ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 2001, p. 1238–1243 Vol. 45, No. 4
0066-4804/01/$04.00+0 DOI: 10.1128/AAC.45.4.1238–1243.2001

Multicenter Survey of the Changing In Vitro Antimicrobial Susceptibilities of Clinical Isolates of *Bacteroides fragilis* Group, *Prevotella, Fusobacterium, Porphyromonas*, and *Peptostreptococcus* Species

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Received 15 September 2000/Returned for modification 1 November 2000/Accepted 24 January 2001

In vitro surveys of antimicrobial resistance among clinically important anaerobes are an important source of information that can be used for clinical decisions in the choice of empiric antimicrobial therapy. This study surveyed the susceptibilities of 556 clinical anaerobic isolates from four large medical centers using a broth microdilution method. Piperacillin-tazobactam was the only antimicrobial agent to which all the isolates were susceptible. Similarly, imipenem, meropenem, and metronidazole were highly active (resistance, <0.5%), whereas the lowest susceptibility rates were noted for penicillin G, ciprofloxacin, and clindamycin. For most antibiotics, blood isolates were less susceptible than isolates from intra-abdominal, obstetric-gynecologic, and other sources. All isolates of the *Bacteroides fragilis* group were susceptible to piperacillin-tazobactam and metronidazole, while resistance to imipenem and meropenem was low (<2%). For these same isolates, resistance rates (intermediate and resistant MICs) to ampicillin-sulbactam, cefoxitin, trovafloxacin, and clindamycin were 11, 8, 7, and 29%, respectively. Among the individual species of the *B. fragilis* group, the highest resistance rates were noted among the following organism-drug combinations: for clindamycin, *Bacteroides distasonis* and *Bacteroides ovatus*; for cefoxitin, *Bacteroides thetaiotaomicron, B. distasonis*, and *Bacteroides uniformis;* for ampicillin-sulbactam, *B. distasonis, B. ovatus*, and *B. uniformis*; and for trovafloxacin, *Bacteroides vulgatus*. For the carbapenens, imipenem resistance was noted among *B. fragilis* and meropenem resistance was seen among *B. fragilis, B. vulgatus*, and *B. uniformis*. With few exceptions all antimicrobial agents were highly active against isolates of *Prevotella, Fusobacterium, Porphyromonas*, and *Peptostreptococcus*. These data further establish and confirm that clinically important anaerobes can vary widely in their antimicrobial susceptibilities. Fortunately most antimicrobial agents were active against the test isolates. However, concern is warranted for what appears to be a significant increases in resistance to ampicillin-sulbactam and clindamycin.

Anaerobic bacteria play an important role in the pathogenicity of mixed aerobic-anaerobic infections, such as intra-abdominal, obstetric-gynecologic (Ob-Gyn), and diabetic foot infections (2). Such mixed infections may afford an optimum situation for the exchange of genetic elements between species of aerobes and anaerobes, resulting in increased virulence and antimicrobial resistance (2). Such exchange of antimicrobial resistance genetic elements has been shown among anaerobes for the agents cefoxitin, imipenem, clindamycin, tetracycline, chloramphenicol, and metronidazole (5–8, 13, 21, 25). Resistance due to β-lactamase production by various anaerobe pathogens has increased appreciably in the last 20 years, especially among the *Bacteroides fragilis* group. Most of the β-lactamases are characterized as cephalosporinases, which confer high rates of resistance to cephalosporins, particularly among non-*fragilis B. fragilis* group species (2).

Although surgery is often the primary mode of intervention in serious mixed aerobic-anaerobic infections, appropriate antimicrobial therapy is also important in preventing the spread of the initial infection or establishment of postsurgical infections. Montravers et al. (14) have shown that the choice of empiric therapy for patients with intra-abdominal infections importantly influences the postsurgical outcome. Using culture and susceptibility data, they reported that with patients judged to be receiving appropriate initial empiric therapy the mortality rate was 16%, whereas the mortality rate with inappropriate initial empiric therapy was 45% ($P < 0.05$). Moreover, Nguyen et al. (17) reported a prospective multicenter observational study involving 128 patients with documented *Bacteroides* bacteremia. In a comparison of the in vitro susceptibilities of the isolates with patient outcome, they found that patients receiving inactive therapy had a mortality rate of 45%, compared to 16% ($P = 0.04$) for patients receiving active therapy. The clinical failure and microbiological persistence rates were significantly higher with patients receiving inactive therapy. Therefore, the use of current antimicrobial data is important for the choice of appropriate antimicrobial agents.

