IDSA LECTURE

Point: Vancomycin Is Not Obsolete for the Treatment of Infection Caused by Methicillin-Resistant *Staphylococcus aureus*

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(See the counterpoint by Deresinski on pages 1543–8)

Since the discovery, development, and US Food and Drug Administration approval of vancomycin in the 1950s, this agent has remained a mainstay for the treatment of infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA). However, because of the development of new antistaphylococcal antibiotics and reports of vancomycin failures, the utility of vancomycin has recently been questioned. Although vancomycin did not undergo the strict US Food and Drug Administration approval process that is in place today to demonstrate efficacy, there is considerable information available that sheds light on the role vancomycin has in infectious diseases pharmacotherapy today. In addition, although we look to in vitro susceptibility testing to assess vancomycin activity against *S. aureus,* we have come to appreciate that resistance of *S. aureus* to vancomycin can be a continuous—rather than a categorical—phenomenon. This has resulted in clinical microbiology laboratories having difficulty identifying *S. aureus* that may not respond to conventional doses of vancomycin. A better understanding is needed of the pharmacodynamic relationship between vancomycin and MRSA as relates to optimal dosing strategies, including consideration for loading doses, and development of rational categorical breakpoints for susceptibility based on clinical outcomes. By better understanding these critical issues, it may be possible to optimize the use of vancomycin, resulting in a cost-effective treatment option for many patients infected with MRSA.

After the discovery of penicillin in 1942, a fermentative by-product of what would later be known as *Penicillium notatum,* it was recognized that nature might be a vast reservoir for new antimicrobials. Pursuit of this concept led to the discovery of natural products, giving us cephalosporins, macrolides, aminoglycosides, and vancomycin.

The bacterium *Streptomyces orientalis* (now classified taxonomically as *Amycolaptosis orientalis*) was isolated from a soil sample from Borneo in 1952. This organism produced a fermentative by-product that was isolated and initially referred to as compound 05865; it was found to have in vitro activity against *Staphylococcus aureus,* including strains that were resistant to penicillin—a growing problem at that time. After extensive efforts to create a purified product, it was ultimately given the name "vancomycin." Soon thereafter, the drug was used for infections caused by penicillin-resistant *S. aureus.* The initial clinical experience with vancomycin was positive, and this ultimately led to an extensive emergency use program and collection of case reports of patient outcomes. On the basis of these "open-label" data, vancomycin received US Food and Drug Administration (FDA) approval in 1958 and became a treatment option for infections caused by

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penicillin-resistant *S. aureus.* By the early 1960s, just a few years after the introduction of methicillin to the market, vancomycin was also recognized as a treatment for cases of methicillin-resistant *S. aureus* (MRSA) infection that were beginning to appear [1].

On 10 October 1962, the Kefauver-Harris Amendments were passed in response to the European thalidomide crisis. These modifications to the Federal Food, Drug, and Cosmetic Act of 1938 added the requirement of efficacy and strengthened the safety requirements for all new drugs that would undergo the FDA approval process. These amendments contained a grandfather clause for drugs marketed in the United States prior to 9 October 1962 and after 25 June 1938 that exempted them from the efficacy requirements of the amended act. One of the drugs exempted was vancomycin.

After the first case of MRSA infection was reported in 1961, MRSA rates initially remained low until the late 1970s, followed by a dramatic increase in resistance and, consequently, in the use of vancomycin over the next 3 decades. Partly because of limited therapeutic options, vancomycin became the drug of choice to treat infections caused by MRSA, even without efficacy data provided to the FDA. Although the increasing prevalence of MRSA has been a catalyst for the development of new antimicrobials, the development of these new agents has, in turn, been a catalyst leading to uncertainties about vancomycin. These factors have led some in recent years to question whether vancomycin has become an obsolete antibiotic for the treatment of infections caused by MRSA [2].

Although vancomycin did not undergo the approval process after its discovery in the 1950s that it would go through today, much information on the pharmacokinetics and pharmacodynamics of vancomycin and the microbiology of *S. aureus* has been published and continues to be generated. The drug, the interactions of the bug and the drug, and the critical measures of the drug's in vitro activity are more understood today. Therefore, in our opinion, the book on vancomycin for the management of MRSA infection is not ready to be closed.

