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Introduction

Vancomycin is the drug of choice for methicillin-resistant *Staphylococcus aureus* (MRSA)[1] but has been associated with significant nephrotoxicity. It remains uncertain, however, to what extent vancomycin is directly responsible. Herein, we critically examine relevant available data in adult patients. We review the pharmacokinetics/pharmacodynamics of vancomycin metabolism and discuss efficacy and safety data. The pathophysiology of vancomycin nephrotoxicity is considered. Risk factors for AKI development are enumerated, and suggestions for practice and further research are given.

Vancomycin has been plagued with concerns about nephrotoxicity since its approval in 1958. Initial preparations were termed "Mississippi mud" and had significant impurities considered the major reason for the nephrotoxicity. Through improved purification procedures, current preparations contain approximately 90 to 95% vancomycin B (the active moiety). The rate of nephrotoxicity with use of modern preparations varies in the literature, with the incidence ranging from as low as 0% in the absence of concurrent nephrotoxins to over 40%[2]. Unfortunately, the majority of studies assessing nephrotoxicity are retrospective, often lacking a control group, and are typically subject to confounding by indication and other biases, as many of the patients are critically ill and have other potential reasons for kidney injury.

Numerous potential risk factors for development of acute kidney injury (AKI) while receiving parenteral vancomycin therapy have been ascertained. Some factors are directly related to vancomycin exposure, such as total daily dose, duration of therapy, method of administration, trough level, and area-under-the-concentration-versus-time (AUC) curve. Others are patient related, including obesity, preexisting kidney disease, severity of illness, and receipt of concurrent nephrotoxins.

Overall, there is only moderate quality evidence linking vancomycin to renal injury. Sinha Ray et al. performed a systematic review and meta-analysis restricted only to randomized controlled trials

(RCTs) and cohort studies that compared vancomycin to another non-glycopeptide antibiotic. Seven RCTs (6 compared to linezolid, 1 to ceftaroline) and 6 cohort studies (all compared to linezolid) were included, suggesting a small risk for AKI[3]. The relative risk for AKI in the RCTs was 2.45 ($p<0.001$), but none were considered at low risk for bias. Only 2 of 6 cohort studies showed significantly worse renal outcomes with vancomycin, and all studies were of moderate or high risk for bias. The strength of causal association was weakened as kidney injury was neither a primary endpoint nor a prespecified secondary outcome in any of the trials.

By contrast, a safety analysis of a RCT comparing daptomycin with either vancomycin plus gentamicin or an antistaphylococcal penicillin plus gentamicin showed a similar rate of a clinically significant decrease in creatinine clearance with vancomycin (10 of 46, 22%) compared to penicillin (16 of 63, 25%)[4]. Both of these groups together, however, had a significantly higher rate than the daptomycin arm, an outcome ascribed to concurrent gentamicin. Carreno et al. reported a RCT of 100 at-risk patients initially prescribed vancomycin in which 51 patients were randomized to continue vancomycin and 49 to receive alternative therapy[5]. No difference in nephrotoxicity was found. Furthermore, it has been repeatedly reported that patients with nephrotoxicity associated with vancomycin use may have improvement of kidney function despite continuation of vancomycin[6,7]. Hence, equipoise remains.

Pharmacokinetics and Pharmacodynamics

Vancomycin is approximately 50% protein bound with a volume of distribution of 0.4-1.0 L/kg and a β-elimination half-life of 3 to 6 hours with normal kidney function[8]. The drug is not metabolized and is eliminated unchanged in the urine. Clearance is linearly related to the glomerular filtration rate. Penetration into tissues is variable, especially into pulmonary epithelial lining fluid in the critically ill, which is of obvious concern when treating MRSA pneumonia[9].

The bactericidal activity of vancomycin is considered time dependent but concentration independent[10]. Increasing concentrations of vancomycin are not associated with enhanced bacterial killing[10]. Rather, the ratio of the 24 hour area-under-the-concentration-versus-time curve to the minimum inhibitory concentration (AUC/MIC) is the pharmacokinetic/pharmacodynamic parameter best correlated with effectiveness[8]. Consensus guidelines published in 2009 by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists (herein referred to as Guidelines) recommend an AUC/MIC of $\geq$400 [8]. Available clinical evidence supports this ratio[11,12].

The 2 most common ways to determine the MIC of staphylococci are broth microdilution (BMD) and the Etest, with the Etest result typically 0.5 to 1.5 times higher after log conversion[13]. Hence, a given AUC will result in a lower ratio if MIC is determined by the Etest. Of note, the Guidelines were derived from data generated using BMD. The BMD method only allows for 2-fold dilutions, i.e. 0.5, 1, 2, 4, 8 mg/L, etc., whereas the Etest is based on a continuous gradient and can give greater discrimination with half-dilution values (e.g. 1.5 mg/L)[14]. In 2006 the Clinical and Laboratory Standards Institute (CLSI) lowered the MIC breakpoint for vancomycin susceptibility from $\leq$4 mg/L to $\leq$2 mg/L by BMD owing to a greater chance for failure at $\geq$4 mg/L[15].

The MICs for vancomycin have been slowly increasing ("MIC creep")[16]. Numerous studies have addressed the effectiveness of vancomycin with higher MICs within the CLSI "susceptible range" with variable conclusions[17-19]. Equipoise remains when the MIC is at the CLSI "susceptible" level of 1.5-2.0 mg/L by Etest or 2.0 mg/L by BMD. The 2009 Guidelines recommend considering alternative therapy[8], but the ISDA 2011 guidelines state vancomycin should be continued irrespective of the MIC unless lack of response occurs[1].

