Review of vancomycin-induced renal toxicity: an update

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***Abstract*:** In recent times the use of larger doses of vancomycin aimed at curbing the increasing incidence of resistant strains of *Staphylococcus aureus* has led to a wider report of acute kidney injury (AKI). Apart from biological plausibility, causality is implied by the predictive association of AKI with larger doses, longer duration, and graded plasma concentrations of vancomycin. AKI is more likely to occur with the concurrent use of nephrotoxic agents, and in critically ill patients who are susceptible to poor renal perfusion. Although most vancomycin-induced AKI cases are mild and therefore reversible, their occurrence may be associated with greater incidence of end-stage kidney disease and higher mortality rate. The strategy for its prevention includes adequate renal perfusion and therapeutic drug monitoring in high-risk individuals. In the near future, there is feasibility of renoprotective use of antioxidative substances in the delivery of vancomycin.

Keywords: Vancomycin, Vancomycin Resistance, Acute Kidney Injury, Nephrotoxicity, Critical Illness, Risk factors

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Introduction

Due to the paucity of methodologically sound studies, there were initial doubts about the causal effect association of vancomycin for acute kidney injury (AKI). Given the multiple confounding predisposing factors, particularly in the critical care setting, proof of causality requires randomized control trials. The ethical implication of conducting such trials led to the preponderance of observational studies [Farber and Moellering, 1983; Hanrahan *et al.* 2015; Burgess and Drew, 2014; Davies *et al.* 2013, 2015]. With glomerular filtration as the principal mode of excretion, the initial wave of reported nephrotoxicity was attributed to the 25–30% formulation content of impurities prior to the late 1970s [Rybak *et al.* 2009; Wood *et al.* 1986]. This assumption was validated by the parallel reduction of vancomycin-related AKI that followed technological improvement in the fermentation process, which led to a 95% level of product purity by 1985 [Bailie and Neal, 1988]. The incidence of vancomycin-induced nephrotoxicity (VIN) was reported to range from 5% to 7% [Farber and Moellering, 1983; Mohammedi *et al.* 2006]. In addition, earlier studies showed there was an inconsistent dose–toxicity relationship while there was failure to establish causality in experimental animal studies [Cantu *et al.* 1994]. Although not in a consistent fashion, data were more supportive of augmented kidney injury with the combined use of vancomycin and other nephrotoxic agents [Rybak *et al.* 1990, 2009; Rostas *et al.* 2014; Paquette *et al.* 2015]. Buoyed by the increasing use of larger doses in clinically complex patients, more recent studies (mostly observational) suggest there may be a rising incidence of VIN [Farber and Moellering, 1983; Hanrahan *et al.* 2015; Burgess and Drew, 2014; Davies *et al.* 2013, 2015].

Definition of vancomycin-induced AKI

Comparison of clinical outcome of vancomycin-related AKI studies is often confounded by variable diagnostic parameters [Rybak *et al.* 2009]. Poor definition of diagnosis may also limit early recognition and prompt intervention concerning VIN. To correct this inadequacy, a good starting point is the recommendation by a committee of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists using the following criteria: at least two or three consecutive elevations in serum creatinine by 0.5 mg/dl or at least 50% increase from the baseline, whichever is greater; the increase

must be documented after several days of vancomycin therapy; and no alternative explanation for the impairment in glomerular filtration rate [Rybak *et al.* 2009]. However, the shortcomings of this recommendation are i) 'several days' need to be specified as number of days and ii) the exclusion of the majority of patients who are likely to suffer from nephrotoxicity in the context of concurrent risk factors that may compromise renal function.

