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Susceptibilities of 394 *Bacteroides fragilis*, Non-*B. fragilis* Group *Bacteroides* Species, and *Fusobacterium* Species to Newer Antimicrobial Agents

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The susceptibilities of 374 selected β-lactamase-producing gram-negative anaerobes (including 22 cefoxitin-resistant strains and 36 strains refractory to the enhancing effect of β-lactamase inhibitors) and 20 β-lactamase-negative strains were tested by agar dilution against selected new agents. The organisms included 217 *Bacteroides fragilis* group strains, 137 non-*B. fragilis* group *Bacteroides* spp., and 40 fusobacteria. All strains were susceptible to piperacillin-tazobactam, imipenem, and meropenem. For the *B. fragilis* group, 96% were susceptible to ampicillin-sulbactam, 95% were susceptible to amoxicillin-clavulanate and cefoperazone-sulbactam, 94% were susceptible to tosufloxacin, 91% were susceptible to cefoxitin, 88% were susceptible to trospectomycin, and 73% were susceptible to cefotetan. For the β-lactamase-positive non-*B. fragilis* group *Bacteroides* spp., ≥94% were susceptible to cefoxitin, amoxicillin-clavulanate, ampicillin-sulbactam, cefoperazone-sulbactam, and trospectomycin, 90% were susceptible to cefotetan, and 85% were susceptible to tosufloxacin (the most resistant strains were *B. bivius* and *B. disiens*). For the β-lactamase-positive fusobacteria, ≥97% were susceptible to amoxicillin-clavulanate, ampicillin-sulbactam, cefoperazone-sulbactam, trospectomycin, and cefoxitin, 90% were susceptible to cefotetan, and 89% were susceptible to tosufloxacin. All agents showed excellent activity against β-lactamase-negative strains (for trospectomycin, 95% were susceptible; for all other drugs, 100% were susceptible). Overall, both carbapenems and piperacillin-tazobactam were most active. Amoxicillin-clavulanate, ampicillin-sulbactam, and cefoperazone-sulbactam lacked activity against some cefoxitin-resistant *B. fragilis* group strains but had excellent activity against other organisms. Tosufloxacin, a new quinolone, had very good activity against *B. fragilis* group strains (94% susceptible), good activity against other β-lactamase-positive strains (≥85% susceptible), and excellent activity against β-lactamase-negative strains (100% susceptible; MIC for 90% of strains, 0.5 μg/ml). Trospectomycin was active against >90% of all strains except for *B. fragilis* group strains (88% susceptible; MIC for 90% of strains, 32 μg/ml). Clinical studies are required to delineate the role of newer agents in the therapy of anaerobic infections.

Gram-negative anaerobic rods are important human pathogens, especially when host defenses are lowered by processes such as surgery, malignancy, trauma, or malnutrition (1, 29). Although the *Bacteroides fragilis* group represents the most important group of anaerobic gram-negative pathogens in humans, infections with non-*B. fragilis* group *Bacteroides* species (including species recently classified as *Prevotella* and *Porphyromonas* [27, 28]) and *Fusobacterium* species are increasingly encountered (1, 29). β-Lactamase production and β-lactam resistance are usually encountered in the *B. fragilis* group. However, β-lactamase production and β-lactam resistance have been increasingly found in non-*B. fragilis* group *Bacteroides*, *Prevotella*, *Porphyromonas*, and *Fusobacterium* species (1–4, 6, 7, 17, 18). Although the addition of inhibitors such as clavulanate, sulbactam, and tazobactam to β-lactams usually lowers the β-lactam MIC to susceptibility levels, this may not always be the case, and susceptibility testing may be indicated in cases of serious infections (1, 2, 4, 17, 18).

