REVIEW

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Vancomycin-Associated Nephrotoxicity: Grave Concern or Death by Character Assassination?

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ABSTRACT

Vancomycin-associated nephrotoxicity was reported in 0% to 5% of patients in the 1980s. This has been confirmed by numerous clinical trials comparing novel anti–methicillin-resistant *Staphylococcus aureus* agents with vancomycin at the Food and Drug Administration-approved dosage of 1 g every 12 hours. Treatment failures of vancomycin in patients with methicillin-resistant *S. aureus* infections have been reported despite in vitro susceptibility. These failures have led to the use of vancomycin doses higher than those approved by the Food and Drug Administration. Higher doses are being administered to achieve goal vancomycin trough concentrations of 10 to 20 μg/mL recommended by several clinical practice guidelines endorsed by the Infectious Diseases Society of America. Recent studies suggest that increased rates of nephrotoxicity are associated with aggressive vancomycin dosing. These increased rates are confounded by concomitant nephrotoxins, renal insufficiency, or changing hemodynamics. These studies also have demonstrated that vancomycin's nephrotoxicity risk is minimal in patients without risk factors for nephrotoxicity. Clinicians unwilling to dose vancomycin in accordance with clinical practice guidelines should use an alternative agent because inadequate dosing increases the likelihood of selecting heteroresistant methicillin-resistant *S. aureus* isolates.

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Nephrotoxicity has been associated with vancomycin since its introduction in the early 1950s.[1] The first reports of vancomycin-associated nephrotoxicity were attributed to poor manufacturing processes. Early lots of the compound were called "Mississippi mud" because impurities produced a muddy, brown appearance. After purification methods were implemented, vancomycin was approved for clinical use by the US Food and Drug Administration in 1958. Vancomycin's approval by the Food and Drug Administration was based on 13 of 15 patients being treated successfully with vancomycin.[1] Lingering safety concerns, as well as the availability of methicillin and cephalothin, limited vancomycin use in early years. Vancomycin use began to increase after methicillin-resistant *Staphylococcus aureus* was first described in 1961.[2] Vancomycin-associated nephrotoxicity was reported in 0% to 5% of patients in the 1980s. Concomitant nephrotoxic agents increase rates of vancomycin-associated toxicity to as high as 35%.[3,4]

Vancomycin treatment failures in patients with methicillin-resistant *S. aureus* infections have been reported despite in vitro susceptibility.[5-7] These failures have led to the use of vancomycin dosages higher than those approved by the Food and Drug Administration (1 g every 12 hours). Higher doses are being administered to achieve vancomycin trough concentrations of 10 to 20 μg/mL recommended by Infectious Diseases Society of America-endorsed clinical prac-

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tice guidelines and consensus statement.[8-10] These recommendations are expert opinion based on pharmacokinetic and pharmacodynamic considerations that have not been validated clinically. Vancomycin trough concentrations less than 10 μg/mL are more likely to select heteroresistant vancomycin resistance in methicillin-resistant *S. aureus* isolates.[11] Because vancomycin dosages more than 2 g per day are not Food and Drug Administration approved, few studies have evaluated the effects of increased vancomycin dosing on nephrotoxicity. All prospective, randomized trials of new anti–methicillin-resistant *S. aureus* compounds have used the Food and Drug Administration-approved vancomycin dose. A recent prospective cohort and retrospective studies suggest increased rates of nephrotoxicity are associated with higher vancomycin doses or trough concentrations.[7,12,13] Defining the incidence and risk factors for nephrotoxicity with higher doses of vancomycin is paramount given the availability of alternative anti–methicillin-resistant *S. aureus* agents that are not nephrotoxic. Nephrotoxicity has been defined as follows: determined by the clinical investigator, an increase of 0.5 mg/dL or 50% or more baseline serum creatinine level in 2 consecutive tests, or a decrease in creatinine clearance to less than 50 mL/min or a decrease of more than 10 mL/min from a baseline creatinine clearance of less than 50 mL/min. This review will critique the current literature of vancomycin-associated nephrotoxicity and make practical methicillin-resistant *S. aureus* treatment recommendations regarding the treatment of methicillin-resistant *S. aureus* in light of the available evidence regarding vancomycin nephrotoxicity.