VANCOMYCIN RESISTANCE IN MRSA

The Clinical and Laboratory Standards Institute (CLSI) recently changed the breakpoint for susceptibility to vancomycin for *S. aureus* from ≤ 4 to ≤ 2 μg/mL on the basis of the high clinical failure rate for vancomycin in patients with organisms with MICs of 4 μg/mL [3]. However, this change is not reflected in the prescribing information for vancomycin, and the FDA breakpoint currently remains at ≤ 4 μg/mL [4]. Although the overall rate of MRSA varies geographically, on average, it is reported to be >50% in most hospitals and, more recently, in some communities. MRSA that also demonstrates true resistance to vancomycin (MIC, ≥ 32 μg/mL) is extremely rare [5]. Six strains of *S. aureus* containing the *vanA* gene located on a plasmid have been reported, likely acquired from vancomycin-resistant *Enterococcus faecalis* present in a polymicrobic milieu, such as a wound infection [6, 7].

The first case of infection caused by *S. aureus* with intermediate susceptibility to vancomycin (VISA) was identified in Japan in 1996 [8]. The mechanism of resistance for these VISA strains relates to overproduction of D-Ala D-Ala in the peptidoglycan cell wall that appears to act as a sponge, absorbing vancomycin before it reaches its target. Outcomes for patients receiving vancomycin for the treatment of infections caused by these VISA strains are poor. However, like high-level vancomycin resistance, intermediate resistance is also a very rare event.

In addition to vancomycin-resistant *S. aureus* (VRSA) and VISA, there are strains of *S. aureus* that display heteroresistance to vancomycin (hVISA). These isolates contain a subpopulation of organisms that exhibit reduced killing with vancomycin in vitro. The MICs are within the susceptible range but are most frequently 2 μg/mL. In a surveillance study of 1357 strains of MRSA isolated during 1997–2000 in 12 Asian countries, no cases of VRSA or VISA were identified; however, 4.3% of the strains displayed heteroresistance to vancomycin by population analysis profiles [9]. The clinical significance of hVISA still remains unclear, partially because these strains were not detected in the clinical microbiology laboratory. In a retrospective evaluation of patients with MRSA bacteremia, the duration of bacteremia was 3 weeks longer in patients with hVISA infection, compared with non-hVISA infection, but only 5 hVISA isolates were recovered over the 12-month study period [10]. It is unclear whether heteroresistance to vancomycin resulted in the prolonged bacteremia or whether therapy with vancomycin caused the heteroresistance to emerge, because the patients with hVISA infection were more likely to have prosthetic joint infections, endocarditis, and abscesses and were more likely to have low initial vancomycin trough concentrations. Although a rabbit endocarditis model demonstrated the emergence of hVISA on vancomycin contributing to clinical failure, an in vitro pharmacodynamic model failed to select for hVISA [11, 12]. Other in vitro models have correlated low levels of vancomycin exposure with the emergence of hVISA, whereas higher-level drug exposures did not select for hVISA phenotypes [13].

Although vancomycin resistance in *S. aureus* is rare as currently defined, it has become clear that not all MRSA strains are created equal, and resistance is not necessarily an all-or-none phenomenon. The perceived low prevalence of VRSA and VISA may be a function of the difficulty of identifying these organisms in the clinical microbiology laboratory. To determine the future utility of vancomycin, methodologies for identifying hVISA, the current prevalence of hVISA, and the overall clinical

significance of hVISA in various types of infections must be ascertained.

DOES VANCOMYCIN "SUSCEPTIBILITY" PREDICT TREATMENT SUCCESS WITH VANCOMYCIN?

Although in vitro susceptibility testing should predict the probability of clinical success, the CLSI defines an organism as "susceptible" to a given antibiotic if the isolates are inhibited by the usually achievable concentrations of an antimicrobial agent when the recommended dose is used for the site of infection [3]. Therefore, a susceptibility breakpoint MIC of 2–4 μg/mL for vancomycin based on recommended serum trough concentrations of 5–10 μg/mL appears to be quite rational, because the serum concentration will always be higher than the MIC in the bloodstream. However, the spectrum of disease caused by *S. aureus* varies from mild to severe skin infection, to respiratory tract infection, to bacteremia, to endocarditis and meningitis, and concentrations of vancomycin at these sites are lower than serum concentrations [14, 15]. In addition, free serum concentrations, which may be a more meaningful pharmacodynamics measure, will also be lower.

