

Vancomycin-Induced Nephrotoxicity

Ahmad Bilal^{*1,2}, Omar Abu-Romeh^{*1,2}, Talla A. Rousan² and Kai Lau^{1,2,3}

¹Section of Nephrology

²Department of Medicine

³VA Medical Center

University of Oklahoma Health Sciences Center

University of Oklahoma Medical Center and VA Medical Center

Oklahoma City, OK

USA

1. Introduction

Nephrotoxicity associated with vancomycin administration has been a topic of debate for over five decades (Tables 1 & 2). Vancomycin is a glycopeptide antibiotic excreted by the kidney and has been used extensively, especially for methicillin-resistant staphylococcus aureus (MRSA) and for many strains of pathogenic staphylococcus epidermidis. The nephrotoxic potential of vancomycin is neither fully appreciated nor well characterized. Previously, most reports of acute kidney injury (AKI) associated with vancomycin had blamed the acute renal failure (ARF) on early, relatively impure formulations of vancomycin (impurities popularly known as Mississippi mud). This conventional belief and the ensuing ambiguity if not controversy in the literature about its nephrotoxic potential have led to common notion that it is rather innocuous. Its popularity as an inexpensive and effective anti-staph medication and its widespread use had contributed to the increased incidence of AKI. But the impurity theory no longer holds because the modern purified preparations are devoid of additives.

The incidence of vancomycin (Van)-induced AKI (Van-AKI) has been on the rise due to (1) the staphylococcal epidemic, (2) the increasing incidence of health-care associated pneumonia (HCAP) and osteomyelitis (due to mounting use of prosthetic hard-wares and more ready diagnosis by routine MRI and CT scans), and (3) wider acceptance and practice of protracted vancomycin administration as outpatient or in nursing homes, where unfortunately physician involvement and toxicity monitoring are inherently less vigorous.

This issue is further compounded by the poor recognition and/or delayed diagnosis due to (1) the outdated notion that vancomycin is relatively benign and safe (Sorrel et al 1985, Kalil et al 2010), (2) the lack of modern guidelines in drug and creatinine monitoring, (3) the recent Infectious Disease (ID) recommendation to target trough levels of 15-20 mg/L in treating MRSA with potentially higher minimal inhibitory concentration (MIC) than the typical sensitivity range of <1 mg/L, (4) the prevailing assumption of renal tolerance based on absolute serum creatinine levels below certain rather arbitrary threshold, instead of using changes in serum creatinine or changes in estimated creatinine clearance from baseline, and

* Both authors contributed equally to the work in this Chapter)

Authors & Publication years	Aim of study	Key Results and Conclusions
Farber et al 1983	Retrospective study of toxicity of preparations of Vancomycin from 1974 to 1981	Possibility of additive toxicity between vancomycin and aminoglycosides should be considered
Sorrell et al 1985	A prospective study of adverse reactions of vancomycin therapy	Vancomycin is a safe drug with minimal side effects as long as levels are kept below 10 mg/L
Bailie et al 1988	Literature review of vancomycin induced nephrotoxicity and ototoxicity.	Area under the curve (AUC) is more important in determining the toxicity of vancomycin as compared to magnitude of peak concentration.
Goetz et al 1993	Prospective study to compare toxicity of vancomycin and aminoglycosides in combination and alone.	Combination of vancomycin and aminoglycosides is more nephrotoxic than individual agents alone
Vance-Bryan et al 1994	Comparative assessment of vancomycin toxicity in young and elderly hospitalized patients	Risk of nephrotoxicity in elderly is greater than young and independent of aminoglycoside administration
Ingram et al 2008	To identify risk factors of nephrotoxicity with continuous vancomycin infusion in outpatient setting	Serum steady-state vancomycin levels >28 mg/L markedly increase the risk of nephrotoxicity
Pritchard et al 2008	Relationship between increasing vancomycin trough concentrations and incidence of nephrotoxicity	Increasing trough vancomycin levels >14 mg/L and length of therapy increase the risk of nephrotoxicity
Lodise et al 2008	To determine nephrotoxic potential of vancomycin based on dosage and compare to linezolid	Vancomycin > 4 g/day are associated with 3-fold increased rates of nephrotoxicity vs. < 4 g/day; both doses associated with higher risks than linezolid
Pertel et al 2009	To determine efficacy and safety of daptomycin vs vancomycin against cellulitis	Daptomycin is superior to vancomycin in treating cellulitis and has with minimal side effect profile
Kalil et al 2010	Linezolid vs vancomycin or teicoplanin for nosocomial pneumonia	Vancomycin and teicoplanin are not associated with more renal dysfunction as compared to linezolid.
Colomo et al 2010	Impact of administration of vancomycin or linezolid to critically ill patients	Vancomycin should be used with caution in critically ill patients with acute renal failure

Table 1. Literature on Vancomycin-induced Nephrotoxicity: Large Epidemiologic Surveys and Drug Toxicity & Efficacy Monitoring Studies

(4) the failure to appreciate AKI causes accumulation of the renally excreted vancomycin, excess of which in turn inflicts further damage to the kidney, setting up a vicious cycle.

Indeed, the literature is replete with observational studies (Table 1) and case reports (Table 2) which in the overall aggregate provide a large body of evidence in support of the contention that vancomycin could be nephrotoxic. Although published studies monitoring

Authors and publication dates	No. of patients	Highest serum vancomycin levels (mg/L)	Other Unexcluded Confounding or Contributing Factors to ARF
Duton and Elmes (1959)	4	Not given	Pre-existing renal disease in all 4; given 6-13 g over 2-5 days & as boluses in 30 min
Farber et al (1983)	12	39 - 65	Use of aminoglycosides, pre-existing renal disease
Odio et al (1984)	4	Not given	Concurrent aminoglycosides, 3 patients had pre-existing renal disease
Frimat et al (1995)	1	50	None
Sokol et al (2004)	1	Not given	Bacteremia, concomitant nephrotoxins (piperacillin/tazobactam, amikacin)
Barraclough et al (2007)	1	66	None
Ladino et al (2008)	5	42 - 86	Sepsis in 1, Bacteremia in 1, and acute allergic interstitial nephritis in 1
Psevdos et al (2009)	2	38.6 - 60.5	HIV
Shah-Khan et al (2011)	1	64.7	Sepsis secondary to Serratia marcescens
Bilal, Abu-Romeh, Rousan & Lau (2011) [current study]	6	38 - 110; Mean \pm SE (70 \pm 10)	None

Table 2. Case reports describing Vancomycin-induced Nephrotoxicity

adverse events in large cohorts usually succeeded in identifying a substantial and statistically significant incidence of renal complications (Bailie et al., (1988); Colomo et al., (2010); Farber et al., (1983); Goetz et al., (1993); Hidayat et al., (2006); Ingram et al., (2008); Lodise et al., (2008); Pritchard et al., (2008); Rybak et al., (1990); Vance-Bryan et al., (1994)), due to the inherently retrospective and epidemiologic nature, most if not all such large-group analyses were unable to capture sufficient key details in the affected individual patients to unequivocally establish a cause-and-effect relationship. There are also growing numbers of case reports, albeit less than two dozen spanning over 50 years, which attributed the AKI to vancomycin (Barraclough et al., (2007); Dangerfield et al., (1960); Dutton & Elmes et al., (1959); Frimat et al., (1995); Ladino et al., (2008); Odio et al., (1984); Psevdos et al., (2009); Shah-Khan et al., (2011); Sokol et al., (2004)). But as will be reviewed in detail below, they often failed to definitely exclude other potential causes of acute renal failure (ARF), including sepsis, allergic interstitial nephritis, urinary tract obstruction, hemodynamic derangements, other concomitant nephrotoxic agents, radio-contrast dyes, ischemia, volume depletion, and other intrinsic renal insults.

2. Objectives

We have three objectives in writing this chapter. One, we shall draw upon the evidence from a thorough review of the published literature and from the detailed analyses of our own experience to argue for the existence of Van-AKI. Two, based on the insights deduced from these two sources, we will describe and characterize the typical picture of Van-AKI,

the renal functional profile in the evolution of the ARF and the recovery. We will also outline the lessons that could be learned for safer but equally effective administration of vancomycin. Three, we will recommend some simple practical guidelines designed to prevent and/or ameliorate the emergence of Van-AKI.

3. Methods

Objective 1: To better document and more firmly establish the existence of Van-AKI

We approached this objective in two ways. First, we performed a systematic search and a careful review of the existing literature (Tables 1 & 2) using Pub-Med, Web of Science, Medline (OVID), Journal Citation Reports (ISI), Cochrane Database of Systematic Reviews, and Current Contents. Secondary references cited from these primary sources were also considered and reviewed with a focus on the published evidence in support of or against the entity of vancomycin nephrotoxicity. Search terms included acute renal failure (ARF), AKI, acute tubular necrosis, nephrotoxicity, renal insufficiency, renal failure, elevated creatinine, decline or deterioration in renal function or glomerular filtration rate or creatinine clearance, all cross-referenced with vancomycin. All studies with sufficient details on methods that are amendable to critical reviews were considered and only those with conclusions supported by the presented data or results were then included in Tables 1 & 2.