Since most clinical microbiology laboratories perform lim-

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TABLE 1. Distribution of anaerobic isolates tested during 1998 and 1999

Organism	No. of isolates	% of total[a]
B. fragilis	180	32 (45)
B. thetaiotaomicron	73	13 (18)
B. ovatus	41	7 (10)
B. vulgatus	33	6 (8)
B. distasonis	27	5 (7)
B. caccae	22	4 (6)
B. uniformis	21	4 (5)
B. stercoris	4	0.1 (1)
Prevotella spp.[b]	65	12
Fusobacterium spp.[c]	22	4
Porphyromonas spp.[d]	19	4
Peptostreptococcus spp.[e]	49	9
Total	556	100

[a] Numbers in parentheses indicate the percentage of *B. fragilis* group isolates.
[b] Isolates consist of *P. bivia* ($n = 48$); *P. intermedia* ($n = 12$); and *P. disiens* ($n = 5$).
[c] Isolates consist of *F. nucleatum* ($n = 19$) and *Fusobacterium* spp. ($n = 3$).
[d] Isolates consist of *P. asaccharolytica* ($n = 18$) and *P. gingiyalis* ($n = 1$).
[e] Isolates consist of *P. asaccharolyticus* ($n = 26$); *P. magnus* ($n = 13$); *P. anaerobius* ($n = 6$); *P. micros* ($n = 1$); *P. prevotii* ($n = 1$); *P. tetradius* ($n = 1$); and *Peptostreptococcus* spp. ($n = 1$).

ited anaerobic bacteriology and often no susceptibility tests, it is important to provide updated survey data to guide physicians in the most effective choices for antianaerobe therapy. The purpose of this multicenter study was to determine the patterns of susceptibility of clinically important anaerobes to a variety of antimicrobial agents. The data were analyzed to determine the most active antimicrobial agents regardless of organism identification, to establish any differences based on the infection source, to compare the susceptibility patterns of individual genus and species groups, and to compare the present results to those of other recent surveys.

MATERIALS AND METHODS

Organisms. A total of 556 nonduplicate, anaerobe isolates were collected at four medical centers (Medical Center of Louisiana, New Orleans, La.; Mayo Clinic, Rochester, Minn.; Carolinas Medical Center, Charlotte, N.C.; and University of Michigan Hospitals, Ann Arbor, Mich.) and transported to a reference laboratory (Medical Center of Louisiana) for testing during 1998 and 1999. This study targeted predominantly intra-abdominal, Ob-Gyn, and body fluid specimens and probably does not reflect the isolation rate of consecutive anaerobes from all sources. The distribution and frequency of test isolates are indicated in Table 1. The sources of the isolates were the following: intra-abdominal, 346 isolates; Ob-Gyn, 112 isolates; blood, 51 isolates; and other (wounds and tissues), 47 isolates. Each isolate was identified using selective growth media, biochemical profiles, and gas-liquid chromatography (9, 24).

Antimicrobial agents. Each of the following agents was provided as a standard laboratory powder by the manufacturer: penicillin G from Eli Lilly (Indianapolis, Ind.); clindamycin from Pharmacia-Upjohn (Kalamazoo, Mich.); ciprofloxacin from Bayer (West Haven, Conn.); trovafloxacin, ampicillin, and sulbactam from Pfizer (Groton, Conn.); imipenem and cefoxitin from Merck (West Point, Pa.); metronidazole from Searle (Skokie, Ill.); piperacillin and tazobactam from Wyeth-Ayerst (St. Davids, Pa.); and meropenem from Zeneca (Wilmington, Del.). All laboratory standard powders were stored at −20°C until used.

