CME CREDIT *EDUCATIONAL OBJECTIVES:* Readers will use vancomycin appropriately

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Vancomycin: A 50-something-year-old antibiotic we still don't understand

ABSTRACT

Because a significant proportion of *Staphylococcus aureus* strains as well as most coagulase-negative staphylococci are resistant to penicillin and semisynthetic beta-lactam drugs, the need for vancomycin and related antibiotics has never been greater. Effective use of vancomycin requires knowledge of dosing parameters and selection of target trough levels appropriate to the specific infection and to the pathogen being treated. For clinicians, it is vital to remain up-to-date with evolving definitions for vancomycin susceptibility, with new interpretations of efficacy, and with information on toxicity.

KEY POINTS

Giving vancomycin by continuous infusion appears to offer no advantage over giving it every 12 hours.

Therapeutic blood levels can be reached more quickly if a loading dose is given, but whether this offers a clinical advantage is unclear.

The trough vancomycin serum concentration should be greater than 10 mg/L to prevent the development of resistance, and trough levels of 15 to 20 mg/L are recommended if the minimum inhibitory concentration (MIC) is 1 mg/L or higher.

Whether *S aureus* is becoming resistant to vancomycin is not clear.

The variable most closely associated with clinical response to vancomycin is the area under the curve (AUC) divided by the MIC (the AUC-MIC ratio), which should be greater than 400.

In the past half-century, vancomycin has gone from near-orphan status to being one of the most often used antibiotics in our formulary. The driving force for its use is clear: the evolution of *Staphylococcus aureus*. At first, vancomycin was used to treat infections caused by penicillin-resistant strains. However, the discovery of methicillin curbed its use for more than 2 decades.[1]

Then, as methicillin-resistant *S aureus* (MRSA) began to spread in the 1980s, the use of vancomycin began to increase, and with the rise in community-associated MRSA infections in the 1990s, it became even more widely prescribed. The recent Infectious Diseases Society of America (IDSA) guidelines for treatment of infections due to MRSA are replete with references to the use of vancomycin.[2]

Another factor driving the use of vancomycin is the increased prevalence of device-associated infections, many of which are caused by coagulase-negative staphylococci and other organisms that colonize the skin.[3] Many of these bacteria are susceptible only to vancomycin; they may be associated with infections of vascular catheters, cardiac valves, pacemakers, implantable cardioverter-defibrillators, orthopedic implants, neurosurgical devices, and other devices.

To use vancomycin appropriately, we need to recognize the changing minimum inhibitory concentrations (MICs), to select proper doses and dosing intervals, and to know how to monitor its use. Despite more than 50 years of experience with vancomycin, we sometimes find ourselves with more questions than answers about its optimal use.

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WHAT IS VANCOMYCIN?

Vancomycin is a glycopeptide antibiotic isolated from a strain of *Streptomyces orientalis* discovered in a soil sample from Borneo in the mid-1950s.[1] It exerts its action by binding to a D-alanyl-D-alanine cell wall precursor necessary for peptidoglycan cross-linking and, therefore, for inhibiting bacterial cell wall synthesis.

Vancomycin is bactericidal against most gram-positive species, including streptococci and staphylococci, with the exception of *Enterococcus* species, for which it is bacteriostatic. Though it is bactericidal, it appears to kill bacteria more slowly than beta-lactam antibiotics, and therefore it may take longer to clear bacteremia.[4]

WHAT IS THE BEST WAY TO DOSE VANCOMYCIN?

Vancomycin is widely distributed to most tissues, with an approximate volume of distribution of 0.4 to 1 L/kg; 50% to 55% is protein-bound. Because of this large volume of distribution, vancomycin's dosing is based on actual body weight.

Despite more than 50 years of experience with vancomycin, we sometimes have more questions than answers

Vancomycin is not metabolized and is primarily excreted unchanged in the urine via glomerular filtration. It therefore requires dosage adjustments for renal insufficiency.