Determining an AUC, and hence the AUC/MIC, is impractical under normal clinical circumstances due to the large number of blood draws required after a single dose. Thus, the Guidelines recommend measurement of trough serum levels at steady state conditions as a surrogate. A trough level <10 mg/L (10 µg/ml) is unlikely to represent a ratio ≥400 and may result in development of resistance, including both vancomycin intermediate *S aureus* (VISA) and heteroresistant VISA (hVISA, wherein a small subpopulation (e.g. 1 per 10^5) of VISA exists within an otherwise susceptible isolate)[20]. Hence, the Guidelines recommend always keeping trough levels above 10 mg/L. A trough level of 15-20 mg/L is recommended to insure an AUC/MIC ≥400 in more serious infections, such as pneumonia, bacteremia, endocarditis, meningitis, and osteomyelitis. This corresponds to guidelines by the American Thoracic Society for healthcare-associated, hospital-acquired, and ventilator-associated pneumonias[21]. Importantly, 3 more recent studies, however, showed that over 50% of patients achieving AUC/MIC ≥400 had trough levels <15mg/L[22-24]. Hence, trough levels at best imperfectly predict AUC/MIC ratios. The use of peak levels has not been shown to increase the predictive ability to identify efficacy or toxicity[25], and is not advocated by the Guidelines. When administered as a continuous infusion, a steady state level of 25-30 mg/L obtained 18 or more hours after dosage adjustment is recommended.

Over 15 cohort studies have compared the effectiveness of trough levels ≥15mg/L versus <15 mg/L. A meta-analysis of these trials found no significant benefit of higher trough concentration on mortality or treatment failure, but there was a higher rate of microbiologic failure in the low trough group[26]. Another meta-analysis evaluated only trials involving patients with documented MRSA infections: 9 studies compared troughs ≥15 mg/L versus <15 mg/L with regard to clinical success, and 11 studies compared such troughs to mortality[27]. There was no significant difference with levels ≥15 mg/L in clinical success (OR 1.07 95% CI 0.68-1.68) or mortality (OR 1.09 95% CI 0.75-1.60), unless accounting for publication bias by the trim-and-fill method for clinical success (OR 1.71 95% CI 1.04-2.81). Similarly, post hoc analysis of 2 trials comparing vancomycin with telavancin for nosocomial pneumonia showed

no difference in cure rate or mortality based on trough levels ≥15 mg/L[28]. Although attainment of Guideline-recommended trough levels for serious infections (≥15 mg/L) correlates only weakly with efficacy, there is a much stronger correlation with nephrotoxicity.

Standard vancomycin dosing as approved by the FDA is 1 gram q12 hour, a dose unlikely to give a ratio ≥400 unless the MIC is ≤0.5 mg/L. Hence, the Guidelines recommend weight based dosing (using actual body weight) at 15-20 mg/kg (not to exceed 2 g/dose) q12 hours, with TDM (trough levels checked at steady state prior to 4th dose if normal renal function). With serious infections a loading dose of 25-30 mg/kg may be considered. A meta-analysis confirmed a benefit to TDM with significantly higher rates of clinical efficacy and significantly reduced nephrotoxicity compared to no TDM[29]. The available evidence for attaining a trough ≥15 mg/L (vs <15 mg/L) may be questionable in terms of predicting an AUC/MIC ≥400 as well as for clinical efficacy, but values <10 mg/L should be avoided to prevent resistance and to attain the target AUC/MIC[24]. TDM is especially necessary in ICU patients. Many have decreased kidney function, but others have augmented renal clearance with lower than expected trough levels[30].

Alternative methods to guide vancomycin dosing by intermittent infusion have been published. One nomogram is based on population pharmacokinetics and is aimed at targeting a trough level of 15-20 mg/L[31]. Based on *a priori* methodology, individual patient data are not required, although one must be careful that a particular patient matches those used to generate the nomogram. Other nomograms are available. Linear regression analysis applying individual patient parameters (*a posteriori*) has been used but does require at least 2 measured serum concentrations and a log linear calculator[32]. Bayesian estimation methodology combines *a priori* population-based data with *a posteriori* individual patient data (which may be limited to just a trough level[23]) to calculate dose and interval most accurately[32], and has higher predicative ability to achieve a specific AUC/MIC[33]. Bayesian methodology may be the fastest

way to achieve therapeutic targets, but requires specific computer software and specialized practitioners and has had limited implementation.

Appropriate dosing is especially problematic in patients receiving renal replacement therapy (RRT), whether by standard thrice-weekly intermittent hemodialysis (IHD)[34], short daily IHD[35], or continuous RRT (CRRT) in the ICU[36]. On the one hand, underdosing may foster resistance. In this regard, vancomycin resistant enterococci, vancomycin-intermediate *S aureus* (VISA), and vancomycin-resistant *S aureus* (VRSA) were all first isolated from hemodialysis patients. On the other hand, many patients receiving hemodialysis have significant residual renal function that contributes to their well-being and should not be glibly sacrificed by overdosing.

