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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 0-5% of patients in the 1980s. This has been confirmed by numerous clinical trials comparing novel anti-methicillin-resistant *Staphylococcus aureus* (MRSA) agents to vancomycin at the Food and Drug Administration (FDA) approved dose of 1 g q12h. Treatment failures of vancomycin in patients with MRSA infections have been reported despite in vitro susceptibility. These failures have led to the utilization of vancomycin doses higher than those approved by the FDA. Higher doses are being administered to achieve goal vancomycin trough concentrations of 10-20 μg/mL recommended by several Infectious Diseases Society of America (IDSA) endorsed clinical practice guidelines. Recent studies suggest that increased rates of nephrotoxicity are associated with aggressive vancomycin dosing. These increased rates are confounded by concomitant nephrotoxins, renal insufficiency, and/or changing hemodynamics. These studies have also 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 since inadequate dosing increases the likelihood of selecting heteroresistant MRSA isolates.

Keywords

vancomycin; nephrotoxicity; adverse events; dose; therapeutic drug monitoring

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Introduction

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 (FDA) in 1958. Vancomycin's approval by the FDA was based on 13 out 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* (MRSA) was first described in 1961.[2] Vancomycin-associated nephrotoxicity was reported in 0-5% of patients in the 1980's. Concomitant nephrotoxic agents increase rates of vancomycin-associated toxicity to as high as 35%.[3, 4]

Vancomycin treatment failures in patients with MRSA infections have been reported despite in vitro susceptibility.[5-7] These failures have led to the utilization of vancomycin doses higher than those approved by the FDA (1 g q 12h). Higher doses are being administered to achieve vancomycin trough concentrations of 10-20 μg/mL recommended by Infectious Diseases Society of America (IDSA) endorsed clinical practice 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 < 10 μg/mL are more likely to select heteroresistant vancomycin resistance in MRSA isolates.11 Since vancomycin doses above 2 grams per day are not FDA approved, few studies have evaluated the effects of increased vancomycin dosing on nephrotoxicity. All prospective, randomized trials of new anti-MRSA compounds have utilized the FDA approved vancomycin dose. A recent prospective cohort and retrospective studies suggest increased rates of nephrotoxicity are associated with higher vancomycin doses and/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-MRSA agents that are not nephrotoxic. Nephrotoxicity has been defined as: 1) determined by the clinical investigator, 2) an increase of 0.5 mg/dL or 50% or more baseline serum creatinine (SCr) level in two consecutive tests, or 3) a decrease in creatinine clearance (CrCl) to < 50 mL/min or a decrease of > 10mL/min from a baseline CrCl of < 50 mL/min. This review will critique the current literature of vancomycin-associated nephrotoxicity and make practical MRSA treatment recommendations regarding the treatment of MRSA in light of the available evidence regarding vancomycin nephrotoxicity.

Vancomycin Nephrotoxicity in Recent Prospective Studies

Numerous clinical trials of anti-MRSA medications have utilized vancomycin 1 g q12h as the comparator (Table 1).[14-24] Most studies did not state a target vancomycin trough concentration or allow vancomycin adjustments according to the local standard of care. Two studies evaluating nosocomial pneumonia targeted vancomycin trough concentrations of 5-10 mcg/mL.25 These clinical trials confirm that nephrotoxicity occurs in a small percentage of patients receiving vancomycin at FDA approved doses. Studies analyzing patients with complicated skin and skin structure infections (cSSSI) documented nephrotoxicity rates to be < 5%.[15-17, 20] More patients receiving vancomycin developed nephrotoxicity compared to tigecycline in one study (3.8% vs 3.4% p=0.005).16 Jaksic et al. 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=0.04).23

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

One randomized controlled trial has evaluated daptomycin vs. 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=0.009). 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 as vancomycin specific data were not reported. The standard treatment arm also contained gentamicin, a known nephrotoxin. The study defined nephrotoxicity as a decrease in CrCl to < 50 mL/min or a decrease of > 10 mL/min from a baseline CrCl of < 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 disease related effects, drug effects, and/or the definition of nephrotoxicity.