Vancomycin's molecular weight is 1,485.73 Da, making it less susceptible to removal by dialysis than smaller molecules. Dosing of vancomycin in patients on hemodialysis depends on many factors specific to the dialysis center, including but not limited to the type of filter used, the duration of filtration, and whether high-flux filtration is used.

Is continuous intravenous infusion better than standard dosing?

Giving vancomycin by continuous infusion has been suggested as a way to optimize its serum concentration and improve its clinical effectiveness.

Wysocki et al[5] conducted a multicenter, prospective, randomized study comparing continuous and intermittent intravenous infusions of vancomycin (the latter every 12 hours) to treat severe hospital-acquired MRSA infections, including bloodstream infections and pneumonia. Although blood concentrations above 10 µg/mL were reached more than 30 hours faster with continuous infusions than with intermittent ones, the microbiologic and clinical outcomes were similar with either method.

James et al[6] compared the pharmacodynamics of conventional dosing of vancomycin (ie, 1 g every 12 hours) and continuous infusion in 10 patients with suspected or documented gram-positive infections in a prospective, randomized, crossover study. While no adverse effects were observed, the authors also found no statistically significant difference between the treatment groups in the pharmacodynamic variables investigated, including the area under the curve (AUC) divided by the MIC (the AUC-MIC ratio).

In view of the currently available data, the guidelines for monitoring vancomycin therapy note that there does not appear to be any difference in patient outcomes with continuous infusion vs intermittent dosing.[7]

Should a loading dose be given?

Another proposed strategy for optimizing vancomycin's effectiveness is to give a higher initial dose, ie, a loading dose.

Wang et al[8] performed a single-center study in 28 patients who received a 25 mg/kg loading dose at a rate of 500 mg/hour. This loading dose was safe, but the authors did not evaluate its efficacy.

Mohammedi et al[9] compared loading doses of 500 mg and 15 mg/kg in critically ill patients receiving vancomycin by continuous infusion. The weight-based loading dose produced higher post-dose levels and a significantly higher rate of clinical cure, but there was no significant difference in the rate of survival to discharge from the intensive care unit.

While the use of a loading dose appears to be safe and likely leads to more rapid attainment of therapeutic blood levels, we lack data on whether it improves clinical outcomes, and further study is needed to determine its role.

WHAT IS THE BEST WAY TO MONITOR VANCOMYCIN THERAPY?

Whether and how to use the serum vancomycin concentration to adjust the dosing has

been a matter of debate for many years. Convincing evidence that vancomycin levels predict clinical outcomes or that measuring them prevents toxicity is lacking.[7]

A consensus statement from the American Society of Health-System Pharmacists, the IDSA, and the Society of Infectious Diseases Pharmacists[7] contains recommendations for monitoring vancomycin therapy, based on a critical evaluation of the available scientific evidence. Their recommendations:

- Vancomycin serum concentrations should be checked to optimize therapy and used as a surrogate marker of effectiveness.
- Trough, rather than peak, levels should be monitored.
- Trough levels should be checked just before the fourth dose, when steady-state levels are likely to have been achieved. More frequent monitoring may be considered in patients with fluctuating renal function.
- Trough levels should be higher than 10 mg/L to prevent the development of resistance.
- To improve antibiotic penetration and optimize the likelihood of achieving pharmacokinetic and pharmacodynamic targets, trough levels of 15 to 20 mg/L are recommended for pathogens with a vancomycin MIC of 1 mg/L or higher and for complicated infections such as endocarditis, osteomyelitis, meningitis, and hospital-acquired pneumonia.
- For prolonged courses, it is appropriate to check vancomycin levels weekly in hemodynamically stable patients and more often in those who are not hemodynamically stable.

IS VANCOMYCIN NEPHROTOXIC?

In the 1950s, vancomycin formulations were sometimes called "Mississippi mud" because of the many impurities they contained.[1] These impurities were associated with significant nephrotoxicity. Better purification methods used in the manufacture of current formulations mitigate this problem, resulting in a lower incidence of nephrotoxicity.