Other factors besides residual renal function contribute to the variability of vancomycin pharmacokinetics during RRT. There may be a prolonged distribution phase, a rebound effect following termination of dialysis, and non-renal clearance[37]. Using standard low-flux dialysis membranes, there is minimal dialytic clearance, and once-weekly dosing suffices[34]. Many patients, however, are now dialyzed on synthetic, high-flux dialyzers using membranes that have a much larger pore size and do have significant vancomycin clearance[38]. These patients require supplemental doses following each dialysis. Vancomycin is often administered during the final hour of a dialysis session, which will result in additional clearance compared to pure post-dialytic administration. Larger doses are required with this method of administration. In contrast, many patients are dialyzed on re-used dialyzers, often up to 15 or more treatments. Such reprocessing results in reduced vancomycin clearance that could result in overdosing[34]. Finally, measurement of vancomycin levels with severe renal failure is problematic depending on the method used. Inactive crystalline degredation products may accumulate and can be measured with the polyclonal fluorescence polarization immunoassay[34].

Various modalities of CRRT are available in the ICU setting, including continuous veno-venous hemodialysis (CVVHD), hemofiltration (CVVHF), and hemodiafiltration (CVVHDF). All use synthetic membranes with significant vancomycin clearance determined primarily by the volume of effluent[36]. Clearances of 15 to 30 ml/min are possible with effluent volumes approaching 3000 ml/hour. A comprehensive discussion of the pharmacokinetics of vancomycin metabolism in various types of intermittent and continuous RRT is beyond the scope of this paper. Suggestions for dosing with both IHD and continuous procedures are provided in Table 1.

Pathophysiology of Vancomycin Nephrotoxicity

In older studies vancomycin was shown to be lethal in experimental animals given exorbitant i.v. doses, and variably showed nephrotoxicity at lower doses[39]. Vancomycin can alter mitochondrial function and induce dose dependent proliferation of proximal tubular cells (PTC) in vitro[40]. Multiple studies have focused on oxidative stress as a potential mechanism of nephrotoxicity, especially involving the proximal tubule. Hence, antioxidants may be protective[41]. In various experimental models, numerous antioxidants have been shown to be protective, including modified superoxide dismutase[42]; the antioxidants erdosteine,[43] α-lipoic acid, Ginkgo biloba extract, and melatonin [44]; and, thymoquinone, caffeic acid phenylethyl esther, vitamin C, vitamin E, N-acetylcysteine, curcumin, tempol, and isoquinelinediol[41]. Most recently, Sakamoto et al. demonstrated that vancomycin induced apoptosis in porcine PTCs via mitochondrial production of reactive oxygen species with peroxidation of the mitochondrial phospholipid cardiolipin[45]. Interestingly, this toxicity could be inhibited by the lipophilic antioxidants vitamin E and mitoTEMPO, but not by water-soluble ones such as vitamin C, n-acetyl cysteine, or glutathione.

Other studies in experimental animals found that agents capable of enhancing renal excretion reduced nephrotoxicity, including cilastatin, imipenem-cilastatin, and fosfomycin[41]. Cilastatin can block

the proximal tubular receptor protein megalin-mediated uptake of vancomycin and inhibit nephrotoxicity in mice[46]. Hence, agents inhibiting oxidative stress and/or reducing renal accumulation may be protective, although human data are lacking and use in patients cannot be endorsed at this time. In contrast, a study of 9 patients with VANT undergoing kidney biopsy demonstrated intratubular casts composed of vancomycin nanospheric aggregates complexed with uromodulin. Notably, these findings were reproduced in mice given large doses of vancomycin[47]. The specific cellular origin of these casts remains to be determined.

Clinical Vancomycin Nephrotoxicity

The Guidelines define nephrotoxicity as a rise in serum creatinine of 0.5 mg/dl or 50% above baseline on 2 consecutive measurements after several days of vancomycin and with no other apparent cause. This is the definition used most frequently, although other studies use the more sensitive risk-injury-failure-loss-ESRD (RIFLE)[48,49] or AKI network (AKIN)[50] criteria for AKI (see Table 2). Herein, vancomycin-associated nephrotoxicity (VANT) refers to the Guideline-based definition of nephrotoxicity and AKI to either the RIFLE or AKIN criteria. Studies using these latter criteria have found most cases to be of lower stages based on creatinine criteria. In one study using AKIN criteria, 92% reached stage 1[50], whereas in 2 studies using RIFLE criteria, 50%[48] and 71%[51] reached only R. No study has specified VANT or AKI stage based purely on urine output criteria. Older studies showed mean increases of serum creatinine from baseline of approximately 1 to 1.5 mg/dl[52].

Various novel blood and urine biomarkers have been studied for their ability to detect impending AKI prior to the standard measures, i.e. serum creatinine and urine output (see Table 3). These include neutrophil gelatinase-associated lipocalin, kidney injury molecule-1, insulin-like growth factor-binding protein 7, and tissue inhibitor of metalloproteinases-2, among others[53]. A number of these have been qualified by the FDA and European Medicine Agency for non-clinical animal toxicology

evaluation of new drug entities (see https://c-path.org/programs/pstc/pstc-tools/). No studies have specifically addressed the utility of any biomarkers for the early detection of vancomycin nephrotoxicity in humans, although limited pre-clinical data exist[54]. An in-depth discussion of biomarkers is beyond the scope of this paper.