Furthermore, quantitative and graded definition of AKI as provided by RIFLE (Risk, Injury, Failure, Loss and End stage kidney disease), AKIN (Acute Kidney Injury Network) and most recently modified by KDIGO (Kidney Disease: Improving Global Outcome) are apt to improve the quality of data on VIN [Mehta *et al.* 2007; Lopes and Jorge 2013]. Recognition of the limitation in estimating kidney injury with the use of serum creatinine has led to the proposal for alternative diagnostic measures. Serum creatinine may remain normal despite a significant kidney injury; and its rise may lag behind for about 48–72 h after an injurious event [Mehta *et al.* 2007]. Given that the suspected mechanism of VIN is principally due to proximal tubular dysfunction, parameters that differentiate disturbance of glomerular filtration from that of tubular function will improve precision of diagnosis [Coca *et al.* 2008]. In this regard, neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule 1 (KIM-1) and interleukin 18 (IL-18) cytokine are preferential biomarkers of tubular inflammation while cystatin C predicts early-onset impairment in glomerular filtration [Coca *et al.* 2008]. Diagnostic accuracy of the individual markers may be improved by a combination of one or more of the parameters. Nevertheless, the usefulness of biomarkers for diagnosis of AKI will invariably require validation in different clinical settings.

Predisposing factors for vancomycin-induced AKI

Recent studies on vancomycin-related AKI frequently suggest that increase in the total amount of drug exposure as measured by plasma trough concentration; area under the curve (AUC) or duration of treatment is the principal determinant of nephrotoxicity. Other risk factors are pre-existing renal impairment, concurrent administration of nephrotoxic agents and its use in high-risk populations including those with obesity, and in the treatment of deep visceral infections.

Vancomycin exposure: higher doses

Although it has been difficult to demonstrate a direct renal injury attributed to vancomycin when given in lower doses in the past, there is consistent evidence that aggressive dosing aimed at curbing the trend of reducing microbial sensitivity is associated with higher incidence of AKI [Hanrahan *et al.* 2015; Elyasi *et al.* 2012; Horey *et al.* 2012; Cano *et al.* 2012]. In a review of the literature by Elyasi and colleagues, vancomycin renal toxicity had a range of 10–20% in patients using conventional doses while the range was 30–40% for those treated with higher doses (10–20 mg/l) [Elyasi *et al.* 2012]. Similarly, in a retrospective study by Hanrahan and colleagues, 8.8% of 159 critically ill patients receiving vancomycin had a new-onset AKI as defined by RIFLE criteria. The plasma trough level of vancomycin was a major correlate of nephrotoxicity [Hanrahan *et al.* 2015]. Implying a causal association, there is also a linear relationship between higher events of AKI and a graded plasma trough concentrations [Horey *et al.* 2012]. Thus there was 3.1%, 10.6%, 23.6% and 81.8% incidence of AKI for those with trough levels of 10–15, 15–20, 20–35 and greater than 35 mg/l, respectively [Horey *et al.* 2012]. In addition, individuals with greater plasma concentration had a more rapid onset of AKI: for trough greater than 20 mg/l the mean duration was 7.4 days and for levels less than 15 mg/; the mean period of onset was 8.8 days [Cano *et al.* 2012].

Furthermore, in a study by Lodise and colleagues, a daily dose of vancomycin in excess of 4 g increases the likelihood of AKI by more than threefold [Lodise *et al.* 2008]. Perhaps demonstrating the strength of the dose–toxicity relationship, there are several case reports of inadvertent use of a supranormal dose of vancomycin that led to severe AKI [Stidham *et al.* 2011; Barraclough *et al.* 2007; Wicklow *et al.* 2006]. In such events, the water solubility and the low protein binding of vancomycin facilitate its rapid removal by acute hemodialysis (HD) procedures. The author has two anecdotal experiences of teenage surgical patients with normal underlying renal function who were inadvertently given high doses of vancomycin that led to plasma trough levels of 54 and 115 mg/l respectively (not published). The former also received a nonsteroidal anti-inflammatory agent for analgesia. In both cases, due to the severity of azotemia, discontinuation of vancomycin and prompt institution of daily HD sessions led to

restoration of serum creatinine to the normal baseline values.