CLINICAL SIGNIFICANCE

- Nephrotoxicity with the vancomycin Food and Drug Administration-approved dosage (1 g every 12 hours) ranges from 0% to 5%.
- Increased nephrotoxicity rates have been observed with aggressive vancomycin dosing. These are likely due to selection biases. Patients receiving aggressive dosing are more likely to receive concomitant nephrotoxins and have other risk factors for nephrotoxicity.
- Vancomycin's nephrotoxic risk is minimal in patients without risk factors for nephrotoxicity. Clinicians unwilling to dose vancomycin in accordance with clinical practice guidelines should use an alternative agent.

VANCOMYCIN NEPHROTOXICITY IN RECENT PROSPECTIVE STUDIES

Numerous clinical trials of anti–methicillin-resistant *S. aureus* medications have used vancomycin 1 g every 12 hours as the comparator (Table).[14-24] Most studies did not state a target vancomycin trough concentration and allowed vancomycin dosing adjustments according to the local standard of care. Two studies evaluating nosocomial pneumonia targeted vancomycin trough concentrations of 5 to 10 μg/mL.[25] These clinical trials confirm that nephrotoxicity occurs in a small percentage of patients receiving vancomycin at Food and Drug Administration-approved doses. Studies analyzing patients with complicated skin and skin structure infections documented nephrotoxicity rates to be less than 5%.[15-17,20] More patients receiving vancomycin developed nephrotoxicity compared with tigecycline in one study (3.8% vs 3.4%, $P = .005$).[16] Jaksic et al[23] assessed the efficacy of linezolid compared with vancomycin of febrile neutropenic patients with cancer determined that significantly more patients treated with vancomycin developed renal failure (0.3% vs 2.3%, $P = .04$).

Few randomized controlled trials using vancomycin for nosocomial pneumonia have reported nephrotoxicity rates. Rubinstein and colleagues[19] observed nephrotoxicity in less than 1% of patients. Another trial described one case of nephrotoxicity in the vancomycin treatment group that resulted in the progression of acute renal failure.[22] A meta-analysis of prospective, randomized controlled trials comparing linezolid with vancomycin or teicoplanin found no difference in nephrotoxicity rates.[26] Nephrotoxicity seems to be an uncommon event in these studies given the sparse reporting of nephrotoxicity.

One randomized controlled trial has evaluated daptomycin versus standard therapy (vancomycin or penicillinase-resistant penicillin ± gentamicin) in patients with *S. aureus* bacteremia and endocarditis.[24] The trial reported higher rates of nephrotoxicity with standard therapy (18.1% vs 6.7%, $P = .009$). These nephrotoxicity rates are higher than other vancomycin comparator studies and may be explained through several rationales. Infective endocarditis can independently have deleterious effects on the kidneys. Potential effects include renal infarction by septic emboli, vasculitic glomerulonephritis, and acute interstitial nephritis.[27] It is not possible to identify the nephrotoxicity rate for vancomycin because vancomycin specific data were not reported. The standard treatment arm also contained gentamicin, a known nephrotoxin. The study defined nephrotoxicity as a decrease in creatinine clearance to less than 50 mL/min or a decrease of more than 10 mL/min from a baseline creatinine clearance of less than 50 mL/min. This definition is inconsistent with studies evaluating vancomycin-associated nephrotoxicity and may have influenced higher nephrotoxicity rates in both groups. Therefore, the higher rates of nephrotoxicity reported could be a result of the disease-related effects, the drug effects, or the definition of nephrotoxicity.

The use of higher vancomycin doses without data from prospective controlled trials has raised new concerns regarding the risk of nephrotoxicity. A prospective cohort study was conducted to determine the effect of aggressive

Table Summary of Nephrotoxicity Incidence in Recent Studies in Patients Treated for Methicillin-resistant *Staphylococcus aureus*