The onset of VANT typically occurs after about 4 to 8 days of therapy. A systematic review by van Hal et al. found a mean range of nephrotoxicity occurrence of 4.3 to 17 days after initiation of vancomycin[55]. Onset as early as 2[56] to 3[57] days of therapy has been reported. In general, about three-quarters of patients will have improvement or resolution by time of discharge[2,58,59], often within a week or less, including patients remaining on vancomycin after onset of nephrotoxicity. Dialysis has been rarely necessary in any study, with an overall incidence of 3% in the van Hal review. As expected, however, VANT is associated with increased mortality[50] and length of stay in the ICU[60] and hospital[50,61].

The vast majority of patients with VANT do not undergo kidney biopsy. It is presumed that the underlying pathophysiology is toxicity to proximal tubular cells, with or without frank necrosis (ATN). In support, several case reports have documented ATN based on clinical evaluation or by renal biopsy[62]. Similarly, acute interstitial nephritis (AIN) has been clinically diagnosed or documented by biopsy[63]. Occasionally, both lesions have been found on biopsy[64]. Various skin lesions have been reported in cases of vancomycin associated AIN, including maculopapular rash, erythema multiforme[63], toxic epidermal necrolysis[63], and the Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome[65]. Infectious glomerulonephritis would also be a consideration when supported by the urinalysis. If there is clinical uncertainty, biopsy is indicated.

Risk Factors

Numerous risk factors have been defined for developing VANT or AKI in patients receiving vancomycin (see Table 4). Various measures of vancomycin exposure have been studied, including use

of a loading dose, maximal dose, duration of therapy, method of administration (intermittent versus continuous infusion), AUC, and trough level. Other risk factors include demographic features, associated medical conditions, severity of illness, pre-existing kidney disease, and concurrent nephrotoxins.

Loading Dose

The Guidelines recommend consideration a loading dose of 25 – 30 mg/kg actual body weight for serious infections. Rosini et al. retrospectively evaluated 1330 patients receiving vancomycin in the Emergency Department (ED) , of which 851 received high doses (>20 mg/kg). VANT occurred in 7.7% with no difference in the high dose group (5.8%) versus the low dose group (11.1%, $p<0.001$)[66]. Results were unchanged using a cutoff of >25 mg/kg. An RCT compared 49 patients receiving a 15 mg/kg initial dose to 50 patients receiving 30 mg/kg in the ED and found no difference in the secondary endpoint of VANT, which overall occurred in only 5% of patients[67]. To date, there is no evidence that a loading dose is associated with increased nephrotoxicity.

High Daily Doses

One retrospective cohort study assessed the nephrotoxicity of high dose vancomycin. Lodise et al. compared 26 patients receiving $\geq$4 g/day vancomycin to 220 patients receiving <4 g/day and 45 patients receiving linezolid and found nephrotoxicity rates of 35%, 11%, and 7%, respectively ($p=0.001$)[68].There was no difference in time to nephrotoxicity between the low dose vancomycin group and the linezolid group. By multivariate analyses, the high dose regimen had an odds ratio of 4.4 ($p=0.003$) for occurrence of nephrotoxicity and a hazard ratio 4.37 ($p<0.001$) for time to its occurrence.

Vancomycin AUC

Several studies compared the relationship between vancomycin exposure as indicated by the AUC and nephrotoxicity. Using a classification and regression tree (CART) analysis in a retrospective

study of 166 patients, Lodise et al. found a significant breakpoint of 1300 mg x h/L with nephrotoxicity rates of 26% and 10% above and below this level ($p=0.05$)[58]. By multivariable analysis, AUC was no longer a significant predictor of nephrotoxicity, while the trough level was. In contrast, a breakpoint of 563 mg x h/L was determined by CART analysis in a recent retrospective study of 127 patients, with significance confirmed by multivariable analysis[69]. Trough levels were not independently predictive in this study. In a smaller study of 31 patients, an AUC of approximately 700 (by visual inspection of a figure) associated with nephrotoxicity compared to about 500 in those without ($p=0.014$), but a specific breakpoint was not established[25]. Comparison of AUC and VANT has not been widely studied.

Vancomycin Trough Levels

Many studies have assessed the relationship between trough levels as a measure of exposure and VANT. In general, there is a major issue with reverse causation, in that reduced kidney function from any cause will lead to an elevated trough level. In an effort to reduce this bias, some studies consider only the initial trough level. Even that, however, does not obviate kidney injury from another cause. Some studies consider mean trough levels, others maximal troughs.

A dose response relationship has been shown repeatedly. Lodise et al. found a 5% rate of nephrotoxicity if the initial trough was <10 mg/L compared to rates of 21% for troughs of 10-15 mg/L, 20% for 15-20 mg/L, and 33% for >20 mg/L ($p<0.05$)[58]. For each mg/L increase, the odds ratio for nephrotoxicity increased by 13%. Horey et al. found nephrotoxicity rates of 5%, 3%, 11%, 24%, and 82% for maximal troughs of 5-10 mg/L, 10.1-15, 15.1-20, 20.1-35, and >35, respectively[48]. Similarly, Barriere et al. showed that renal adverse events occurred in 0% of patients with median trough levels <10 mg/L compared to 3% if 10-<15 and 17% if >15 ($p<0.01$)[28]. Cano et al. found that nephrotoxicity increased from 7% at initial trough <10 mg/L, but increased up to 34% at >20 mg/L ($p=0.0003$ for trend)[60]. Wunderink et al. noted 18% nephrotoxicity with day 3 trough <15 mg/L versus 22% at 15-20mg/L versus

37% if ≥20 mg/L (significance not assessed)[70]. In contrast, Kullar et al. found no more significant nephrotoxicity with troughs of 15-20 mg/L (13%) compared to 10-15 mg/L (17%) and <10 mg/L (15%), although the rate was significantly higher if >20 mg/L (27%, p=0.032)[61]. The question remains as to whether higher exposure as reflected in higher troughs causes VANT or whether trough levels rise as a result of its occurrence.