Susceptibility testing. Each isolate was tested by a broth microdilution method based on recommendations of the NCCLS (15). Antimicrobial agents were prepared in serial twofold dilutions within a dilution range of 0.008 to 256 μg/ml in Anaerobic broth MIC (Difco). Ampicillin was combined with sulbactam in a 2:1 ratio, and serial twofold dilutions of piperacillin were combined with tazobactam at a fixed concentration of 4 μg/ml. For fastidious isolates, 5% lysed horse blood was added to the medium. The inoculum was prepared by suspending colonies from a 24-to-48-h anaerobic sheep blood agar plate 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. 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 *Bacteroides fragilis* ATCC 25285, *Bacteroides thetaiotaomicron* ATCC 29741, and *Eubacterium lentum* ATCC 43055.

β-lactamase testing. β-lactamase production was detected using a nitrocephin test (Cefinase; BBL, Cockeysville, Md.).

Data management. MICs were collated to determine the mode MICs, MICs at which 50% of the isolates are inhibited (MIC_{50}s), and MIC_{90}s and the percentage of isolates susceptible to each test antimicrobial agent, based on NCCLS recommendations (15, 16). A resistant breakpoint of ≥4 μg/ml was used for ciprofloxacin, which has been previously published (22).

RESULTS AND DISCUSSION

The distribution of the test isolates is shown in Table 1. Ninety-one percent were anaerobic gram-negative bacilli (predominately the *B. fragilis* group), and 9% were anaerobic gram-positive cocci (*Peptostreptococcus*). The percent distribution of the various *B. fragilis* group species validates the expected isolation rates from the types of infections cultured. β-lactamase production was as follows: for the *B. fragilis* group, 97.5%; for *Prevotella* spp., 100%; for *Fusobacterium* spp., 4.5%; for *Porphyromonas* spp., 21%; and for *Peptostreptococcus* spp., 0%. All β-lactamase-producing isolates were considered resistant to penicillin G regardless of the MICs, as recommended by the NCCLS (16).

The susceptibility results for all 556 isolates as a group are listed in Table 2. Overall, the isolates were susceptible to the majority of the test antimicrobial agents, with the least activity occurring for ciprofloxacin, penicillin G, and clindamycin. Piperacillin-tazobactam was the only antimicrobial agent active against all the isolates, which may be important in the choice of empiric therapy for mixed infections. Low resistance rates (includes intermediate and resistant MICs) were noted for imipenem, meropenem, and metronidazole (<0.5%). Table 3 illustrates the susceptibility patterns of the isolates grouped by isolation source. Overall, fewer isolates from blood were susceptible to the antimicrobial agents than organisms recovered from other sources, which included less susceptibility to carbapenems and metronidazole (≤4%). These data are important, since it has been shown by a comparison with uninfected controls that bacteremia due to the *B. fragilis* group in patients

TABLE 2. Antimicrobial activities of the various antimicrobials against all anaerobes (556 isolates) tested

Antimicrobial agent	MIC (μg/ml)				%S[a]
	Range	Mode	50%	90%	
Piperacillin-tazobactam	0.06–32	0.06	0.12	2	100
Ampicillin-sulbactam	0.03–64	1	1	8	92
Penicillin G	0.015–32	32	8	32	19
Cefoxitin	0.015–32	4	4	16	94
Imipenem	0.015–8	0.03	0.06	0.25	99.8
Meropenem	0.015–32	0.12	0.12	0.5	99.1
Ciprofloxacin	0.015–32	4	4	32	25
Trovafloxacin	0.015–16	0.25	0.25	2	94
Clindamycin	0.015–16	16	0.25	16	77
Metronidazole	0.12–64	0.5	0.5	2	99.1

[a] Percent susceptible.