Although the MIC is the parameter that is routinely measured in the clinical microbiology laboratory to determine susceptibility of *S. aureus* to vancomycin, the classification as "susceptible" may not predict therapeutic efficacy with vancomycin, and several studies have evaluated other parameters. In a study of 80 patients with *S. aureus* bacteremia, a ratio of minimum bactericidal concentration to MIC of >32—not whether the organism had an MIC outside the susceptible range—was correlated with vancomycin failure [16]. In a more recent evaluation of relationships between vancomycin efficacy and vancomycin susceptibility in patients with MRSA bacteremia, 100% of isolates were considered to be "susceptible," according to the MIC, to vancomycin, but only 23% clinically responded to vancomycin. However, an increase in vancomycin efficacy was associated with the subset of isolates with lower vancomycin MICs and with those isolates that demonstrated an increased in vitro killing of vancomycin after 72 h of incubation with 16 μg/mL vancomycin [17]. Decreased clinical efficacy of vancomycin has also been associated with strains that contain type II accessory gene regulator proteins [18, 19]. However, the patients included in these analyses were identified because vancomycin treatment was failing, so this may not reflect a "real-life" situation. Therefore, these results should be validated with prospective studies or with cohorts of consecutive patients with MRSA infection.

To summarize the above, there appears to be an in vitro/in vivo disconnect between what we have traditionally called vancomycin "susceptibility" and clinical success with vancomycin treatment for serious infections, such as complicated pneumonia and bacteremia. Although the perceived lack of utility of vancomycin is not due to the development of "resistance" at the current CLSI- or FDA-defined levels, this assumes that the breakpoint for resistance adequately distinguishes clinical successes and clinical failures. Understanding the relationships between the microbiologic activity of vancomycin against MRSA and in vivo concentrations of vancomycin should enhance our understanding of the overall clinical utility of vancomycin for the treatment of serious infections caused by MRSA.

VANCOMYCIN PHARMACODYNAMICS

In the neutropenic murine thigh–infection model, the pharmacodynamic parameter that best predicted the activity of vancomycin was the ratio of the area under the curve (AUC) to the MIC (AUC/MIC) [20]. When evaluating vancomycin-susceptible *S. aureus,* VISA, and hVISA in this model, the AUC/MIC ratio required for a static effect was similar for all these organisms [21]. However, the dose required for a 2-$\log_{10}$ kill was 2.5-fold higher for hVISA, compared with VISA. The authors concluded that a free AUC/MIC ratio of ~500 was needed to optimize vancomycin pharmacodynamics for hVISA—a ratio that is only achievable in humans with much higher-than-usual doses or lower MICs. In a study of patients with lower respiratory tract infections due to *S. aureus,* an AUC/MIC threshold of >400 was associated with greater clinical response and microbiological eradication, compared with patients with an AUC/MIC ratio of <400 [22]. No relationship was identified between vancomycin % time>MIC and infection response.

In another study, Jeffres et al. [23] evaluated the effect of vancomycin pharmacokinetics on mortality in patients with health care–associated MRSA pneumonia. Although a reduction in mortality with higher vancomycin trough concentrations or AUCs, compared with lower trough concentrations, was not observed, the clinical outcome relative to MIC was not reported, because disk diffusion was used for susceptibility testing for vancomycin—a method that is unable to detect MRSA with reduced susceptibility to vancomycin (figure 1). However, information on the pharmacokinetics of different vancomycin dosing strategies was provided. In patients with a mean trough concentration of 9.4 μg/mL, the mean AUC (±SD) achieved was 318 ± 111 μg/h/mL; in patients with a mean trough concentration of 20.4 μg/mL, the mean AUC (±SD) achieved was 418 ± 152 μg/h/mL. On the basis of the pharmacokinetics, organisms with MICs of 2 μg/mL and 0.5 μg/mL have a probability of achieving an AUC/MIC ratio of >400, using Monte-Carlo simulation, of 0% and 100%, respectively (figure 2). Therefore, on the basis of the pharmacodynamic profile of vancomycin and MRSA, one would expect a high probability

