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Antimicrobial Susceptibility Testing for Glucose-Nonfermenting Gram-Negative Bacteria: the Tip of the Iceberg

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We read with great pleasure the recently published manuscript by Caverly and colleagues who studied the *in vitro* activities of four β-lactam–β-lactamase inhibitors (BL-BLIs), including ceftazidime-avibactam, ceftolozane-tazobactam, meropenem-vaborbactam, and piperacillin-tazobactam, against 420 isolates of the following glucose-nonfermenting Gram-negative bacteria: *Burkholderia* spp., *Achromobacter* spp., *Stenotrophomonas maltophilia*, and *Pandoraea* spp. (1). The authors used the reference antimicrobial susceptibility test method and interpretive criteria for results established by the Clinical and Laboratory Standards Institute (CLSI) for the BL-BLIs against *Pseudomonas aeruginosa*. Meropenem-vaborbactam had the greatest activity against *Burkholderia* spp. and *Achromobacter* spp. among the four tested antibiotics. However, the activity of the four BL-BLIs against *Stenotrophomonas maltophilia* and *Pandoraea* spp. was minimal, with ranges of 11% to 40% and 0% to 5%, respectively (1).

The CLSI and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) define guidelines to interpret antimicrobial resistance in the United States and Europe, respectively, and set antimicrobial MIC breakpoints based on clinical, microbiological, pharmacodynamic, and pharmacokinetic profiles of the antimicrobials for particular pathogens (2, 3). The CLSI has established breakpoints for the *Burkholderia cepacia* complex (Bcc) and *S. maltophilia* for a limited number of antimicrobials, including ceftazidime, minocycline, levofloxacin, trimethoprim-sulfamethoxazole, chloramphenicol, and ticarcillin-clavulanate in addition to meropenem exclusively for *S. maltophilia* and cefiderocol for Bcc only (2, 4). The susceptibility testing for *Achromobacter* spp., *Pandoraea* spp., and *Burkholderia gladioli* established by the CLSI is defined by MIC breakpoints for other non-*Enterobacteriaceae*, which include *Pseudomonas* spp. (not *P. aeruginosa*) and other glucose nonfermenters, excluding *Acinetobacter* spp., Bcc, *Burkholderia mallei*, *Burkholderia pseudomallei*, and *S. maltophilia*, which have separate breakpoints set by CLSI for each (2). Yet, there are not CLSI breakpoints for the four BL-BLIs against the glucose-nonfermenting bacteria except for *P. aeruginosa* (2). One caveat is that CLSI has established meropenem-vaborbactam MIC breakpoints for *Enterobacteriaceae* only (interpreted as susceptible if MIC is $\leq$4/8 μg/ml, intermediate if 8/8 μg/ml, and resistant if $\geq$16/8 μg/ml), but there is not an MIC breakpoint for the glucose nonfermenters, including *P. aeruginosa* (2). On the other hand, EUCAST has established *P. aeruginosa* MIC breakpoints for meropenem-vaborbactam that are interpreted differently (susceptible if MIC is $\leq$8/8 μg/ml and resistant if $>$8/8 μg/ml) (3). Trimethoprim-sulfamethoxazole is the only antibiotic with defined MIC breakpoints for *S. maltophilia* by EUCAST (3). Due to the broad MIC distribution of the Bcc group for the relevant antibiotics, EUCAST recommends against *in vitro* susceptibility testing for Bcc. Similarly, there are not MIC breakpoints by EUCAST for *Achromobacter* spp. and *Pandorea* spp. (3). In the setting of a lack of standardized

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susceptibility testing for several antibiotics against the glucose nonfermenters, predicting the *in vitro* activity of antibiotics based on CLSI breakpoints established for *P. aeruginosa* could be justified only in specific circumstances where the observed MIC falls several dilutions away from the susceptibility range. However, interpreting MICs included within one to two dilutions from the susceptibility range established for another pathogen should be taken with "a grain of salt."

Despite the Generating Antibiotic Incentives Now (GAIN) Act passed in 2012 as a section of the FDA Safety and Innovation Act to endorse the development of new antibiotics and antimicrobial resistance tests (5, 6) and the 21st Century Cures Act signed in 2016 to accelerate drug and medical device development (7), additional actions and incentives are crucial to facilitate pharmacokinetic-pharmacodynamic and clinical studies for novel antimicrobials that are required to set up interpretative breakpoints that guide antimicrobial therapy and improve patient outcomes (6).

In conclusion, there is an urgent need to develop standardized antimicrobial susceptibility testing for the glucose-nonfermenting Gram-negative bacteria and harmonize the CLSI and EUCAST standards in the era of rapid emergence of multidrug-resistant and difficult-to-treat infections.

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