Antibiotic Tolerance and Combination Therapy

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The recent paper by Haaber et al. (1) highlights another mechanism by which bacterial pathogens may evade the effects of antibiotics. The combination of colistin with vancomycin against *Staphylococcus aureus* may be antagonistic and may lessen the effectiveness of glycopeptide antibiotic. Colistin, it seems, induces gene expression in *S. aureus* which mimics the vancomycin-intermediate (VISA) phenotype. This induction is reversible when the colistin is removed.

This article is very timely. Therapeutic options for many infections, particularly those caused by Gram-negative bacteria, are diminishing. Many researchers and clinicians are looking for alternative treatment options and combination antibiotic therapy for recalcitrant multidrug-resistant (MDR) infections. Synergies between agents that might otherwise seem counterintuitive have been described. For example, combination therapy with colistin and vancomycin has been shown to be effective *in vitro* and in *in vivo* models against MDR *Acinetobacter baumannii* (2, 3). Driven by desperation for new therapeutic options for these highly resistant organisms, a number of researchers have shown interest in the combination of colistin with glycopeptide agents (see Claeys et al. [4] for a review).

While colistin and vancomycin are an unlikely combination for treating *S. aureus* infection, the findings of Haaber et al. suggest that caution should be exercised if combination therapy is to be employed clinically. Simultaneous colonization of patients with *S. aureus* and *A. baumannii* has been documented (5). Moreover, it is not uncommon for infections to have a polymicrobial etiology. For example, Sancho et al. determined that 20.2% of bacteremia cases in critically ill patients are polymicrobial in nature, with *A. baumannii* and *S. aureus* being one of the more common combinations (6). Treating such a polymicrobial infection with the colistin-vancomycin combination might be effective against the Gram-negative pathogen, but the colistin-induced vancomycin-intermediate phenotype might exacerbate the Gram-positive infection.

Ultimately, the challenge to maximize both the effectiveness and the longevity of our current antibiotic inventory might require innovative approaches to how we use them. This serves as a useful reminder that such applications have to be considered holistically—new treatment regimens may have unforeseen implications. Clinicians should exercise caution testing colistin-vancomycin combination therapy when there is a high likelihood of polymicrobial infection.

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