Second, we carefully and objectively analyzed the data from 101 consecutive patients evaluated for ARF (from among a total of 153 cases referred for renal consultation in the course of the month of services (Table 3). The renal consultative service was provided to adult patients admitted to the Hospitals of the University of Oklahoma Health Sciences Center (OUHSC) with a 450-bed capacity for acute or tertiary care. After excluding pre-renal and post-renal causes for ARF using the traditional or conventional clinical criteria and renal ultrasound, we found intra-renal insults in 78 patients from among the 101 with ARF (Table 4). Additional diagnostic studies and analyses of the clinical presentation and subsequent course allowed us to assign an etiologic factor accounting for the intra-renal ARF (Table 5). We have identified 6 patients with ARF with clinical and laboratory data and subsequent recovery course that unequivocally support the causal role of vancomycin in the AKI.

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| 1. Inter- or concurrent issues in patients with known end-stage renal diseases (N=41). |
| 2. Issues unrelated to acute kidney injury (AKI), acute renal failure (ARF) or chronic kidney diseases (N=11). |
| electrolytes disorders n=4 |
| transplantation issues n=2 |
| fluid management n=4 |
| drug overdose n=1 |
| 3. AKI or ARF (N=101). |

Table 3. Indications for Renal Consultations (analysis of the 153 cases seen over a month)

In analyzing the potential etiologies of their AKI, we have vigorously ruled out sepsis, bacteremia, urinary tract obstruction, volume depletion, and any conceivable concomitant nephrotoxic antibiotics or intra-renal or intrinsic insults so that we could convincingly pin down vancomycin as the principal culprit. Based on serial drug levels, daily and

cumulative administered doses, the temporal relationship between drug administration and changing renal function, the profile of renal failure, and the course of recovery upon stopping vancomycin, we believe other confounding variables could be excluded with a high degree of certainty. As opposed to the previous era when vancomycin was typically and invariably administered to patients along with an aminoglycoside or amphotericin B (typically for overt or presumed sepsis, bacteremia, or neutropenic fever), the recent practice of treating HCAP with triple antibiotics consisting of vancomycin but no other known nephrotoxins has provided a unique opportunity to witness and document AKI in the absence of other nephrotoxic insults. The absence of bacteremia or sepsis also helps eliminate a key confounding variable that previously precluded isolation of vancomycin as the culprit. Similarly, with the heightened detection and increased diagnosis of osteomyelitis by CT or MRI, more and more patients have been treated with long-term antibiotic regimen composed of vancomycin but not aminoglycoside. Since these patients are relatively asymptomatic and generally free of bacteremia on pre-treatment blood cultures, their subsequent development of AKI could reasonably be attributed to the adverse effects of antibiotics like vancomycin. Thus these two groups of patients (vancomycin-treated HCAP or osteomyelitis of undefined pathogens) have unwittingly provided a wonderful chance for clinicians to document the diagnosis of Van-AKI, an entity which had previously been questioned and debated because of the presence of other potential but unexcluded nephrotoxic insults.

- A. Post-renal or obstructive nephropathy
(N=4 or 4% of all AKI).
- B. Pre-renal (N=19 or 19% of all AKI)
volume depletion, n=8;
hemodynamic issues, n=11;
(atrial fibrillation, bleeding, myocardial
ischemia, or hypotension).
- C. Intra-renal insults (N=78 or 77% of all AKI).

Table 4. Acute Kidney Injury (AKI) or Acute Renal Failure (ARF) (N=101)

Objective 2: To describe and characterize the clinical and renal function profile for a typical Van-AKI, using lessons and insights from the reviewed literature and our own experience

To this end, we examined and tested the validity of the various independent risk factors proposed from the literature, namely serum vancomycin levels, total dose administered, and the duration of administration in our group of 6 patients. We attempted to generate insights from our own experience and that of the literature by doing the following statistical analyses. We first grouped their demographic data and clinical characteristics including hematologic data. We abstracted and tabulated the various parameters and indices of vancomycin therapy and longitudinal renal function, for each patient and also the entire group, using 100/serum creatinine as the estimate of creatinine clearance (CrCl) (Table 6). We analyzed their serial serum creatinine (and the associated CrCl) by calculating group means (and variance as standard errors), throughout the entire course of their AKI (Figure 7), starting from their initial baseline, to the days just before serum vancomycin reached its peak, through the days of peak vancomycin levels, then the days of peak serum creatinine,

	Number	% of Intra-renal Insults
(1) Sepsis or septic shock	(45)	(58%)
(2) Unknown or multifactorial	(11)	(14%)
(3) Allergic interstitial nephritis	(7)	(9%)
(4) Radio-contrast dye	(3)	(4%)
(5) Rhabdomyolysis	(2)	(3%)
(6) Nephrotoxic antibiotics	(10)	(13%)
(a) Colistin	(1)	(1.3%)
(b) Amphotericin B	(1)	(1.3%)
(c) Vancomycin	(4 solo) (4 major)	(5%)

Table 5. For Intra-renal insults (N = 78 or 77% of the 101 cases of Acute Kidney Injury)

the days of nadir vancomycin levels, and finally to the days of nadir serum creatinine at maximal recovery 60 days after the initiation of vancomycin. We also plotted serial vancomycin levels against the renal functional profile to evaluate and define the temporal relationships between drug levels and kidney function during the evolution of and recovery from AKI (Fig 7).

Objective 3: To generate and provide simple practical guidelines and recommendations to minimize vancomycin nephrotoxicity

Inferences from the analyses performed for Objective 2 will provide the basis for us to formulate the proposed guidelines designed to prevent and /or ameliorate the emergence of Van-AKI. These will be elaborated as a narrative in the Results section and presented in a tabulated format (Table 7) in the final Conclusion and Recommendations.

4. Findings

Results for objective 1: Evidence for the existence of Van-AKI

Towards objective 1, the findings of our current studies reported here belong to two sections. In the first section (A), we have performed and will present a comprehensive, systematic, and an up-to-date literature review to draw on all described indirect and circumstantial evidence cited to support the concept and the existence of Van-AKI. In the second section (B), we shall describe the 6 patients we personally saw and helped manage who were consulted for acute renal failure and in whom we found compelling evidence for the diagnosis of Van-AKI. We will detail their presentation and the clinical course of their ARF. We shall provide serial laboratory findings to document the causality of vancomycin, including their recovery course following the discontinuation of the offending agent.

(A) Evidence for Van-AKI based on literature review

The literature has provided two independent sources of indirect evidence in support of the issue of Van-AKI. The first body of evidence (1) (Table 1) comes from several epidemiologic

surveys and drug toxicity monitoring studies performed in sizable patient cohorts taking vancomycin, which suggested an association between the drug and acute elevation of serum creatinine (Farber et al. (1983), Sorrell et al. (1985), Bailie et al. (1988), Rybak et al. (1990), Goetz et al. (1993), Vance-Bryan et al. (1994), Hidayat et al. (2006), Lodise et al. (2008), Pritchard et al. (2008), Ingram et al. (2008), Pertel et al. (2009), Kalil et al. (2010), Rodriguez Colomo et al. (2010). The second body of evidence (2) (Table 2) is based on the growing number of case reports describing the association between acute nephrotoxicity and vancomycin (Dutton & Elmes et al.(1959), Dangerfield et al. (1960), Odio et al. (1984), Frimat et al. (1995), Sokol et al. (2004), Barraclough et al. (2007), Ladino et al. (2008), Psevdos et al. (2009)).

(A) (1): Epidemiologic and drug toxicity monitoring studies

These studies have collectively provided four lines of evidence implicating vancomycin in the pathophysiology of AKI: (a) Correlation between acute rise in serum creatinine and high serum vancomycin levels (Rybak et al 1990, Hidayat et al 2006, Ingram et al 2008, Lodise et al 2008, Pritchard et al 2008); (b) Increased incidence of acute renal failure (or potentiation of nephrotoxicity) when vancomycin was also administered concurrent with aminoglycosides (Farber et al 1983, Rybak et al 1990, Goetz et al 1993); (c) Increased incidence of AKI with prolonged duration of vancomycin therapy (Hidayat et al, 2006, Pitchard et al 2008); (d) Increased incidence of AKI with vancomycin compared to linezolid in comparable cohorts with similar patient characteristics (Lodise et al 2008, Colomo et al, 2010). The studies providing these four lines of evidence will be presented in the same order.

- a. ARF was more often associated with a higher steady-state or trough serum vancomycin levels and linked to higher daily doses.

Rybak et al reported in 1990 that higher serum trough vancomycin levels were associated with the development of elevated serum creatinine (Rybak et al., 1990). In the ensuing two decades, this observation was not only confirmed but also extended by the studies of Hidayat et al (2006), Ingram et al (2008), and Lodise et al (2008).