Reference	Design	Patients	Intervention	Nephrotoxicity
Arbeit et al[15]	Prospective, multicenter, double-blind, randomized controlled trial	Complicated skin and skin-stricture infections N = 1092	Daptomycin IV 4 mg/kg every 24 h vs vancomycin IV 1 g every 12 h or penicillinase-resistant penicillin 4-12 g every 24 h	2.2% vs 2.7% (P = NS)
Ellis-Grosse et al[16]	Prospective, multicenter, double-blind, randomized controlled trial Analysis of 2 phase 3 studies	Complicated skin and skin-stricture infections N = 833	Tigecycline IV 100 mg ×1, then 50 mg every 12 h vs vancomycin IV 1 g every 12 h plus aztreonam IV 2 g every 12 h	3.4% vs 3.8% (P = .005)
Weigelt et al[17]	Prospective, multicenter, open-label, randomized controlled trial	Complicated skin and skin-stricture infections N = 1180	Linezolid IV 600 mg every 12 h vs vancomycin IV or PO 1 g every 12 h	Not reported
Wilcox et al[20]	Prospective, multicenter, open label, randomized controlled trial	Catheter-related bloodstream infections and complicated skin and skin-stricture infections N = 726	Linezolid 600 mg every 12 h vs vancomycin IV 1 g every 12 h	0.8% vs 2.5% (P = NS)
Fagon et al[18]	Prospective, multicenter, open-label, randomized controlled trial	Nosocomial pneumonia N = 298	Quinupristin/dalfopristin IV 7.5 mg/kg every 8 h vs vancomycin 1 g every 12 h Each with aztreonam IV 1-2 g every 8 h	Not reported
Rubinstein et al[19]	Prospective, multicenter, double-blind, randomized controlled trial	Nosocomial pneumonia N = 396	Linezolid IV 600 mg every 12 h vs vancomycin IV 1 g every 12 h Each with aztreonam IV 1-2 g every 8 h	Not reported
Wunderink et al[21]	Prospective, multicenter, double-blind, randomized controlled trial	Nosocomial pneumonia Gram-positive N = 623	Linezolid IV 600 mg every 12 h vs vancomycin IV 1 g every 12 h Each with aztreonam IV 1-2 8 h	Linezolid: 1 patient with kidney failure Vancomycin: 2 patients with kidney failure
Wunderink et al[22]	Prospective, multicenter, open-label	Methicillin-resistant *Staphylococcus aureus* ventilator-associated pneumonia N = 50	Linezolid IV 600 mg every 12 h vs vancomycin IV 1 g every 12 h	Not reported
Hidayat et al[7]	Prospective, cohort study	Nosocomial methicillin-resistant *S. aureus* infections Comparing high trough (15-20 μg/mL) vs low trough (<15 μg/mL) N = 95	Vancomycin IV dosed to achieve trough concentration of 4 to 5 times the minimum inhibitory concentration of the methicillin-resistant *S. aureus* strain	12% vs 0% (P = .01)
Jeffres et al[12]	Retrospective, cohort study	Methicillin-resistant *S. aureus* healthcare-associated pneumonia N = 94	Vancomycin IV 30 mg/kg/d in 2 divided doses to achieve a trough concentration of 15-20 μg/mL	42.6%
Fowler et al[24]	Prospective, open-label, randomized controlled trial	Bacteremia and endocarditis N = 235	Daptomycin IV 6 mg/kg every 24 h (left-sided endocarditis received gentamicin 1 mg/kg every 8 h) vs vancomycin IV 1 g every 12 h or penicillinase-resistant penicillin 2 g every 4 h plus gentamicin 1 mg/kg every 8 h	6.7% vs 18.1% (P = .009)
Lodise et al[13]	Retrospective cohort study	Gram-positive infection Comparing vancomycin high dose IV (n = 26) vs standard dose IV (n = 220) vs linezolid (n = 45) N = 291	Vancomycin high dose IV ≥ 4 g/d vs standard dose IV < 4 g/d vs linezolid	34.6% vs 9.7% vs 2.4% (P = .001)
Stevens et al[14]	Prospective, multicenter, open-label, randomized controlled trial	Definitive or empiric methicillin-resistant *S. aureus* infection N = 460	Linezolid IV 600 mg every 12 h vs vancomycin IV 1 g every 12 h Each with aztreonam or gentamicin per physician	0% vs 1% (P = .139)
Jaksic et al[23]	Prospective, multicenter, double blind, randomized controlled trial	Patients with cancer with febrile neutropenia and proven or suspected Gram-positive bacterial infection N = 605	Linezolid IV 600 mg every 12 h vs vancomycin IV 1 g every 12 h Concomitant Gram-negative and antifungal therapy was allowed with each group.	0.3% vs 2.3% (P = .04)

IV = intravenous; NS = not significant; PO = by mouth.

vancomycin dosing on nephrotoxicity.[7] Patients with methicillin-resistant *S. aureus* infection were treated with vancomycin to attain trough concentrations of 15 μg/mL or greater. The investigators defined nephrotoxicity as an increase of 0.5 mg/dL or 50% or more from the baseline serum creatinine level in 2 consecutive tests. All 11 patients

(11.6%) who developed nephrotoxicity had vancomycin trough concentrations of 15 μg/mL or more. Higher mean vancomycin trough concentrations (19 vs 15.8 μg/mL; $P = .03$) and longer durations of therapy (17 vs 11 days; $P = .004$) were associated with nephrotoxicity. Ten of the 11 patients who developed nephrotoxicity received concomitant nephrotoxic agents. Four of these patients also had preexisting renal disease. Only 2% of patients who did not receive concomitant nephrotoxic agents developed nephrotoxicity. It is difficult to decipher whether the elevated vancomycin concentrations were a cause of nephrotoxicity or elevated as a result of nephrotoxicity.