Over the last several years, organizations such as the American Thoracic Society and the IDSA have recommended targeting higher vancomycin trough concentrations.[10] The consequent widespread use of higher doses has renewed interest in vancomycin's potential nephrotoxicity.

Lodise et al,[11] in a cohort study, examined the incidence of nephrotoxicity with higher daily doses of vancomycin (≥ 4 g/day), lower daily doses (< 4 g/day), and linezolid (Zyvox). They defined nephrotoxicity as an increase in serum creatinine of 0.5 mg/dL or a decrease in calculated creatinine clearance of 50% from baseline on 2 consecutive days.

The incidence of nephrotoxicity was significantly higher in the high-dose vancomycin group (34.6%) than in the low-dose vancomycin group (10.9%) and in the linezolid group (6.7%) (P = .001). Additional factors associated with nephrotoxicity in this study included baseline creatinine clearance less than 86.6 mL/minute, weight greater than 101.4 kg (223.5 lb), and being in an intensive care unit.

Hidayat et al[12] investigated outcomes in patients with high vs low vancomycin trough levels (≥ 15 mg/L vs < 15 mg/L) in a prospective cohort study. Sixty-three patients achieved an average vancomycin trough of 15 to 20 mg/L, and of these, 11 developed nephrotoxicity, compared with no patients in the low-trough group (P = .01). Of the 11 who developed nephrotoxicity, 10 were concomitantly taking other potentially nephrotoxic agents.

Vancomycin needs dosage adjustment for renal insufficiency

Comment. The data on vancomycin and nephrotoxicity are mostly from studies that had limitations such as small numbers of patients, retrospective design, and variable definitions of nephrotoxicity. Many of the patients in these studies had additional factors contributing to nephrotoxicity, including hemodynamic instability and concomitant exposure to other nephrotoxins. Additionally, the sequence of events (nephrotoxicity leading to elevated vancomycin levels vs elevated vancomycin levels causing nephrotoxicity) is still debatable.

The incidence of nephrotoxicity associated with vancomycin therapy is difficult to determine. However, based on current information, the incidence of nephrotoxicity appears to be low when vancomycin is used as monotherapy.

IS *S AUREUS* BECOMING RESISTANT TO VANCOMYCIN?

An issue of increasing importance in health care settings is the emergence of vancomycin-intermediate *S aureus* (VISA) and vancomycin-resistant *S aureus* (VRSA). Eleven cases of VRSA were identified in the United States from 2002 to 2005.[13] All cases of VRSA in the United States have involved the incorporation of enterococcal vanA cassette into the *S aureus* genome.[14] While true VRSA isolates remain rare, VISA isolates are becoming more common.

Heteroresistant VISA: An emerging subpopulation of MRSA

Another population of *S aureus* that has emerged is heteroresistant vancomycin-intermediate *S aureus* (hVISA). It is defined as the presence of subpopulations of VISA within a population of MRSA at a rate of one organism per 10^5 to 10^6 organisms. With traditional testing methods, the vancomycin MIC for the entire population of the strain is within the susceptible range.[15] These hVISA populations are thought to be precursors to the development of VISA.[16]

The presence of hVISA may be associated with vancomycin treatment failure

The resistance to vancomycin in hVISA and VISA populations is due to increased cell wall thickness, altered penicillin-binding protein profiles, and decreased cell wall autolysis.

While the true prevalence of hVISA is difficult to predict because of challenges in microbiological detection and probably varies between geographic regions and individual institutions, different studies have reported hVISA rates between 2% and 13% of all MRSA isolates.[15–17]

Reduced vancomycin susceptibility can develop regardless of methicillin susceptibility.[18]

While hVISA is not common, its presence is thought to be a predictor of failing vancomycin therapy.[15]

Factors associated with hVISA bacteremia include high-bacterial-load infections, treatment failure (including persistent bacteremia for more than 7 days), and initially low serum vancomycin levels.[15]

'MIC creep': Is it real?