Since the new millennium, the widespread use of vancomycin has led to the expected emergence of strains of methicillin resistant staphylococcus aureus (MRSA) that have only intermediate sensitivity to vancomycin, based on higher than the classical minimum inhibitory concentration (MIC) of 1 mg/L. Accordingly, the Infectious Disease (ID) guidelines have recommended higher trough concentrations like between 15-20 mg/L (Rybak et al., 2009) in order to maximize the chances of eradicating such infections. One unintended consequence was the apparent rise in the incidence of AKI by following such guidelines too rigidly but without closer vigilance of the level of renal function.

Thus, in a prospective study on the efficacy and toxicity of vancomycin during treatment of these relatively resistant MRSA strains by targeting and achieving the higher trough level of 15-20 mg/L, Hidayat et al. (2006) not only noted a higher mortality rate and a poorer end-of-treatment response, but also the development of nephrotoxicity in the subset of patients with demonstrably higher trough levels.

In 2008, Ingram et al. performed a retrospective cohort study of 102 adults to identify risk factors for nephrotoxicity during continuous outpatient vancomycin administration between 2004 and 2007. The incidence of nephrotoxicity, defined as $\geq 50\%$ increase in baseline serum creatinine, was about 15.7%. Based on their analyses, a steady-state serum vancomycin concentration of ≥ 28 mg/L was thought to be an independent risk factor for developing nephrotoxicity.

Since the published new ID guidelines to keep trough level between 15-20 mg/L for resistant strains of MRSA, a good number of clinicians have increased the dose to >4 g/day

to achieve the recommended required trough levels. This approach has afforded an opportunity for Lodise et al. (2008) to conduct a retrospective cohort study to describe the impact of ≥ 4 g/day of vancomycin on renal function. They found a 3-fold greater incidence of nephrotoxicity in patients receiving >4 g vancomycin/day (34.6 %) versus those receiving <4 g /day (10.9%). In the same review, these investigators also found a much lower incidence of renal failure in similar patients who received only linezolid (6.7%) as opposed to either > 4 or < 4 g /day of vancomycin ($P=0.001$).

Pritchard et al. (2008) conducted a retrospective analysis of ~ 3,000 courses of vancomycin given between 2003 and 2007. The aim of their study was to determine the relationship between vancomycin trough concentrations and nephrotoxicity. They noted that trough levels >14 mg/L was an independent risk factor for renal injury among others to be elaborated below.

In contrast, when serum trough vancomycin levels were prospectively limited to the lower range of 5 to 10 mg/L and if peak levels were kept ~ 28 mg/L, in 1985, Sorrel et al found no AKI with vancomycin (when used alone in two patients) and < 8% incidence of AKI even if combined with an aminoglycoside among the 54 patients studied. Taken together, these findings indicate that vancomycin must be considered nephrotoxic, especially at high serum levels, although it was found to be relatively safe at low trough or steady-state levels.

Parenthetically, Bailie et al. (1988) had reviewed the utility of peak serum levels as an indicator of vancomycin induced nephrotoxicity and ototoxicity. They determined that peak vancomycin concentration per se may be relatively minor in producing and predicting nephrotoxicity as opposed to the total area under the serum concentration-time curve (AUC).

b. Increased incidence of AKI when vancomycin was concurrently administered with an aminoglycoside.

At least three to four studies have found the synergistic nephrotoxic potential between vancomycin and aminoglycosides. In a retrospective study, Farber et al in 1983 found that more patients who received both vancomycin and gentamicin (12 of 34) had suffered from nephrotoxicity as compared to those getting vancomycin alone (3 of 60) with a p value of <0.001 . In the studies by Sorrel et al (1985), AKI was found in 4 of 54 vancomycin-treated patients, but all 4 had also received aminoglycosides. In contrast, no AKI was found in the two on vancomycin alone.

These findings, however, were not uniformly observed (Downs et al. in 1989, Cimino et al. in 1987, Mellor et al. in 1985), perhaps due to intrinsic differences in their patient characteristics, definitions of acute renal failure, and the divergence in their study methods. In contrast, in 1990 Rybak et al. confirmed that the combination of aminoglycosides and vancomycin was more nephrotoxic than either drug alone.

The prospective studies by Goetz & Sayer published in 1993 provided corroboration for the additive nephrotoxic potential between vancomycin and aminoglycosides. The incidence of nephrotoxicity was 19% in patients receiving vancomycin alone, 12% in patients receiving an aminoglycoside alone and 24% in patients receiving combined vancomycin and an aminoglycoside.

c. Increased incidence of AKI with prolonged vancomycin administration.

Several studies have led to the conclusion that prolonged therapy with vancomycin was a risk factor for AKI (Goetz & Sayer 1993, Hidayat et al 2006, Pritchard et al 2008). Besides showing the synergism between aminoglycosides and vancomycin in causing AKI, Goetz & Sayer observed that a duration of >21 days posed greater risk for renal toxicity. In

the prospective studies by Hidayat et al on targeting higher trough vancomycin levels for MRSA strains with high MIC, they not only confirmed the previous association between high trough levels and nephrotoxicity, but also a link between prolonged treatment and AKI.

The retrospective review by Pritchard et al in 2008 also identified the duration of vancomycin administration as an independent risk factor. In their studies of ~ 3,000 courses of vancomycin given between 2003 and 2007, they observed that therapy over 7 days was associated with AKI. They also suggested baseline serum creatinine > 1.7 mg/dl as another independent risk factor. It is however unclear if this association merely reflects a heightened sensitivity of the clinicians to AKI, an enhanced detection of renal failure with an already elevated baseline creatinine, and/or intrinsically greater susceptibility of chronically diseased kidneys to new and acute insults.

d. Increased incidence of AKI or slower recovery from pre-existing ARF if treated with vancomycin versus linezolid.

In the retrospective review by Lodise et al (2008) on the impact of ≥ 4 g/day of vancomycin, they also found a significantly lower incidence of renal failure in patients on linezolid (6.7% vs. 34.6% in patients on > 4 g /day or 10.9 % in those on < 4 g /day) ($P=0.001$). In the treatment of nosocomial pneumonia, Kalil et al (2010) performed a meta-analysis to test the hypothesis of the superiority of linezolid over vancomycin. But they found no significant difference in either vancomycin efficacy or risks of renal dysfunctions, although the study was not powered to compare the nephrotoxic potential between the two drugs.

Rodriguez Colomo et al. (2010) conducted a retrospective, multicenter observational study in patients in intensive care unit with pre-existing renal failure. They found that those patients treated with linezolid had a better renal recovery than those treated with vancomycin, implying either continued nephrotoxic susceptibility or superimposed injury with vancomycin in these cohorts.

In brief, despite the mounting body of indirect evidence summarized above suggesting a role of vancomycin in AKI, firm and unambiguous proofs for a cause-and-effect linkage remain elusive. Virtually all of the studies cited and reviewed above did not offer sufficient details on those individual patients with presumed Van-AKI to allow independent and objective confirmation of a causal and unequivocal relationship. Inherent in the nature of these large-cohort surveys and drug toxicity monitoring studies, despite showing statistical significance among different cohorts, none of the other known and potential etiologic factors for the ARF could be readily evaluated in individual affected patients, let alone vigorously excluded. For instance, the evolution of their serial renal function and the subsequent clinical course after cessation of vancomycin were either not provided or extractable from those individuals afflicted with AKI. A larger prospective study with sufficient clinical details is therefore needed to objectively eliminate all other confounding variables and to prove the implied cause-and-effect relationship.

(A) (2): Evidence for Van-AKI based on published case reports

Between 1956 and 1986, 57 cases of ARF were described in the course of vancomycin administration and had been attributed to vancomycin. However, over a half of them were reported within the first 6 years of vancomycin use, when impurities were considered to be the most likely culprit (Bailie & Neal 1988)

Although they spanned out over 5 decades in the medical literature, there have been but fewer than two dozen well documented cases of ARF which can be confidently and

objectively attributed to vancomycin (Dutton & Elmes et al (1959), Dangerfield et al (1960), Odio et al (1984), Frimat et al (1995), Sokol et al (2004), Barracough et al (2007), Ladino et al (2008), Psevdos et al (2009), Shah-Khan et al (2011)) (Table 2).

A very early case series was described by Dutton & Elmes (1959) who reported that 4 out of 9 vancomycin-treated patients developed renal failure (Table 2). The authors did not measure vancomycin or report drug levels. Unfortunately, all 4 affected patients had suffered from pre-existing renal diseases. Most remarkably, they had all received relatively high doses of vancomycin (between 6-13 grams over 2-5 days). One described method of administration involved rather rapid direct injection in 20 ml saline over only 5 minutes. In retrospect, the high dose and the bolus injection might have resulted in excessive blood and renal tissue concentrations and contributed to the high rates of acute nephrotoxicity, as clearly demonstrated by the dosage comparison studies of Lodise et al (2008).

