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Multicenter Study of In Vitro Susceptibility of the *Bacteroides fragilis* Group, 1995 to 1996, with Comparison of Resistance Trends from 1990 to 1996

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Antimicrobial resistance, including plasmid-mediated resistance, among the species of the *Bacteroides fragilis* group is well documented. An analysis of the in vitro susceptibility of *B. fragilis* group species referred between 1995 and 1996 as well as during a 7-year (1990 to 1996), prospective, multicenter survey of over 4,000 clinical isolates of *B. fragilis* group species was undertaken to review trends in the percent resistance to and geometric mean MICs of the antibiotics tested. There was a trend toward a decrease in the geometric mean MICs of most β-lactam antibiotics, while the percent resistance to most agents was less affected. Within the species *B. fragilis*, the geometric mean MICs showed significant ($P < 0.05$) decreases for piperacillin-tazobactam, ticarcillin-clavulanate, piperacillin, ticarcillin, ceftizoxime, cefotetan, and cefmetazole; a significant increase was observed for clindamycin and cefoxitin. For the non-*B. fragilis* species, a significant decrease in the geometric mean MICs was observed for meropenem, ampicillin-sulbactam, ticarcillin-clavulanate, piperacillin, ticarcillin, ceftizoxime, and cefmetazole; a significant increase was observed for cefoxitin. Significant increases in percent resistance were observed within the *B. fragilis* strains for ticarcillin and ceftizoxime and within the non-*B. fragilis* isolates for cefotetan. Significant increases in percent resistance among all *B. fragilis* group species were observed for clindamycin, while imipenem showed no significant change in resistance trends. The trend analysis for trovafloxacin was limited to 3 years, since the quinolone was tested only in 1994, 1995, and 1996. During the 7 years analyzed, there was no resistance to metronidazole or chloramphenicol observed. The data demonstrate that resistance among the *B. fragilis* group species has decreased in the past several years, the major exception being clindamycin. The majority of the resistance decrease has been for the β-lactams in *B. fragilis*, compared to other species. The reasons for these changes are not readily apparent.

Antimicrobial resistance among *Bacteroides fragilis* and related species has been known to vary among institutions, species, and countries (1, 2, 4, 5). Furthermore, the past decade has seen an increase in resistance in this group of anaerobic pathogens (17, 19). *B. fragilis* is the most common anaerobic organism to seed the human bloodstream, with an attributable mortality of 19.3% (15), and it is the most common anaerobic isolate complicating intra-abdominal sepsis (6, 12). Appropriate antimicrobial therapy has been shown to be associated with an improved outcome (11), and there has been at least one study which has documented that there is a relationship between in vitro antibiotic sensitivity and outcome of *Bacteroides* infections, although this is still considered controversial (16, 18).

There has been an ongoing need to document changing patterns of antimicrobial resistance among *B. fragilis* group species, especially with the recognition of both in vitro and in vivo transfer of antimicrobial resistance among the species of the *B. fragilis* group (23). For over 15 years, a multicenter survey of resistance of *Bacteroides* to a variety of antimicrobials has been conducted in the United States by using the methodology described in this report (1, 2, 4, 5, 9, 17–19, 22, 24, 25). This report describes the susceptibility of members of the *B. fragilis* group isolated from 1995 to 1996 and analyzes the trends over a 7-year period, 1990 to 1996.

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MATERIALS AND METHODS

Medical centers. Eight medical centers participated in the study from 1995 to 1996. Two of the centers, the University of Florida and Danbury Hospital, referred isolates during 1995 only. The participating medical centers were as follows: Danbury Hospital, Danbury, Conn.; Duke University Medical Center, Durham, N.C.; Loyola University Medical Center, Maywood, Ill.; New England Medical Center, Boston, Mass.; Pittsburgh Veterans Administration Medical Center, Pittsburgh, Pa.; University of Florida Medical Center, Jacksonville, Fla.; University of Michigan Medical Center, Ann Arbor, Mich.; and Wadsworth Veterans Administration Hospital, West Los Angeles, Calif.