Vancomycin exposure: longer duration

Studies have also demonstrated the strong relationship between AKI and other similar measures of vancomycin exposure. In this regard, longer duration of therapy exceeding 7 days correlate with higher risk of nephrotoxicity in multiple studies [Hanrahan *et al.* 2015; Cano *et al.* 2012; Wong-Beringer *et al.* 2011; van Hal *et al.* 2013; Contreiras *et al.* 2014]. In one of these studies, there was 12% greater incidence of AKI for each additional day of treatment with vancomycin [Cano *et al.* 2012]. In another study, 21% of the patients on high-dose therapy (trough 15–20 mg/l) for more than 1 week, and 30% of those treated for more than 2 weeks sustained nephrotoxicity [Hidayat *et al.* 2006]. None of the patients on low-dose vancomycin (<15 mg/l) had AKI.

Vancomycin exposure: impaired glomerular filtration

Susceptibility to vancomycin renal toxicity is profoundly affected by clinical events that compromise glomerular filtration. Hence severity of acute illness [Acute Physiology and Chronic Health Evaluation (APACHE) II score], hemodynamic instability, and concurrent administration of nephrotoxic agents are recognized strong determinants of AKI [Hanrahan *et al.* 2015; Horey *et al.* 2012; Wong-Beringer *et al.* 2011]. In a retrospective study, there was 14% greater risk of VIN for those with higher APACHE II score while the concurrent use of aminoglycoside accounted for an 18-fold greater probability [Hanrahan *et al.* 2015]. Despite correction of confounding variables in regression analysis, coadministration of other agents that worsen renal perfusion including loop diuretics, vasopressors, angiotensin-converting enzyme inhibitors, and nonsteroidal anti-inflammatory drugs also increased the odds of developing AKI by 43-, 18-, 5- and 19-fold respectively [Matson *et al.* 2015].

The major shortcoming of these studies is the inability to deduce if there is causal association given that data on trough level of vancomycin were obtained in parallel with the incidence of AKI. However, these findings were corroborated by studies in which trough concentration was measured prior to the estimation of serum creatinine [Cano *et al.* 2012; van Hal *et al.* 2013]. After accounting for the temporal effect, the incidence of AKI was 21–28% in patients with other risk profiles compared with 7% in those lacking additional renal risk [Wong-Beringer *et al.* 2011]. In two similar studies corrected for this variable, the odds ratio for AKI among patients with vancomycin trough level at least 15 mg/l was 3.1 and 5.0 respectively [Cano *et al.* 2012; van Hal *et al.* 2013].

Vancomycin exposure: synergism with nephrotoxic agents

Although there is a low rate of renal toxicity with modest doses, vancomycin reduces the threshold for kidney injury while using other agents with potential nephrotoxicity. Such synergism has been observed with the combination of vancomycin and piperacillin–tazobactam [Burgess and Drew, 2014]. In a retrospective cohort, 8% of 99 adults treated with vancomycin had AKI while combination with piperacillin–tazobactam accounted for 16.3%. Similarly, there is a threefold greater occurrence of AKI when this combination was compared with the controls who were treated with a concurrent cefepime [Gomes *et al.* 2014]. Furthermore, in a pediatric study, concurrent use of vancomycin with acyclovir, amphotericin B and piperacillin–tazobactam significantly increased the risk of AKI respectively [Knoderer *et al.* 2015]. A major limitation of retrospective data is the uncertainty of the adverse renal impact while using other agents that were not part of the study. However, a similar pattern of results was realized in a prospective trial of 168 patients that compared three therapeutic modalities: AKI occurred in 5% of those treated with vancomycin, 22% of those who had vancomycin and aminoglycoside, and 11% of those treated with gentamicin only [Rybak *et al.* 1990].