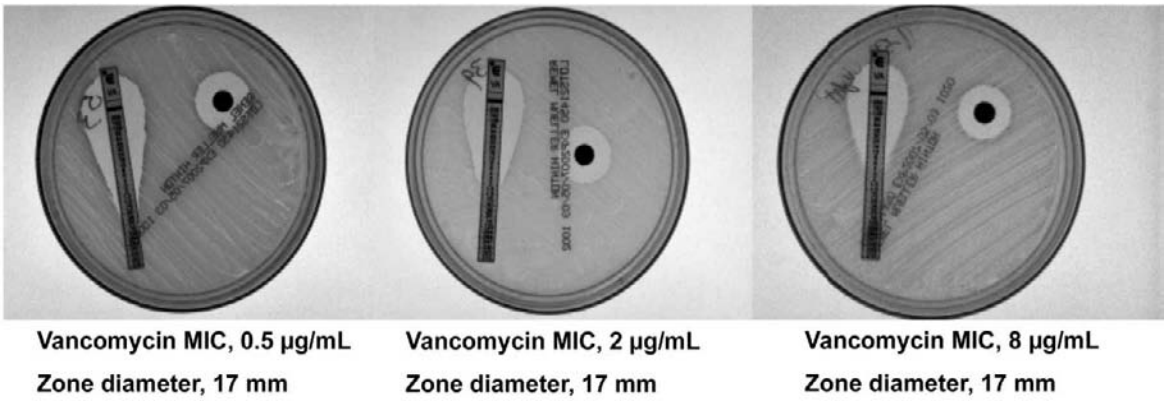

Figure 1. Inability of disk diffusion to detect methicillin-resistant *Staphylococcus aureus* with reduced susceptibility to vancomycin. (Photo provided by J.F.M.)

of suboptimal vancomycin AUC/MIC ratios for patients infected with organisms with vancomycin MICs of ⩾2 μg/mL, regardless of whether high or lower dosing is used, resulting in a poor clinical and microbiological response in patients with health care–associated MRSA pneumonia. Patients with pneumonia due to MRSA with a vancomycin MIC of 2 μg/mL have been demonstrated to have poor clinical outcomes when treated with vancomycin, compared with patients infected with organisms with MICs of 0.5–1 μg/mL [17, 19, 24]. However, MRSA with a vancomycin MIC of 2 μg/mL is considered to be susceptible according to vancomycin prescribing information [4], as well as the CLSI [3].

VANCOMYCIN MIC DRIFT IN *S. AUREUS*

The clinical relevance of MRSA with vancomycin MICs of 2 μg/mL would be low if these organisms represented a small proportion of the overall bacterial population. In an evaluation of >35,000 strains of *S. aureus* isolated during 1998–2003, the percentage of *S. aureus* isolates with MICs of 2 μg/mL ranged from 4.7% to 7.8% over the study period, and there was no upward trend over time ($MIC_{50/90}$, 1 μg/mL each year) [25]. However, others have reported more apparent shifts over time. Steinkraus et al. [26] demonstrated an increase in the vancomycin MIC among MRSA isolates recovered from blood cultures from 2001 to 2005 (figure 3). The increase in the geometric mean MIC was primarily a function of fewer strains with MICs of 0.5 μg/mL and of more strains with MICs of 1 and 2 μg/mL, with 8% of MRSA isolates recovered in 2005 having vancomycin MICs of 2 μg/mL. In a recent analysis of 116 consecutive blood culture isolates from a large tertiary care hospital in the Texas Medical Center (Houston) from August 2005 to December 2006, 30% of the strains had MICs of 2 μg/mL; however, no trend over time could be identified (A. Wanger and J.F.M.; unpublished data.)

ARE WE ADMINISTERING THE CORRECT VANCOMYCIN DOSE AT THE RIGHT TIME AND SHOULD WE USE A LOADING DOSE?

With vancomycin failure rates being reported as high as 50%–60% for complicated bacteremia and 40% for pneumonia with routine doses, some have advocated aiming to achieve trough concentrations of ⩾15 μg/mL, but no prospective trials have been conducted to fully answer this question [27]. However, the importance of initiating antibiotic treatment early for patients with *S. aureus* bacteremia has been demonstrated, and isolation of MRSA was the most significant factor contributing to delayed treatment for *S. aureus* bacteremia [28].