TABLE 3. Comparison of the in vitro activities of various antimicrobial agents against all anaerobes from each source category

Antimicrobial agent	Results for anaerobe source category[a]							
	Intra-abdominal (346)		Ob-gyn (112)		Blood (51)		Other (47)	
	MIC_{90}[b]	%S[c]	MIC_{90}	%S	MIC_{90}	%S	MIC_{90}	%S
Piperacillin-tazobactam	4	100	2	100	2	100	4	100
Ampicillin-sulbactam	8	92	8	98	16	88	16	81
Penicillin G	32	16	32	25	32	14	32	34
Cefoxitin	16	94	16	96	16	90	32	89
Imipenem	0.25	100	0.12	100	0.25	98	0.5	100
Meropenem	0.5	99.1	0.25	100	1	96	1	100
Ciprofloxacin	32	23	16	30	32	23	32	38
Trovafloxacin	2	93	2	96	2	94	2	92
Clindamycin	16	74	4	87	16	71	16	79
Metronidazole	2	99.7	2	97	1	98	2	100

[a] Numbers in parentheses indicate the number of isolates tested.
[b] MIC_{90}s of antimicrobial agents are expressed in micrograms per milliliter.
[c] Percent susceptible isolates.

with intra-abdominal infections is an independent risk factor of mortality (risk ratio = 4.9) (19). Conversely, Ob-Gyn isolates were the most susceptible group overall, particularly to ampicillin-sulbactam, cefoxitin, and clindamycin. For certain antimicrobial agents, significant differences in susceptibility were noted among the various sources. For penicillin G, intra-abdominal isolates were less susceptible than Ob-Gyn isolates ($P < 0.03$) and "other" ($P < 0.01$) isolates. Other isolates were less susceptible to ampicillin-sulbactam than were Ob-Gyn isolates ($P < 0.001$), while for clindamycin Ob-Gyn isolates showed greater susceptibility than intra-abdominal ($P < 0.01$) or blood ($P < 0.02$) isolates. The *B. fragilis* group isolates comprised >70% of all isolates tested, and their susceptibility results are presented in Table 4. Piperacillin-tazobactam and metronidazole were active against all isolates, followed by low resistance rates (<2%) to imipenem and meropenem. Cefoxitin and trovafloxacin were active against >90% of isolates; however, trovafloxacin was eightfold more active by weight (MIC_{90}s). Ampicillin-sulbactam was active against 89% of isolates, compared to 71% for clindamycin. A comparison of susceptibility results among the various medical institutions showed significant differences ($P < 0.05$) only within the *B. fragilis* group for ampicillin-sulbactam and clindamycin. Ampicillin-sulbactam was significantly less active in New Orleans (87% susceptible) and Michigan (81% susceptible) than in North Carolina (97% susceptible), and the rate of susceptibility to clindamycin was significantly lower in Michigan (57%) than at the other three institutions (72 to 79%). These isolated differences had no significant effect on the overall susceptibility rate. Using susceptibility of the *B. fragilis* group to cefoxitin as a phenotypic marker, we found that among cefoxitin-susceptible isolates, 98.6% were susceptible to ampicillin-sulbactam, compared to 85% for cefoxitin-resistant isolates. Similarly, with clindamycin as a phenotypic marker, 92% of clindamycin-susceptible isolates were susceptible to ampicillin-sulbactam, compared with 81% for clindamycin-resistant isolates. Interestingly, MIC_{90}s for imipenem and meropenem rose eightfold each, and resistance rates rose 3 and 8%, respectively, for cefoxitin-resistant isolates. No isolate was susceptible to penicillin G based on β-lactamase production and/or MICs. Previously we reported a five-year study (3) on the in vitro activity of various antimicrobial agents against >2,800 *B. fragilis* group isolates. The overall resistance rates (5-year range) compared to the present data are as follows: piperacillin-tazobactam, 0.2% (0 to 0.4%) versus 0%; ampicillin-sulbactam, 1% (0.6 to 1.4%) versus 11%; cefoxitin, 6% (5 to 8%) versus 8%; imipenem, 0.1% (0 to 0.2%) versus 0.2%; and clindamycin, 14% (5 to 19%) versus 29%. Two recent reports by Snydman et al. (22, 23) have revealed increases in resistance rates to cefoxitin and clindamycin, up to 15 and 16%, respectively. In a Spanish study, Betriu et al. (6) reported resistance rates to cefoxitin and clindamycin of 13 and 34%, respectively, and in South Africa resistance rates were 32 and 29% to the same two agents, respectively (12). In both of those studies no metronidazole resistance was detected and resistance to imipenem and meropenem was ≤0.5%; these results are similar to ours. The fact that some laboratories identify isolates only as *B. fragilis* or non-*B. fragilis* species, the fact that low numbers of certain non-*B. fragilis* species may be isolated and susceptibility tested, and the ease of presenting the two groups in antibiograms instead of as individual species supports a susceptibility analysis of the *B. fragilis* species as a group and of the non-*B. fragilis* species as a separate group. Historically, the non-*B. fragilis* species of the *B. fragilis* group have been reported to be more resistant to many antimicrobials, especially the β-lactam agents. Table 5 indicates that the differences between the two groups have narrowed or in some cases the trend is reversed. Although the piperacillin-tazobactam MIC_{90} increased from 1 μg/ml for the *B. fragilis* species to 4 μg/ml for the non-*B. fragilis* species, no resistant isolates were detected. Only slight increases in resistance to ampicillin-sulbactam, cefoxitin, and trovafloxacin were noted among non-*B. fragilis* species compared to results for the *B. fragilis* species. More resistant isolates were seen among the *B. fragilis* species than among non-*B. fragilis* species for imipenem and meropenem. The largest increases in resistance for the non-*B. fragilis* species were noted for ciprofloxacin and clindamycin. Snydman et al. (23) recently reported similar results, indicating that resistance rates to many antimicrobials, especially β-lactams, had decreased among the *B. fragilis* group. They also reported that resistance to imipenem, meropenem, and trovafloxacin was more frequent among the *B. fragilis* species than among non-*B. fragilis* species. However, the latter group exhibited more resistance