Vancomycin exposure: high-risk populations

Nosocomial pneumonia. Hospital-acquired pneumonia, particularly when due to MRSA, is frequently associated with critical illness. Optimal antibiotic exposure may be limited by the concurrent use of assisted ventilation. Therapeutic success is determined by antibiotic availability on the epithelial lining fluid of the alveolar compartments [Rodvold *et al.* 2011]. Due to its water solubility, penetration of vancomycin across the alveolar capillary membrane is low, estimated as 5–41% [Rybak *et al.* 2009]. To overcome the poor

lung bioavailability, higher doses of vancomycin to achieve serum level with AUC greater than 345 may be warranted [Moise *et al*. 2000]. With plasma protein binding of 50–55% for vancomycin it may be extremely difficult to achieve adequate AUC/minimal inhibitory concentration (MIC) value for pathogen with MIC greater than 1 mg/; [Rybak *et al*. 2009; Harigaya *et al*. 2009]. Consequently there is a recommendation for aggressive dosing to attain a trough level of 15–20 mg/l. However, this has led to increasing reports ofVIN [Harigaya *et al*. 2009].Thus in a retrospective analysis of multi-institutional patients with critical health care associated pneumonia [Improving Medicine through Pathway Assessment of Critical Therapy of Hospital-Acquired Pneumonia (IMPACT-HAP) trial], nephrotoxicity occurred in 15.4% of 188 vancomycin-treated patients [Cano *et al*. 2012]. Similarly, aggressive treatment in 94 patients with pneumonia due to MRSA resulted in 42.6% of renal toxicity. Given the large doses required and to circumvent nephrotoxicity, alternative therapy (e.g. linezolid) is recommended if MIC is greater than 2 mg/l [Rybak *et al*. 2009; Chastre *et al*. 2014].

Intensive care unit. Larger doses of vancomycin are often required in patients in intensive care unit because the offending pathogens are less susceptible to the antibiotic. There is multiplefold greater MIC compared with the noncritically ill controls [Roberts *et al*. 2014]. In addition, apart from renal hypoperfusion in these patients, altered volume of distribution of vancomycin, a hydrophilic compound, aggravates susceptibility to renal injury [Roberts *et al*. 2014; Bagshaw *et al*. 2008]. In severe sepsis, increase in the volume of distribution ultimately results from widespread endothelial injury and excess administration of resuscitative fluids. Furthermore, as evident in animal experiments, endotoxemia *per se* increases the intrarenal distribution of vancomycin while there is a reduction in its elimination kinetics [Ngeleka *et al*. 1989]. Finally, due to the variability of pharmacokinetic parameters and the greater susceptibility to renal injury, therapeutic drug monitoring has been recommended in critically ill patients [Roberts *et al*. 2011].

Vancomycin exposure: obesity

Due to increases in both adipose tissue and skeletal muscle mass, there is a greater volume of distribution of vancomycin in patients with obesity compared with the healthy controls [Grace, 2012]. In addition, the increase in blood volume and cardiac output results in augmented renal delivery. Studies have examined the impact of greater drug exposure imposed by the use of unadjusted body weight to calculate the dose of vancomycin in patients with obesity [Davies *et al*. 2015; Matson *et al*. 2015]. Apparently influenced by the retrospective design, the results of such studies are inconsistent. Few studies showed higher vancomycin trough concentration in the absence of weight adjustment but most data found no difference in comparison with the controls [Heble *et al*. 2013; Le *et al*. 2015; Eiland and Sonawane, 2014]. Because sample sizes of the studies are often small, there may be a lack of adequate power to detect a significant difference. In addition, study outcome may reflect the imperfection of body mass index (deduced from height and weight) in the determination of adiposity. In a retrospective study of 530 patients stratified by body mass index (>30 kg/m^2), APACHE II score greater than 21 was the only variable associated with nephrotoxicity in a regression analysis [Davies *et al*. 2015]. There was no significant relationship between obesity and a higher risk of nephrotoxicity [Davies *et al*. 2015; Matson *et al*. 2015]. However, a different outcome was obtained in another study: there was fivefold greater likelihood of attaining a serum vancomycin greater than 20 mg/l in patients with exogenous obesity [Richardson *et al*. 2015].

Another factor that influences the outcome of these studies may be the threshold of the dose required for renal effect of vancomycin. This is best illustrated in a study with an adequate proportion of patients who have morbid obesity (weight $>$ 100 kg) [Lodise *et al*. 2008]. The requirement of disproportionately larger doses of vancomycin (calculated by actual body weight) led to a significant association with a greater number of events of VIN. Finally, given the predisposition of critically ill patients with obesity to succumb to AKI, more comprehensive studies on the renal impact and dosing strategy of vancomycin are needed in this population [Danziger *et al*. 2016].