The development of new β-lactam–β-lactamase inhibitor combinations, as well as new broad-spectrum β-lactams and other compounds, mandates susceptibility testing surveys with standardized techniques of clinical strains isolated within 1 to 3 years of the surveys (4, 6, 17, 18). In this study, we used standardized methods to examine the susceptibilities of 217 *B. fragilis* group strains, 137 non-*B. fragilis* group *Bacteroides*, *Prevotella*, and *Porphyromonas* (127 β-lactamase-positive) strains, and 40 *Fusobacterium* (30 β-lactamase-positive) strains isolated within 3 years of the survey to amoxicillin, amoxicillin-clavulanate, ampicillin-sulbactam, cefoperazone, cefoperazone-sulbactam, piperacillin, piperacillin-tazobactam, cefoxitin, cefotetan, imipenem, meropenem, tosufloxacin (a new fluoronaphthyridine [11, 13]), and trospectomycin (a spectinomycin derivative [5, 20, 33]).

MATERIALS AND METHODS

Bacterial strains. Organisms were obtained from sources described previously (4, 17, 18) and were all recent clinical isolates from normally sterile sites, isolates obtained from blood cultures, and isolates obtained from material from orofacial, pulmonary, intra-abdominal, upper genital tract, and other infections. Most strains were obtained prior to the institution of antimicrobial therapy. Prior to being tested, organisms were checked for purity as described previously (1–4, 17, 18). Identification was done by standard methods (1, 16, 29). To facilitate the presentation of data, we use the old classification of non-*B. fragilis* group *Bacteroides* species (27, 28) throughout the paper.

β-Lactamase and susceptibility testing. β-Lactamase test-

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ing was done by the nitrocefin disk method (Cefinase disks; BBL Microbiology Systems, Cockeysville, Md.) as described previously (3). Testing of susceptibility to amoxicillin and amoxicillin-clavulanate (SmithKline Beecham Pharmaceuticals, Philadelphia, Pa.); ampicillin-sulbactam, cefoperazone, and cefoperazone-sulbactam (Pfizer Pharmaceuticals, New York, N.Y.); piperacillin and piperacillin-tazobactam (Lederle Laboratories, Pearl River, N.Y.); cefoxitin and imipenem (Merck Sharp and Dohme Laboratories, West Point, Pa.); cefotetan and meropenem (ICI Pharmaceuticals Group, Wilmington, Del.); tosufloxacin (Abbott Laboratories, North Chicago, Ill.); and trospectomycin (The Upjohn Co., Kalamazoo, Mich.) was performed by agar dilution (2), as recommended by the National Committee for Clinical Laboratory Standards (NCCLS) (23), with Wilkins-Chalgren agar alone (for the *B. fragilis* group) or supplemented with 5% sterile defibrinated sheep blood (for other organisms). Quality control strains (*B. fragilis* ATCC 25285 and *B. thetaiotaomicron* ATCC 29741) were included each day a run was performed. Plates contained serial doubling dilutions of antimicrobial agents (amoxicillin, 0.125 to 256 μg/ml; amoxicillin-clavulanate, ampicillin-sulbactam, cefoperazone, cefoperazone-sulbactam, piperacillin, piperacillin-tazobactam, cefoxitin, cefotetan, and trospectomycin, 0.5 to 64 μg/ml; and imipenem, meropenem, and tosufloxacin, 0.03 to 8 μg/ml). Clavulanate and sulbactam were added to β-lactams in 1:2 ratios, and tazobactam was added to piperacillin in a 1:8 ratio. The susceptibility breakpoints used were 4 μg/ml (amoxicillin and tosufloxacin), 8 μg/ml (amoxicillin-clavulanate [for the β-lactam component], imipenem, and meropenem), 16 μg/ml (ampicillin-sulbactam [for the β-lactam component]), 32 μg/ml (cefoperazone, cefoperazone-sulbactam [for the β-lactam component], cefoxitin, cefotetan, and trospectomycin), and 64 μg/ml (piperacillin and piperacillin-tazobactam [for the β-lactam component]). The MICs of any β-lactam–β-lactamase inhibitor combination were expressed as concentrations of the β-lactam portion of the combination.