Dangerfield et al (1960) described nephrotoxicity in 11 out of 85 patients in their series. They defined nephrotoxicity as an otherwise unexplained elevation in serum creatinine $\geq 0.5\text{mg/dl}$. Eight of these patients had no pre-existing renal disease. Follow up demonstrated a return to baseline renal function in 3-4 weeks. No serum vancomycin concentrations were reported. More importantly, no details on these 11 patients were provided for an objective review or an independent confirmation that no other factors could have contributed to the ARF. Since patients with serious infections requiring vancomycin therapy could have concurrent sepsis, hemodynamic derangements, volume depletion and/or dehydration, it remains unclear if the well known etiologies for AKI had been systematically and definitively excluded, especially if the criterion for ARF was a simply fixed serum creatinine elevation of 0.5 mg/dl irrespective of the starting baseline levels. The actual drop in glomerular filtration rate (GFR) is relatively minor ($\sim 10\text{ ml/min}$ or $\sim 10\%$) if serum creatinine rose from a baseline of 2 to 2.5 mg/dl, which could be easily explained by many pre-renal factors. In contrast, a rise in serum creatinine from a baseline of 1 to 1.5 mg/dl could easily reflect $\sim 33\text{ ml/min}$ or $\sim 33\%$ drop in GFR. Thus at the very best, these generalized descriptions offer no stronger evidence for Van-AKI than that inferred from large efficacy and toxicity studies reviewed and commented above [(A) (1); Table 1].

Each of the report by Frimat et al (1995) and by Barracough et al (2007) described a case in which they found no alternative explanations for the ARF except vancomycin (Table 2). In the former report, the patient received 39 grams of vancomycin over 17 days, with a peak drug level of 50 mg/L. The patient needed 2 sessions of hemodialysis before the renal function very slowly recovered over > 2 months. In the latter report, the patient had a peak vancomycin level of 66 mg/L and had no other plausible explanation for ARF. Kidney function recovered to baseline in 5-6 weeks. In our opinion, these 2 cases demonstrated rather convincingly the causal relationship between vancomycin and the associated ARF, very similar to our 6 patients to be described below (see Fig 1-6 and Table 6).

In 2008 Ladino et al. presented a case series of 5 patients believed to be Van-AKI. Vancomycin levels were reported to be between 42-86 mg/L and renal function recovered in 3-4 weeks after stopping vancomycin. These authors believed that they had ruled out other causes of ARF. However, in three of the five, there were equally viable etiologic explanations. Thus, one patient had full-blown sepsis, another had bacteremia, and the third had evidence for acute interstitial nephritis (AIN), making it difficult to accept vancomycin as the principal or sole culprit.

In 2011 a case of renal biopsy-proven acute tubular necrosis (ATN) was reported. The authors attributed the ARF to 5 g of intravenous vancomycin given in $< 24\text{ h}$ to a 103-kg

young man with chills, high fever, tachycardia and catheter infected with *Serratia* (Shah-Khan et al (2011)). He appeared to be septic from a PICC line and exit site infection although peripheral blood culture was negative and there was no frank hypotension. Serum creatinine rose from 0.97 to 4.26 mg/dl in a day and required three hemodialysis treatments for several days of severe oliguria, a serum vancomycin of 64.7 mg/L on day 4, and a sustained elevation of creatinine > 9 mg/dl from days 4 to 9. Although urine output rose to 1-2.5 liters a day since day 5, serum creatinine remained elevated at 1.24 mg/dl even by day 30. The AKI in this man confirmed the observation and caution by Lodise et al (2008) that >4 g of vancomycin /day posed extra nephrotoxic risks. The rapidity of his functional recovery, albeit incomplete, might be related to the single day of brief exposure to vancomycin although excessive in total quantity.

The difficulty of identifying in 5 decades even 2 dozen cases of definite or probable Van-AKI serve to explain the uncertainty and continued controversy regarding the nephrotoxicity of vancomycin. Although there have been many other reports of vancomycin-associated nephrotoxicity, most of them turned out to have been very poorly documented. In most of them, some other renal insults could be easily identified to explain their ARF if only the clinical details were more meticulously, comprehensively, and/or objectively analyzed. In general, often overlooked and/or frequently missed were the concomitant aminoglycosides or nephrotoxic medications, coexisting sepsis or bacteremia, hypotension, hemodynamic factors, pre-existing renal diseases, radio-contrast dye insults, and/or allergic interstitial nephritis. In all objectivity, these factors proved to be the more reasonable and probable etiologies for the ARF without necessarily invoking vancomycin.

To offer more vigorous evidence for Van-AKI, we will describe in the following section B our 6 patients. We shall provide sufficient details to demonstrate the causal role of vancomycin, having carefully considered and then excluded most if not all described confounding factors or other potential etiologies. In all six patients, we shall also provide complete information about their entire clinical course showing the temporal evolution of the AKI (in an individual set of three figures per patient as well as a separate case report for each). High-lighted will be the initial renal dysfunctions and the subsequent recovery upon cessation of vancomycin, against the temporal profile of the rising and falling serial vancomycin levels (Figs 1-6).

Results for objective 1:

(B) Evidence for VAN-AKI derived from 6 cases observed at OUHSC

Of the 101 cases referred for acute renal failure (ARF) (Table 4), 78 (77%) were attributable to intra-renal causes (Table 5), as opposed to pre-renal factors like hemodynamic etiologies or volume depletion (19 or 19%), or post-renal causes like obstructive nephropathy (4 or 4%). Among the 78 patients with AKI due to intra-renal etiologies (Table 5), 45 (or 58%) could be attributed to sepsis or septic shock, 11 (or 14%) to multiple or unidentifiable factors, 7 (or 9%) to allergic interstitial nephritis, 3 (or 4%) to radio-contrast dye insults, 2 (or 2.6 %) to rhabdomyolysis, and 10 (or 13%) to nephrotoxic antibiotics. Of the 10 patients with antibiotic-induced AKI, one was linked to colistin, another to amphotericin B, 4 solely caused by vancomycin and 4 principally due to vancomycin. We shall focus on 6 of these 8 (4 solely due to vancomycin and two others with vancomycin as the uncontested primary etiology). Demographic details and clinical characteristics at baseline for the entire group are tabulated in Table 6A. The usual pre-renal and obstructive etiologies were excluded by conventional clinical and laboratory studies. None exhibited signs of hypotension, sepsis or

bacteremia despite mild leukocytosis. There were no physical, hematologic or urinary evidence to suggest allergic interstitial nephritis. Although two patients had received radio-contrast dye injection, these were temporally unrelated to the AKI.

These 6 cases will also be individually presented in narrative form, along with an accompanying 3-part figure per patient. Three of them were treated for MRSA or Health Care Associated Pneumonia (HCAP) (Cases 1, 4, 5) and three for osteomyelitis from proven or presumed MRSA (Cases 2, 3, 6) (Table 6A). The individual figure serves to illustrate the changes in serum creatinine (A), changes in 100/serum creatinine, as an estimate of CrCl (B), and changes in the levels of serum vancomycin (C) as a function of time from the first day of vancomycin therapy through day 80 since the initiation or the last day of follow-up whichever was longer (Fig 1-6). Thus individually and collectively these 6 cases offer the strongest support for the concept and diagnosis of Van-AKI, especially in the context of the previously reviewed literature.

Case I:

A 48-year-old white man was admitted to the general internal medicine ward with delirium tremens, diverticulitis, and community acquired pneumonia. He had a past medical history significant for rheumatic fever, rheumatic heart disease, history of infective endocarditis 6 years earlier with septic emboli. There was also a history of diverticulitis and alcoholism. His heart rate was 125 beats/minute and his blood pressure was 143/85 mmHg. The patient was agitated and hallucinating, but otherwise physical examination was unremarkable. Initially white blood cell count was 11.1 K/mm³ and hemoglobin of 12.4 g/dL. Blood chemistries were significant for Na of 130 mEq/L, K of 2.6 mEq/L, and Cl of 85 mEq/L. His serum creatinine was 0.93 mg/dl. He had elevated liver enzymes and bilirubin (aspartate aminotransferase 306 units/L, alanine aminotransferase 126 units/L, total alkaline phosphatase 203 units/L, and total bilirubin 2.7 mg/dl), which all eventually resolved in the course of general and specific therapy during his hospitalization. Serum alcohol level was < 10 mg/dl. Chest X ray revealed perihilar right lower lobe and left lower lobe pneumonia as well as right middle and left lingular pneumonia. Computed tomography (CT) scan of the abdomen and pelvis with intravenous and oral contrast showed findings consistent with sigmoid diverticulitis. Blood and urine cultures were negative.

The patient was given lorazepam as needed for alcohol withdrawal symptoms. Regarding his antibiotic regimen, he was initially started on moxifloxacin 400 mg intravenous once daily; the antibiotic regimen was changed on day 3 to vancomycin, piperacillin/tazobactam, and ciprofloxacin given his poor clinical response. Later on day 5, levofloxacin substituted ciprofloxacin for the same reason. Vancomycin was initially started at a dose of 1 g intravenously q12 h (from hospital days 3 through 5). The dose was increased to 1 g intravenously q8 h on day 6 because of a low vancomycin trough level of < 5 mg/L. The dose was further increased on day 7 when trough level was 8 mg/L.