Vancomycin toxicity in chronic kidney disease

The renal consequence of aggressive dosing of vancomycin is of particular significance in patients with chronic kidney disease (CKD) [Spadaro *et al*. 2015]. This is because approximately one third of

the patients admitted into the intensive care unit had a pre-existing CKD [Uchino *et al.* 2005]. Due to impaired renal autoregulation, critically ill patients with CKD are more likely to sustain AKI than those with normal renal function [Hoste *et al.* 2003]. Coadministration of vancomycin with other nephrotoxic agents (as in aminoglycosides) has been associated with greater severity of AKI and a lower probability of renal recovery [Paquette *et al.* 2015]. Incomplete renal recovery accelerates the progression of CKD, and may result in higher rates of cardiovascular morbidity and fatality [D'Hoore *et al.* 2015; Panwar *et al.* 2013].

The clinical issue encountered in patients with end-stage kidney disease (ESKD) is different. It is principally driven by the common use of a central line for vascular access. Seventy-seven percent of these patients had sepsis compared with 23% recorded for those dialyzed with either arteriovenous fistulas or grafts [Decker *et al.* 2010]. Case fatality rate from septicemia is quite high, about 20%. This is partly because MRSA accounts for more than 40% of the bacterial infection in this population [Klevens *et al.* 2008]. Given its common use as empirical treatment, there are reports of resistant pathogens: Vancomycin resistant enterococcus (VRE), Vancomycin intermediate staphylococcus aureus (VISA) and Vancomycin resistant staphylococcus aureus (VRSA) in the dialysis population [Pai and Pai, 2006; Fridkin, 2001; Centers for Disease Control and Prevention, 2002]. Hence a diligent dosing regimen of vancomycin is important to avoid compromise of the residual renal function. A fixed loading dose (1 g of intravenous vancomycin) given at the end of initial HD, and 0.5–1 g maintenance dose after subsequent dialysis provides adequate pre-HD drug level in 96% of patients (5–20 ug/ml) [Decker *et al.* 2010]. Other studies have found a relative advantage with a weight-based calculation of the loading doses [Brown *et al.* 2011]. This may be facilitated by the use of a preprogramed dose calculator [Vandecasteele *et al.* 2011].

Vancomycin-induced nephrotoxicity: pediatric studies

Studies on vancomycin-induced renal toxicity have been performed mostly in the adult population. There are few pediatric clinical trials and where available they are mostly of retrospective design [Goren *et al.* 1989; Nahata, 1987]. Although past studies had implied there was rarity of vancomycin-induced AKI in children, more recent data suggest otherwise. The incidence rate of vancomycin-associated AKI ranges from 12.6% to 27.2%. In a regression analysis of a study of 175 children, the likelihood of AKI increased by 16% with each 5 mg/kg vancomycin dosing and by 11% with every additional day of treatment [Sinclair *et al.* 2014]. Furthermore, there is fivefold higher incidence with a concurrent use of nephrotoxic drugs. Other notable determinants of VIN are critical illness, pretreatment kidney injury, and age less than 12 months [Knoderer *et al.* 2015; Ragab *et al.* 2013; Totapally *et al.* 2013]. Nevertheless, AKI is often modest in degree and it is frequently reversible. Although higher mortality rate occurred in patients who sustained AKI, there was restoration of baseline serum creatinine in the majority, 87% of the patients [Oktem *et al.* 2005].