Hidayat et al. [24] conducted a cohort analysis of 95 hospitalized adults who received vancomycin for MRSA infection (primarily pneumonia with and without concurrent bacteremia). Patients who achieved a target trough concentration of ⩾15 μg/mL within the first 24 h of treatment had a faster

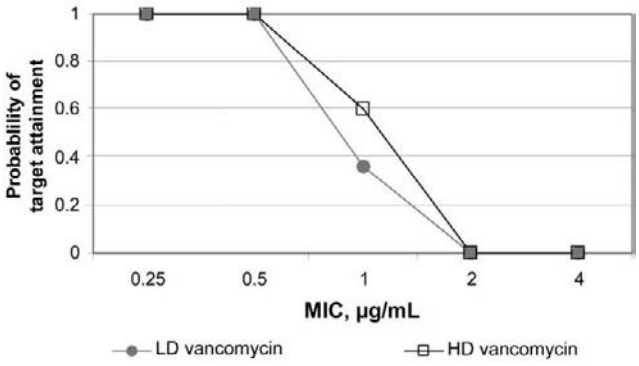

Figure 2. Probability of achieving a ratio of the area under the curve to the MIC of >400 for high-dose (HD) vancomycin treatment (trough concentration, >15 μg/mL) and low-dose (LD) vancomycin treatment (trough concentration, ⩽15 μg/mL). Adapted from Jeffres et al. [23].

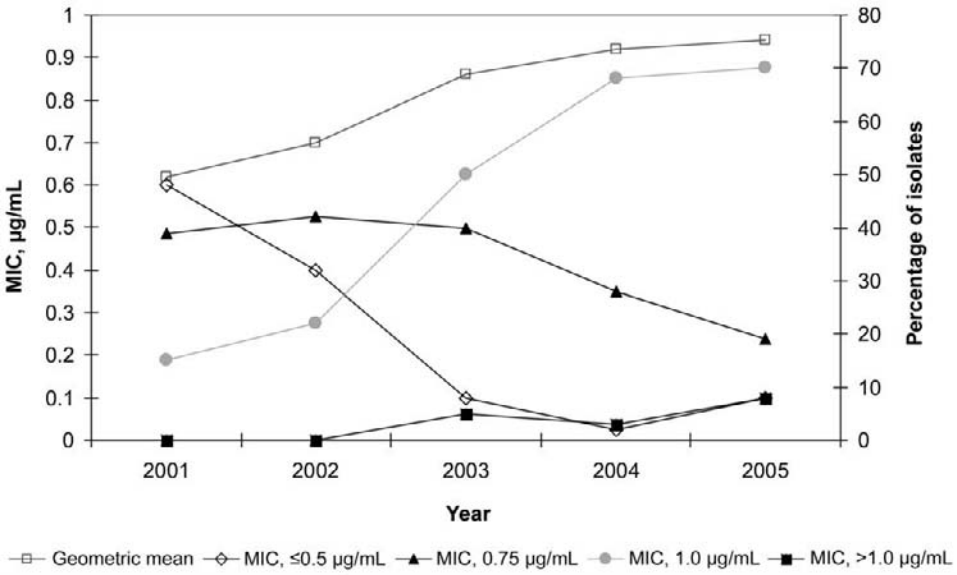

Figure 3. Vancomycin MICs for 668 blood culture isolates from 2001–2005. Data are from Steinkraus et al. [26]

clinical response, compared with patients who did not achieve this target trough concentration (76% vs. 56%; $P = .05$); however, efficacy was similar at the end of treatment. In addition, patients infected with organisms with an MIC of $\geqslant 2$ μg/mL were more likely to experience therapy failure than were patients infected with organisms with an MIC of $\leqslant 1$ μg/mL, despite reaching a trough concentration of $\geqslant 15$ μg/mL (85% vs. 62%; $P = .02$). This suggests that both the vancomycin dose and the vancomycin MIC are important variables for managing MRSA pneumonia.

Vancomycin loading doses of 15–25 mg/kg were components of early vancomycin dosing nomograms [29, 30]. However, this practice was not used in recent clinical trials [31, 32]. On the basis of the increase in hVISA associated with initial low vancomycin concentrations [10], various in vitro observations associated with the emergence of hVISA with low vancomycin exposures [13], reports of clinical failures with hVISA [12], and the improved outcomes associated with early empirical [28] plus aggressive vancomycin dosing [24, 33], the need for vancomycin loading doses should be reevaluated.

WHAT HAS BEEN PROVEN TO GIVE BETTER CLINICAL OUTCOMES THAN VANCOMYCIN?