As noted above, various guidelines recommend trough levels of ≥15 mg/L to 20 mg/L, although minimal evidence supporting efficacy exists. In contrast, numerous studies have assessed the safety of this recommendation by comparing nephrotoxicity rates above and below 15 mg/L. At least 2 meta-analyses analyzed these studies. Van Hal et al. identified 15 studies and found an odds ratio of 2.67 (95% CI 1.95-3.65) for nephrotoxicity with troughs ≥15 mg/L. This finding persisted if restricted to studies evaluating only initial troughs[17]. More recently, Tongsai and Koomanachai analyzed 10 studies involving only patients with MRSA infection and found an OR of 2.14 (95% CI 1.42-3.23) for nephrotoxicity with troughs ≥15 mg/L and an adjusted OR of 3.33 (95% CI 1.91-5.79) in 3 studies providing sufficient data for combining adjusted ORs[27]. Hence, the evidence for potential harm with attaining troughs ≥15 mg/L is more compelling than the evidence for potential benefit.

Duration of Vancomycin

Some studies find no significant relation of nephrotoxicity to duration of therapy[48,50,71,72], but more often a positive result is found[2,51,59,60,73-75]. Significantly positive durations include ≥7 days[57,59], ≥14 days[2], and >15 days[75]. One study found a significant 12% increase in OR for each additional day of therapy[60], and another study found a 4% increased OR for each additional day[76]. Based on available evidence, it is improbable that less than 48-72 hours of vancomycin exposure is sufficient to cause nephrotoxicity. Hence, we feel it is safe to include vancomycin in initial broad spectrum coverage, with consideration of continuation based on severity of illness, risk, and culture results.

Method of Administration

The Guidelines recommend intermittent infusion as the preferred method of administration. Others advocate continuous infusion[77]. Several observational studies and 2 RCTs assessed the nephrotoxicity of continuous infusion versus intermittent infusion. An earlier meta-analysis of 1 RCT and 5 observational studies found a relative risk of 0.6 (95% CI 0.4-0.9, p=0.02) for nephrotoxicity with continuous infusion[78]. Subsequently, an observational study of 1430 ICU patients by Hanrahan et al. found an adjusted OR for nephrotoxicity of 8.2 ($p \leq 0.001$) with intermittent infusion, although nephrotoxicity was higher with continuous infusion in unadjusted analyses[76]. A 2014 meta-analysis added this study, as well as another small trial of 55 patients, to the prior studies and found a trend for reduced nephrotoxicity with continuous infusion (risk ratio 0.8, p=0.3), although only the unadjusted analysis of the Hanrahan study was used for consistency[79]. There was no mortality benefit to continuous infusion. A more recent meta-analysis did not include the Hanrahan study but did include 5 additional studies and found a risk ratio of 0.61 (95% CI 0.47-0.80, p<0.001) with continuous infusion, with no difference in treatment failure or mortality[80]. The optimal method of administration remains uncertain, and the guideline endorsed approach of intermittent infusion remains the clinical standard.

Demographics

The demographic features of age, race, and sex have generally not been found to be significantly associated with nephrotoxicity in patients receiving vancomycin with occasional exceptions for older age[75] and black race[74]. The one notable demographic feature is obesity, which remains problematic. The Guidelines recommend doses based on actual body weight, not ideal body weight. In addition to a greater volume of distribution, clearance is significantly increased relative to non-obese patients, at least with normal renal function[81]. Despite increased clearance, however, dosing based actual body weight may result in higher trough levels, even with doses caped at 2,000 mg/dose. Richardson et al.

found a significantly higher incidence of trough levels > 20 mg/L with BMI $\geq$ 30 (19% versus 4%)[82]. Obesity has also been significantly associated with nephrotoxicity in some studies, although not all. In a retrospective analysis of 337 patients, 23% developed nephrotoxicity [75]. Weight above 100 kg was a significant predictor by multivariate analysis (OR 2.74). In a study of 246 patients receiving vancomycin, nephrotoxicity was significantly associated with TBW $\geq$ 101.4 kg by multivariable analysis[68]. In another study of 270 veterans, the risk for nephrotoxicity increased by 1.02 for every 1 kg increase in body weight[48]. In contrast, a study of 530 patients found that obesity was not associated by multivariable analysis with nephrotoxicity [49]. Based on available evidence, we feel obesity is a risk factor. We recommend a loading dose and subsequent dosing based on actual body weight. TDM is necessary, with trough levels closely followed starting with the third or fourth dose.