Mechanisms of vancomycin-induced nephrotoxicity

Although the mechanism underlying renal toxicity from vancomycin is not fully understood, experimental studies supported proinflammatory oxidation, mitochondrial dysfunction and cellular apoptosis as the principal modes of injury. Oxidative phosphorylation by vancomycin induces free oxygen radicals and thereby reduces the activity of defensive antioxidative enzymes including superoxide dismutase and catalases. In experimental animals, coadministration (or pretreatment) of rats with antioxidative compounds that express superoxide dismutase attenuated proximal renal tubular injury with a favorable histological outcome [Oktem *et al.* 2005; Nishino *et al.* 2003]. Superoxide production by vancomycin causes depolarization of mitochondrial membrane potential with a release of cytochrome C, and a subsequent activation of both caspases 9 and 3 [Arimura *et al.* 2012; Humanes *et al.* 2015]. The latter is involved in apoptotic cell death. In support of apoptotic mechanism, overactivation of poly (adenosine diphosphate ribose) polymerase 1 (PARP-1) activity, a pathway involved in DNA repair, has been demonstrated in rats administered vancomycin [Dalaklioglu *et al.* 2010]. In this study, concurrent treatment with 1,5-isoquinelinediol, a PARP inhibitor, attenuated the intensity of the renal injury. Similarly, by reducing vancomycin cellular uptake, cilastatin inhibited dehydropeptidase on brush border modulated the apoptotic activity observed in a culture medium of porcine renal proximal tubular epithelial cells [Humanes *et al.* 2015].

Histological aspects of kidney injury

Given that vancomycin renal toxicity often occurs in the setting of critical illness and it is frequently self limiting, there is hardly any justification for kidney biopsy in most patients. Hence there are no systematic studies on the pattern of histological injury. However, there are multiple case reports of patients who have had kidney biopsy as clinically indicated [Wicklow *et al.* 2006; Wu *et al.* 2007; Hong *et al.* 2007; Plakogiannis and Nogid, 2007; Zuliani *et al.* 2005]. The histological findings on the majority of such reports are acute interstitial nephritis, a few of which were associated with non-caseating granuloma lesions. There are also rare instances of acute tubular necrosis [Wicklow *et al.* 2006; Wu *et al.* 2007; Hong *et al.* 2007; Plakogiannis *et al.* 2007]. In some of the reports, there were concurrent dermatological features: diffuse erythematous plaques, erythema multiforme and fatal toxic epidermal necrolysis [Plakogiannis *et al.* 2007; Hsu, 2001]. Despite the bias inherited in these reports they provide direct pathological evidence for a possible mechanism of injury in selected patients.

Apparently due to a rising frequency of use, vancomycin is increasingly recognized as a major etiological factor in Drug Rash with Eosinophilia and Systemic Symptoms (DRESS syndrome), a distinct but severe hypersensitivity reaction. Characteristic features include skin rash, fever, eosinophilia, atypical lymphocytes, lymphadenopathy and visceral involvement [Zuliani *et al.* 2005]. As part of the visceral components, acute interstitial nephritis occurs in about 10%. In a review of inpatient consultation at a Boston tertiary hospital over an 18-month period, six patients fulfilled the clinical criteria for DRESS syndrome [Blumenthal *et al.* 2012]. Eighty-three percent of these events were attributed to vancomycin, and there was elevated human herpesvirus 6 immunoglobulin G titer in 60% of the patients. Outcome is favorable with prompt withdrawal of the offending drugs and early institution of steroids but case fatality rate was close to 10% [Zuliani *et al.* 2005].

Prevention of vancomycin-induced AKI

Although most vancomycin nephrotoxic events are deemed reversible, available data support there is prolonged hospitalization, increased mortality rate and higher incidence of ESKD from AKI of any cause [Prendecki *et al.* 2016]. For this reason, awareness of these complications particularly in critically ill patients may allow prompt intervention. Customized dosing of vancomycin on the basis of patient characteristics, baseline creatinine clearance, pattern of microbial resistance, MIC of the pathogen involved, and specific population pharmacokinetics may be advantageous [Roberts *et al.* 2014]. However, there is need for comprehensive studies on the decision-making process for customized vancomycin dose adjustment on the basis of these parameters [van Hal *et al.* 2013].