A corollary to the premise that vancomycin is obsolete is that other antibiotics are superior, yet such data are generally lacking. Vancomycin has demonstrated clinical outcomes comparable to those of tigecycline, telavancin, oritavancin, ceftobiprole, and daptomycin in blinded clinical trials for patients with complicated skin and skin structure infections (cSSTIs), including those caused by MRSA [34–38]. In an open-label study of cSSTI, linezolid demonstrated a 94% rate of clinical cure (436 of 462 patients), compared with vancomycin's rate of 90% (394 of 436), in the clinically evaluable population ($P = .023$) [32]. The suggested superiority of linezolid is currently being validated in a prospective, randomized clinical trial (http://clinicaltrials.gov). Dalbavancin, in turn, was comparable to linezolid in a prospective, blinded clinical trial [39]. Although linezolid is an option for treatment of cSSTI, a 90% clinical response rate among the vancomycin-treated patients does not make the latter obsolete, particularly when it is used for nonfatal diseases, such as skin infections. Moreover, in light of the small absolute increase in clinical cure in the large population of patients enrolled, a balance of the cost of treatment and the emergence of resistance would need to be carefully considered prior to declaring linezolid (or other expensive therapies with similar efficacy) as a first-line treatment for cSSTI.

Vancomycin has also served as a comparator agent for more-severe diseases with higher mortality rates, such as bacteremia and ventilator-associated pneumonia. Daptomycin was comparable to nafcillin or vancomycin with gentamicin (for 4 days) in patients with *S. aureus* bacteremia; however, this study had a total of 139 patients in the per protocol set. Thus, it did not enroll enough patients to identify those problem organisms that have been associated with vancomycin failure [31]. In addition, associations with increasing daptomycin MICs with increased vancomycin MICs have been observed [40, 41], further complicating the strategy of using daptomycin for patients for whom vancomycin treatment fails.

Vancomycin performed comparably to linezolid in 2 randomized, double-blind studies in patients with nosocomial pneumonia [42, 43]. However, when the 2 studies were combined, the subset of patients with ventilator-associated MRSA

pneumonia who were treated with linezolid had a higher overall clinical cure rate (59% [36 of 61 patients] vs. 35% [22 of 62 patients]) [44]. Because there was no difference in the overall *S. aureus* subset, the benefit seen in the MRSA subset raises questions about the MSSA subset and the validity of this post hoc analysis. A larger randomized study aimed at reproducing this observation is being conducted (http://clinicaltrials.gov).

CONCLUSIONS

To summarize, we believe that vancomycin is not obsolete. Indeed, the case can be made that it is not the drug that is the problem, but that there are some difficult-to-treat organisms and difficult-to-treat infections. Unfortunately, the ability to identify these bugs in the routine clinical microbiology laboratory is challenging. Efforts to identify relationships between adequate therapy and clinical outcomes for MRSA infection with vancomycin have been disappointing, likely because isolates with microbiologic properties that may increase the risk for clinical failure are not recognized and because the MIC is in the "susceptible" range. Although there was a reduction in the CLSI's vancomycin breakpoint for susceptibility from 4 μg/mL to 2 μg/mL, one study demonstrated that 80% of the organisms with MICs of 2 μg/mL were demonstrated to have hVISA phenotypes [45]. Because hVISA and *S. aureus* with MICs of 2 μg/mL have been associated with poor clinical outcomes, it may be that an even lower susceptibility breakpoint may be needed. Although organisms with MICs of 2 μg/mL may be problematic, these organisms are infrequent in the overall population and appear to be a problem primarily in more-serious deep-seated infections. To adequately evaluate the efficacy of vancomycin for these problem organisms, large numbers of patients must be enrolled in the clinical trials for them to be adequately represented.

Finally, the existence of substantial evidence to support the superiority of alternative agents to vancomycin for MRSA infections is lacking. Millions of doses of vancomycin are administered for MRSA infections each year. Although there have been reports of newer antibiotics that have suggested better outcomes in some clinical scenarios, overall, vancomycin has not had inferior performance, and care should be taken in correlating statistically significant differences with clinical or economic relevance. In fact, vancomycin has been established as a safe drug, with no drug-drug interactions, that can be administered fairly infrequently through a peripheral vein, and it is inexpensive. Although some have advocated closing the book on this "useless" drug, we feel that the book remains open and that we need to study further the factors that would allow for the optimal use of vancomycin and to maximize its clinical utility. These factors include optimal dosing strategies of vancomycin that complement the pharmacodynamic properties of the drug and the microbiological identification of organisms that would be predicted to have a low probability of failing vancomycin therapy with a low likelihood of the selection of variants with reduced susceptibility to vancomycin.

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