Bacterial isolates. Nonduplicated clinical isolates of the *B. fragilis* group species collected from the eight centers during 1995 and 1996 were referred for susceptibility testing to the New England Medical Center. The isolates were shipped on prereduced chopped meat agar slants (Carr Scarborough Microbiologicals, Stone Mountain, Ga.) and were stored frozen (−70°C) until time of testing. The identification of the isolates was confirmed by means of standard methodology (7, 21). In all tests, *B. fragilis* ATCC 25285 and *Bacteroides thetaiotaomicron* ATCC 29741 were used as controls. All runs in which control values were beyond the limits specified by the National Committee for Clinical Laboratory Standards (NCCLS) were repeated. For the 7-year analysis of trends, data for isolates from 1990 to 1994 (19) were added.

TABLE 1. Distribution of the *Bacteroides* species isolates from 1995 and 1996

Species	No. of isolates	% of total
B. fragilis	513	53.4
B. thetaiotaomicron	137	14.3
B. ovatus	114	11.9
B. distasonis	88	9.2
B. vulgatus	59	6.1
B. uniformis	29	3.0
B. caccae	18	1.9
B. stercoris	3	0.3
Total isolates	961	100.1

Antimicrobial agents. Standard powders were obtained from the following manufacturers: cefoxitin and imipenem, Merck Sharp and Dohme (West Point, Pa.); ampicillin, sulbactam, and trovafloxacin, Pfizer Inc. (New York, N.Y.); ticarcillin and clavulanic acid, SmithKline-Beecham (Philadelphia, Pa.); piperacillin and tazobactam, Wyeth-Ayerst Pharmaceuticals (St. Davids, Pa.); cefotetan and meropenem, Zeneca Pharmaceuticals (Wilmington, Del.); clindamycin and cefmetazole, Pharmacia Upjohn (Kalamazoo, Mich.); and metronidazole and chloramphenicol, Sigma Chemical (St. Louis, Mo.).

The antimicrobial powders were solubilized according to manufacturers' specifications. The stock antimicrobial solutions were prepared at 20 times the desired test concentration and kept frozen at −70°C until the day of use. Susceptibilities to metronidazole and chloramphenicol were screened at two concentrations, 1 and 8 μg/ml. Imipenem and meropenem were tested at a concentration range of 0.125 to 8 μg/ml, and trovafloxacin was tested at 0.12 to 16 μg/ml. Cefotetan was tested at a range of 0.25 to 256 μg/ml. All other antibiotics were tested at a range of 0.12 to 128 μg/ml. To prepare the combinations of β-lactam–β-lactamase inhibitors, constant amounts of clavulanic acid (2 μg/ml) and tazobactam (4 μg/ml) were combined with serial twofold dilutions of ticarcillin and piperacillin, respectively; ampicillin-sulbactam was tested at a fixed ratio of 2:1.

Susceptibility testing. The susceptibilities of all the isolates collected from 1990 to 1996 were determined by a modified agar dilution method using brain heart infusion agar (BBL; Becton Dickinson, Cockeysville, Md.) supplemented with 5% sheep erythrocytes and 0.005% vitamin K_1 (22). The antibiotic-containing plates were prepared in house on the day of the test by adding serial twofold dilutions of the corresponding antibiotics to molten agar. The bacteria were grown to logarithmic phase in brain heart infusion-supplemented broth (Carr Scarborough Microbiologicals) and were diluted with the same broth to $\sim 10^7$ CFU/ml. A Steers replicator was used to deliver the inocula (10^4 CFU/spot) onto the surface of the agar plates. The plates were incubated for 48 h in an anaerobic chamber (Coy Systems, Grand Lake, Mich.) at 37°C. The MIC was defined as the lowest concentration of antibacterial agent that inhibited visible growth. The interpretive criteria for resistance breakpoints were based on recommendations by the Subcommittee on Antimicrobial Susceptibility Testing of the NCCLS (10). These are the breakpoints used during the 6 years of the study period (10). We used the resistance breakpoint for full resistance, as intermediate susceptibility was considered susceptibility.

Data analysis. Data were stored using Lotus 1-2-3 (Lotus Development, Cambridge, Mass.). Statistical calculations were performed using SAS, version 6.12 (SAS Institute Inc.). Resistance rates between groups were compared using the chi-square test for categorical data, and resistance rates within groups were compared using McNemar's test for paired data. Trends were analyzed using regression methods. Resistance rates over time were compared using the Wald chi-square test extracted from univariate logistic regression analyses predicting resistance from year to year. Geometric mean MICs over time were compared using the *t* test extracted from univariate linear regressions predicting mean MICs from year to year. An alpha level of 0.05 was used to determine statistical significance.