TABLE 4. Comparison of the various antimicrobial agents against the 401 isolates of *B. fragilis* group

Antimicrobial agent	MIC (μg/ml)				%S[a]
	Range	Mode	50%	90%	
Piperacillin-tazobactam	≤0.06–32	0.12	0.25	4	100
Ampicillin-sulbactam	≤0.03–>64	1	2	16	89
Penicillin G	≤0.015–>32	8	8	>32	0
Cefoxitin	≤0.015–>32	4	4	16	92
Imipenem	≤0.015–8	0.03	0.06	0.25	99.8
Meropenem	≤0.015–>32	0.12	0.12	0.5	98.8
Ciprofloxacin	≤0.015–>32	4	8	32	10
Trovafloxacin	≤0.008–>16	0.25	0.25	2	92.8
Clindamycin	≤0.008–>16	>16	1	>16	71
Metronidazole	≤0.12–4	0.5	0.5	1	100

[a] Percent susceptible isolates.

TABLE 5. Comparison of the in vitro activities of the various antimicrobial agents against isolates of the *B. fragilis* and non-*B. fragilis* species

Antimicrobial agent and species groups	No. of isolates tested	MIC (μg/ml)				%S[a]
		Range	Mode	50%	90%	
Piperacillin-tazobactam						
B. fragilis	180	0.06–32	0.12	0.12	1	100
Non-*B. fragilis*	221	0.06–16	2	0.5	4	100
Ampicillin-sulbactam						
B. fragilis	180	0.5–64	1	2	8	92
Non-*B. fragilis*	221	0.03–64	1	2	16	87
Penicillin G						
B. fragilis	180	0.5–32	8	8	32	0
Non-*B. fragilis*	221	0.015–32	32	8	32	0
Cefoxitin						
B. fragilis	180	0.25–32	4	4	16	93
Non-*B. fragilis*	221	0.015–32	4	4	16	91
Imipenem						
B. fragilis	180	0.015–8	0.03	0.06	0.25	99.4
Non-*B. fragilis*	221	0.015–2	0.12	0.06	0.25	100
Meropenem						
B. fragilis	180	0.03–32	0.06	0.12	0.5	98.3
Non-*B. fragilis*	221	0.015–8	0.12	0.12	0.5	99.1
Ciprofloxacin						
B. fragilis	180	0.5–32	4	4	32	13
Non-*B. fragilis*	221	0.03–32	32	16	32	6
Trovafloxacin						
B. fragilis	180	0.015–4	0.25	0.25	2	93
Non-*B. fragilis*	221	0.015–16	0.5	0.5	2	92
Clindamycin						
B. fragilis	180	0.015–16	0.25	0.25	16	77
Non-*B. fragilis*	221	0.015–16	16	1	16	67
Metronidazole						
B. fragilis	180	0.12–2	0.5	0.5	1	100
Non-*B. fragilis*	221	0.12–4	0.5	0.5	1	100

[a] Percent susceptible isolates.

to piperacillin-tazobactam, ampicillin-sulbactam, and clindamycin.