Also worrisome, the average vancomycin MIC for *S aureus* has been shifting upward, based on reports from several institutions, although it is still within the susceptible range.[19,20] However, this "MIC creep" likely reflects, at least in part, differences in MIC testing and varying methods used to analyze the data.[19,20]

Holmes and Jorgensen,[21] in a single-institution study of MRSA isolates recovered from bacteremic patients from 1999 to 2006, determined that no MIC creep existed when they tested vancomycin MICs using the broth microdilution method. The authors found the MIC_{90} (ie, the MIC in at least 90% of the isolates) remained less than 1 mg/L during each year of the study.

Sader et al,[22] in a multicenter study, evaluated 1,800 MRSA bloodstream isolates from nine hospitals across the United States from 2002 to 2006. Vancomycin MICs were again measured by broth microdilution methods. The mode MIC remained stable at 0.625 mg/L during the study period, and the authors did not detect a trend of rising MICs.

The inconsistency between reports of MIC creep at single institutions and the absence of this phenomenon in large, multicenter studies seems to imply that vancomycin MIC creep is not occurring on a grand scale.

Vancomycin tolerance

Another troubling matter with *S aureus* and vancomycin is the issue of tolerance. Vancomycin tolerance, defined in terms of increased minimum bactericidal concentration, represents a loss of bactericidal activity. Tolerance to vancomycin can occur even if the MIC remains in the susceptible range.[23]

Safdar and Rolston,[24] in an observational study from a cancer center, reported that of eight cases of bacteremia that was resistant to vancomycin therapy, three were caused by *S aureus*.

Sakoulas et al[25] found that higher levels of vancomycin bactericidal activity were associated with higher rates of clinical success; however, they found no effect on the mortality rate.

The issue of vancomycin tolerance remains controversial, and because testing for it is impractical in clinical microbiology laboratories,

its implications outside the research arena are difficult to ascertain at present.

IS VANCOMYCIN STILL THE BEST DRUG FOR *S AUREUS*?

MIC break points have been lowered

In 2006, the Clinical Laboratories and Standards Institute lowered its break points for vancomycin MIC categories for *S aureus*:

- Susceptible: ≤ 2 mg/L (formerly ≤ 4 mg/L)
- Intermediate: 4–8 mg/L (formerly 8–16 mg/L)
- Resistant: ≥ 16 mg/L (formerly ≥ 32 mg/L).

The rationales for these changes were that the lower break points would better detect hVISA, and that cases have been reported of clinical treatment failure of *S aureus* infections in which the MICs for vancomycin were 4 mg/L.[26]

Since 2006, the question has been raised whether to lower the break points even further. A reason for this proposal comes from an enhanced understanding of the pharmacokinetics and pharmacodynamics of vancomycin.

The variable most closely associated with clinical response to vancomycin is the AUC-MIC ratio. An AUC-MIC ratio of 400 or higher may be associated with better outcomes in patients with serious *S aureus* infection. A study of 108 patients with *S aureus* infection of the lower respiratory tract indicated that organism eradication was more likely if the AUC-MIC ratio was 400 or greater compared with values less than 400, and this was statistically significant.[27] However, in cases of *S aureus* infection with a vancomycin MIC of 2 mg/L or higher, this ratio may not be achievable.

A prospective study of 414 MRSA bacteremia episodes found a vancomycin MIC of 2 mg/L to be a predictor of death.[28] The authors concluded that vancomycin may not be the optimal treatment for MRSA with a vancomycin MIC of 2 mg/L.[28] Additional studies have also suggested a possible decrease in response to vancomycin in MRSA isolates with elevated MICs within the susceptible range.[25,29]

Recent guidelines from the IDSA recommend using the clinical response, regardless of the MIC, to guide antimicrobial selection for isolates with MICs in the susceptible range.[2]

Combination therapy with vancomycin

As vancomycin use has increased, therapeutic failures with vancomycin have become apparent. Combination therapy has been suggested as an option to increase the efficacy of vancomycin when treating complicated infections.