On hospital day 10, vancomycin trough level was found to be 68 mg/L. Vancomycin was therefore discontinued. Creatinine level ranged between 0.57 and 0.93 mg/dl during the first 9 hospital days, but it increased to 2.34 mg/dl on day 10 and continued to rise to a peak of 4.69 mg/dl on day 15 (Fig 1A). Urinalysis done on day 10 of hospital stay was normal with no urinary sediment. Renal ultrasound was unremarkable. Serum creatinine started to decline after that and reached 1.07 mg/dl on day 33 (two days prior to his discharge). Random vancomycin levels were checked periodically after stopping the drug. Level declined to 5 mg/L on day 20. The patient improved clinically throughout his hospital stay

with resolution of his pneumonia and improvement of the diverticulitis. He was discharged with follow up in the general medicine clinic after completing his course of antibiotics.

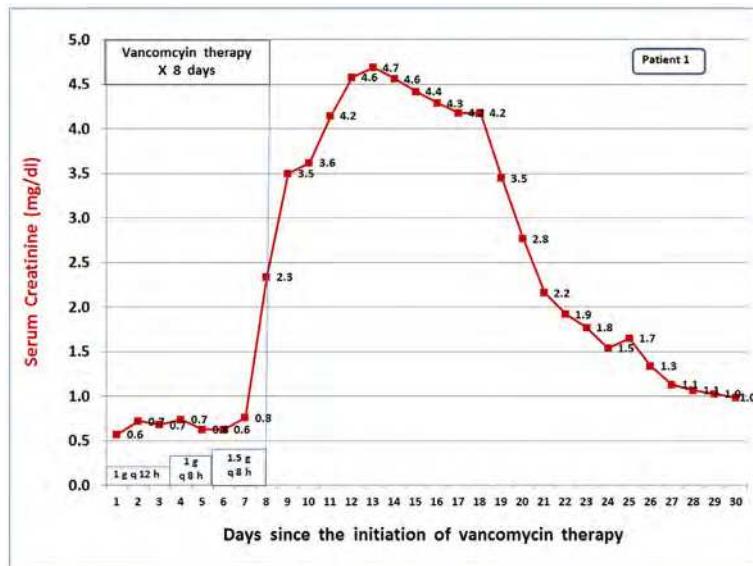


Fig. 1. A

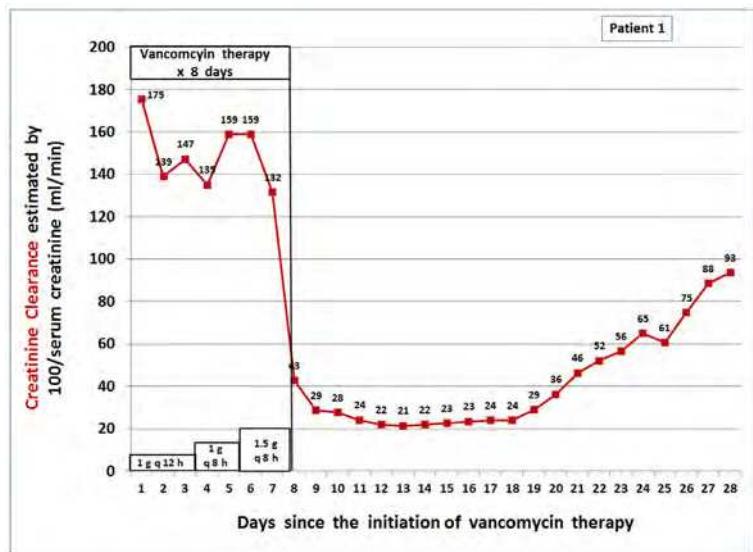


Fig. 1. B

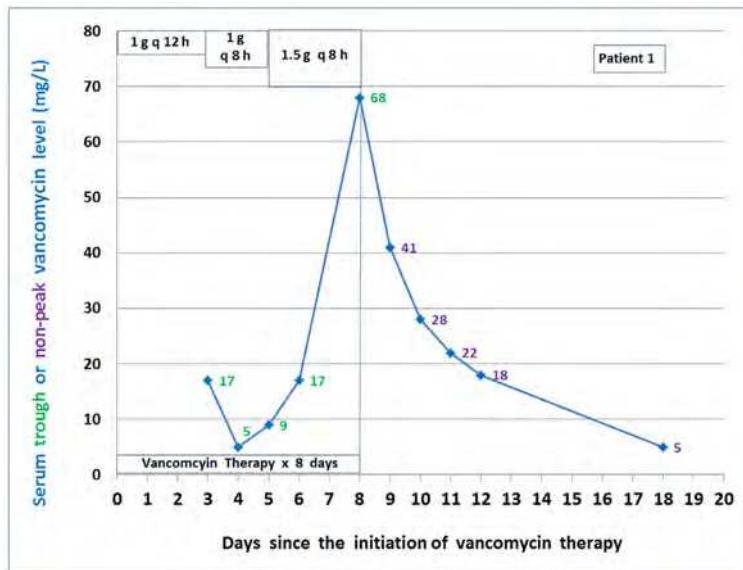


Fig. 1. C

We believed his acute kidney injury (AKI) was secondary to direct vancomycin nephrotoxicity based on the temporal relationship between the continually escalating dosage and documented excessive trough vancomycin levels on the one hand and the worsening kidney function on the other hand. Although he had received IV contrast on day 1, his serum creatinine did not rise until day 8. All pre-renal hemodynamic factors and post-renal causes were excluded, as were the absence of other intrinsic nephrotoxins. His recovery upon stoppage of vancomycin gave additional credence to our formulation. Although he had pneumonia, at no times did he have bacteremia or any signs of sepsis or hypotension. There were also no signs of allergic interstitial nephritis by serial exam, blood or urine eosinophilia. The patient was on multiple medications when he developed his AKI, including vancomycin, levofloxacin, piperacillin/tazobactam, ondansetron, enoxaparin, lorazepam, morphine sulfate, omeprazole, sucralfate, and thiamine. But all these medications (except for vancomycin and enoxaparin, the latter replaced by unfractionated heparin) were continued during his subsequent renal recovery, arguing against any possible pathogenic role in the AKI.

Case 2:

This was a 53-year-old man with recurrent and recalcitrant osteomyelitis admitted for acute renal failure. He was known to suffer from diabetes mellitus, hypertension, chronic hepatitis C infection, alcohol abuse, and cocaine dependence. The patient sustained a right ankle fracture secondary to a fall and status post intramedullary nailing for fusion of right tibiotalar and subtalar joints. The patient's course was complicated by two episodes of right ankle osteomyelitis post surgery; the first episode happened about four months after the surgery which was treated with intravenous vancomycin and piperacillin/tazobactam in addition to the removal of 2 screws from the right foot. The second episode took place five months thereafter. At that time he underwent removal of the remaining screws and nail and

was started on intravenous vancomycin at 1 g every 12 h with an intended duration of treatment for eight weeks.

On a regular out-patient follow up towards the end of antibiotic therapy, the patient was found to have a creatinine of 6.9 mg/dl from a baseline of 1.1 mg/dl (Fig 2A). On admission, he did not have any significant complaints. Outpatient medications included amlodipine, clonidine, glipizide, hydrochlorothiazide, lisinopril, hydrocodone, insulin, omeprazole, tramadol, and naproxen. Lisinopril dose had been constant for at least two years prior to admission. The patient admitted to taking two tablets of naproxen 500 mg daily for about seven months previously for pain relief.

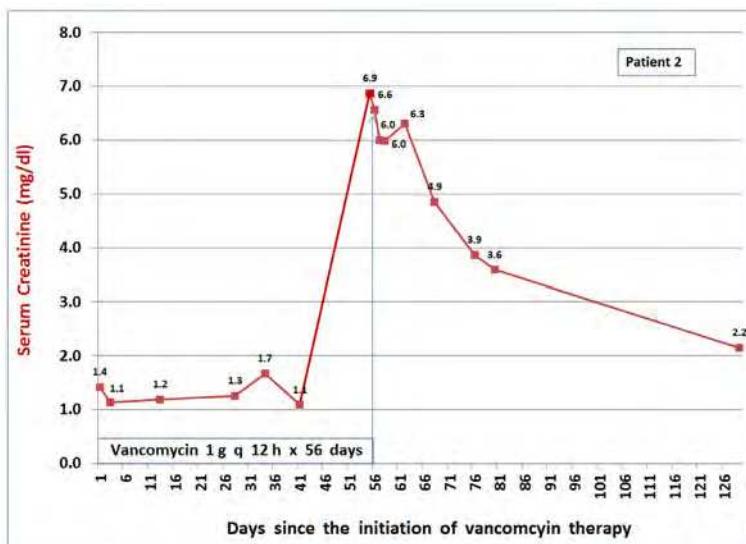


Fig. 2. A

Examination was significant for right ankle pitting edema and for a sinus tract over the lateral malleolus draining serous fluid. Initial laboratory revealed a white blood cell count of 7.3 K/mm³ and hemoglobin of 10.0 g/dl. Chemistry was significant for BUN of 63 mg/dl, bicarbonate of 16 mEq/L, and creatinine 6.87 mg/dl. Previously, his serum trough vancomycin levels ranged between 11.5 mg/L and 20.9 mg/L since the initiating the antibiotics, with a level of 11.5 mg/L measured two weeks prior to admission (Fig 2C). On admission, random vancomycin level was however found to be 67 mg/L. Urine was positive for eosinophils. Urine creatinine was 87.6 mg/dl and urine protein 37 mg/dl, yielding a ratio of 0.42. Renal ultrasound revealed horseshoe kidneys with dimensions of 11.3 x 5.3 x 5.1 cm and 11.1 x 5.1 x 4.7 cm respectively for the right and left kidneys.