RESULTS

Distribution of the isolates. Table 1 lists the distribution of the isolates by species within the *B. fragilis* group for 1995 and 1996. *B. fragilis*, the most commonly isolated species, constituted more than half of the total isolates referred. *B. thetaiotaomicron* was the second most common species, followed by *Bacteroides ovatus*, *Bacteroides distasonis*, and *Bacteroides vulgatus*. Less commonly seen were *Bacteroides uniformis*, *Bacteroides caccae*, and *Bacteroides stercoris*.

Susceptibilities of the isolates. All 961 isolates were susceptible to metronidazole and chloramphenicol at concentrations of ≤1 and ≤8 μg/ml, respectively (data not shown). The susceptibility rates of the *B. fragilis* group for 1995 and 1996 to 13 antibiotics are shown in Table 2. There appeared to be a trend for the resistance rates to be higher for the 1995 isolates than for the 1996 isolates; however, the difference in rate per year was only significant for piperacillin and trovafloxacin ($P = 0.004$ and 0.015, respectively). The most active of all agents were the carbapenems, imipenem and meropenem, with only one resistant strain isolated in 1995 and none in 1996. Both antibiotics showed similar MICs (geometric means, MICs at which 50% of the isolates are inhibited [MIC_{50}s], and MIC_{90}s) which were the lowest among the drugs evaluated.

The combinations of β-lactams with β-lactamase inhibitors were the second most active agents. Within this group, piperacillin-tazobactam was the most active of the three combinations, with no 1995 isolate showing resistance and only one resistant strain isolated in 1996. Although the MICs for piperacillin-tazobactam were considerably higher than those of imipenem and meropenem, the percent resistance for the 2-year period was the same as for the carbapenems. Ticarcillin-clavulanate was the second most active agent of this group, but its activity was not significantly different from that of piperacillin-tazobactam. Ampicillin-sulbactam was the least active of the β-lactam-β-lactamase inhibitor combinations, but only a few isolates were resistant. The rare strains resistant to ticarcillin-clavulanate and ampicillin-sulbactam (3 and 12, respectively) were isolated in both 1995 and 1996. Piperacillin was significantly more active than ticarcillin in both 1995 and 1996 isolates ($P < 0.001$).

Cefoxitin was significantly more active than the other three cephalosporins ($P < 0.001$ for all three comparisons); it was approximately three times more active than ceftizoxime and cefmetazole and slightly over five times more active than cefotetan. Ceftizoxime and cefmetazole had statistically equivalent activities, while cefotetan was significantly less active than both ceftizoxime and cefmetazole ($P < 0.001$ for both). The resistance rates for clindamycin were similar for both years, and its activity was slightly higher than that of ceftizoxime ($P = 0.051$). Trovafloxacin, at a breakpoint of 8 μg/ml, showed activity similar to that of cefoxitin ($P = 0.283$) but was significantly more active than clindamycin ($P < 0.001$).

Resistance rates. Table 3 shows the 2-year combined resistance rates by species within the *B. fragilis* group. The only strain resistant to the carbapenems was *B. fragilis*, while the only strain resistant to piperacillin-tazobactam was *B. uniformis*. Resistance to ticarcillin-clavulanate was observed in two strains of *B. fragilis* and one strain of *B. uniformis*. Twelve isolates were resistant to ampicillin-sulbactam: five *B. fragilis*, two *B. distasonis*, two *B. thetaiotaomicron*, one *B. ovatus*, and two *B. uniformis*. *B. vulgatus* was the most resistant of the species against both clindamycin and trovafloxacin. The highest mean resistance rate for all antibiotics was noted among *B. ovatus* isolates (19.4%). The lowest mean resistance rates were noted for *B. vulgatus* (8.4%) and *B. fragilis* (9.1%).

