Counterpoint: Vancomycin and *Staphylococcus aureus*—An Antibiotic Enters Obsolescence

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(See the point by Mohr and Murray on pages 1536–42)

The efficacy of vancomycin for the treatment of patients with infections due to *Staphylococcus aureus* is impaired by its poor tissue penetration and by its relatively weak antibacterial activity—an activity that is declining as *S. aureus* evolves. Neither dose escalation nor use of vancomycin in combination with other antibiotics that have antistaphylococcal activity has been demonstrated to safely enhance its therapeutic efficacy. Although no clinical trials suggest superiority of vancomycin over any comparator, some have provided evidence of its inferiority. Strong consideration should be given to the use of alternative agents in the treatment of serious *S. aureus* infections.

The efficacy of vancomycin in the treatment of infection due to *Staphylococcus aureus* has, in recent years, come under increasing scrutiny. As a result, the role of vancomycin in modern therapeutics has become controversial, and the Infectious Diseases Society of America, in its infinite wisdom, decided that fighting the battle over vancomycin in Toronto, Ontario, at its 2006 annual meeting would save us from having to fight it in the streets of the United States. As a consequence of that decision, a debate took place in which I was assigned the task of taking the position that vancomycin has outlived its usefulness. This essay is based on my arguments presented at that meeting, where I restricted my focus to the treatment of infection due to *S. aureus*.

**METHICILLIN-SUSCEPTIBLE S. AUREUS (MSSA)**

Vancomycin is often used as initial empirical therapy in patients with suspected infections due to gram-positive organisms, as well as in the specific treatment of known MSSA infection, either because of the presence of β-lactam allergy or for convenience (such as when impaired renal function allows infrequent dosing). The evidence is quite clear, however, that vancomycin is inferior to at least some β-lactams for the treatment of bacteremia and endocarditis due to MSSA. For instance, a retrospective study of 123 patients undergoing long-term hemodialysis who developed bacteremia due to MSSA found that vancomycin treatment was associated with a significantly greater risk of failure than was treatment with cefazolin (31.2% vs. 13%; *P* = .02), and use of this glycopeptide was an independent risk factor for failure [1]. In a prospective, multicenter, observational study, vancomycin therapy was associated with a significantly greater risk of failure, with persistence of bacteremia for >7 days and/or relapsed bacteremia occurring in 13 (19%) of 70 of patients receiving this antibiotic, compared with no failures among 18 persons treated with nafcillin [2]. Thus, the evidence is strong that vancomycin is not an acceptable alternative therapy for patients with MSSA infection.
METHICILLIN-RESISTANT S. AUREUS (MRSA)

The activity of vancomycin against S. aureus is weak and is getting weaker. This increasing impotence, together with vancomycin’s poor tissue penetration, may prove to be problems that cannot safely be overcome by such strategies as dose escalation.

“MIC CREEP”

Owing, at least in part, to the recognition of the poor therapeutic performance of vancomycin, the Clinical and Laboratory Standards Institute (CLSI) implemented a downward revision in vancomycin breakpoints [3]. Despite this change, vancomycin resistance (MIC, ≥16 µg/mL) remains a remarkably rare phenomenon, and vancomycin-intermediate S. aureus (VISA; MIC, 4–8 µg/mL) is also infrequently encountered. Unfortunately, the confluence of 2 phenomena—MIC creep (i.e., a gradual reduction in susceptibility of S. aureus to vancomycin) and the poor response to therapy of patients infected with S. aureus isolates whose MICs lie at the higher end of the range of susceptibility (MIC, ≤2 µg/mL)—make the continued use of vancomycin increasingly problematic.

At least 3 US centers, each geographically distant from the others, have reported MIC creep in recent years, but MICs have remained within the range considered to be susceptible by current CLSI criteria. In a small study at a Houston, Texas, teaching hospital, the vancomycin MIC₉₀ for MSSA increased from 0.12 µg/mL to 2.0 µg/mL, and that of MRSA increased from 0.25 µg/mL to 2.0 µg/mL between 1985 and 2004 [4]. Between 2002 and 2005, the geometric mean MIC of bloodstream MRSA isolates increased from 0.9 µg/mL to 1.4 µg/mL at a Boston, Massachusetts, teaching hospital [5]. At a similar institution in Los Angeles, California, analysis of 6003 S. aureus clinical isolates found a significant upward MIC shift over several years, with isolates with an MIC of 1.0 µg/mL replacing those with an MIC <1.0 µg/mL [6]. As a consequence, the proportion of isolates with an MIC of 1.0 µg/mL increased from 19.9% in 2000 to 70.4% (P<.01) in 2004 [6]. The nationwide consequences of this phenomenon are evident from the finding by The Surveillance Network Database–USA (Focus Technologies) that 16.2% of 241,605 recent S. aureus isolates tested had an MIC of 2 µg/mL [7]. Thus, it appears that a progressive reduction susceptibility to vancomycin is inevitable in all venues in which the drug is extensively used.