RETROSPECTIVE STUDIES OF VANCOMYCIN NEPHROTOXICITY

Greater emphasis has been placed on retrospective data because of the deficit of prospective studies evaluating nephrotoxicity with vancomycin dosages greater than 2 g per day (Table 1).[12,13] The following studies defined nephrotoxicity as an increase in serum creatinine of 0.5 mg/dL or a more than 50% increase from baseline serum creatinine. This definition is based on a retrospective study that noted increases in serum creatinine of 0.5 mg/dL or more in hospitalized patients to be associated with a 6.5-fold increase in the odds of death, a 3.5-day increase in length of stay, and approximately $7500 dollars in excess hospital costs.[28] No study has evaluated the effect of vancomycin-associated nephrotoxicity on these outcomes.

Jeffres et al[12] evaluated patients with methicillin-resistant *S. aureus* health-care associated pneumonia (n = 94) and observed that 42.6% of patients developed nephrotoxicity while receiving vancomycin. Patients with mean vancomycin trough concentrations of 15 μg/mL or more and those who received vancomycin for 14 days or more were identified as having an increased risk of nephrotoxicity. Patients who experienced nephrotoxicity also had significantly higher Acute Physiology and Chronic Health Evaluation II scores. The 2 groups might not have been comparable because higher Acute Physiology and Chronic Health Evaluation II scores are associated with an increased severity of illness. Patients who developed nephrotoxicity also were more likely to have recent vasopressor use and have a blood urea nitrogen to serum creatinine ratio greater than 20. Both of these factors are markers of hemodynamic instability and might independently cause renal injury.

Lodise et al[13] reported significantly increased nephrotoxicity rates in patients receiving 4 g or more per day compared with those receiving less than 4 g vancomycin per day (34.6% vs 10.9%, $P = .001$).[13] Linezolid was used as a second control with 6.7% of patients developing nephrotoxicity. At baseline, significantly more patients in the nephrotoxic group were intensive care unit residents and had significantly lower creatinine clearance (60 vs 72.5 mL/min $P = .02$). The study also identified a relationship with high trough concentrations of vancomycin and nephrotoxicity (18.5 ± 7.4 vs 12 ± 4.9; $P = .001$). Patients receiving 4 g or more of vancomycin per day may represent 2 distinct populations. The investigators did not report what percentage of patients received weight-based doses in accordance with Infectious Diseases Society of America-endorsed guidelines. Only 5 of the 26 patients receiving 4 g or more per day weighed more than 100 kg. This means that most patients receiving 4 g or more per day received vancomycin dosages ≥ 40 mg/kg/d, which is significantly higher than the guideline-recommended 30 mg/kg/d. On the other hand, the few patients weighing more than 100 kg may have received less than guideline-recommended doses given the large standard deviation associated with patient weight.

A retrospective study observed that 10 of 35 patients (29%) who received ≥ 5 days of vancomycin (target trough concentrations of 15-20 μg/mL) developed nephrotoxicity.[29] Nine of the 10 patients who developed nephrotoxicity received concomitant nephrotoxic agents. Therapy was continued in 7 of the 10 patients without further decline in renal function. Five of these 7 patients had their serum creatinine concentrations return to baseline by discharge or at their follow-up visit. Although this study is limited by its small sample size and confounding nephrotoxins, it suggests that discontinuation of high-dose vancomycin in the setting of nephrotoxicity might not be required.