Analysis of the strains that showed resistance to either the carbapenems or the β-lactam–β-lactamase inhibitor combinations (data not shown) indicated that for all but 4 of 13 strains (69.2%) the carbapenem MICs were elevated (≥2 μg/ml), as were those of ticarcillin-clavulanate and cefoxitin (≥32 μg/ml); for seven strains, the MICs of piperacillin-tazobactam were elevated (≥32 μg/ml); all but five strains were highly resistant to clindamycin (MIC ≥ 256 μg/ml); and two strains (15.4%) were resistant to trovafloxacin (MIC ≥ 8 μg/ml). Twelve strains were resistant to ampicillin-sulbactam; one strain was

TABLE 2. Susceptibilities of the isolates[a] from all species in the *B. fragilis* group isolated in 1995 and 1996

Antibiotic	Year	MIC (μg/ml)[b]				% Resistant	Resistance breakpoint[c]
		Range	Geometric mean	50%	90%		
Imipenem	1995	≤0.12–16	0.38	0.25	1	0.2	16
	1996	<0.12–8	0.32	0.25	1	0	
Meropenem	1995	≤0.12–16	0.40	0.25	1	0.2	16
	1996	<0.12–8	0.32	0.25	1	0	
Piperacillin-tazobactam	1995	≤0.25–64	0.91	0.5	8	0	128/4
	1996	≤0.25–>256	1.26	1	8	0.2	
Ampicillin-sulbactam	1995	0.5–>256	2.93	2	8	1.7	32/8
	1996	≤0.25–64	2.24	2	8	0.8	
Ticarcillin-clavulanate	1995	≤0.25–>256	1.48	1	8	0.4	128/2
	1996	≤0.25–128	0.97	1	8	0.2	
Piperacillin	1995	0.5–>256	24.44	16	>256	24.7	128
	1996	1–>256	20.98	16	128	17.2	
Ticarcillin	1995	0.5–>256	53.84	32	>256	32.4	128
	1996	1–>256	38.25	32	>256	27.6	
Cefoxitin	1995	0.5–>256	13.52	16	32	7.9	64
	1996	1–>256	15.12	16	32	5.4	
Ceftizoxime	1995	0.5–>256	31.63	32	>256	21.2	128
	1996	1–>256	20.34	16	128	17.5	
Cefotetan	1995	2–512	23.85	16	128	33.5	64
	1996	1–512	22.70	16	128	37.2	
Cefmetazole	1995	2–>256	16.52	16	64	20.2	64
	1996	2–>256	18.98	16	64	23.2	
Clindamycin	1995	0.5–>256	1.58	0.5	>256	16.4	8
	1996	≤0.25–256	1.58	0.5	256	16.0	
Trovafloxacin	1995	≤0.12–16	1.10	1	4	3.7	8
	1996	≤0.25–16	1.05	1	4	7.3	

[a] Number of isolates in 1995 was 481, number in 1996 was 480.
[b] 50% and 90%, MIC_{50} and MIC_{90}, respectively.
[c] NCCLS-recommended breakpoint for resistance; strains with MICs at or above this MIC are considered resistant.

resistant to ticarcillin-clavulanate but not ampicillin-sulbactam. Analysis of cross-resistance among the 971 isolates showed obvious cross-resistance among the β-lactam antibiotics but no significant cross-resistance between nonrelated antibiotics. The resistance patterns of clindamycin and cefoxitin were significantly different ($P < 0.001$), as were those of clindamycin and trovafloxacin ($P < 0.001$). The resistance patterns of clindamycin and ceftizoxime were marginally different ($P = 0.051$), while those of trovafloxacin and ceftizoxime were significantly different ($P < 0.001$).

Resistance trends. Table 4 shows an analysis of the trends in antimicrobial resistance from 1990 to 1996, a 7-year period including more than 4,000 isolates. The trends are analyzed as predicted annual changes in geometric mean MICs (μg/ml) and percent resistance (expressed as the annual percent change). For the isolates of the *B. fragilis* species, a significant decrease ($P < 0.05$) in the geometric mean MIC was observed for piperacillin-tazobactam, ticarcillin-clavulanate, piperacillin, ticarcillin, ceftizoxime, cefotetan, and cefmetazole. A significant increase in the geometric mean MIC was observed for

TABLE 3. Percent resistance[a] of isolates to antibiotics tested by species of the *B. fragilis* group