MIC CREEP AND POOR THERAPEUTIC RESPONSE TO VANCOMYCIN

Although it may be argued that such increases in MICs that, nonetheless, remain within the range considered to be susceptible are meaningless, such is not the case. A retrospective study of 30 selected patients with MRSA bacteremia found that the frequency of successful therapy with vancomycin was 55.6% in the 9 patients infected with an isolate for which the MIC was ≥0.5 µg/mL, but it was only 9.5% in those whose isolate had an MIC of 1 or 2 µg/mL [8]. There is, therefore, a gradation of responses to vancomycin therapy that depends upon the MIC of infecting isolates within the “susceptible” range. Because many clinical laboratories only report results at the breakpoint, clinicians are often not aware of the actual MIC and cannot make therapeutic decisions on this basis.

LIMITATIONS OF THE CLINICAL LABORATORY IN DETECTING REDUCED SUSCEPTIBILITY AND RESISTANCE TO VANCOMYCIN

In addition to the problem the clinician faces when clinical laboratories only report results at the breakpoint, some automated antimicrobial susceptibility testing devices may fail to detect isolates with an MIC of 2 µg/mL [5]. Furthermore, VISA strains with an MIC of 4 µg/mL may not be detected with the use of screening agar plates containing vancomycin, 6 µg/mL, nor are they reliably detected by some automated devices [9]. In addition, standard clinical laboratory testing does not detect S. aureus with vancomycin heteroresistance (hVISA), which was found to be present in 2.16% of >6000 MRSA isolates (with great variation in frequency) from the multiple participating centers [10, 11]. Vancomycin therapy given to patients with hVISA infection is associated with even poorer responses than those seen with patients infected with “fully susceptible” strains of MRSA [12, 13].

Other features that may impair the therapeutic response to vancomycin that are not detected in the clinical microbiology laboratory include its susceptibility to an inoculum effect and its relatively sluggish pace of bactericidal activity [14–16]. The latter is further exaggerated by anaerobic conditions, stationary planktonic growth, and growth as biofilm [17–22]. The poor bactericidal activity of vancomycin against some strains of S. aureus is such that these are considered to be tolerant to this glycopeptide, as demonstrated by either time-kill assays or major discrepancies between minimum bactericidal concentration and MIC [8, 23, 24]. Slowed bactericidal activity and tolerance have been correlated with refractoriness of infections with gram-positive organisms to treatment with vancomycin and to a reduced likelihood of clinical success in the treatment of patients with MRSA bacteremia [8, 23, 24].

THE PENETRATION OF VANCOMYCIN INTO TISSUE IS POOR

The limited penetration of the bulky (molecular weight, 1449 Daltons) hydrophilic vancomycin molecule [25] into a variety of tissues contributes to its limited therapeutic efficacy. The concentration achieved in epithelial lining fluid of the lung in patients undergoing mechanical ventilation is only ~14% of that in serum.
Penetration into soft tissue of patients undergoing cardiac surgery in whom vancomycin was administered by continuous infusion was also limited, with a tissue-to-plasma ratio of 0.3 in nondiabetic subjects and of only 0.1 in diabetic subjects [27].

**INCREASING THE DOSE OF VANCOMYCIN MAY NOT SAFELY OVERCOME ITS POOR ACTIVITY AND LIMITED TISSUE PENETRATION**

Because the ratio of the 0–24 area under the curve (AUC	extsubscript{0–24}) to the MIC appears to be the best pharmacodynamic predictor of response to therapy with vancomycin [25], it may be surmised that dose escalation could overcome problems regarding limited potency and tissue penetration. Taking this into account, the current guidelines of the Infectious Diseases Society of America and the American Thoracic Society recommend maintenance of a trough serum concentration of 15–20 μg/mL—a concentration higher than that previously generally targeted—for the treatment of patients with severe health care-associated pneumonia (HCAP) due to MRSA [28]. Whether dose escalation will, however, improve therapeutic outcomes remains to be determined; the results to date are not encouraging.

