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In Vitro Activities of Polymyxin B, Imipenem, and Rifampin against Multidrug-Resistant *Acinetobacter baumannii*

In a previous issue of this journal, Yoon et al. reported the activities of polymyxin B, imipenem, and rifampin in double and triple combinations against multidrug-resistant strains of *Acinetobacter baumannii* (7). These organisms have emerged as important nosocomial pathogens responsible for outbreaks of pneumonia, bacteremia, and sepsis among critically ill patients throughout the world (2, 3). As treatment options are limited, studies demonstrating enhanced activity with combinations of one or more agents are welcomed as they may be useful in selecting and guiding therapy. Yoon et al. have used standard checkerboard microtiter plate and time-kill assays against eight isolates of *A. baumannii* and conclude that bactericidal synergy can be obtained using polymyxin B in combination with imipenem or rifampin and using all three agents combined. In drawing their conclusions, Yoon et al. have defined synergy in checkerboard assays as a fractional inhibitory concentration index (FICI) of <1.0. We are concerned that this interpretation of the FICI overemphasizes the significance of their findings. It is widely accepted that variability in MIC determinations means the true value may lie within a three-dilution range (6). When testing two antibiotics, this effect is cumulative, and the errors are subsequently incorporated in the FICI score. In view of this, the editorial policies of many journals, including *Antimicrobial Agents and Chemotherapy* (1) and the *Journal of Antimicrobial Chemotherapy* (5), require FICI data of <0.5 to be defined as synergy. We feel the inclusion of a third antibiotic is not sufficient reason to merit the use of different criteria for interpreting FICI data. In fact, these scores will carry even greater inbuilt error and should therefore be interpreted at least as conservatively as FICI data derived from testing with two antibiotics. If the results of Yoon et al. are reinterpreted using these criteria, then only three of their double combinations and two of their triple combinations are in fact synergistic, with the remainder having only additive, if any, effect. Some authors have suggested more stringent criteria, with a FICI of ≤ 0.25 obtained in at least five replicate experiments (6). If these criteria are used, then none of the combinations tested by Yoon et al. are synergistic. Combinations of imipenem, rifampin, and colistin have been found to be effective in animal models (4), and these combinations may yet prove to be the most effective means of treating multidrug-resistant *Acinetobacter* infections. However, until there is a well-designed clinical trial of the safety and efficacy of these regimens, clinicians should remain cautious in extrapolating the existing in vitro and animal data to humans.

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Authors' Reply

We agree with Drs. Wareham and Bean on all issues that they have mentioned. The recent editorial by Odds (3) that those authors discuss and earlier papers by Berenbaum (1, 2) demonstrate the mathematics of synergy and present the pitfalls of using a fractional inhibitory concentration index (FICI) of <1.0 to define synergy. The paper by Dr. Berenbaum (1) and the letter by Drs. Wareham and Bean present the larger picture of synergy, of which mathematics is only a part. The results of time-kill studies from our paper in reference 4 showing data on the MICs of each antibiotic alone and in double and triple combinations at one-fourth the MICs are more convincing than the FICI data. Serum bactericidal assays may be an even better assessment of the antibiotic interactions. In prior years, a strict definition of synergy prevented the unnecessary use of two agents against a susceptible organism. Now that multiresistant pathogens such as *A. baumannii* have become resistant and/or poorly responsive to most or all antibiotics, any enhanced activity provided by a second agent, whether additive or synergistic, may be important clinically. Nevertheless, we agree with Drs. Wareham and Bean, as stated in our discussion, that clinical trials will be necessary to establish the value of antibiotic combinations for the treatment of *Acinetobacter* infections.

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