
Skin and soft tissue	280	3.4	64.2	10.2	19.2	2.0
Abscess or wound	112	2.8	66.0	6.8	15.9	7.5
Bile	15	0.0	79.8	6.4	6.6	6.4
Bone	22	0.0	66.9	14.2	18.9	0.0
Blood	163	1.8	71.4	3.8	17.0	5.0
Fecal	16	0.0	75.0	12.5	12.5	0.0
Perinatal	40	13.4	37.3	2.6	13.4	32.8
Lower respiratory tract	10	10.0	70.0	0.0	0.0	20.0
Pelvic	69	1.4	60.9	5.9	20.3	11.8
Drainage	28	0.0	77.3	8.7	7.0	7.0

species in the group, *B. fragilis* continued to be the most susceptible to the β-lactam drugs. *B. distasonis*, *B. vulgatus*, and *B. thetaiotaomicron* were more resistant, particularly to the cephamycins: cefoxitin, moxalactam, and cefotetan. Cefotetan showed the highest variation in activity among the species. The lowest cefotetan resistance rate was found with *B. fragilis* (8%), and the highest rate was found with *B. ovatus* (83%). Piperacillin and clindamycin showed less species variation in activity. Imipenem and ticarcillin-clavulanic acid showed essentially no variation.

The distribution of *B. fragilis* species by clinical site is seen in Table 5. *B. fragilis*, the species isolated most frequently, was found in 63% of cultures. Conversely, non-*B. fragilis* isolates accounted for 37% of all clinical isolates. *B. distasonis* and *B. vulgatus* species were found at statistically significantly higher rates in perinatal isolates, while *B. fragilis* species were found at lower rates. *B. fragilis* species were isolated from blood, skin and soft tissue, and drainage sites more frequently than chance would allow. *B. ovatus* was isolated less frequently from the bloodstream than expected. The resistance rates by site of isolation are seen in Table 6. Blood isolates tended to be more resistant to most antibiotics except imipenem, ticarcillin-clavulanic acid, chloramphenicol, and metronidazole, for which very low or no resistance was found. Perinatal isolates were generally more resistant to β-lactam antibiotics and less resistant to clindamycin. Bone isolates tended to be more resistant, but the sample size was too small to draw conclusions. The tendency toward higher rates of β-lactam drug resistance in perinatal sites is probably accounted for by the high percentage of recovery of the more β-lactam-resistant *B. distasonis* and *B. vulgatus* species. The increased resistance of the blood isolates, however, cannot be explained in a similar fashion. Fecal isolates were generally more susceptible.

Analysis of drug cross resistance is seen in Table 7. Cefoxitin-, piperacillin-, moxalactam-, and cefotetan-resistant isolates were highly resistant to the other β-lactams and modestly more resistant to clindamycin. Isolates resistant to ceftizoxime, cefotaxime, cefoperazone, and ceftazidime were not as highly cross resistant. Clindamycin-resistant isolates had statistically significant higher resistance rates to piperacillin, moxalactam, cefotaxime, and cefotetan. The *B. distasonis* isolate, which was resistant to imipenem and ticarcillin-clavulanic acid, was resistant to all other β-lactams and clindamycin. It was susceptible to chloramphenicol and metronidazole.

DISCUSSION

The results of our study indicate that several of the currently available β-lactam antimicrobial agents are active against the *B. fragilis* group of organisms. Imipenem and ticarcillin-clavulanic acid were the most active β-lactam drugs, while cefoxitin, piperacillin, and moxalactam also

TABLE 6. Resistance rates of *B. fragilis* group

Site of isolation	No. of isolates	% Resistant to the following antimicrobial agent[a]:											
		IMP	TIM	FOX	PIP	MOX	CTT	ZOX	CTX	CPZ	TAZ	CLN	TET
All isolates tested	1,203[b]	0.2	0.2	8.2	11.3	15.3	25.5	39.0	40.2	54.2	68.0	6.7	63.0
Intra-abdominal	408	0.0	0.0	6.1	9.0	16.3	27.5	30.5	33.6	49.7	66.5	5.3	64.0
Skin and soft tissue	280	0.0	0.0	9.3	8.8	13.9	23.4	39.3	45.5	54.3	66.8	6.9	69.0
Abscess or wound	112	1.5	1.5	8.5	15.4	16.5	28.5	36.5	45.5	60.6	68.2	7.1	57.0
Bile	15	0.0	0.0	0.0	0.0	13.1	33.3	66.7	34.9	49.3	66.7	6.4	75.0
Bone	22	0.0	0.0	14.5	18.1	27.2	25.0	36.3	45.3	63.8	81.8	0.0	67.0
Blood	163	0.0	0.0	10.7	15.8	12.4	20.8	42.8	44.9	60.5	69.3	10.3	79.0
Fecal	16	0.0	0.0	0.0	0.0	6.3	0.3	88.0	35.7	44.0	86.0	0.0	50.0
Perinatal	40	0.0	0.0	10.8	21.0	32.5	20.0	37.5	45.0	52.5	62.5	0.0	63.0
Lower respiratory tract	10	0.0	0.0	10.0	30.0	10.0	10.0	20.0	30.0	50.0	50.0	20.0	
Pelvic	69	0.0	0.0	1.5	10.2	11.7	22.5	37.2	43.6	53.2	74.4	6.0	50.0
Drainage	28	0.0	0.0	10.5	14.4	14.4	27.2	40.0	51.9	67.9	73.3	14.1	75.0

[a] No resistance was found to chloramphenicol or metronidazole. Abbreviations are defined in Tables 2 and 3. Resistance breakpoints were taken at the lower values of Table 1.