One study examined the effect of administration of 2 different doses of vancomycin on *S. aureus* colonization of multiple anatomic sites in patients receiving the drug for treatment of osteomyelitis [29]. In this trial, administration of vancomycin in a dosage of 40 mg/kg per day, with a trough target of 20–25 μg/mL, was no more effective than a dosage of 20 mg/kg per day, with a trough target of 10–15 μg/mL, in reducing the frequency of MRSA colonization [29]. In a large, randomized therapeutic trial involving patients with *S. aureus* bacteremia or endocarditis [30], there was reported to be no correlation between trough vancomycin concentration and outcome [31]. In addition, a retrospective examination of 132 patients with HCAP at a single Midwestern institution was unable to identify a correlation between either vancomycin trough serum concentration or estimated AUC and survival [32]. This lack of correlation was true, even among a subset of patients whose trough serum vancomycin concentrations were ≧15 μg/mL; in this group, the mean values in survivors and nonsurvivors were 20.8 ± 3.4 μg/mL and 20.4 ± 5.2 μg/mL, respectively [32]. A case-control study did find a statistically nonsignificant trend toward better outcomes in patients whose trough free (i.e., non–protein-bound) vancomycin concentrations were ≧4-fold higher than the MIC of their *S. aureus* isolates after their initial antibiotic dose [33]. Response rates in those infected with an MIC of 2 μg/mL were significantly lower than in those whose isolates had a lower MIC (61% vs. 90%; *P* = .004), and target attainment did not benefit persons infected with isolates with higher MICs [33].

It might be argued that the reason for a lack of improved efficacy with administration of higher doses of vancomycin was simply that the dose was insufficiently escalated. Some work has attempted to define a target AUC	extsubscript{0–24}/MIC ratio that, if achieved, provides reasonable assurance of therapeutic efficacy. A retrospective analysis of patients with respiratory tract infections from whom *S. aureus* was recovered and who received vancomycin identified a ratio of ≧400 (using the AUC of total drug concentration) as being associated with more-rapid bacterial eradication [27]. This analysis was, however, complicated by the administration of ≧1 antibiotic in addition to vancomycin to these patients. A Monte Carlo pharmacokinetic/pharmacodynamic simulation using European Committee on AntimicrobialSusceptibility Testing data (excluding those for VISA strains) [34] and pharmacokinetic data from 46 patients in the intensive care unit receiving vancomycin (one-half of whom had a creatinine clearance rate ≤50 mL/min, but none of whom were receiving renal replacement therapy), determined that a daily dose of 42 mg/kg was required to assure a 90% probability of achieving an AUC	extsubscript{0–24}/MIC ratio of 400 [35]. The corresponding approximate mean total daily doses required for 95% and 100% probabilities of achieving this target were 56 mg/kg and 70 mg/kg, respectively [35].

A target ratio of 400 that was calculated using the total (bound plus unbound drug concentration) corresponds, when only the free (non–protein-bound) fraction of the antibiotic is considered, to an AUC	extsubscript{0–24}/MIC ratio of ~160, using an estimated 60% protein binding for vancomycin. Studies using the neutropenic mouse thigh infection model, however, concluded that the appropriate target AUC	extsubscript{0–24}/MIC for enhanced success is ~500 [36]. If this is accurate, at least in neutropenic individuals, the corresponding target using total vancomycin concentrations is 833, and achieving this target in a 70-kg individual infected with a strain of *S. aureus* with an MIC of 1 μg/mL would require doses approximately twice as high as those indicated above.

These data suggest that dose escalation of vancomycin may not improve its therapeutic efficacy. At the same time, they do not address the possibility that higher-than-usual doses may be associated with increased toxicity. In one retrospective study, nephrotoxicity developed in 6 (15%) of 40 patients whose trough antibiotic concentration was ≧15 μg/mL but in 0 of 19 patients with higher trough concentrations [37]. That study was complicated, however, by the receipt of other potentially nephrotoxic agents by some patients. A much more compelling indication of the potential adverse consequences of dose escalation arose from a retrospective analysis of 94 patients with HCAP due to MRSA who were treated with vancomycin as a single agent [38]. In that study, nephrotoxicity (defined as a ≥25% decrease in creatinine clearance rate) developed in 30 (59%) of 51 patients whose vancomycin trough serum concentrations were >15 μg/mL but
in only 13 (30%) of those with lower trough concentrations (\( P = .0006 \)) [38].