Comparison of the susceptibility rates for the individual species of the *B. fragilis* group (Table 6) is important not only for empiric therapy of anaerobic infections but for epidemiologic reasons as newer species, such as *Bacteroides caccae, Bacteroides eggerthii, Bacteroides stercoris*, and *Bacteroides uniformis*, become more prevalent. Piperacillin-tazobactam was active against isolates of all species with MIC_{90}s of 1 to 8 μg/ml, as was metronidazole, with MIC_{90}s of 1 μg/ml for all test species. In 1994 (3), members of our group and other colleagues reported detection of clinical isolates of *B. fragilis, B. thetaiotaomicron*, and *Bacteroides distasonis* that were resistant to piperacillin-tazobactam, whereas Betriu et al. (6) found resistance only among *B. fragilis* isolates and Snydman et al. (23) reported resistance by a single *B. uniformis* isolate. Numerous reports (3, 6, 23) indicate the continued in vitro activity of metronidazole against the *B. fragilis* group species. However, Rotimi et al. (20) reported clinical failures due to metronidazole-resistant isolates of the *B. fragilis* group and detected high-level cross-resistance to imipenem, meropenem, piperacillin, piperacillin-tazobactam, clindamycin, and cefoxitin.

For ampicillin-sulbactam, resistance rates varied from 8 to 23% among the various species, with the highest rates occurring with the non-*B. fragilis* species. These data show decreased activity of ampicillin-sulbactam against the *B. fragilis* group compared to a previous report (3) indicating resistance rates ranging from 0 to 5% among the various species. Others (6, 23) have also reported higher rates of resistance to ampicillin-sulbactam among non-*B. fragilis* species but not as high as in the present study. Cefoxitin resistance in the present study varied among the species from 5 to 19%, with the highest resistance rates occurring among *B. uniformis* isolates. Betriu et al. (6) reported 28% resistance among *B. thetaiotaomicron* isolates, and Snydman et al. (23) reported 14% resistance among *B. thetaiotaomicron* and *Bacteroides ovatus* isolates, respectively.

All resistance to imipenem in previous studies (6, 23) has occurred with *B. fragilis* isolates, which is similar to our results. Meropenem resistance has also been reported (6, 23) for *B. fragilis* isolates, but we report here resistance among *B. vulgatus* and *B. uniformis* isolates. For trovafloxacin we report here that resistance rates varied from 1 to 24% for the various species, which is similar to that previously reported (23).

Clindamycin susceptibility rates among the *B. fragilis* group have continued to decrease significantly (11). Here we report clindamycin susceptibility rates that vary from 77% among *B. thetaiotaomicron* to 59% for *B. distasonis* and *B. ovatus*. The distribution of resistance rates in the 1994 survey (3) was similar to those presented here, but the present resistance rates are higher. Others (6, 4) have reported clindamycin resistance rates as high as 33% for *B. fragilis*, 36% for *B. thetaiotaomicron*, 49% for *B. distasonis*, and 46% for *B. caccae*. Recently Oteo et al. (18) reported an overall rate of resistance to clindamycin of 49% for the *B. fragilis* group. Taken together, these reports

TABLE 6. Susceptibilities of the *B. fragilis* group species to the various test antimicrobial agents[a]