Antibiotic(s)	% Resistance of:					
	B. fragilis	*B. distasonis*	*B. thetaiotaomicron*	*B. ovatus*	*B. vulgatus*	Other[b]
Imipenem	0.2	0	0	0	0	0
Meropenem	0.2	0	0	0	0	0
Piperacillin-tazobactam	0	0	0	0	0	2.0
Ampicillin-sulbactam	1.0	2.3	1.5	0.9	0	4.0
Ticarcillin-clavulanate	0.4	0	0	0	0	2.0
Piperacillin	21.3	20.5	19.9	25.7	17.0	16.0
Ticarcillin	30.0	33.3	29.9	35.4	15.3	30.0
Cefoxitin	4.7	13.6	5.1	14.2	1.7	8.0
Ceftizoxime	20.1	17.1	21.2	23.9	5.1	18.0
Cefotetan	14.9	59.5	68.4	70.6	21.4	48.9
Cefmetazole	5.9	39.8	44.5	54.9	8.5	30.0
Clindamycin	13.8	11.4	20.2	20.7	26.8	16.0
Trovafloxacin	5.7	1.1	3.6	6.2	13.6	6.0
Total no. of strains	513	88	137	114	59	50

[a] Resistance at NCCLS-recommended resistance breakpoints (Table 2).
[b] Includes the following: 29 *B. uniformis* isolates, 18 *B. caccae* isolates, and 3 *B. stercoris* isolates.

TABLE 4. Resistance trends over time (1990 to 1996) by antibiotic and *B. fragilis* versus non-*B. fragilis* species

Antibiotic(s) and bacterial group	Geometric mean MIC (all years combined)	Predicted annual % change in MIC	*P* value	% Resistant (all years combined)	Predicted annual % change in resistance	*P* value
Imipenem						
B. fragilis	0.35	−0.44	0.622	0.39	−19.18	0.252
Non-*B. fragilis*	0.43	0.72	0.470	0.28	−37.79	0.098
Meropenem						
B. fragilis	0.36	−2.97	0.151	0.08	72.36	0.580
Non-*B. fragilis*	0.42	−4.65	0.017	0.00	0.00	N/A[a]
Piperacillin-tazobactam						
B. fragilis	0.68	−3.99	0.002	0.43	−11.69	0.465
Non-*B. fragilis*	3.21	3.44	0.052	0.68	7.52	0.631
Ampicillin-sulbactam						
B. fragilis	2.85	−1.19	0.179	1.08	−0.35	0.973
Non-*B. fragilis*	3.50	−3.51	0.002	3.09	−6.16	0.365
Ticarcillin-clavulanate						
B. fragilis	1.30	−5.33	<0.001	0.61	−15.22	0.259
Non-*B. fragilis*	2.38	−3.51	0.037	1.55	−9.23	0.327
Piperacillin						
B. fragilis	27.80	−5.79	<0.001	23.33	4.27	0.100
Non-*B. fragilis*	38.26	−3.51	0.020	26.85	−0.96	0.725
Ticarcillin						
B. fragilis	51.84	−2.59	0.031	28.92	7.80	0.002
Non-*B. fragilis*	55.18	−3.37	0.015	32.25	1.01	0.699
Cefoxitin						
B. fragilis	11.21	3.56	<0.001	4.15	7.28	0.190
Non-*B. fragilis*	18.42	2.31	0.027	8.49	2.92	0.506
Ceftizoxime						
B. fragilis	39.08	−6.09	<0.001	21.73	5.56	0.038
Non-*B. fragilis*	32.50	−8.17	<0.001	20.00	0.07	0.981
Cefotetan						
B. fragilis	16.27	−4.54	<0.001	19.16	−4.47	0.100
Non-*B. fragilis*	54.80	1.67	0.295	63.49	5.17	0.048
Cefmetazole						
B. fragilis	15.05	−6.55	<0.001	11.46	−17.27	<0.001
Non-*B. fragilis*	35.68	−3.13	0.007	48.48	−3.64	0.133
Clindamycin						
B. fragilis	1.14	4.04	0.036	10.91	15.10	<0.001
Non-*B. fragilis*	2.00	1.27	0.598	16.49	8.18	0.017
Trovafloxacin[b]						
B. fragilis	0.99	2.09	0.603	7.18	−5.09	0.75
Non-*B. fragilis*	1.15	0.28	0.943	5.95	−9.63	0.595

[a] Nonapplicable.
[b] The data are for the years 1994 to 1996.

cefoxitin and clindamycin. For this same group of isolates, a significant decrease in the percent resistance was observed only for cefmetazole, while increases were shown for ticarcillin, ceftizoxime, and clindamycin.