On day 1, vancomycin was discontinued along with stopping lisinopril and naproxen. Creatinine started to trend down reaching 2.15 mg/dl about 10 weeks later (Fig 2A). Since all medications except vancomycin had previously been taken without producing any renal toxicity, the temporal relationship between the high vancomycin level and elevated creatinine strongly suggests Vancomycin-AKI. His subsequent clinical course of a slow but steady recovery upon cessation of vancomycin lends further support to this formulation.

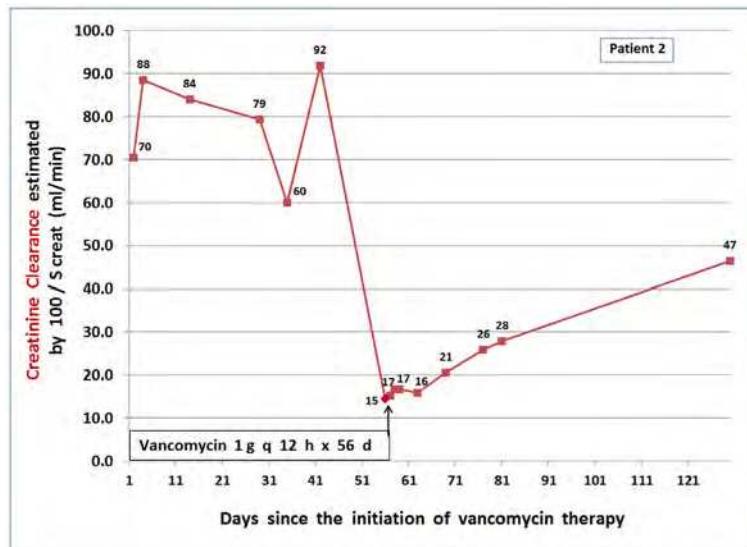


Fig. 2. B

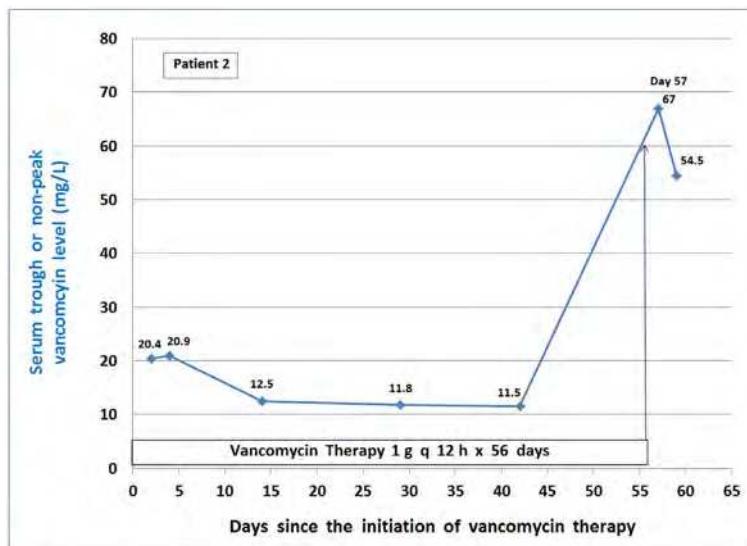


Fig. 2. C

We found no other stigmata of allergic interstitial nephritis (to either vancomycin) or other potential offending agents. Similar to the other patients, all pre-renal and post-renal factors had been carefully considered and excluded, including the absence of other known intra-renal insults in our patient.

Case 3:

This patient was a 56 year old man admitted for chronic open draining wound on right foot. He had a history of diabetes mellitus of unknown duration, although he was not taking any medications for diabetes. He reported chronic drainage from his right foot with worsening pain. Otherwise, the review of system was negative, notably for the absence of fever, chills, vomiting, diarrhea, dyspnea, and chest pain. He denied taking any NSAID or recent hospitalizations.

On admission he was normotensive and afebrile. He had no orthostatic hypotension. The big toe on his right foot had a large ulcer with purulent drainage and surrounding cellulitis. Nuclear scan confirmed osteomyelitis. Blood cultures and wound cultures were negative. His serum creatinine was 0.9 mg/dl on admission. He was treated with 1 g vancomycin q 12 h. On hospital day 3 his creatinine was 2.56 mg/dl and rose to a peak of 7.4 on hospital day 12, falling down to 4.85 at the time of discharge (Fig 3A).

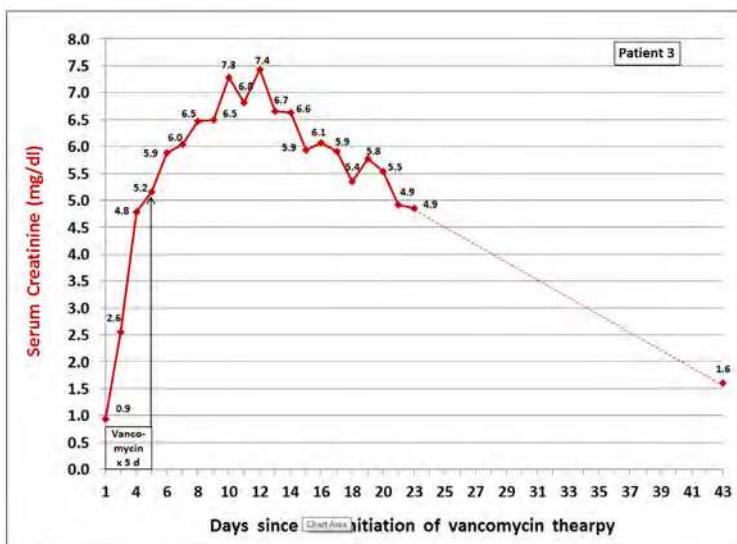


Fig. 3. A

Throughout his hospital stay, he was normotensive and received no other potential nephrotoxic insults including radio-contrast dyes. Due to persistent though mild leukocytosis and a low grade fever, he had undergone above knee amputation on his right side on hospital day 9. This was also prompted by the consideration that he had failed medical treatment and the wound was deemed to have very poor chance of healing based on vascular studies and transcutaneous oxygen tension gradients. He had received 2 g of vancomycin daily for the first 5 hospital days and given his extremely high serum trough or random vancomycin levels (Fig 3C) and the temporal relationship with the acute rise in serum creatinine, his AKI was best explained by vancomycin. In addition, all other etiologic factors, both pre-renal and post-renal causes, had been vigorously excluded. Three weeks after discharge, his amputation wound was healing well and his serum creatinine fell to 1.6 mg/dl, towards his normal baseline although still significantly elevated considering the loss of his right leg (Fig 3 A).

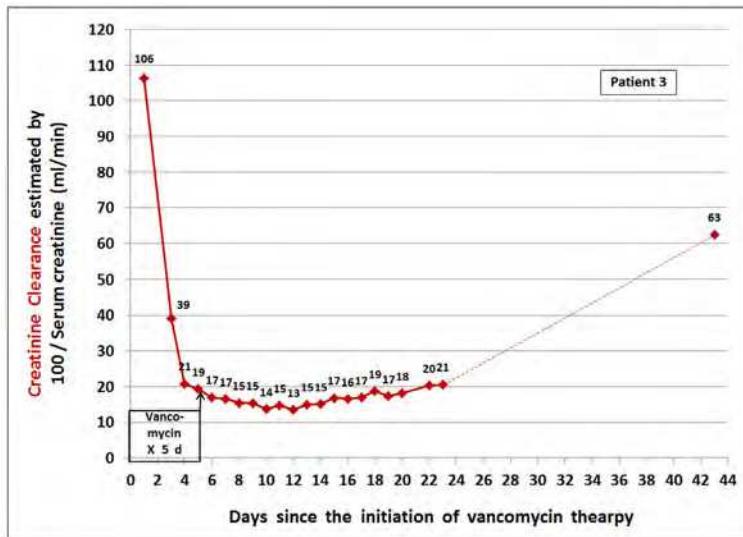


Fig. 3. B

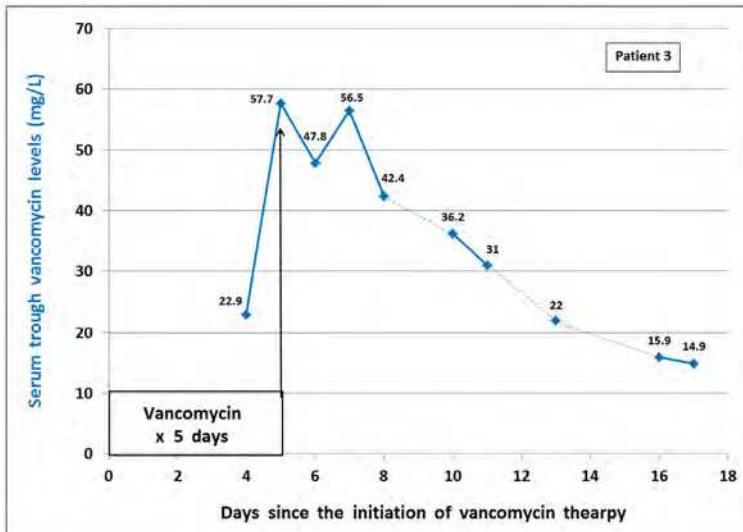


Fig. 3. C

Case 4:

This patient was a 33 year old man with a past medical history of Hirschsprung disease as a child admitted to the trauma service of our Medical Center after an alleged assault. He was intubated at the scene and subsequently treated for multiple facial fractures, right orbital fractures and intracranial hemorrhage. His hospital course was significant for

having developed left lower lobe pneumonia attributed to MRSA cultured from the tracheal aspirate on the fourth hospital day. This was treated initially with vancomycin 1.5 g every 8 h. After 3 doses, trough vancomycin level was 10 mg/L. Thus vancomycin was increased to 2 g every 8 h, a regimen which was continued for the ensuing 10 days. His vancomycin trough levels on days 4, 5 and 9 of administration were respectively 15, 17 and 20 mg/L (Fig 4C).