The utilization 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 vancomycin dosing on nephrotoxicity.[7] Patients with MRSA infection were treated with vancomycin to attain trough concentrations > 15 μg/mL. The investigators defined nephrotoxicity as an increase of 0.5 mg/dL or 50% or more from the baseline serum creatinine (SCr) level in two consecutive tests. All eleven patients (11.6%) that developed nephrotoxicity had vancomycin trough concentrations ≥ 15 μg/mL. Higher mean vancomycin trough concentrations (19 vs 15.8 μg/mL; p=0.03) and longer durations of therapy (17 vs 11 days; p=0.004) were associated with nephrotoxicity. Ten of the 11 patients who developed nephrotoxicity received concomitant nephrotoxic agents. Four of these patients also had pre-existing 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 due to the deficit of prospective studies evaluating nephrotoxicity with vancomycin doses greater than 2 grams per day (Table 1).[12, 13] The following studies defined nephrotoxicity as an increase in SCr of 0.5 mg/dL or a > 50% increase from baseline SCr. This definition is based on a retrospective study which noted increases in SCr ≥ 0.5 mg/dL in hospitalized patients to be associated with 6.5 fold increase in the odds of death, a 3.5 day increase in length of stay, and near 7,500 dollars excess hospital costs.[28] No study has evaluated the effect of vancomycin-associated nephrotoxicity on these outcomes.

Jeffres et al. evaluated patients with MRSA health-care associated pneumonia (n = 94) and observed that 42.6% of patients developed nephrotoxicity while receiving vancomycin.[12] Patients with mean vancomycin trough concentrations ≥ 15 μg/mL and those who received vancomycin for ≥ 14 d were identified as having an increased risk of nephrotoxicity. Patients

that experienced nephrotoxicity also had significantly higher Acute Physiology and Chronic Health Evaluation II (APACHE II) scores. The two groups may not have been comparable since higher APACHE II scores are associated with an increased severity of illness. Patients who developed nephrotoxicity were also more likely to have recent vasopressor use and have blood urea nitrogen (BUN) to SCr ratio > 20. Both of these factors are markers of hemodynamic instability and may independently cause renal injury.

Lodise et al. reported significantly increased nephrotoxicity rates in patients receiving ≥ 4 g per day compared with those receiving < 4 g vancomycin per day (34.6% vs. 10.9%, p=0.001).[13] Linezolid was utilized 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 CrCl (60 vs 72.5 ml/min p=0.02). The study also identified a relationship with high trough concentrations of vancomycin and nephrotoxicity (18.5 ± 7.4 vs 12 ± 4.9 p=0.001). Patients receiving ≥ 4 grams of vancomycin per day may represent two distinct populations. The investigators did not report what percentage of patients received weight-based doses in accordance with IDSA endorsed guidelines. Only 5 of the 26 patients receiving ≥ 4 grams per day weighed greater than 100 kilograms. This means that most patients receiving ≥ 4 grams per day received vancomycin doses ≥ 40 mg/kg/day, which is significantly higher than the guideline-recommended 30 mg/kg/day. On the other hand, the few patients weighing more than 100 kilograms may have received less than guideline-recommended doses given the large standard deviation associated with patient weight.

A retrospective study observed that 10 out 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 may 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. assessed aminoglycoside and glycopeptide renal toxicity in intensive care patients.30 The study concluded that toxicity from vancomycin and/or aminoglycosides are not confined to the proximal tubules, but may involve the medullary region of the nephron. However, the authors did not specify which patients were on 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 (ATP) 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 may have a role in preventing vancomycin-associated nephrotoxicity. Nephrotoxicity in humans due to 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 due to the paucity of prospective, 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 an American Society of Health Systems Pharmacists (ASHP), the Infectious Disease Society of America (IDSA), and Society of Infectious Diseases Pharmacists (SIDP) 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 (e.g. baseline renal insufficiency, concomitant nephrotoxic drugs) that warrant close monitoring or selection of an alternative agent.