For the isolates of the non-*B. fragilis* species, a significant decrease in geometric mean MIC was shown for meropenem, ampicillin-sulbactam, ticarcillin-clavulanate, piperacillin, ticarcillin, ceftizoxime, and cefmetazole, while a significant increase was found for cefoxitin. For this group of isolates, no significant decrease in the percent resistance was observed for any of the antibiotics, while increases were observed for cefotetan and clindamycin.

DISCUSSION

At the completion of this study period in 1996, after 16 years of ongoing surveillance of the in vitro susceptibility of the *B. fragilis* group, no strains resistant to either metronidazole or chloramphenicol had been isolated. The carbapenems, imipenem and meropenem, and the β-lactam–β-lactamase inhibitor combinations, piperacillin-tazobactam, ticarcillin-clavulanate, and ampicillin-sulbactam, continue to be the most active β-lactam antibiotics against this group of pathogens. However, strains resistant to these agents have been isolated, albeit rarely. The relative activity of these antibiotics appears to be related not only to the type and amount of β-lactamase produced by the isolate but also to factors such as differences in penicillin binding proteins and the ability of the antibiotic to permeate the outer membrane of the bacterial cell, or to combinations of these factors (3, 8, 13, 14, 26, 27). Although there was no cross-resistance between the carbapenem-resistant strain and the strain resistant to piperacillin-tazobactam, the antibiotic(s) in question showed elevated MICs for both strains. The strain resistant to the carbapenems was also resistant to ticarcillin-clavulanate, ampicillin-sulbactam, ticarcillin, and the cephalosporins but not to piperacillin, while the piperacillin-tazobactam-resistant isolate was resistant to all other β-lactams with the exception of ticarcillin-clavulanate. These differences in activities merit further characterization of the mechanisms of the resistance produced by these isolates. Within the β-lactam–β-lactamase inhibitor combinations, resistance appears to be closely related to the intrinsic activity of the β-lactam component (i.e., piperacillin is more active than ticarcillin, and ticarcillin is more active than ampicillin) and to the amount of inhibitor in the combination.

Cefoxitin was the most active of the cephalosporins evalu-

ated. Its activity was significantly higher than that of ceftizoxime, piperacillin, cefmetazole, ticarcillin, or cefotetan. The percentage of isolates resistant to cefoxitin (approximately 6%) appears to have been quite stable over the last 7 years; however, a significant increase in the geometric mean MIC was observed during this same period, which could serve as a predictor for a possible increase in future resistance rates.

Rates of resistance to clindamycin, although they did not increase during 1995 and 1996, continued to be high (16%), and a significant trend for an increase in resistance from 1990 to 1996 raises questions about the usefulness of this antibiotic in today's therapeutic armamentarium against the *B. fragilis* group. Trovafloxacin, the quinolone with anaerobic activity, was similar to cefoxitin but significantly exceeded the activity of clindamycin. The trend of susceptibility of *B. fragilis* group species to trovafloxacin was unchanged over the 3 years of testing, although this agent has only been available for clinical use since 1998.

B. ovatus was the most resistant of the *B. fragilis* group species. This observation is in contrast to previous years, when the highest resistance to all antibiotics was noted among isolates of *B. distasonis*. Resistance to the carbapenems occurred in a *B. fragilis* isolate, and resistance to ampicillin-sulbactam was also found in five isolates of this species, two of which were also resistant to ticarcillin-clavulanate. Of interest is the observation that isolates of *B. uniformis*, a species that has been included in the study only since 1990, showed resistance to all three of the β-lactam–β-lactamase inhibitor combinations. Resistance among *B. fragilis* and *B. vulgatus* continues to be lower than among the rest of the other species. Nonetheless, resistance to the carbapenems, ticarcillin-clavulanate, and ampicillin-sulbactam occurred in *B. fragilis* strains, and the highest rates of resistance to both clindamycin and trovafloxacin were observed among isolates of *B. vulgatus*. Similar association of this species and resistance to trovafloxacin was previously observed by Snydman and McDermott (20). The association of resistance with specific antibiotic-species combinations implies that complete identification (genus and species) of isolates by clinical laboratories will help in the selection of therapy and that susceptibility testing panels with currently used antibiotics should be reevaluated to include those antibiotics with low rates of resistance.