His serum creatinine was 1.3 mg/dl on admission. After repletion of his extracellular fluid volume, it dropped to 0.6 and stayed in that range for a week (Fig 4A). On days 9 to 10 of vancomycin therapy, his serum creatinine began to climb slightly to 0.9 mg/dl. It rose to 1.2 on day 11 and to 2.8 mg/dl on day 12 of vancomycin administration. It peaked and plateaued at 3.5 to 3.6 mg/dl two weeks after the initiation of vancomycin (Fig 4A). Of note, his serum trough vancomycin level was found to be 110 mg/L eight hours after the last dose of vancomycin. Although there was a peripheral eosinophilia of 12.5% with a peak absolute count of 1,400 ten days after the last dose of vancomycin, his serum creatinine level then was already trending down, arguing against an allergic interstitial nephritis. There was no significant granulocytosis despite an intermittent low-grade fever and mild leukocytosis. All blood cultures drawn throughout his hospital course were negative. *Hemophilus influenzae* grew out from his tracheal aspirate on hospital day 9 and treated for 9 days with piperacillin/tazobactam. The patient was hemodynamically stable throughout his hospital stay and he made a slow but steady and significant physical recovery to be able to transfer to a full rehabilitation center on hospital day 36. At that time his serum creatinine had also returned to 0.84 mg/dl, very close to his normal baseline.

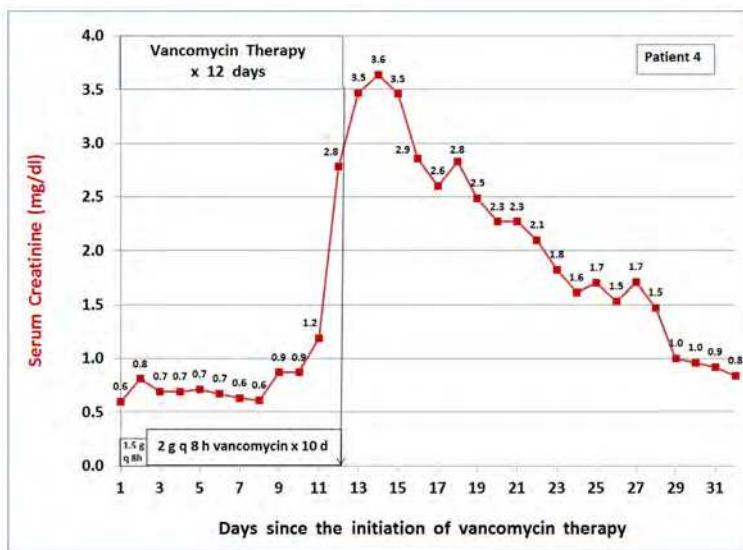


Fig. 4. A

Although he had received IV contrast on day 1, his serum creatinine had remained in the normal range and stable over the first 2 weeks of his hospitalization. All known nephrotoxic insults, pre-renal and post-renal factors were excluded as potential explanation for his AKI.

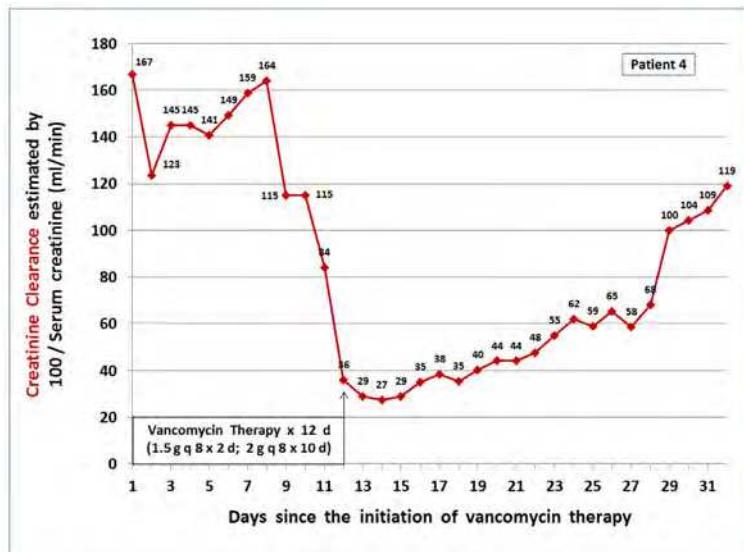


Fig. 4. B

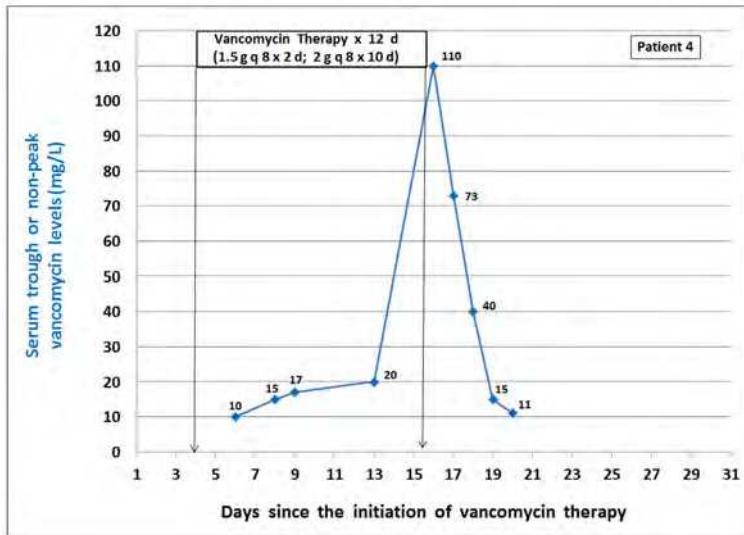


Fig. 4. C

Thus we believe his clinical course and renal function profile were best explained by acute vancomycin nephrotoxicity. His kidney recovery 3 weeks after stopping vancomycin was also consistent with the typical picture of improved serum creatinine over this time frame as in classical Van-AKI shown here and in the few documented cases published in the literature.

Case 5:

This man was a 75 year old resident of a skilled nursing facility admitted to our medical center because of altered mental status. He had a history of dementia and old cerebrovascular accidents and his outside medications included no nephrotoxic medications.

On examination, he appeared to be confused and disoriented, responsive only to painful stimuli. His blood pressure was 126/70 mm Hg. His pulse rate was 67. Temperature was 36.1 C and his respiratory rate was 18. On room air, his pulse oxygen saturation was 95%. He had coarse crackles in left lower lobe with decreased air entry. No other sources of infection were found on physical examination.

The white blood cell count was 11.3 K/mm³. A chest X ray showed left lower lobe consolidation and a small pleural effusion. A CT scan of the head revealed no acute intracranial process. His serum creatinine was 2.42 mg/dl (versus a baseline of 1.5mg/dl). He was thought to be volume depleted. After receiving intravenous fluids, his serum creatinine returned to normal and on day 5, it was 1.11 mg/dl. In the mean time he was given vancomycin 1g q12 h and piperacillin/tazobactam 2.25 g q 6 h (adjusted dose for his renal function) for the treatment of his HCAP. On day 5 of his admission, he was discharged back to nursing home to complete a 2 week course of HCAP treatment.

Six days later, he was re-admitted to the hospital, again with altered mental status and decreased oral intake. His serum creatinine was elevated to 3.45 mg/dl (Fig 5 A). He was hemodynamically stable with blood pressure of 147/96 mm Hg and a pulse rate of 89. White blood cell count was 8.4 K/mm³. Serum Na was 153 mEq/L and K was 3.8 mEq/L. BUN was 15 mg/dl. The urine fractional excretion of Na (FENA) was 13.8%, suggestive of intrinsic or intra-renal disease. Despite intravenous fluids, his serum creatinine continued to rise during the first few days (Fig 5A).