Antimicrobial agent	Results (MIC_{90} of drug[b]/% susceptibility of bacteria) with:							
	B. fragilis group	*B. fragilis*	*B. thetaiotaomicron*	*B. distasonis*	*B. ovatus*	*B. vulgatus*	*B. uniformis*	*B. caccae*
Piperacillin-tazobactam	4/100	1/100	4/100	8/100	4/100	2/100	2/100	1/100
Ampicillin-sulbactam	16/89	8/92	8/90	32/67	16/88	16/88	16/86	8/96
Penicillin G	>32/0	>32/0	>32/0	>32/0	>32/0	>32/0	16/0	>32/0
Cefoxitin	16/92	16/93	16/90	32/89	16/95	16/91	>32/81	16/96
Imipenem	0.25/99.8	0.25/99.4	0.12/100	0.5/100	0.25/100	0.25/100	0.25/100	0.12/100
Meropenem	0.5/98.8	0.5/98	0.5/100	0.5/100	0.5/100	0.5/97	0.5/95	0.5/100
Ciprofloxacin	32/9.5	32/13	32/7	16/7	>32/0	>32/6	>32/14	>32/5
Trovafloxacin	2/93	2/93	2/99	2/96	2/93	16/76	2/91	2/91
Clindamycin	>16/71	>16/71	>16/77	>16/59	>16/59	>16/70	>16/76	>16/73
Metronidazole	1/100	1/100	1/100	1/100	1/100	1/100	1/100	1/100

[a] A total of 401 *B. fragilis* group isolates were tested. See Table 1 for the number of isolates tested for each species.
[b] MIC_{90}s are expressed in micrograms per milliliter.

TABLE 7. Comparison of the in vitro activities of the various antimicrobial agents against clinical isolates of *Prevotella, Fusobacterium, Porphyromonas*, and *Peptostreptococcus*

Organism (n[a]) and antimicrobial agents	MIC (μg/ml)				%S[b]
	Range	Mode	50%	90%	
Prevotella spp. (65)					
Piperacillin-tazobactam	≤0.06–8	≤0.06	≤0.06	≤0.06	100
Ampicillin-sulbactam	≤0.03–8	0.5	1	4	100
Penicillin G	≤0.015–>32	8	4	16	17
Cefoxitin	≤0.015–16	1	1	4	100
Imipenem	≤0.015–0.12	0.03	0.03	0.06	100
Meropenem	≤0.015–0.5	0.03	0.03	0.12	100
Ciprofloxacin	≤0.015–>32	8	8	16	35
Trovafloxacin	≤0.008–4	1	1	1	97
Clindamycin	≤0.008–>16	0.015	0.015	4	89.2
Metronidazole	≤0.12–4	2	2	2	100
Fusobacterium spp. (22)					
Piperacillin-tazobactam	≤0.06–1	≤0.06	≤0.06	0.12	100
Ampicillin-sulbactam	≤0.03–4	≤0.03	≤0.03	0.25	100
Penicillin G	≤0.015–8	≤0.015	≤0.015	0.5	91
Cefoxitin	≤0.015–16	≤0.015	0.03	0.5	100
Imipenem	≤0.015–0.25	≤0.015	≤0.015	0.03	100
Meropenem	≤0.015–0.25	≤0.015	≤0.015	0.12	100
Ciprofloxacin	≤0.015–16	≤0.015	0.5	2	96
Trovafloxacin	≤0.008–4	≤0.008	0.12	0.5	96
Clindamycin	≤0.008–>16	≤0.008	0.015	0.12	91
Metronidazole	≤0.12–8	≤0.12	≤0.12	2	100
Porphyromonas spp. (19)					
Piperacillin-tazobactam	≤0.06–8	≤0.06	≤0.06	1	100
Ampicillin-sulbactam	≤0.03–2	0.03	0.12	1	100
Penicillin G	≤0.015–16	≤0.015	0.03	4	79
Cefoxitin	≤0.015–>32	≤0.015	0.25	4	95
Imipenem	≤0.015–1	≤0.015	0.03	0.06	100
Meropenem	≤0.015–1	≤0.015	0.03	0.25	100
Ciprofloxacin	≤0.015–4	1	1	4	90
Trovafloxacin	≤0.015–1	1	0.5	1	100
Clindamycin	≤0.008–8	0.015	0.015	8	90
Metronidazole	≤0.12–2	2	2	2	100
Peptostreptococcus (49)					
Piperacillin-tazobactam	≤0.06–8	≤0.06	≤0.06	0.25	100
Ampicillin-sulbactam	≤0.03–16	≤0.03	0.12	0.5	96
Penicillin G	≤0.015–8	≤0.015	0.06	0.5	94
Cefoxitin	≤0.015–16	≤0.015	0.06	2	100
Imipenem	≤0.015–1	≤0.015	≤0.015	0.06	100
Meropenem	≤0.015–2	≤0.015	≤0.015	0.25	100
Ciprofloxacin	≤0.015–16	2	1	8	86
Trovafloxacin	≤0.008–8	0.5	0.25	2	94
Clindamycin	≤0.008–>16	0.25	0.12	2	92
Metronidazole	≤0.12–>64	≤0.12	0.5	2	94