We analyzed the data using the currently recommended NCCLS breakpoints for fully resistant strains. Although NCCLS medium was not employed, the medium used for testing has been employed for 17 years (1, 2, 4, 17, 18, 24, 25). Given the good growth of *Bacteroides* in most media, the medium employed should not affect the analysis. While the breakpoints have not been validated in this medium, they have been used in most recent surveys and form a basis of comparison over time (17–20).

It appears from the comparison of the results from 1995 and 1996 to those of previous years that resistance rates for most of the antibiotics evaluated may be decreasing (5, 17, 19). Explanations for this change are not readily apparent but could be due to decreased β-lactam use, alternative agents, and combinations which include metronidazole. Continued surveillance should establish the nature of the trend.

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REFERENCES

1. **Cornick, N. A., G. J. Cuchural, D. R. Snydman, N. V. Jacobus, P. Iannini, G. Hill, T. Cleary, J. P. O'Keefe, C. Person, and S. M. Finegold.** 1990. The antimicrobial susceptibility patterns of the *Bacteroides fragilis* group in the United States, 1987. J. Antimicrob. Chemother. **25:**1011–1019.
2. **Cuchural, G. J., F. P. Tally, N. V. Jacobus, S. L. Gorbach, K. Aldridge, T. Cleary, S. M. Finegold, G. Hill, P. Iannini, J. P. O'Keefe, and C. Pierson.** 1984. Antimicrobial susceptibilities of 1,292 isolates of the *Bacteroides fragilis* group in the United States: comparison of 1981 with 1982. Antimicrob. Agents Chemother. **26:**145–148.
3. **Cuchural, G. J., M. H. Malamy, and F. P. Tally.** 1986. β-Lactamase-mediated imipenem resistance in *Bacteroides fragilis*. Antimicrob. Agents Chemother. **30:**645–648.
4. **Cuchural, G. J., F. P. Tally, N. V. Jacobus, K. Aldridge, T. Cleary, S. M. Finegold, G. Hill, P. Iannini, J. P. O'Keefe, and C. Pierson.** 1988. Susceptibility of the *Bacteroides fragilis* group in the United States: analysis by site of isolation. Antimicrob. Agents Chemother. **32:**717–722.
5. **Cuchural, G. J., F. P. Tally, N. V. Jacobus, T. Cleary, S. M. Finegold, G. Hill, P. Iannini, J. P. O'Keefe, and C. Pierson.** 1990. Comparative activities of new β-lactam agents against members of the *Bacteroides fragilis* group. Antimicrob. Agents Chemother. **34:**479–480.
6. **Gorbach, S. L., and J. G. Bartlett.** 1974. Anaerobic infections. N. Engl. J. Med. **290:**1177–1184, 1237–1245.
7. **Holdemann, L. V., E. P. Cato, and W. E. Moore.** 1977. Anaerobic laboratory manual, 4th ed. Virginia Polytechnic Institute, Blacksburg, Va.
8. **Hurlbut, S., G. J. Cuchural, and F. P. Tally.** 1990. *Bacteroides distasonis* mediated by a novel β-lactamase. Antimicrob. Agents Chemother. **30:**117–120.
9. **Jacobus, N. V., G. J. Cuchural, and F. P. Tally.** 1989. In-vitro susceptibility of the *Bacteroides fragilis* group and the inoculum effect of newer β-lactam antibiotics on this group of organisms. J. Antimicrob. Chemother. **24:**675–682.
10. **National Committee for Clinical Laboratory Standards.** 1997. Methods for antimicrobial susceptibility testing of anaerobic bacteria, 4th ed., vol. 13. Approved standard M11-A4. National Committee for Clinical Laboratory Standards, Villanova, Pa.
11. **Nguyen, M. H., V. L. Yu, A. J. Morris, L. McDermott, M. W. Wagener, L. Harrell, and D. R. Snydman.** Antimicrobial resistance and clinical outcome for *Bacteroides* bacteremia: results from a multicenter, prospective observational trial. Clin. Infect. Dis., in press.