[b] Thirty isolates were from miscellaneous sites not included in the major categories.

TABLE 7. Analysis of cross resistance[a]

Subset of isolates resistant to:	No. of isolates	% Cross resistant to[b]:								
		FOX	PIP	MOX	CTT	ZOX	CTX	CPZ	TAZ	CLN
Isolates tested	531	5	11	15	26	37	41	54	68	5
FOX	41	100	86	86	91	86	93	86	100	14
PIP	48	48	100	77	80	85	96	100	100	15
MOX	63	39	60	100	87	60	89	89	100	11
CTT	66	29	48	70	100	46	69	74	100	8
ZOX	148	14	34	28	30	100	88	95	92	9
CTX	159	15	43	39	44	85	100	96	97	7
CPZ	203	12	35	30	34	81	88	100	95	7
TAZ	320	10	23	28	49	50	64	75	100	7
CLN	32	10	28	38	46	53	65	69	75	100

[a] Data of the 1985 isolates that had MICs available for all drugs. Imipenem, ticarcillin-clavulanic acid, metronidazole, and chloramphenicol are not included because of their uniformly excellent activity.

[b] Abbreviations and resistance breakpoints are described in Tables 2 and 3.

possessed good activity. The latter drugs have been shown to be effective in the treatment of infections caused by *B. fragilis* (6–8). Cefotetan displayed poor activity for the non-*B. fragilis* species included in the *B. fragilis* group. Accurate species identification or susceptibility testing should probably be performed before the empiric use of cefotetan. Ceftizoxime showed poor activity very similar to that of cefotaxime. Cefoperazone and ceftazidime were the least active β-lactam drugs tested.

Generally, resistance to β-lactam drugs in the *B. fragilis* group is the result of β-lactamase inactivation of the drug. The excellent activity of imipenem and cefoxitin is probably due to intrinsic stability of these molecules to β-lactamase degradation (2, 3, 9, 12). Ticarcillin-clavulanic acid is highly active because the clavulanic acid component of this combination acts as a β-lactamase inhibitor and allows the ticarcillin component to escape β-lactamase-mediated destruction. The rank order of β-lactam drug activities seen in Table 1 probably is analogous to the rank order of resistance to *B. fragilis* β-lactamase destruction by the various compounds.

Chloramphenicol and metronidazole continued to be the most active non-β-lactam agents. Clindamycin resistance among the 1985 isolates remained equal to the resistance rate of 1981 (5%). The high resistance rates and high MIC_{90}s of cefotaxime, cefoperazone, ceftazidime, ceftizoxime, and tetracycline indicate that these drugs should not be considered adequate therapy when used alone to treat infections involving the *B. fragilis* group of organisms. A recent study of the treatment of appendicitis with cefotaxime and cefoperazone as compared with moxalactam supports this opinion (6).

The isolation rates of the various species suggest that *B. fragilis* is more invasive than the other members of the group. The excess rate of bloodstream isolation is of interest and may be related to virulence factors such as capsule production by this species. Increased resistance at some clinical sites may be a result of increased rates of infection with more resistant species, such as perinatal sites. The increased rate of resistance in blood isolates cannot be accounted for on the basis of the species recovered, especially with the higher rates of recovery of the generally more susceptible *B. fragilis* species. Higher rates of antibiotic resistance may be related to prior antibiotic administration selecting for more resistant organisms and hence biasing the sample, as is probably the case with bone isolates. Alternatively, virulence factors which may result in increased rates of bacteremia or bacterial invasion of other sites may be linked to antimicrobial agent resistance factors.

The data on cross resistance suggest that patients with *B. fragilis* group infections who failed therapy owing to a possible drug resistance to cefoxitin, piperacillin, moxalactam, or cefotetan should be switched to imipenem, ticarcillin-clavulanic acid, metronidazole, or chloramphenicol pending susceptibility testing. Patients with isolates resistant to ceftizoxime, cefotaxime, cefoperazone, or ceftazidime are probably common, and most of these isolates will be susceptible to imipenem, ticarcillin-clavulanic acid, cefoxitin, clindamycin, chloramphenicol, or metronidazole.

Local susceptibility patterns are of great importance for guiding empiric therapy of infections caused by this group of organisms, since these infections are frequently serious and life threatening.

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