SESSION XVI—NEW ANTIBIOTICS

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NEW ANTIBIOTICS TO TREAT ANAEROBIC INFECTIONS

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The discovery and development of new antimicrobial agents has slowed in the past decade. The newest agents approved by the FDA to treat anaerobic infections, including intra-abdominal and skin and soft tissue infections, are ertapenem, doripenem, tigecycline, and moxifloxacin. Numerous *in vitro* studies as well as clinical trials, have been conducted and reported on these drugs. Controversy still surrounds the interpretation of *in vitro* studies, including the incidence of fluoroquinolone resistance in *B. fragilis* group species. The organisms covered by these compounds vary but generally include some *B. fragilis* gp. species, clostridia, and peptostreptococci. *In vitro*, doripenem has similar anaerobic activity to the other approved carbapenems; tigecycline is broadly active in vitro against usual and unusual anaerobes; in one tigecycline study, it was against all gram-positive strains and 228 of 232 gram-negative anaerobes at ≤1 ug/ml with one strain of *Prevotella oralis* that was nonsusceptible at 8 ug/ml. *B. fragilis* strains with MICs of 8 ug/ml are also reported. Moxifloxacin susceptibilities have been variable between different *B. fragilis* group isolates, according to studies published amongst different laboratories and according to the clinical source of the isolate (e.g., pelvic vs. intra-abdominal vs. skin and soft tissue) and the control strain performance readings. Faropenem remains in development with MIC_{90}s of 1 mg/L for many Gram-negative and Gram-positive anaerobes. One study reported that only 5 strains of the *B. fragilis* group (1.1% of all anaerobes tested) were resistant to faropenem, and another noted 2/176 strains of *B. fragilis* gp had faropenem MICs of 64 mg/ml and imipenem MICs of >32 ug/ml. New MRSA-active cephalosporins, ceftobiprole (a pyrrolidinone cephem), and ceftaroline both have limited anaerobic activity against *B. fragilis* and other gram-negatives. Ceftobiprole had MIC_{90}s (ug/ml) against *A. prevotii,* 0.125; *F magna,* 0.5; *P. asaccharolyticus*, 1; *P. anaerobius*, 4. Drugs with aerobic gram-positive activity also tend to have *in vitro* activity against gram-positive anaerobes, such as televancin, daptomycin (a cyclic lipopeptide), and dalbavancin (a glycopeptide). Dalbavancin's *in vitro* activity against 120 anaerobic isolates from pretreatment diabetic foot infections showed an MIC_{90} of ≤0.125 mg/ml against *C. perfringens,* other clostridia, *Peptoniphilus asaccharolyticus, Finegoldia magna*, and *Anaerococcus prevotii.* Tinidazole, a nitroimmidazole, are also being evaluated. Several new agents are under development for *C. difficile* associated diarrhea including OPT-80 (aka tiacumicin B, lipiarmycin or PAR-101).

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ANTIBIOTIC PHARMACODYNAMICS

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Pharmacodynamic parameters integrate both pharmacokinetic and MIC data. Such parameters include: the time (t) for which antibiotic concentration remains above the MIC (t > MIC), the ratio between the peak (C_{max}) concentration and MIC (C_{max}/MIC); and the ratio between the area under the serum concentration – time curve (AUC) and the MIC (AUC/MIC) (3). To optimize antibiotic activity, it is important to know whether the drug kills in a concentration-dependent or independent fashion. Concentration-dependent (or time-independent) antibiotics kill at a greater rate and to a greater extent with increasing antibiotic concentrations, whereas concentration-independent (time-dependent) agents kill bacteria at the same rate and to the same extent once an appropriate antibiotic concentration has been achieved. For example, clindamycin, β-lactams, and fluoroquinolone antibiotics exhibit concentration-independent activity (T > MIC) against anaerobic bacteria. Time-kill data suggests that the antimicrobial activity is maximized near the MIC of the organism. Alternatively, metronidazole provides concentration-dependent killing which enables greater manipulation of dosing regimens.