[a] n, number of isolates tested.
[b] Percent susceptible isolates.

lead one to question the use of clindamycin as the antianaerobic component of the "gold standard" regimen of clindamycin-gentamicin.

Four isolates of *B. stercoris* were tested and were susceptible to all test antimicrobial agents except penicillin G (25% susceptible) and ciprofloxacin (25% susceptible).

Table 7 compares the in vitro activities of the various antimicrobial agents against clinical isolates of non-*Bacteroides* anaerobes. The *Prevotella* isolates were susceptible to all the antimicrobial agents except penicillin G (83% resistant), ciprofloxacin (65% resistant), trovafloxacin (3% resistant), and clindamycin (11% resistant). Eighty-three percent of *Prevotella* isolates were β-lactamase producers and had penicillin MICs of ≥1 μg/ml, while the non-β-lactamase producers (17%) had penicillin MICs of ≤0.06 μg/ml. The most active agents were piperacillin-tazobactam, imipenem, and meropenem based on MIC_{90}s. Overall, *Fusobacterium* isolates were highly susceptible to all antimicrobial agents, including penicillin G and ciprofloxacin. Four strains showed high-level resistance (MICs of >16 μg/ml) to clindamycin. Among the *Porphyromonas* isolates, 21% produced β-lactamase and had penicillin MICs of ≥4 μg/ml, while non-β-lactamase producers (79%) had penicillin MICs of ≤0.5 μg/ml. Most (≥90%) of these same isolates were susceptible to the other antimicrobials, including ciprofloxacin. Ninety percent or more of the *Peptostreptococcus* isolates were susceptible to all the antimicrobial agents except ciprofloxacin. Lubbe et al. (12) reported a high susceptibility rate of *Prevotella, Porphyromonas, Fusobacterium*, and *Peptostreptococcus* isolates to cefoxitin, imipenem, meropenem, and trovafloxacin. They also reported clindamycin resistance among *Porphyromonas* and *Peptostreptococcus* isolates and, surprisingly, metronidazole resistance among *Porphyromonas* isolates. Ackermann et al. (1) have recently reported clindamycin resistance among *Prevotella* spp. (9% resistant) and *Fusobacterium* spp. (30% resistant). In our study two *Fusobacterium* isolates were resistant to penicillin G; however, only one isolate was β-lactamase positive. Könönen et al. (10) recently reported that penicillin resistance among oral isolates of *Fusobacterium* spp., both β-lactamase positive and β-lactamase negative, showed overlapping MICs based on the current NCCLS breakpoint.

This study illustrates the dynamic changes that are occurring among anaerobic pathogens and antimicrobial resistance when compared to previously published surveys. Our study indicates that for the present test population of clinical isolates, the most active agents were piperacillin-tazobactam, metronidazole, imipenem, and meropenem. These data are important for the empiric choice of antimicrobials for anaerobic infections. Trovafloxacin was also very active in vitro, but unfortunately due to toxicity trovafloxacin is no longer available as a first-line agent for anaerobic infections. This study also illustrates the high variability of resistance patterns among not only the well-known species but also the more recently recognized and less frequently isolated species of the *B. fragilis* group. In this regard, it is worrisome to document such a high level of clindamycin resistance in most of our test groups. Fortunately our data do not support the increased resistance to imipenem reported in Japan and the resistance to metronidazole reported for the *B. fragilis* group in Kuwait and for *Prevotella* and *Porphyromonas* isolates in South Africa. However, we must remain vigilant through additional surveys such as this to detect significant changes in antimicrobial resistance.

ACKNOWLEDGMENTS

This study was supported in part by research grants from Wyeth-Ayerst Laboratories and Pfizer Pharmaceuticals.

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