Alternative anti-MRSA 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. Thrombocyopenia and anemia occur in approximately 6-7% of patients and is more common after 2 weeks of therapy. Leukopenia occurs in approximately 3-4% of patients. These rates are similar to comparator drugs. Linezolid is also a weak monoamine oxidase inhibitor which 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 FDA 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. observed the clonal spread of linezolid-resistant coagulase-negative staphylococci in 25 patients. The authors postulated that linezolid's selection pressure could also cause the clonal spread of linezolid-resistant MRSA.[38]

Myopathy is the hallmark adverse event during daptomycin therapy, occuring in <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 HMBCoA reductase inhibitors due to the increased risk of myopathic effects. Additionally, daptomycin is bound by pulmonary surfactant and is not effective against pneumonia.[36] Fowler et al. observed that daptomycin MICs increased to the nonsusceptible range in 6 of 19 patients with persistent or relapsing MRSA infection. All six patients previously received vancomycin.[24] 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 may not be an optimal agent for bacteremia or urinary tract infections due to low serum and urine concentrations. Additional data are needed before tigecycline is routinely used for these infections. Quinupristin/dalfopristin is not widely used due to a significant number of patients experiencing myalgias and/or arthralgias.[36] A central line is required for administration due to the high incidence of infusion-related reactions. Quinupristin/dalfopristin is also an inhibitor and substrate of cytochrome P450 3A4.

While newer anti-MRSA 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 MRSA infection. The literature analyzing anti-MRSA 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-MRSA medication for endocarditis. Linezolid use for endocarditis is limited to case reports.[40] Newer anti-MRSA medications only have limited data for surgical prophylaxis or use in patients with osteomyelitis or meningitis.

Vancomycin remains a viable option for the treatment of MRSA infections.[14-21, 23, 24] Therefore, it is imperative to conduct studies evaluating the true incidence of nephrotoxicity with vancomycin dosing regimens utilized to achieve the target trough concentrations in many IDSA 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 FDA 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 FDA 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-FDA approved dosing regimens.

Conclusion

Increased vancomycin trough concentrations have been recommended based on expert opinion by several IDSA endorsed guidelines. Three published studies have suggested that there is a significant association between increased vancomycin trough concentrations and nephrotoxicity. There is currently insufficient data to identify the true incidence of nephrotoxicity associated with aggressive vancomycin dosing. Limitations of the existing data include: 1) the available data is observational in nature, 2) the lack of prospective, randomized, controlled trials, and 3) the 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 dosing of 30 mg/kg/day 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 (mg/kg) on the incidence of nephrotoxicity would provide a better measure of evaluating vancomycin-associated nephrotoxicity than those evaluating vancomycin trough concentrations.

Alternative anti-MRSA therapies may 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 MRSA infections until further data evaluating vancomycin-associated nephrotoxicity are available. Data have shown that most cases of nephrotoxicity occur in patients who have additional risk factors including those with baseline renal insufficiency (CrCl $\leq$ 50 ml/min), changing hemodynamics (requiring vasopressors, BUN:SCr > 20), and with concomitant nephrotoxins. Patients with these risk factors who receive vancomycin should be

monitored closely for the development of nephrotoxicity. Alternative anti-MRSA therapies may 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 utilize an alternative agent as inadequate dosing increases the likelihood of selecting heteroresistant MRSA isolates.