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TARGETING SELENIUM METABOLISM IN STICKLAND FERMENTORS: NOVEL NARROW-SPECTRUM ANTIMICROBIAL DRUG DEVELOPMENT

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Selenium metabolism has been evaluated as a target for antimicrobial development in two anaerobes. *Clostridium difficile* is a nosocomial pathogen whose incidence and importance are on the rise. Previous work in our laboratory characterized the central role of selenoenzyme-dependent Stickland reactions in *C. difficile* metabolism. *Treponema denticola* has also been shown to require selenium for growth, due to the need for production of selenoenzymes involved in Stickland reactions. This unique pathway may be a valid target for antimicrobial development. This study examines the effect of a known inhibitor of selenoenzymes, auranofin, on *C. difficile* and *T. denticola* growth. Auranofin potently inhibits the growth of *C. difficile,* but does not similarly effect the growth of other toxigenic clostridia (*C. perfringens* and *C. tetani*) that do not produce selenoproteins. Auranofin also inhibited growth of *T. denticola* at similar (low micromolar to high nanomolar) concentrations. Addition of selenium in the form of selenite or L-selenocysteine to the growth media significantly reduces the inhibitory action of auranofin on growth of either anaerobe. Moreover, auranofin inhibits the incorporation of radioisotope selenium (^{75}Se) in selenoproteins in *E. coli*, the prokaryotic model for selenoprotein synthesis, without impacting protein synthesis. We also have identified, using mass spectrometry, a stable complex formed upon reaction of auranofin with hydrogen selenide, and have evidence this complex is present in culture medium during the treatment of these anaerobic pathogens with auranofin. Hydrogen selenide is a required metabolic precursor for selenoprotein synthesis. These data strongly suggest that auranofin interferes with selenium metabolism upstream of the selenoprotein synthesis machinery. This clearly shows proof of principle that targeting of selenium metabolism in anaerobic pathogens that carry out Stickland fermentations can be a viable avenue for narrow-spectrum antimicrobial drug development.

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COMPARATIVE IN VITRO ACTIVITY OF DORIPENEM AGAINST RECENT CLINICAL ANAEROBIC ISOLATES WITH EMPHASIS ON THE *BACTEROIDES FRAGILIS* GROUP

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The carbapenems currently available for clinical use (imipenem, meropenem and ertapenem) have been the most active *in vitro* agents against the *B. fragilis* group. Doripenem, a new carbapenem with excellent activity against a broad spectrum of bacterial pathogens, very recently received FDA approval for clinical use. We evaluated and compared its activity against 567 recent clinical isolates with that of other antianaerobic agents using CLSI recommended procedures. The isolates tested included 404 *Bacteroides* spp., 41 *Clostridium* spp., 51 *Peptostreptococcus* spp. and 31 *Propionibacterium* spp. Multi-drug resistant strains were included in the test.

The results of the evaluation *vs* the *Bacteroides spp*. showed that doripenem was as active as imipenem and meropenem and two to four fold more active than ertapenem. Against this group of pathogens, doripenem was as active as piperacillin:tazobactam, more active than ampicillin:sulbactam and showed considerable better activity than cefoxitin, clindamycin, and moxifloxacin. Four *Bacteroides spp*. isolates, resistant to metronidazole showed variable resistance to doripenem. Doripenem was very active *vs C. perfringes* strains. Doripenem and meropenem were the most active carbapenems *vs C. difficile*. A multi-resistant isolate of *Clostridium spp.* (resistant to most agents including imipenem) showed elevated MICs of 8 μg/ml *vs* doripenem, ertapenem and meropenem. Doripenem was very active *vs Peptostreptococcus spp*., including strains resistant to metronidazole, moxifloxacin, vancomycin and clindamycin. All *Propionibacterium spp.* isolates were susceptible to doripenem and the comparative agents with the exception of metronidazole.

The results of this evaluation indicate that doripenem—with its broad spectrum of activity, given the increasing resistance of *B. fragilis* group isolates to routinely used antibiotics, and the frequent isolation of anaerobic pathogens—is an ideal agent for the treatment of mixed infections.