12. **Nichols, R. L., and J. W. Smith.** 1993. Wound and intraabdominal infections: microbiological considerations and approaches to treatment. Clin. Infect. Dis. **16**(Suppl. 4)**:**S266–S272.
13. **Piddock, L. V. J., and R. Wise.** 1987. Cefoxitin resistance in *Bacteroides* species: evidence indicating two mechanisms causing decreased susceptibility. J. Antimicrob. Chemother. **19:**161–170.
14. **Rasmussen, B. A., Y. Gluzman, and F. P. Tally.** 1990. Cloning and sequencing of the class b β-lactamase gene (*ccrA*) from *Bacteroides fragilis* metallo-β-lactamase TAL3636. Antimicrob. Agents Chemother. **34:**1590–1592.
15. **Redondo, M. C., M. D. J. Arbo, J. Grindlinger, and D. R. Snydman.** 1995. Attributable mortality of bacteremia associated with the *Bacteroides fragilis* group. Clin. Infect. Dis. **20:**1492–1496.
16. **Rosenblatt, J. E., and I. Brook.** 1993. Clinical relevance of susceptibility testing of anaerobic bacteremia. Clin. Infect. Dis. **16**(Suppl. 4)**:**S446–S448.
17. **Snydman, D. R., G. J. Cuchural, and The National Anaerobic Susceptibility Study Group.** 1994. Susceptibility variations in *Bacteroides fragilis*: a national survey. Infect. Dis. Clin. Pract. **3**(Suppl. 1)**:**S34–S43.
18. **Snydman, D. R., G. J. Cuchural, L. McDermott, and M. Gill.** 1992. Correlation of various in-vitro testing methods with clinical outcomes in patients with *Bacteroides fragilis* group infections treated with cefoxitin: a retrospective analysis. Antimicrob. Agents Chemother. **36:**540–544.
19. **Snydman, D. R., L. McDermott, G. J. Cuchural, D. W. Hecht, P. B. Iannini, L. J. Harrell, S. G. Jenkins, J. P. O'Keefe, C. L. Pierson, J. D. Rihs, V. L. Yu, S. M. Finegold, and S. L. Gorbach.** 1996. Analysis of trends in antimicrobial resistance patterns among clinical isolates of *Bacteroides fragilis* group species from 1990 to 1994. Clin. Infect. Dis. **23**(Suppl. 1)**:**S54–S65.
20. **Snydman, D. R., and L. McDermott.** 1996. Analysis of the in vitro activity of trovafloxacin (CP-99,219) against *Bacteroides* species. Infect. Dis. Clin. Pract. **5**(Suppl. 3)**:**S96–S100.
21. **Summanen, P., E. J. Baron, D. M. Citron, C. A. Strong, H. Wexler, and S. M. Finegold.** 1993. Wadsworth anaerobic bacteriology manual, 5th ed. Star Publishing, Belmont, Calif.
22. **Tally, F. P., N. V. Jacobus, J. G. Bartlett, and S. L. Gorbach.** 1975. Susceptibility of anaerobes to cefoxitin and other cephalosporins. Antimicrob. Agents Chemother. **7:**128–132.
23. **Tally, F. P., D. R. Snydman, S. L. Gorbach, and M. H. Malamy.** 1979. Plasmid-mediated, transferable resistance to clindamycin and erythromycin in *Bacteroides fragilis*. J. Infect. Dis. **139:**83–88.
24. **Tally, F. P., G. J. Cuchural, N. V. Jacobus, S. L. Gorbach, K. Aldridge, T. Cleary, S. M. Finegold, G. Hill, P. Iannini, J. P. O'Keefe, and C. Pierson.**

1983. Susceptibility of the *Bacteroides fragilis* group in the United States in 1981. Antimicrob. Agents Chemother. **23:**536–540.
25. **Tally, F. P., G. J. Cuchural, N. V. Jacobus, S. L. Gorbach, K. Aldridge, T. Cleary, S. M. Finegold, G. Hill, P. Iannini, J. P. O'Keefe, and C. Pierson.** 1985. Nationwide study of the susceptibility of the *Bacteroides fragilis* group in the United States. Antimicrob. Agents Chemother. **28:**675–677.
26. **Wexler, H. M., and S. Halebian.** 1990. Alterations to the penicillin-binding proteins in the *Bacteroides fragilis* group: a mechanism for non-β-lactamase mediated cefoxitin resistance. J. Antimicrob. Chemother. **26:**7–20.
27. **Yotsuji, A., S. Minami, M. Inoue, and S. Mitsuhashi.** 1983. Properties of a novel β-lactamase produced by *Bacteroides fragilis*. Antimicrob. Agents Chemother. **24:**925–929.