TABLE 1. β-Lactamase-positive organisms tested

Species	No. of strains
B. fragilis group	217
B. fragilis	97
B. thetaiotaomicron	60
B. ovatus	8
B. distasonis	23
B. vulgatus	18
B. uniformis	7
B. eggerthii	4
Non-*B. fragilis* group *Bacteroides*[a]	127
B. bivius (*Prevotella bivia*)	58
B. disiens (*Prevotella disiens*)	11
B. melaninogenicus (*Prevotella melaninogenica*)	15
B. intermedius (*Prevotella intermedia*)	7
B. ureolyticus	6
B. oralis (*Prevotella oralis*)	15
B. capillosus	5
B. oris or *B. buccae* (*Prevotella oris* or *Prevotella buccae*)	3
B. gingivalis (*Porphyromonas gingivalis*)	1
B. splanchnicus	2
B. loescheii (*Prevotella loescheii*)	4
Fusobacterium	30
F. mortiferum	13
F. varium	13
F. nucleatum	1
F. necrophorum	2
F. gonidiaformans	1

[a] New names given in the recent reclassification of some of these species are given in parentheses.

RESULTS

The β-lactamase-positive organisms tested in the current study included 217 *B. fragilis* group strains, 127 non-*B. fragilis* group *Bacteroides* strains (predominantly *B. bivius*, black-pigmented strains, *B. oralis*, and *B. disiens*), and 30 fusobacteria (mainly *Fusobacterium mortiferum* and *F. varium*) (Table 1). Susceptibility data for β-lactamase-producing strains are shown in Table 2. In the latter table as well as subsequent tables, breakpoints for amoxicillin-clavulanate and ampicillin-sulbactam are presented as 4 μg/ml, as well as the current NCCLS recommendations of 8 and 16 μg/ml, for the β-lactam components, respectively. However, data given in the text represent those obtained with NCCLS breakpoints only. Differences in the β-lactam susceptibilities of members of the *B. fragilis* group were similar to those reported previously (18). The addition of clavulanate to amoxicillin lowered the MIC for 90% of strains (MIC_{90}) from >256 to 4 μg/ml, with 97% of the strains being susceptible (19% were susceptible to amoxicillin alone). Similarly, the addition of sulbactam to ampicillin lowered the MIC_{90} to 8 μg/ml, with 98% of the strains being susceptible. When sulbactam was added to cefoperazone, the MIC_{90} dropped from >64 to 16 μg/ml, with 96% of the strains being susceptible (33% were susceptible to cefoperazone alone). The addition of tazobactam to piperacillin lowered the MIC_{90} from >64 to 16 μg/ml, with 100% of the strains being susceptible (79% were susceptible to piperacillin alone). All strains were susceptible to imipenem (MIC_{90}, 2 μg/ml) and meropenem (MIC_{90}, 1 μg/ml). Cefoxitin was slightly more active than was cefotetan, especially against the *B. fragilis* group. Tosufloxacin was most active against the *B. fragilis* group (94% susceptible) and less active against other gram-negative rods (85 to 89% susceptible). Most tosufloxacin-resistant non-*B. fragilis* group *Bacteroides* strains were *B. bivius* and *B. disiens* (21% resistant). Trospectomycin showed good activity against all strains tested, especially non-*B. fragilis* group *Bacteroides* strains and fusobacteria (≥94% susceptible).

Susceptibility data for strains susceptible and resistant to the enhancing effect of inhibitors upon companion β-lactams are presented in Table 3. While there was no significant lowering of amoxicillin or ampicillin MIC_{90}s with the addition of clavulanate or sulbactam, respectively, for resistant strains, MIC_{90}s were lowered fourfold with the addition of sulbactam to cefoperazone and tazobactam to piperacillin. β-Lactam MICs were generally higher against cefoxitin-resistant than against cefoxitin-susceptible β-lactamase-producing strains (Table 4), but the enhancing effect of inhibitors was observed in both groups. Although cefoxitin was slightly more active than was cefotetan against cefoxitin-susceptible strains, 23% of cefoxitin-resistant strains were susceptible to cefotetan.