DISCUSSION

Although vancomycin-associated nephrotoxicity has been studied in humans and animals, its exact mechanism remains to be elucidated. Le Moyec et al[30] assessed aminoglycoside and glycopeptide renal toxicity in intensive care patients. The study concluded that toxicity from vancomycin and aminoglycosides are not confined to the proximal tubules but might involve the medullary region of the nephron. However, the authors did not specify which patients were receiving concomitant or monotherapy. A toxicogenomic study analyzing responses to high-dose vancomycin in mice reported gene expression changes in the inflammation and complement pathway response. These changes suggest a link between vancomycin-induced nephrotoxicity and complement activation.[31] Another proposed mechanism is that vancomycin exposure increases cell proliferation in the renal proximal tubule epithelial cells. Stimulation of oxygen consumption and elevated cellular adenosine triphosphate concentrations supports the role of vancomycin as a cause of oxidative phosphorylation, which produces oxygen free radicals leading to the injury.[32] A study using rat models determined oxidative stress in the renal proximal tubule cells is the underlying pathogenesis of nephrotoxicity.[33,34] The authors concluded that administration of antioxidants might have a role in preventing vancomycin-associated nephrotoxicity. In humans, nephrotoxicity resulting from vancomycin monotherapy has been shown to be reversible at typical doses and even higher dose regimens.[29,35]

It is difficult to determine the exact nephrotoxic potential of higher vancomycin doses because of the paucity of pro-

spective, randomized, controlled trials. Only one prospective cohort study has assessed higher vancomycin dosing regimens and nephrotoxicity.[7] This study's major limitation was that most patients who developed nephrotoxicity received concomitant nephrotoxins. Observational data analyzing higher vancomycin doses and nephrotoxicity are compromised by the presence of a selection bias.[12,13] Patients with a greater severity of illness and an increased baseline risk of nephrotoxicity are more likely to receive aggressive vancomycin dosing. Selection biases make the previous studies inadequate to accurately identify the rate of nephrotoxicity associated with higher vancomycin dosing. This conclusion is in agreement with the American Society of Health Systems Pharmacists, Infectious Diseases Society of America, and Society of Infectious Diseases Pharmacists consensus statement acknowledging that there is limited evidence to suggest an association between nephrotoxicity and a specific vancomycin concentration.[10] The existing literature provides insight to patients at an increased risk of nephrotoxicity (eg, baseline renal insufficiency, concomitant nephrotoxic drugs) that warrant close monitoring or selection of an alternative agent.

Alternative anti–methicillin-resistant *S. aureus* medications, such as linezolid, daptomycin, and tigecycline, are not considered to cause nephrotoxicity. It is important to consider all aspects of drug safety and efficacy as opposed to only evaluating nephrotoxicity. Linezolid use is associated with myelosuppression and neuropathies. Thrombocytopenia and anemia occur in approximately 6% to 7% of patients and is more common after 2 weeks of therapy. Leukopenia occurs in approximately 3% to 4% of patients. These rates are similar to comparator drugs. Linezolid also is a weak monoamine oxidase inhibitor that can cause serotonin syndrome when co-administered with commonly prescribed medications, such as serotonin reuptake inhibitors or tricyclic antidepressants.[36] Patients with febrile neutropenia treated with linezolid had significantly longer time to absolute neutrophil count recovery compared with vancomycin.[23] The Food and Drug Administration recently issued an alert regarding the use of linezolid in patients with intravascular catheter-related bloodstream.[20,37] Specifically, patients with a Gram-negative infection (with or without Gram-positive organisms) or no pathogen at baseline had an increased likelihood of mortality. Therefore, empiric use of linezolid against catheter-related infections may result in worse outcomes. The reason for this is currently unknown. Potoski et al[38] observed the clonal spread of linezolid-resistant coagulase-negative staphylococci in 25 patients. The authors postulated that linezolid's selection pressure also could cause the clonal spread of linezolid-resistant methicillin-resistant *S. aureus*.

Myopathy is the hallmark adverse event during daptomycin therapy, occurring in less than 1% of patients. Therefore, creatine phosphokinase levels should be monitored weekly. Creatinine phosphokinase should be monitored more frequently in patients with renal insufficiency or patients receiving 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors because of the increased risk of myopathic effects. In addition, daptomycin is bound by pulmonary surfactant and is not effective against pneumonia.[36] Fowler et al[24] observed that daptomycin mean inhibitory concentrations increased to the nonsusceptible range in 6 of 19 patients with persistent or relapsing methicillin-resistant *S. aureus* infection. All 6 patients previously received vancomycin. This clinical association between vancomycin exposure and daptomycin heteroresistance in *S. aureus* has been confirmed in the laboratory.[39]

Tigecycline is associated with significant nausea and vomiting.[36] Tigecycline might not be an optimal agent for bacteremia or urinary tract infections because of low serum and urine concentrations. Additional data are needed before tigecycline is routinely used for these infections. Quinupristin/dalfopristin is not widely used because of a significant number of patients experiencing myalgias or arthralgias.[36] A central line is required for administration because of the high incidence of infusion-related reactions. Quinupristin/dalfopristin also is an inhibitor and substrate of cytochrome P450 3A4.