Severity of Illness

Severity of illness impacts development of AKI in patients receiving vancomycin. In less sick patients, VANT is uncommon (<5%). For example, in prospective RCTs restricted to vancomycin use for complicated skin and skin structure infections, adverse renal event rates of 2.7%[83] and 3.8%[84] were reported, although criteria of renal injury were not specified. In the critically ill, other causes of AKI besides vancomycin use frequently coexist, such as sepsis, hemodynamic stress, contrast exposure, and concurrent nephrotoxic medications, and AKI may develop in a quarter to a half of such patients. In observational studies of VANT, severity of illness, as assessed by Acute Physiology and Chronic Health Evaluation (APACHE) II score[49,85], Charlson Comorbidity Index[72], Sequential Organ Failure Assesment[76], or by residence in the ICU[50,58,68], was found by multivariable analysis to be an independent risk factor for kidney dysfunction. Other comorbid conditions significantly associated with nephrotoxicity include hypotension[48,72] heart failure[74], cancer[50,73,74], impaired kidney function[50,58], and prior AKI[50].

It remains uncertain to what degree vancomycin is directly responsible in any individual case when multiple factors are involved. The only RCT to date with a primary renal endpoint included 100 patients initially prescribed vancomycin with ≥2 risk factors for AKI who were randomized to either continue therapy as planned or use an alternative agent[5]. There was no difference between groups in either the Guideline based nephrotoxicity definition or AKIN defined AKI. Furthermore, equipoise remains as to whether a critically ill patient receiving vancomycin who develops AKI can continue therapy with TDM or should be switched to an alternative agent. More data are clearly needed to provide guidance in the critically ill.

Concurrent Nephrotoxins

Multiple other agents capable of decreasing kidney function are often administered to patients receiving vancomycin, especially ICU patients. Potential toxins include aminoglycosides, amphotericin, acyclovir, calcineurin inhibitors, chemotherapy, and intravenous contrast. Other agents capable of affecting kidney function include vasopressors, loop diuretics, and renin-angiotensin system blockers. In some studies, these agents are lumped together as concurrent nephrotoxin exposure[73], other times they are considered individually in multivariable analyses. Dose and duration are rarely provided. The individual agents most extensively studied include aminoglycosides and piperacillin-tazobactam.

Both preclinical studies and human data support the potential synergistic nephrotoxicity of vancomycin and aminoglycosides. Wold and Turnipseed found no evidence of nephrotoxicity after administering either 150 mg/kg of vancomycin or 60 mg/kg of tobramycin alone to rats, but significant nephrotoxicity occurred with the combination[39]. Wood et al. in an animal model found no nephrotoxicity of vancomycin alone, but the combination of vancomycin and tobramycin resulted in higher serum creatinine and greater histologic damage than tobramycin alone[86].

Initial studies in humans were performed decades ago and were generally not controlled for confounding factors. Farber and Moellering found nephrotoxicity in 12 of 34 (35%) patients receiving concomitant vancomycin and aminoglycosides compared to only 5% of 60 patients receiving vancomycin without aminoglycosides[87]. Of note, 2 patients with nephrotoxicity on vancomycin alone had high trough levels and were able to continue the drug after dosage adjustment with improvement of renal function. Sorrell and Collignon showed nephrotoxicity in in 4 of 28 patients receiving vancomycin and aminoglycosides compared to 0 of 25 not on the latter; 2 of the 4 had improvement of kidney function with cessation of aminoglycosides despite continuation of vancomycin[88]. Ryback et al. compared nephrotoxicity in 168 patients receiving vancomycin alone, 63 receiving vancomycin together with an aminoglycoside, and 103 receiving aminoglycosides alone (with or without a beta-lactam)[89]. Nephrotoxicity occurred in 5%, 22%, and 11%, respectively, a highly significant difference. Recently, Hanrahan et al. studied 158 critically ill patients receiving vancomycin and noted AKI by RIFLE criteria in 14 (8.9%)[90]. By multivariable analysis, concurrent use of aminoglycosides was highly associated with development of AKI (OR 18.9, p=0.002), although, a separate group receiving aminoglycosides in the absence of vancomycin was not compared.

By contrast, several earlier studies reported no significant increase in nephrotoxicity comparing the vancomycin/aminoglycoside combination with either agent alone. When these positive and negative studies were combined in a 1993 meta-analysis, combination therapy did have a significant 13% ($p<0.01$) higher rate of nephrotoxicity than vancomycin alone and a 4% ($p<0.05$) higher rate than aminoglycosides alone[91]. A more recent study found no difference in nephrotoxicity with addition of gentamycin to vancomycin by multivariate analysis[68]. As noted earlier, in an RCT of patients with staphylococcal bacteremia, vancomycin plus gentamicin was no more nephrotoxic than a penicillin plus gentamicin, but both regimens were significantly more toxic than daptomycin without an aminoglycoside[4]. It remains uncertain whether the enhanced rate of nephrotoxicity reported with

vancomycin use in combination with aminoglycosides is the result of severity of underlying illness, the nephrotoxicity of aminoglycosides per se, or a true nephrotoxic synergy between the agents.

The combination of piperacillin-tazobactam (PTZ) with vancomycin was first noted to potentially result in enhanced nephrotoxicity compared to vancomycin without PTZ in several abstracts published in 2011. Subsequent studies have been conflicting. For example, Meaney et al. found a significant adjusted OR of 5.36 of AKI when PTZ was added to vancomycin therapy in 125 adult patients[72]. Gomes et al. studied 224 adults receiving vancomycin and found a significantly higher AKI incidence when PTZ was added (35% vs 13%, P<0.0001)[92]. Propensity score matching confirmed this significance (p=0.003). Kim et al. showed a significantly reduced OR (0.14) of vancomycin monotherapy compared to combination with PTZ by multivariable analysis in 228 adult patients that was confirmed in a propensity score analysis (OR=0.17)[93]. Fodero et al. studied 453 veterans receiving vancomycin and noted a significant OR (3.21) for nephrotoxicity with concomitant PTZ by multivariable analysis[94].