β-Lactam MICs were much higher against β-lactamase-positive than against β-lactamase-negative strains (Table 5). With the exception of trospectomycin (95% susceptible), all β-lactamase-negative strains were susceptible to all antimicrobial agents tested. Of note was the significantly lower MIC_{90} of tosufloxacin against β-lactamase-negative strains

TABLE 2. Susceptibilities and MIC_{90}s of 13 agents against 374 β-lactamase-producing *Bacteroides* species and fusobacteria

Antimicrobial agent[a]	% of the following strains susceptible at the MIC breakpoint (MIC_{90} [μg/ml]):			
	B. fragilis group (*n* = 217)	Other *Bacteroides* species (*n* = 127)	Fusobacteria (*n* = 30)	All (*n* = 374)
Amoxicillin (4)	5 (>256)	34 (128)	60 (32)	19 (>256)
Amoxicillin-clavulanate (4/8)	88/95 (8)	97/98 (2)	90/97 (4)	91/97 (4)
Ampicillin-sulbactam (4/16)	74/96 (16)	96/100 (4)	93/100 (4)	83/98 (8)
Piperacillin (64)	67 (>64)	96 (64)	93 (64)	79 (>64)
Piperacillin-tazobactam (64)	100 (16)	100 (4)	100 (16)	100 (16)
Cefoperazone (32)	18 (>64)	56 (>64)	53 (>64)	33 (>64)
Cefoperazone-sulbactam (32)	95 (16)	97 (8)	100 (16)	96 (16)
Cefoxitin (32)	91 (32)	99 (16)	97 (8)	94 (32)
Cefotetan (32)	73 (64)	90 (32)	90 (32)	80 (64)
Imipenem (8)	100 (2)	100 (2)	100 (2)	100 (2)
Meropenem (8)	100 (1)	100 (1)	100 (1)	100 (1)
Tosufloxacin (4)	94 (4)	85 (8)	89 (8)	91 (4)
Trospectomycin (32)	88 (>32)	94 (32)	97 (16)	91 (32)

[a] Numbers in parentheses are MIC breakpoints (in micrograms per milliliter) indicating susceptibility; data for amoxicillin-clavulanate and ampicillin-sulbactam are shown in the new NCCLS breakpoints and also at 4 μg/ml for comparison with the new NCCLS ampicillin and amoxicillin breakpoints of 4 μg/ml.

(0.5 μg/ml) than against β-lactamase-positive strains (4 μg/ml).

DISCUSSION

The results of this study confirm the enhancing effect of clavulanate, sulbactam, and tazobactam added to β-lactams against β-lactamase-producing anaerobic gram-negative rods (2, 4, 8, 10, 12, 14, 17, 18, 22, 25). Higher β-lactam MICs against *B. fragilis* group strains than against β-lactamase-positive non-*B. fragilis* group *Bacteroides* strains and fusobacteria have also been described before (4, 17, 18). A lower degree of enhancement with piperacillin-tazobactam than with amoxicillin-clavulanate, ampicillin-sulbactam, and cefoperazone-sulbactam probably reflects lower concentrations of tazobactam than of the other two inhibitors in the combinations; however, in all cases, MICs of piperacillin-tazobactam were in the susceptibility range. A higher degree of enhancement may well have been demonstrated with the use of fixed concentrations of inhibitors, as previously used by us (2, 4, 17, 18), rather than the fixed ratios recommended by the NCCLS (23).

β-Lactam MICs for resistant strains were usually in the susceptibility range, notwithstanding the lack of enhance-

TABLE 3. Susceptibilities and MIC_{90}s of 13 agents against β-lactamase-producing *Bacteroides* species and fusobacteria for which drug activity was enhanced or not enhanced by the addition of a β-lactamase inhibitor to a β-lactam agent

Antimicrobial agent[a]	% of the following strains susceptible at the MIC breakpoint (MIC_{90} [μg/ml]):	
	Susceptible (*n* = 338)[b]	Resistant (*n* = 36)[c]
Amoxicillin (4)	12 (>256)	86 (8)
Amoxicillin-clavulanate (4/8)	92/97 (4)	83/94 (8)
Ampicillin-sulbactam (4/16)	82/97 (8)	92/100 (4)
Piperacillin (64)	77 (>64)	97 (64)
Piperacillin-tazobactam (64)	100 (16)	100 (16)
Cefoperazone (32)	29 (>64)	72 (64)
Cefoperazone-sulbactam (32)	96 (16)	94 (16)
Cefoxitin (32)	94 (32)	97 (16)
Cefotetan (32)	79 (64)	89 (32)
Imipenem (8)	100 (2)	100 (2)
Meropenem (8)	100 (1)	100 (1)
Tosufloxacin (4)	92 (4)	97 (4)
Trospectomycin (32)	90 (32)	94 (16)