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Table 1

Summary of Nephrotoxicity Incidence in Recent Studies in Patients Treated for MRSA

Reference	Design	Patients	Intervention	Nephrotoxicity
Arbeit (2004)[15]	P, MC, DB, RCT	cSSSIs N=1092	Daptomycin IV 4 mg/kg q24h vs Vancomycin IV 1 g q12h or PRP 4-12 g q24h	2.2% vs 2.7% (p=ns)
Ellis-Grosse (2005)[16]	P, MC, DB, RCT Analysis of two phase 3 studies	cSSSIs N=833	Tigecycline IV 100 mg x1, then 50 mg q12h vs Vancomycin IV 1 g q12h plus Aztreonam IV 2 g q12h	3.4% vs 3.8% (p=0.005)
Weigelt (2005)[17]	P, MC, OL, RCT	cSSSIs N=1180	linezolid IV 600 mg q12h vs Vancomycin IV or PO 1 g q12h	Not reported
Wilcox (2009)[20]	P, MC, OL, RCT	Catheter-related blood stream infections and cSSSIs N=726	Linezolid 600 mg q12h vs Vancomycin IV 1 g q12h	0.8% vs 2.5% (p=ns)
Fagon (2000)[18]	P, MC, OL, RCT	Nosocomial pneumonia N=298	Quinupristin/dalfopristin IV 7.5 mg/kg q8h vs Vancomycin 1 g q12h Each with aztreonam IV 1-2g8h	Not reported
Rubinstein (2001) [19]	P, MC, DB, RCT	Nosocomial pneumonia N=396	Linezolid IV 600 mg q12h vs Vancomycin IV 1 g q12h Each with aztreonam IV 1-2g8h	Not reported
Wunderink (2003)[21]	P, MC, DB, RCT	Nosocomial pneumonia Gram-positive N=623	Linezolid IV 600 mg q12h vs Vancomycin IV 1 g q12h Each with aztreonam IV 1-2 8h	Linezolid: One patient with kidney failure Vancomycin: Two patients with kidney failure
Wunderink (2008)[22]	P, MC, OL	MRSA VAP N=50	Linezolid IV 600 mg q12h vs Vancomycin IV 1 g q12h	Not reported
Hidayat[7] (2006)	P, C	Nosocomial MRSA 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 MIC of the MRSA strain	12% vs 0% (p=0.01)
Jeffres (2007)[12]	R, C	MRSA HCAP N=94	Vancomycin IV 30 mg/kg/day in 2 divided doses to achieve a	42.6%

Reference	Design	Patients	Intervention	Nephrotoxicity
			trough concentration of 15-20 μg/mL	
Fowler (2006)[24]	P, OL, RCT	Bacteremia and endocarditis N=235	Daptomycin IV 6 mg/kg q24h (left-sided endocarditis received gentamicin 1 mg/kg q8h) vs vancomycin IV 1 g q12h or PRP 2 g q4h plus gentamicin 1mg/kg q8h	6.7% vs 18.1% (p=0.009)
Lodise (2008)[13]	R, C	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 per day vs standard dose IV < 4 g per day vs linezolid	34.6% vs 9.7% vs 2.4% (p=0.001)
Stevens (2002)[14]	P, MC, OL, RCT	Definitive or empiric MRSA infection N= 460	Linezolid IV 600 mg q12h vs Vancomycin IV 1 g q12h Each with aztreonam or gentamicin per physician	0% vs 1% (p=0.139)
Jaksic[23] (2006)	P, MC, DB, RCT	Cancer patients with febrile neutropenia and proven or suspected gram-positive bacterial infection N=605	Linezolid IV 600 mg q12h vs Vancomycin IV 1 g q12h Concomitant gram-negative and antifungal therapy was allowed with each group	0.3% vs 2.3% (p=0.04)

P= prospective; R= retrospective; RCT= randomized controlled trial; C= cohort study; DB= double-blind; MC= multicenter; OL= open-label; cSSSIs= complicated skin and skin-stricture infections; HCAP = Healthcare associated pneumonia PRP= penicillinase-resistant penicillin; MIC= minimum inhibitory concentration; MRSA= Methicillin resistant *Staphylococcus aureus*; VAP= ventilator associated pneumonia