Therapeutic drug monitoring

Although studies on the cost effectiveness of therapeutic monitoring are erroneously based on short-term outcome, there is suggestion of its benefit in high-risk clinical settings that include the following: patients who are being treated with a combination of vancomycin and a nephrotoxic agent (e.g. aminoglycosides); patients with CKD or ESKD and those who are undergoing HD; patients who are being treated with higher than usual doses of vancomycin (e.g. doses >4 g per day), which may include patients with pneumonia, endocarditis, osteomyelitis and meningitis; and critically ill patients who are likely to experience rapid changes in renal function [Darko *et al.* 2003]. Therapeutic effectiveness of vancomycin is independent of its concentration but it correlates with the duration at which the drug plasma level exceeds the MIC of the pathogen [Rybak *et al.* 2009]. Hence 24 h AUC relative to the MIC of the pathogen is recommended for the assessment of both efficacy and toxicity [Neely *et al.* 2014]. However, due to multiple blood samples and the complexity of AUC calculation, despite uncertain reliability trough levels are often used as the surrogates [Haeseker *et al.* 2015; Prybylski, 2015]. In a large-scale population study, compared with 24 h AUC/MIC ratio, vancomycin trough was poorly predictive of mortality rate in patients with staphylococcal bacteremia [Prybylski, 2015].

To overcome the aforementioned limitations, there are available strategies aimed at reducing the number of blood samples and to facilitate customization of antibiotic therapy [Roberts *et al.* 2014]. Normogram allows for adjustment of doses by comparing a measured concentration at a given time point with an expected therapeutic range for the same period on a graph [Brown *et al.* 2011; Pea *et al.* 2009; Kullar *et al.* 2011]. Nonlinear regression analysis derived from timed

collection of vancomycin concentration allows dose prediction using data projected from a population pharmacokinetic model (e.g. AUC). Looking into the future, Roberts and colleagues proposed the use of software packages with the capacity for prediction of dose for an individual based on Bayesian posterior pharmacokinetic parameters [Roberts *et al*. 2014; Burton *et al*. 1989]. Estimation of such parameters will be derived from input of data on patient characteristics, MIC of the pathogen and *a priori* population PK indices. The latter have been developed for children and adults with ESKD, malignancy, critical illness and neutropenia [Le *et al*. 2015; Haeseker *et al*. 2016; Camaione *et al*. 2013; Abdel Hadi *et al*. 2015; Revilla *et al*. 2010].

Drug modification

There is a recent attempt to enhance therapeutic efficacy while reducing renal toxicity of vancomycin by improving the drug delivery system [Yang *et al*. 2015]. This is achieved by liposomal modification of the water-soluble vancomycin hydrochloride, and wrapping the product with nanosuspension of chitosan using a electrostatic deposition technique. In comparison with the native vancomycin, intravenous injection of the liposomal variant in experimental mice showed much higher AUC values while there was a reduction of the renal tissue distribution. Similarly, synthesis of lipophilic vancomycin carbonhydrate analogs that exhibit greater than a 250-fold binding affinity against VanA and VanB strains of VRE has the potential of minimizing renal injury considerably [Yarlagadda *et al*. 2015]. Furthermore, to overcome the reduction in the affinity produced by a resistant pathogen (by alteration of vancomycin binding site on cell wall), structural modification of the antibiotic for dual binding to D-Ala-d-Ala and D-Ala-D-Lac terminals has been designed [Xie *et al*. 2011]. With the change in the ligand, there is a 600-fold increase in the binding strength relative to the native vancomycin compound.

Dosing strategy

Although drug monitoring may not be necessary in the majority of patients (with MIC <1 mg/l for the offending organism), such practice may improve effectiveness, reduce adverse effects and optimize cost–benefit in populations otherwise at high risk. As previously indicated, effective treatment with vancomycin requires attainment of a long duration of serum value that is well above the MIC of the pathogen being treated. Therefore the dosing regimen that takes into consideration the ratio of 24 h AUC and MIC will be cost beneficial [Cole and Riordan, 2013]. In addition, although validity studies are needed, data on children and young adults indicated vancomycin dosing based on body surface area is more likely than a weight-based regimen to achieve isometric 24 h AUC values [Camaione *et al*. 2013].