[a] Numbers in parentheses are MIC breakpoints (in micrograms per milliliter) indicating susceptibility; data for amoxicillin-clavulanate and ampicillin-sulbactam are shown at the new NCCLS breakpoints and also at 4 μg/ml for comparison with the new NCCLS ampicillin and amoxicillin breakpoints of 4 μg/ml.

[b] Strains for which the activity of a β-lactam was enhanced by the addition of a β-lactamase inhibitor.

[c] Strains for which the activity of a β-lactam was not enhanced by the addition of a β-lactamase inhibitor. Strains (*n*) included *B. fragilis* (2), *B. distasonis* (4), *B. vulgatus* (1), *B. gingivalis* (1), *B. splanchnicus* (1), *B. melaninogenicus* (2), *B. intermedius* (1), *B. bivius* (7), *B. disiens* (1), *F. necrophorum* (1), *F. mortiferum* (5), and *F. varium* (10).

TABLE 4. Susceptibilities and MIC_{90}s of 13 agents against cefoxitin-susceptible and cefoxitin-resistant β-lactamase-producing *Bacteroides* species and fusobacteria

Antimicrobial agent[a]	% of the following strains susceptible at the MIC breakpoint (MIC_{90} [μg/ml]):	
	Cefoxitin susceptible (*n* = 352)	Cefoxitin resistant (*n* = 22)[b]
Amoxicillin (4)	20 (>256)	0 (>256)
Amoxicillin-clavulanate (4/8)	93/97 (4)	68/86 (16)
Ampicillin-sulbactam (4/16)	87/98 (8)	32/91 (16)
Piperacillin (64)	81 (>64)	55 (>64)
Piperacillin-tazobactam (64)	100 (16)	100 (16)
Cefoperazone (32)	35 (>64)	5 (>64)
Cefoperazone-sulbactam (32)	96 (16)	86 (32)
Cefoxitin (32)	100 (32)	0 (>64)
Cefotetan (32)	84 (64)	23 (>64)
Imipenem (8)	100 (2)	100 (2)
Meropenem (8)	100 (1)	100 (2)
Tosufloxacin (4)	91 (4)	82 (8)
Trospectomycin (32)	91 (32)	86 (>32)

[a] Numbers in parentheses are MIC breakpoints (in micrograms per milliliter) indicating susceptibility; data for amoxicillin-clavulanate and ampicillin sulbactam are shown at the new NCCLS breakpoints and also at 4 μg/ml for comparison with the new NCCLS ampicillin and amoxicillin breakpoints of 4 μg/ml.

[b] Strains (*n*) included *B. fragilis* (12), *B. thetaiotaomicron* (6), *B. distasonis* (1), *B. vulgatus* (1), *B. buccae* (1), and *F. varium* (1).

TABLE 5. Susceptibilities and MIC_{90}s of 13 agents against 374 β-lactamase-producing *Bacteroides* species and fusobacteria and 20 non-β-lactamase-producing strains

Antimicrobial agent[a]	% of the following strains susceptible at the MIC breakpoint (MIC_{90} [μg/ml]):	
	β-Lactamase positive (n = 374)	β-Lactamase negative (n = 20)[b]
Amoxicillin (4)	19 (>256)	100 (0.5)
Amoxicillin-clavulanate (4/8)	91/97 (4)	—[c]
Ampicillin-sulbactam (4/16)	83/98 (8)	—
Piperacillin (64)	79 (>64)	100 (4)
Piperacillin-tazobactam (64)	100 (16)	—
Cefoperazone (32)	33 (>64)	100 (4)
Cefoperazone-sulbactam (32)	96 (16)	—
Cefoxitin (32)	94 (32)	100 (2)
Cefotetan (32)	80 (64)	100 (16)
Imipenem (8)	100 (2)	100 (0.12)
Meropenem (8)	100 (1)	100 (0.12)
Tosufloxacin (4)	91 (4)	100 (0.5)
Trospectomycin (32)	91 (32)	95 (32)

[a] Numbers in parentheses are MIC breakpoints (in micrograms per milliliter) indicating susceptibility; data for amoxicillin-clavulanate and ampicillin-sulbactam are shown at the new NCCLS breakpoints and also at 4 μg/ml for comparison with the new NCCLS ampicillin and amoxicillin breakpoints of 4 μg/ml.