By contrast, Moenster et al. could not find a significant difference for AKI by multiple logistic regression analysis with the addition to vancomycin of either PTZ or cefepime in 139 diabetic patients with osteomyelitis[95]. Likewise, Hammond et al. compared vancomycin-TZB with vancomycin-cefepime in 122 critically ill patients and found no significant difference in AKI incidence, AKI duration, or need for dialysis [96].

Two recent meta-analyses addressed this issue. Giuliano et al. evaluated 6 studies published only in abstract form and the 9 studies outlined above[97]. There was overall OR of 3.65 (95% CI 2.16-6.17, p<0.001, I^2=83.5%) for development of nephrotoxicity or AKI with vancomycin and PTZ compared to vancomycin +/- β-lactam. This remained significant after removal of either abstracts or low quality studies. The increased risk remained significant in studies compared to vancomycin alone (OR 3.98, 95% CI 2.75-5.76) but not in studies compared to vancomycin plus a β-lactam (OR 3.0, 95% CI 0.9-9.73).

Hammond et al. evaluated 14 published studies, including 11 in adults[98]. The combination of vancomycin with PTZ again had an adjusted OR for nephrotoxicity or AKI of 3.11 (95% CI 1.77-5.47). By contrast to the findings of Giuliano et al., the OR was not significant when the combination was compared to vancomycin alone, but was significant when compared to vancomycin + a β-lactam.

Subsequently, the 2 largest single center series were published. Navelkele et al. compared 279 propensity-matched patients receiving vancomycin + PTZ to 279 receiving vancomycin plus cefipime and found AKI rates of 29% and 11%, respectively ($p<0.0001$)[56]. By multivariable analysis, the group receiving PTZ had a hazard ratio for AKI of 4.27 (95% CI 2.73-6.68). Rutter et al. propensity matched 1,633 patients receiving vancomycin + PTZ to 578 receiving vancomycin + cefipime and found AKI rates of 21.4% and 12.5%, respectively ($p<0.0001$)[57]. By multivariable analysis, the OR for the PTZ group was 2.18 (95% CI 1.64-2.94).

The potential mechanism of enhanced toxicity of this combination remains uncertain. Piperacillin-tazobactam is not considered to be a nephrotoxin, but support for potential nephrotoxicity comes from post hoc analysis of a randomized controlled trial of 1200 critically ill patients which showed receipt of PTZ was associated with impaired renal recovery [99]. Acute interstitial nephritis has been reported with PTZ in case reports. It is possible that an AIN induced by PTZ could complicate toxic proximal tubulopathy or AIN induced by vancomycin.

In our opinion, the enhanced nephrotoxicity of this combination appears real. This regimen should be used carefully and only under the guidance of an antimicrobial stewardship program with TDM. In support, a recent retrospective study of 320 patients receiving vancomycin-PTZ found an alarming 33% incidence of AKI[100]. Associated factors that were significantly associated with AKI and were potentially modifiable by antimicrobial stewardship included a vancomycin loading dose, longer duration of dual therapy, and concomitant nephrotoxins.

Conclusion

Vancomycin used at currently recommended doses is minimally nephrotoxic when used in non-critically ill patients with less serious infections. In sicker patients with multiple risk factors for AKI, VANT occurs much more commonly, but it remains uncertain to what degree vancomycin is directly responsible. In our opinion, it is safe to initiate therapy with vancomycin in critically ill patients with multiple risk factors for AKI pending culture results with use of TDM and antibiotic stewardship (see Table 5). Trough levels should be obtained within 48 to 72 hours by which time initial culture results should be available. Decisions regarding continuation of vancomycin therapy can be individualized, based on culture result, MIC (if staphylococci are isolated), AKI risk, and side-effect profile of alternative agents. Loading doses are safe. Trough levels with intermittent dosing should always be >10 mg/L to prevent resistance. It remains uncertain whether Guideline based trough levels of 15 – 20 mg/L are more efficacious than 10 – 15 mg/L in serious infections. Trough levels of 15 – 20 mg/L, however, are clearly associated with greater VANT than levels <15 mg/L, but it remains uncertain whether these levels are the cause or the result of the nephrotoxicity. Combination with PTZ should be avoided or duration minimized. In patients receiving vancomycin who develop AKI that is not easily correctible with fluid resuscitation or discontinuation of other agents, cessation of vancomycin should be considered. This very important issue clearly warrants a large, multicenter RCT to answer definitively. Further issues need research as well, preferably with RCTs (see Table 6).

Table 1
Suggestions for Vancomycin Dosing During RRT

Modality	Recommendation	Comments
Thrice Weekly Intermittent Hemodialysis – Low Flux membrane	Standard LD (20 – 25 mg/kg) based on actual body weight MD: Approximately 15 – 20 mg/kg qweek	Follow trough levels, especially with serious infections
Thrice Weekly Intermittent Hemodialysis – High Flux Membrane	Standard LD as above MD: 10 mg/kg in last hour of each dialysis	Add an additional 250 mg to end of week MD Follow trough levels
Short Daily Dialysis – High Flux Membrane	Standard LD as above MD: 10 mg/kg after every other dialysis	Validated for MIC $\leq$ 1 mg/L; above that , use alternative agent
Continuous RRT	Standard LD as above MD: Consider 500 – 750 mg/q12 hour or 15 – 20 mg/kg when random level at desired trough	Consider residual renal function Follow trough level

LD: loading dose; MD: maintenance dose; RRT: renal replacement therapy.