Although newer anti–methicillin-resistant *S. aureus* medications show great promise, none has the versatility to replace vancomycin in all situations given the currently available literature. Vancomycin is well tolerated and is used empirically for any type of methicillin-resistant *S. aureus* infection. The literature analyzing anti–methicillin-resistant *S. aureus* medications in patients with serious infections is lacking. Only daptomycin and linezolid have been prospectively evaluated for use in patients with bacteremia.[20,24] The daptomycin study is the only prospective study evaluating a novel anti–methicillin-resistant *S. aureus* medication for endocarditis. Linezolid use for endocarditis is limited to case reports.[40] Newer anti–methicillin-resistant *S. aureus* medications have only limited data for surgical prophylaxis or use in patients with osteomyelitis or meningitis.

Vancomycin remains a viable option for the treatment of methicillin-resistant *S. aureus* infections;[14-21,23,24] therefore it is imperative to conduct studies evaluating the true incidence of nephrotoxicity with vancomycin dosing regimens used to achieve the target trough concentrations in many Infectious Diseases Society of America-endorsed guidelines. Determining the mechanism of vancomycin-associated nephrotoxicity is important to potentially develop methods to prevent this adverse event.

Several pharmacokinetic studies have demonstrated that vancomycin should be dosed on actual body weight.[41] This information has been incorporated into clinical practice guidelines.[8-10] The Food and Drug Administration has not evaluated this information for inclusion in vancomycin's prescribing information. Vancomycin has been available as a generic product for decades. Conducting the required studies for inclusion of new pharmacokinetic-pharmacodynamic guided dosing regimens is not fiscally sound for

generic drug manufacturers. This mismatch between clinical practice guidelines and Food and Drug Administration-approved prescribing information has resulted in patients receiving doses lacking a rigorous evaluation of efficacy and safety. Incorporating new pharmacokinetic and pharmacodynamic concepts for generic medications is imperative in infectious diseases given the lack of novel agents being developed. Mechanisms are needed to hasten the safe and effective incorporation of advances requiring non-Food and Drug Administration-approved dosing regimens.

CONCLUSIONS

Increased vancomycin trough concentrations have been recommended based on expert opinion by several Infectious Diseases Society of America-endorsed guidelines. Three published studies have suggested that there is a significant association between increased vancomycin trough concentrations and nephrotoxicity. There are currently insufficient data to identify the true incidence of nephrotoxicity associated with aggressive vancomycin dosing. Limitations of the existing data include the following: The available data are observational in nature; there is a lack of prospective, randomized, controlled trials; and there is difficulty in discerning whether vancomycin concentrations are a cause of nephrotoxicity or are only increased because of nephrotoxicity. An ongoing prospective, randomized controlled trial assessing linezolid versus vancomycin weight-based dosage of 30 mg/kg/d will hopefully offer further information on the use of high-dose vancomycin in patients.[42] In the meantime, studies evaluating the effect of vancomycin dose (milligrams/kilogram) on the incidence of nephrotoxicity would provide a better measure of evaluating vancomycin-associated nephrotoxicity than those evaluating vancomycin trough concentrations.

Alternative anti–methicillin-resistant *S. aureus* therapies might be without risk of nephrotoxicity, but are not benign. We recommend that vancomycin remain a first-line treatment option for patients with known or suspected methicillin-resistant *S. aureus* infections until further data evaluating vancomycin-associated nephrotoxicity are available. Data have shown that most cases of nephrotoxicity occur in patients with additional risk factors, for example: baseline renal insufficiency (creatinine clearance ≤ 50 mL/min), changing hemodynamics (requiring vasopressors, blood urea nitrogen: serum creatinine > 20), and concomitant nephrotoxins. Patients with these risk factors who receive vancomycin should be monitored closely for the development of nephrotoxicity. Alternative anti–methicillin-resistant *S. aureus* therapies might be considered for patients with these additional risk factors. Providers who are uncomfortable using weight-based dosing for patients receiving vancomycin due to nephrotoxicity concerns should use an alternative agent because inadequate dosing increases the likelihood of selecting heteroresistant methicillin-resistant *S. aureus* isolates.

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