Continuous instead of intermittent infusion of vancomycin has been suggested as a cost-effective means of achieving the pharmacodynamics goal (24 h AUC/MIC $>$ 400) [Revilla *et al*. 2010; Wysocki *et al*. 2001]. It requires less frequent blood sampling while achieving rapid onset of the desired plasma concentration at a steady state [Revilla *et al*. 2010; Wysocki *et al*. 2001; Hong *et al*. 2015]. In addition it is associated with a slower onset of AKI but there was no difference in either efficacy or the rate of renal toxicity [Hanrahan *et al*. 2015; Hong *et al*. 2015; DiMondi and Rafferty, 2013]. The argument that goes against the use of continuous infusion is the relative long half life of vancomycin and the concentration-independent therapeutic effectiveness. It has been postulated that the poor selection of patients who will benefit optimally from continuous infusion may account for the difficulty in demonstrating its advantage over the intermittent mode of administration [Vandecasteele *et al*. 2011]. Prospective randomized trials in critically ill patients that controls for the confounding effects of the degree of pathogen resistance (MIC) may clarify the definitive role of continuous infusion of vancomycin.

Therapeutic strategy for vancomycin-induced AKI

Given the increasing burden of vancomycin-induced AKI, particularly in patients with complex life-threatening clinical conditions, the preventive strategies discussed above remain the ultimate goal of minimizing mortality rate in this population [Hsu *et al.* 2016]. Nevertheless, despite the inherent challenges encountered in the past years, there is need for a continued effort towards achieving optimal therapeutic interventions [Okusa *et al.* 2016]. In this regard, the model of AKI that is most susceptible to pharmacological modulation is that due to pro-oxidative inflammation as in contrast-induced nephropathy [Huang *et al.* 2016]. In view of a similar pathophysiology,

in the face of vancomycin cytotoxicity, renal perfusion must be maintained by ensuring there is adequate intravenous hydration. This measure will potentially reverse renal vasoconstriction as induced by free oxygen radicals while reducing vancomycin toxic exposure to the proximal tubular cells by optimizing renal clearance.

Antioxidative therapy

Antioxidative biological agents that have been successfully used in animal studies are hexamethylenediamine-conjugated superoxide dismutase, erdosteine, vitamin E, vitamin C, N-acetylcysteine, caffeic acid phenethyl ester, and recombinant human erythropoietin [Elyasi *et al.* 2012; Oktem *et al.* 2005; Nishino *et al.* 2003; Cetin *et al.* 2007; Ocak *et al.* 2007]. However, in at least one study, there was a benefit from the use of iron-chelating antioxidant, 2,3-dihydroxybenzoic acid but there was no protection from 4-hydroxyl-2,2,6,6-tetramethylpiperidine-1-oxyl (Tempol; Sigma-Aldrich Co. LLC; 3050 Spruce St., St. Louis MO 63178), a superoxide dismutase mimetic compound [Naghibi *et al.* 2007]. These therapeutic agents enhance the survival of renal tubular cells by reducing DNA fragmentation, apoptosis and necrosis; and in certain instances by the modulation of autophagy [Huang *et al.* 2016]. Nevertheless, in contrast to the effect of cilastatin previously discussed, it is unclear if antioxidative strategy would place a limitation on the bactericidal activity of vancomycin [Humanes *et al.* 2015]. Clinical trials are therefore needed to validate the renal protective advantage of these agents in the human population.

In summary, data available on vancomycin-induced renal toxicity showed limitation in proving a causal effect association because of the inherent methodology flaws that include lack of temporal relationship, retrospective design, inadequate study power (limited by sample size) and strong interference by confounding variables. However, there seems to be a trend in support of a dose–response relationship: higher vancomycin doses in several clinical settings correlate with renal toxicity. In addition, most reported studies are supportive of synergistic effects of vancomycin with other nephrotoxic agents and in clinical conditions that compromise glomerular filtration. There is a need for standardization of vancomycin-induced renal injury to facilitate early diagnosis, prompt intervention and for the sake of comparative analysis of research studies. In this regard, upcoming novel diagnostic biomarkers of AKI may be of potential application.

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