[b] Strains (n) included *B. buccae* (1), *B. melaninogenicus* (1), *B. intermedius* (2), *B. oralis* (2), *B. bivius* (1), *B. ureolyticus* (1), *B. capillosus* (2), *F. nucleatum* (4), *F. necrophorum* (4), *F. varium* (1), and *F. gonidiaformans* (1).

[c] —, results were not valid, as most β-lactamase negative strains were inhibited by the β-lactamase inhibitor alone at the tested concentration.

ment by the inhibitors. In many cases, the addition of sulbactam to cefoperazone and tazobactam to piperacillin led to a two- to fourfold drop in β-lactam MICs for resistant strains; however, enhancement was greater for organisms susceptible to the effect of an inhibitor than for organisms resistant to the effect of an inhibitor with these two combinations. Previous studies with resistant strains have documented some enhancement (lower than that with susceptible strains) with some combinations of β-lactams and inhibitors (2). Higher β-lactam MICs, probably reflecting a permeability barrier, against cefoxitin-resistant strains have been described before (18). The slightly higher MIC_{90}s of cefotetan (64 μg/ml) than of cefoxitin (32 μg/ml) confirmed previous findings (8, 26, 31). However, with a susceptibility breakpoint of 32 μg/ml (23, 32), it is doubtful whether this difference is of much clinical importance.

The MICs of all β-lactams against all β-lactamase-negative organisms were low. It is also interesting to note that tosufloxacin MICs were significantly lower for β-lactamase-negative than for β-lactamase-positive strains. Johnson and coworkers reported similar findings with trospectomycin and tetracycline (21). A permeability barrier to non-β-lactams may be the mechanism for this phenomenon in enzyme-producing strains. In contrast to the findings of Johnson et al. (21), however, we did not observe lower trospectomycin MICs against non-enzyme-producing strains. Additionally, trospectomycin MICs higher than those reported by Jacobus and Tally (20) were found. Differences in strains or techniques may account for these discrepancies.

In summary, imipenem and meropenem had the lowest MIC_{90}s and were active against all strains tested. β-Lactamase-mediated resistance to imipenem (and presumably meropenem) is extremely rare at the present time (4, 9, 15, 17–19, 24, 30), and gram-negative anaerobes can be assumed to be susceptible to carbapenems. All combinations of β-lactam–β-lactamase inhibitors tested in the current study showed very good to excellent activities against test organisms, with piperacillin-tazobactam being the most active. Both cephamycins showed good activity, with cefoxitin being slightly more active than cefotetan. Trospectomycin, at a proposed breakpoint of 32 μg/ml (33), was active against 91% of strains. The tosufloxacin MIC_{90} (4 μg/ml) was 1 to 2 doubling dilutions higher than those reported by Fernandes et al. (1 μg/ml for *B. fragilis* and 2 μg/ml for other *Bacteroides* species) (11) and Fujimaki et al. (1.56 μg/ml) (13) in limited studies of 21 and 34 anaerobic gram-negative rods, respectively. However, 91% of all strains were susceptible to this drug at a proposed breakpoint of 4 μg/ml; the lower activity against non-*B. fragilis* group *Bacteroides* species mainly involved *B. bivius* and *B. disiens* (21% resistant). Additionally, tosufloxacin (MIC_{90}, 4 μg/ml) showed significantly greater activity against gram-negative anaerobic rods than did quinolones such as ciprofloxacin (MIC_{90}, 8 to 50 μg/ml) and ofloxacin (MIC_{90}, 12.5 μg/ml) (11, 13). On the basis of the current results, available agents can be selected for therapy and experimental agents can be selected for clinical evaluation.

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