Rifampin plus vancomycin is controversial.[30] The combination is theoretically beneficial, especially in infections associated with prosthetic devices. However, clinical studies have failed to convincingly support its use, and some have suggested that it might prolong bacteremia. In addition, it has numerous drug interactions to consider and adverse effects.[31]

Gentamicin plus vancomycin. The evidence supporting the use of this combination is weak at best. It appears that clinicians may have extrapolated from the success reported by Korzeniowski and Sande,[32] who found that methicillin-susceptible *S aureus* bacteremia was cleared faster if gentamicin was added to nafcillin. A more recent study[33] that compared daptomycin (Cubicin) monotherapy with combined vancomycin and gentamicin to treat MRSA bacteremia and endocarditis showed a better overall success rate with daptomycin (44% vs 32.6%), but the difference was not statistically significant.

Gentamicin has some toxicity. Even short-term use (for the first 4 days of therapy) at low doses for bacteremia and endocarditis due to staphylococci has been associated with a higher rate of renal adverse events, including a significant decrease in creatinine clearance.[34]

Clindamycin or linezolid plus vancomycin is used to decrease toxin production by *S aureus*.[30]

While combination therapy with vancomycin is recommended in specific clinical situations, and the combinations are synergistic in vitro, information is lacking about clinical outcomes to support their use.

Tolerance to vancomycin can occur even if the MIC remains in the susceptible range

Don't use vancomycin when another drug would be better

Vancomycin continues to be the drug of choice in many circumstances, but in some instances its role is under scrutiny and another drug might be better.

Beta-lactams. In patients with infection due to methicillin-susceptible *S aureus*, failure rates are higher with vancomycin than with

beta-lactam therapy, specifically nafcillin.[35–37] Beta-lactam antibiotics are thus the drugs of choice for treating infection with beta-lactam-susceptible strains of *S aureus*.

Linezolid. In theory, linezolid's ability to decrease production of the *S aureus* Panton-Valentine leukocidin (PVL) toxin may be an advantage over vancomycin for treating necrotizing pneumonias. For the treatment of MRSA pneumonia, however, controversy exists as to whether linezolid is superior to vancomycin. An analysis of two prospective, randomized, double-blind studies of patients with MRSA pneumonia suggested that initial therapy with linezolid was associated with better survival and clinical cure rates,[38] but a subsequent meta-analysis did not substantiate this finding.[39] An additional comparative study has been completed, and analysis of the results is in progress.

Daptomycin, approved for skin and soft-tissue infections and bacteremias, including those with right-sided endocarditis, is a lipopeptide antibiotic with a spectrum of action similar to that of vancomycin.[40] Daptomycin is also active against many strains of vancomycin-resistant enterococci. As noted above, in the MRSA subgroup of the pivotal comparative study of treatment for *S aureus* bacteremia and endocarditis, the success rate for daptomycin-treated patients (44.4%) was better than that for patients treated with vancomycin plus gentamicin (32.6%), but the difference was not statistically significant.[33,41]

The creatine phosphokinase concentration should be monitored weekly in patients on daptomycin.[42] Daptomycin is inactivated by lung surfactant and should not be used to treat pneumonia.

Other treatment options approved by the US Food and Drug Administration (FDA) for MRSA infections include tigecycline (Tygacil), quinupristin-dalfopristin (Synercid), telavancin (Vibativ), and ceftaroline (Teflaro).

Tigecycline is a glycylcycline with bacteriostatic activity against *S aureus* and wide distribution to the tissues.[43]

Quinupristin-dalfopristin, a streptogramin antibiotic, has activity against *S aureus*. Its use may be associated with severe myalgias, sometimes leading patients to stop taking it.

Telavancin, recently approved by the FDA, is a lipoglycopeptide antibiotic.[44] It is currently approved to treat complicated skin and skin structure infections and was found to be not inferior to vancomycin. An important side effect of this agent is nephrotoxicity. A negative pregnancy test is required before using this agent in women of childbearing potential.

Ceftaroline, a fifth-generation cephalosporin active against MRSA, has been approved by the FDA for the treatment of skin and skin structure infections and community-acquired pneumonia.[45]

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