Table 2
Current Criteria for Diagnosing and Staging Acute Kidney Injury

RIFLE Criteria	Stage	Creatinine-Based Criteria	Urine Output-Based Criteria
	R	Rise of serum creatinine of ≥ 50% within 7 days **or** GFR decrease by 25%	<0.5 ccs/kg/hr for 6 consecutive hours
	I	Rise of serum creatinine of >100% **or** GFR decrease by 50%	<0.5 ccs/kg/hr for 12 consecutive hours
	F	Rise of serum creatinine of >200% **or** GFR decrease by 75% **or** renal replacement therapy	<0.3 ccs/kg/hr for 24 hours or anuria for 12 hours
	L	Complete loss of function for more than 4 weeks	
	E	End stage renal disease	
AKIN Criteria	1	Rise of serum creatinine of ≥ 50% or increase of ≥0.3 mg/dl in <48 hours	<0.5 ccs/kg/hr for 6 consecutive hours
	2	Rise of serum creatinine of >100%	<0.5 ccs/kg/hr for 12 consecutive hours
	3	Rise of serum creatinine of >200% or renal replacement therapy	<0.3 ccs/kg/hr for 24 hours or anuria for 12 hours

Note: Satisfaction of **either** creatinine-based criteria **or** urine output-based criteria is sufficient for diagnosis and staging. Both are not required.
RIFLE: Risk, Injury, Failure, Loss, End-Stage-Renal-Disease[49]: AKIN: Acute Kidney Injury Network[52]: GFR: glomerular filtration rate

Table 3 Novel Biomarkers	
Blood	Cysatatin-C
	Neutrophil gelatinase associated lipocalin-2
	Retinol binding protein
	IL-18
	TNF-receptor-1
Urine	Neutrophil gelatinase associated lipocalin-2
	Kidney injury molecule-1
	Liver type fatty acid binding protein
	n-acetyl-β-d-glucosaminidase
	Tissue inhibitor of metalloproteinases-2
	IFG-binding protein-7
	Glutathione-S-transferase
	IL-18

Table 4 **Potential Risk Factors for Vancomycin Nephrotoxicity**	
Vancomycin Exposure Variables	Loading Dose Total Daily Dose AUC Trough Level Duration Continuous vs Intermittent Infusion
Patient Specific Factors	Obesity Severity of Illness ICU Residence Chronic Kidney Disease Concurrent Nephrotoxin Exposure Concurrent Aminoglycosides Concurrent Piperacillin-Tazobactam

Table 5

Approaches to Reduce Vancomycin Nephrotoxicity

Recommendation	Comment
Weight based dosing of 15-20 mg/kg	Use actual body weight and combine with therapeutic drug monitoring. Consider nomograms in patients with renal insufficiency
Consider a loading dose of 25 – 30 mg/kg for severe infections (bacteremia, endocarditis, pneumonia, osteomyelitis, meningitis)	There is no evidence of increased nephrotoxicity with a loading dose
Use intermittent rather than continuous administration	Continuous infusion has limited evidence for reducing toxicity and is cumbersome to use.
Do not obtain peak vancomycin concentrations	Peak concentrations do not predict efficacy or toxicity
Maintain trough concentration 10-15 mg/L for non-severe infections	>15 mg/L correlates weakly with improved efficacy, but at the expense of a clear association with toxicity.
Maintain tough concentrations 15-20 mg/L for serious infections	Increased potential toxicity balanced against severity of infection
Consider cessation of vancomycin should AKI develop after at least 2 days of therapy	Effective but not nephrotoxic alternatives exist e.g. daptomycin for MRSA bacteremia/endocarditis or linezolid for MRSA pneumonia
Tailor duration of therapy to efficacy and not to prevent nephrotoxicity	Duration of therapy should be directed to microbiologic control. Toxicity may increase with prolonged therapy, but evidence base is weak.
Concomitant use with piperacillin-tazobactam or an aminoglycoside should be paired with TDM and ongoing assessment of need for concurrent therapy	There is moderate evidence of synergistic toxicity to be balanced against potential need for efficacy
TDM should be used in patients at high risk for toxicity, prolonged therapy or impaired renal function	Toxicity in patients with limited comorbidities treated for less than 10 days is very uncommon
Obtain TDM before the fourth dose after starting or adjusting therapy if stable renal function	Assumptions linking trough levels to AUC are based upon a steady state concentration

Table 6 **Areas for Further Research**
1.) Comparison of vancomycin to alternative therapy in the critically ill with a **primary renal endpoint** of AKI. Urine output criteria should be incorporated as well as creatinine criteria. 2.) The role of serum and/or urine biomarkers for earlier diagnosis of nephrotoxicity 3.) Continuation of vancomycin with TDM versus discontinuation should AKI develop. 4.) Dosing based on Baysean methodology. 5.) The optimal trough for serious infections. 6.) The optimal dosing strategy: continuous versus intermittent infusion. 7.) The optimal dosing strategy for the morbidly obese. 8.) Comparison of vancomycin/piperacillin-tazobactam with vancomycin/cefepime (or alternative regimens). 9.) Antioxidants for nephroprotection. 10.) Cilastatin for nephroprotection.

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