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Review article

Antimicrobial susceptibility of anaerobic bacteria

Trends in antimicrobial resistance among *Bacteroides* species and *Parabacteroides* species in the United States from 2010–2012 with comparison to 2008–2009

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ABSTRACT

The susceptibility trends for *Bacteroides fragilis* and related species against various antibiotics were determined using data from 3 years of surveillance (2010–2012) on 779 isolates referred by 7 medical centers. The antibiotic test panel included imipenem, ertapenem, meropenem, ampicillin-sulbactam, piperacillin-tazobactam, cefoxitin, clindamycin, moxifloxacin, tigecycline, linezolid, chloramphenicol and . MICs were determined using the agar dilution CLSI reference method. Carbapenem resistance remained low (range 1.1%–2.5%) and unchanged from 2008 to 9 through 2010–2012. Resistance also remained low to the beta-lactam/beta-lactamase inhibitor combinations (1.1%–4.4%). While resistance to clindamycin and moxifloxacin remained high; rates were lower for *B. fragilis* in 2010-12 (24% and 19% respectively) compared to the earlier time frame of 2008-9 (29% and 35% respectively for the earlier time frame). There were notable species and resistance associations which have been demonstrated previously. No resistance to metronidazole or chloramphenicol resistance was seen. These data demonstrate the continued variability in resistance among *Bacteroides* and *Parabacteroides* species, but do demonstrate that carbapenems and beta-lactam/beta-lactamase inhibitor combinations remain very active throughout the United States.

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1. Introduction

Transferable resistance to clindamycin and tetracycline in *Bacteroides fragilis* was first recognized in the mid 1970's. Given that most laboratories do not test anaerobic bacteria for susceptibility, we instituted a national survey on the susceptibility of the *Bacteroides fragilis* group to help guide clinicians and assess trends over time [1,2].

An important observation while conducting the national survey was the variation of the susceptibilities within the species and the association of antibiotic resistance with particular species within the group [3,4]. In our prior analysis, we noted an increasing rate of carbapenem resistance among some species [5], which is consistent with results seen in other surveys throughout the world [6–12]. This report summarizes our survey data from 2010 to 2012 and contrasts the rates of resistance over time for select agents.

2. Materials and methods

2.1. Medical centers

Seven medical centers participated in the study and represented various geographical areas in the USA:Tufts Medical Center, Boston, MA (Snydman, McDermott, Jacobus), Loyola University, Maywood, IL (Hecht), RM Alden Research Laboratory, Santa Monica, CA (Goldstein), Duke University Medical Center, Durham, NC (Harrell), New York Presbyterian Hospital/Weill Cornell Medical Center, New York, NY (Jenkins), University of Michigan Medical Center, Ann Arbor, MI (Newton) and Mayo Clinic, Rochester, MN (Patel).

2.2. Bacterial isolates

As in previous studies, the isolates included in this study, referred to as *Bacteroides fragilis* group, include *Bacteroides* species as well as former members of the group reclassified as *Parabacteroides* sp. (See listing of bacterial isolates in Table 1.). Non-duplicated clinical isolates of the *B. fragilis* group and *Parabacteroides* were referred as a convenience sample for antimicrobial susceptibility testing to the Special Studies Laboratory at Tufts Medical Center, Boston, MA by the medical centers participating on the survey. The isolates were shipped on pre-reduced agar slants and stored until the time of testing. A total of 779 isolates were analyzed. The identification of the isolates was confirmed using API, RapidANA II, and/or standard methodology as described in the Wadsworth Anaerobic Laboratory Manual [13].

2.3. Antimicrobial agents

Standard powders of the antibiotics were obtained from the following manufacturers: cefoxitin, ertapenem and imipenem, Merck and Co., West Point, PA; ampicillin and sulbactam, piperacillin and tazobactam, linezolid and tigecycline, Pfizer, Inc., New York, NY; doripenem, Johnson and Johnson, Raritan, NJ; meropenem, Astra-Zeneca Pharmaceuticals, Wilmington, DE; moxifloxacin, Bayer Pharmaceuticals, West Haven, CT, and clindamycin, metronidazole and chloramphenicol, Sigma Chemical, St. Louis, MO. Aliquots of stock solutions prepared at 10x the highest testing concentrations, were kept frozen at −80 °C. None of the aliquots were refrozen after thawing.

2.4. Antimicrobial susceptibility testing

MICs were determined by the agar dilution method following CLSI recommendations and as described in previous publications [14,15]. In all tests, *B. fragilis* ATCC 25285 and *B. thetaiotaomicron* ATCC 29741 were used as controls. Tests were repeated when the MICs of the control organisms were outside of the CLSI specified range [14,15]. One exception to testing serial two-fold dilutions to the agents was chloramphenicol where screening levels at two dilutions were run (Table 1).

2.5. Data analysis

Data were stored and analyzed in Microsoft Excel spreadsheets. Breakpoints for resistance for all the antibiotics, with the exception of tigecycline and doripenem, were those established by CLSI [14,15]. FDA established breakpoints for resistance for anaerobes were used for tigecycline [16]. Since there are currently no CLSI breakpoints available for doripenem and no resistant FDA breakpoint exists, the resistance breakpoint for doripenem was selected to be the same as imipenem and meropenem, namely, 16 μg/mL.

3. Results

A summary of frequency of isolation, and the resistance rates of the antibiotics for the period of the study, 2010–2012, is shown in Table 1. As previously reported, *B. fragilis* continues to be the most common isolate (58.4% for the 3 years of the study), followed by *B. thetaiotaomicron* (17.3%) [5]. The frequency of isolation for the species *B. ovatus, Parabacteroides distasonis* and *B. vulgatus* through the 3 years varied from 4 to approximately 8%. *B. uniformis* represented 3.3% of the species, and *B. caccae* 1.7%. Other *Bacteroides* species, which include *Parabacteroides goldsteinii*, *B. eggerthii*, *Parabacteroides merdae*, *B. dorei, B. instestinalis, B. splanchnicus, Parabacteroides johnsonii,* and *B. stercoris* were analyzed and reported together since their frequency of isolation was uncommon.

The rates of resistance to 12 antimicrobial agents by species is shown in Table 1. Within all the species of the *B. fragilis* group, *B. fragilis* continues to be the most susceptible to most of the agents tested. All isolates of *B. fragilis* were susceptible to metronidazole and chloramphenicol. Carbapenems were quite active against *B. fragilis* with small differences between imipenem (1.1% resistance), meropenem (2.2% resistance) and ertapenem (2.4% resistance). The beta-lactam/beta-lactamase inhibitor combinations also had excellent activity with resistance rates comparable to the carbapenems. Tigecycline resistance was 2.4%. Linezolid also had excellent activity with a resistance rate of 0.7%. Resistance to clindamycin was 24.4%, and to moxifloxacin 19.1%.

The rates of resistance of the antibiotics against the non-*fragilis* species (*distasonis, ovatus, thetaiotaomicron, uniformis, vulgatus* and 'other') are also listed in Table 1. Notably moxifloxacin and clindamycin were much less active against the non-*fragilis* species. For