Correspondence

Vancomycin Minimum Inhibitory Concentrations and Outcome in Patients With Severe Staphylococcus aureus Infection

To the Editor—As Holland and Fowler point out in their excellent commentary [1], there are many unresolved issues in the measurement and clinical interpretation of vancomycin minimum inhibitory concentrations (MICs). There is, however, one major omission from their otherwise comprehensive review of published, peer-reviewed outcome studies versus MIC in serious methicillin-resistant Staphylococcus aureus (MRSA) infection: the results that have recently been reported from 2 double-blind, randomized, phase III, non-inferiority Assessment of Telavancin for Treatment of Hospital-acquired Pneumonia (ATTAIN) 0015 and 0019 studies. These studies compared telavancin (10 mg/kg given intravenously every 24 hours) with vancomycin (1 g given intravenously every 12 hours) in a total of 1503 patients with Gram-positive hospital-acquired pneumonia, most of whom were not documented to have bacteremia [2]. Telavancin was significantly more effective than vancomycin in the subset of patients with monomicrobial S. aureus infections with vancomycin MIC $\geq 1 \mu g/mL$ (as measured by broth microdilution) (87.1% vs 74.3%; $P = .03$).

This result implies an MIC-dependent response to vancomycin but, crucially, also implies that telavancin was superior to vancomycin in those isolates with a raised MIC. This break point could be considered broadly equivalent to that of $>1.5 \text{ mg/L}$ obtained using the E test, as reported by Holmes et al [3]. Patients randomized to vancomycin could subsequently be changed to a $\beta$-lactam if they were in the methicillin-susceptible S. aureus (MSSA) arm. Unfortunately, we are not told enough details about the $\beta$-lactam therapy given in the study by Holmes et al [3], nor is it clear how many patients with MSSA infection received empiric vancomycin therapy or whether the subset of 72 patients given only $\beta$-lactam all had MSSA infection.

Our current knowledge base on vancomycin MIC versus outcome in MSSA consists of 3 studies. Importantly, the 2 ATTAIN studies [2], suggest that alternative therapy is indicated when the MIC is elevated, challenging the conclusions of Holland and Fowler about the use of alternatives to vancomycin in such cases. There may well be advantages of changing from vancomycin in cases with raised MIC. Indeed, it may seem perverse to conclude otherwise, while accepting the collateral effects associated with raised MIC, whether there are changes to the organism’s pathogenic potential or patient factors.

Several published studies allude to increased persistence of MRSA with raised MICs, particularly heteroresistant vancomycin-intermediate S. aureus strains [4, 5], and many of the studies mentioned by Holland and Fowler [1] refer to an inferior clinical response, but not necessarily higher mortality. Paradoxically, mortality has even been described as lower in MRSA strains with raised vancomycin MICs in the United Kingdom [6]. It is probable that differences in strains and patient populations complicate interpretation of the data. There are also many pathways leading to raised vancomycin MICs, with numerous possible mutations being described [7], so the conclusions of any one study may not be widely applicable. Furthermore, many methodological issues in the measurement of vancomycin MICs need to be clarified [8], not the least of which is the use of stored organisms, as in the study by Holmes et al. Elevated vancomycin MICs may be unstable and lost during storage or passage without vancomycin [9]. Our own observations (unpublished) on vancomycin MICs (at time of isolation) show no relationship to in-hospital survival in MSSA bacteremia.

Although the narrow therapeutic margin of vancomycin and the current break point stress the capability of current MIC test systems to give clinically meaningful results, it is too early to write off the clinical significance of elevated vancomycin MICs as an indication to consider alternative therapy. The MIC has, after all, been the cornerstone of our major advances in the understanding of antibiotic pharmacokinetics and pharmacodynamics in the past 30 years.

Note

Potential conflicts of interest. I. M. G. is on the speakers bureau and/or acting as a consultant for many companies producing novel therapies for MRSA.

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3. Holmes NE, Turnidge JD, Munchhof WJ, et al. Antibiotic choice may not explain poorer outcomes in patients with Staphylococcus aureus bacteremia and high vancomycin minimum MICs.