**VANCOMYCIN HAS PROVEN TO BE INFERIOR TO SOME COMPARATORS IN RANDOMIZED CLINICAL TRIALS**

There appears to be no clinical trial evidence that is indicative of the superiority of vancomycin over any rationally chosen comparator agent, but some trials have demonstrated its possible inferiority. In an analysis that combined data from 2 clinical trials involving a total of 1867 patients with complicated skin and skin-structure infections (719 of which were due to MRSA), the rate of clinical cure was 90.6% among telavancin recipients and 86.4% among those assigned to receive vancomycin (\( P = .60 \)) [39]. A similar trend, also approaching statistical significance, was achieved with regard to bacterial eradication, which was observed in 89.9% and 85.4% of subjects (\( P = .053 \)), respectively [39]. A statistically significant difference in the frequency of bacteriological eradication, achieved in 92% of telavancin recipients and 68% of vancomycin recipients (\( P = .04 \)), was reached in 1 of the 2 individual trials [40].

In a randomized trial involving patients with bacteremia or endocarditis, success was achieved in those with MRSA infection among 20 (44.4%) of 45 persons given daptomycin and in only 14 (31.8%) of 44 of those given vancomycin plus gentamicin for the first 4 days—a trend favoring the lipopeptide that, however, did not reach statistical significance (95% CI for the difference, −7.4 to 32.6) [30].

More dramatic differences have been identified in randomized trials involving other comparators. Bacteriological eradication was achieved in 90% of patients with complicated skin and skin-structure infections due to MRSA who were randomized to receive dalbavancin, but this happened in only 82% of those given vancomycin [41]. It was similarly achieved in 88.6% of linezolid recipients and only 66.9% (\( P < .001 \)) of vancomycin recipients with complicated skin and skin-structure MRSA infections [42]. Bacterial eradication was also achieved significantly more frequently in linezolid recipients than in vancomycin recipients with complicated skin and soft-tissue infections of the lower extremities due to MRSA [43].

Finally, although no significant difference was detected in either of the 2 individual trials, a post hoc pooled analysis of results from each found that linezolid treatment in patients with HCAP due to MRSA was associated with significantly improved survival (80%), compared with vancomycin therapy (63.5%; \( P = .022 \)) [44]. Similar improved survival among persons given linezolid was detected when the analysis was limited to those with ventilator-associated pneumonia [45].

**USING VANCOMYCIN IN COMBINATION WITH A SECOND ANTISTAPHYLOCOCCAL ANTIBIOTIC DOES NOT IMPROVE ITS THERAPEUTIC EFFICACY**

Vancomycin is commonly administered together with a second agent with antistaphylococcal activity, most often rifampin and/or gentamicin. In a small, randomized trial involving a total of 42 patients with endocarditis due to MRSA, the addition of rifampin to vancomycin was associated with an apparent prolongation of bacteremia (9 vs. 7 days) [46]. There has been, in contrast, no reported clinical trial evaluating the combination of gentamicin and vancomycin versus vancomycin alone. Even short durations (e.g., 4 days) of adjunctive gentamicin therapy, however, have been associated with an apparently increased risk of nephrotoxicity [30]. Thus, although the addition of gentamicin adds toxicity to a therapeutic regimen, there is no evidence supporting any benefit, making its use for the purpose of attempting to improve the efficacy of vancomycin therapy, at best, questionable.

**CONCLUSIONS**

To the extent that vancomycin may have once been a moderately effective antistaphylococcal antibiotic, currently available in vitro and clinical data indicate it is no longer so. *S. aureus* has evolved; vancomycin has not. The intrinsic characteristics of the drug that impede its penetration to the site of infection have, of course, not changed. In contrast, the concentration required to inhibit the growth of this organism is progressively increasing. Available evidence provides scant hope that either increasing the dose of vancomycin or administering it in combination with a second agent that has antistaphylococcal activity will improve its efficacy. These strategies require further randomized clinical trials for their validation or rejection. In the meantime, the only argument for “staying the course” with vancomycin appears to be its low acquisition cost relative to newer agents—a benefit that is, on closer but more comprehensive examination, illusory [47]. Although it may not be time to completely “cut and run,” it is time to consider the use of alternative, more effective antistaphylococcal antibiotics.

**EPILOGUE**

Vancomycin was derived from a streptomyecete recovered from a sample of soil obtained in the Borneo rain forest [48]. Its use was limited at first because of toxicity resulting from impurities; the appearance of vancomycin in vials was such that it was likened to “Mississippi mud.” In recent decades, its use increased dramatically and, along with this increased use, its
efficacy as an antistaphylococcal agent began to be questioned. These questions have now been answered:

There is an antibiotic called mud
That’s proving to be quite a dud.
Its provenance is jungle
Its use is a bungle
It just won’t get rid of your crud.

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References