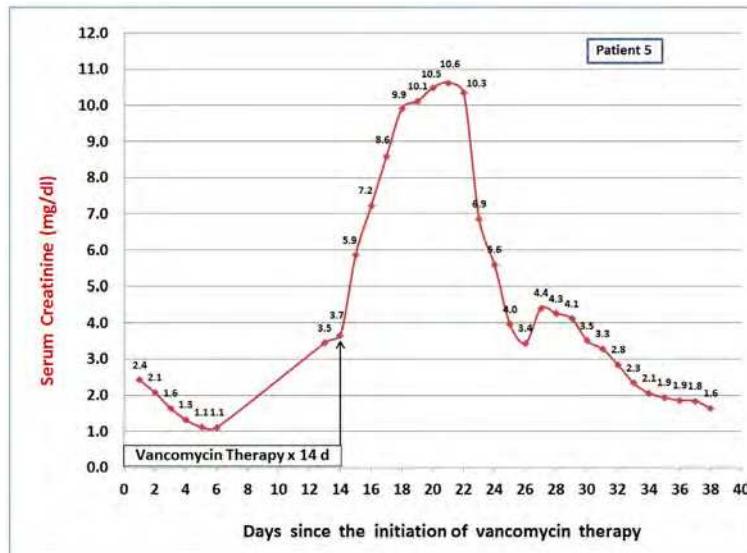


Fig. 5. A

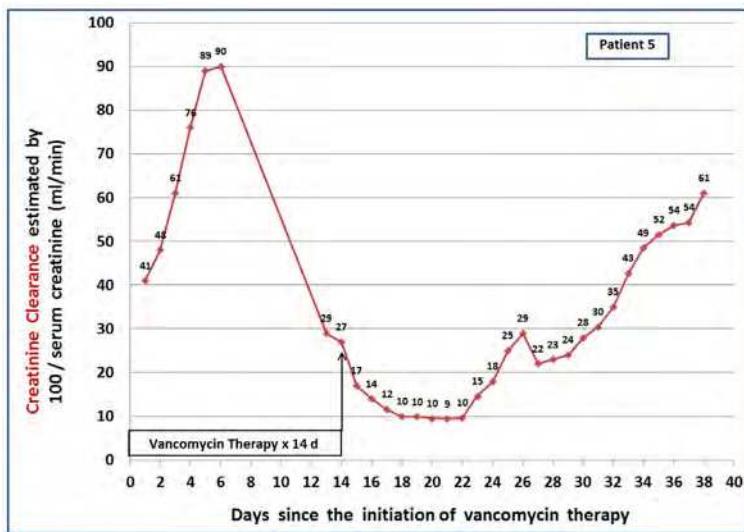


Fig. 5. B

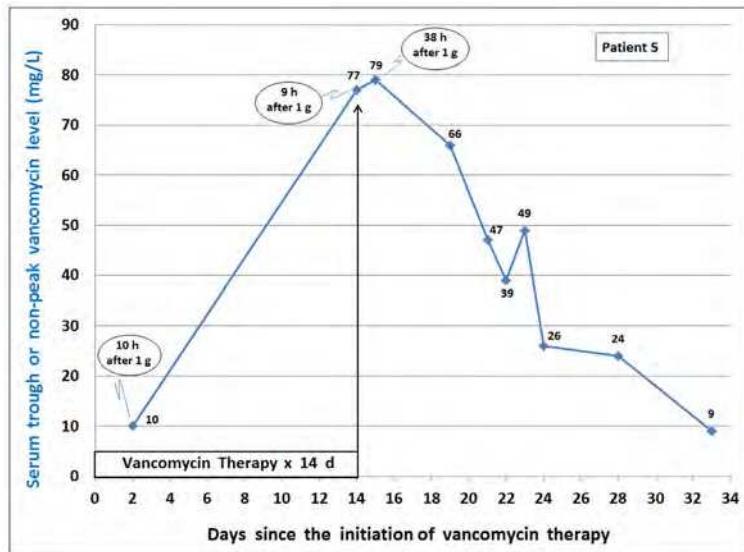


Fig. 5. C

In the nursing home his vancomycin level was not monitored. On re-admission, the vancomycin level (77 mg/L) was found to be in toxic range. Vancomycin was thus discontinued. 5 days later serum creatinine was 6.6mg/dl and it continued to climb to a peak level of 10.3 mg/dl on hospital day 7 (Fig 5A).

Patient appeared clinically stable and euvolemic. A kidney ultrasound did not show any obstruction. Of note other causes of acute renal failure were ruled out. He did not have acute interstitial nephritis as there was no rash, peripheral eosinophilia or eosinophiluria. He showed no signs of sepsis and his blood cultures remained negative. He did not receive any nephrotoxic agents or radio-contrast dyes. His antibiotics were switched to ciprofloxacin 400 mg IV q 24 h and cefepime 1g q12 h.

On days 7 and 9 of his second hospitalization, he underwent two sessions of hemodialysis to help manage his oliguria and to help remove the cumulated vancomycin. After the hemodialysis his serum creatinine and serum vancomycin levels both trended down. As vancomycin disappeared from his system, his kidney function improved significantly. Although he required furosemide drip to help manage his oliguria, he became relatively polyuric in the recovery phase of his AKI. Four weeks after discontinuation of vancomycin, his serum creatinine was 1.64 mg/dl close to though still higher than his best baseline value. But he was vastly improved and able to be discharged. At that time vancomycin level was 9 mg/L.

Case 6:

This patient was a 65 year old man hospitalized for hand osteomyelitis. He had a significant and complicated past and ongoing medical history due to uncontrolled type 2 diabetes mellitus, hypertension, hyperlipidemia, atrial fibrillation, previous stroke, degenerative joint disease of his left hip and knee, status-post knee replacement, gastroesophageal reflux disease, diabetic neuropathy, and a chronic but recently resolved MRSA diabetic left foot ulcer.

His present illness related to his left thumb pain that was initially treated with local steroid injections by his outside doctor. Subsequently, he had a draining ulcer at the first metacarpal joint of his left hand. Four days prior to his transfer from a local hospital to our medical center, MRI showed first metacarpal osteomyelitis and tendonitis. He was started on vancomycin, initially at a dose of 1.5 g every 18 hours three days before the transfer. On the 2nd hospital day with us, gram stain and culture from the left thumb wound showed MRSA. MRSA was also confirmed by intra-operative bone biopsy culture on the 3rd hospital day. Vancomycin was continued targeting 24-h trough levels \geq 15 mg/L.

The patient was discharged on the 5th hospital day to complete a prolonged course of vancomycin at a dose of 1.5 g daily at the recommendation of ID consultants. Blood for vancomycin levels and basic metabolic profile was drawn and checked by home health nurse once weekly. After two weeks, his vancomycin dose was increased to 2.0 g daily. Four more weeks later, it was further raised to 2.5 g daily to keep level >15 mg/L (Fig 6C). Three weeks after the last dose increase, although the 24-h trough levels finally reached 17-19 mg/L (Fig 6C), his serum creatinine had also risen from 1.3 to 2.3 mg/dl (Fig 6 A). This represented a further hike from initial baseline of 0.8 at the start of vancomycin therapy.

Meloxicam, an NSAID, and lisinopril, which he had taken for years, were temporarily stopped, along with holding his vancomycin for 3 days. When his serum creatinine appeared to stop rising and seemed to stabilize at \sim 2.1 mg/dl, vancomycin was resumed albeit at a reduced dose of 1 g daily. This was however stopped completely due to the persistent elevation of his serum creatinine at 2 mg/dl (Fig 6A). By having excluded obstruction with renal ultrasound, pre-renal or hemodynamic factors, bacteremic or septic etiologies and other intra-renal insults, we believe his subacute decline in renal function (Fig

6B), at least in retrospect, was best explained by the protracted vancomycin exposure with unmeasured peak levels which could have inflicted steady but sustained chronic damage.

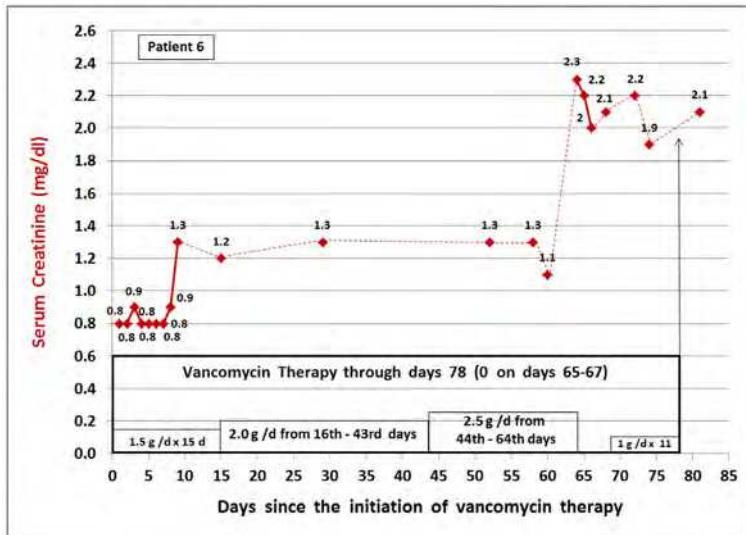


Fig. 6. A

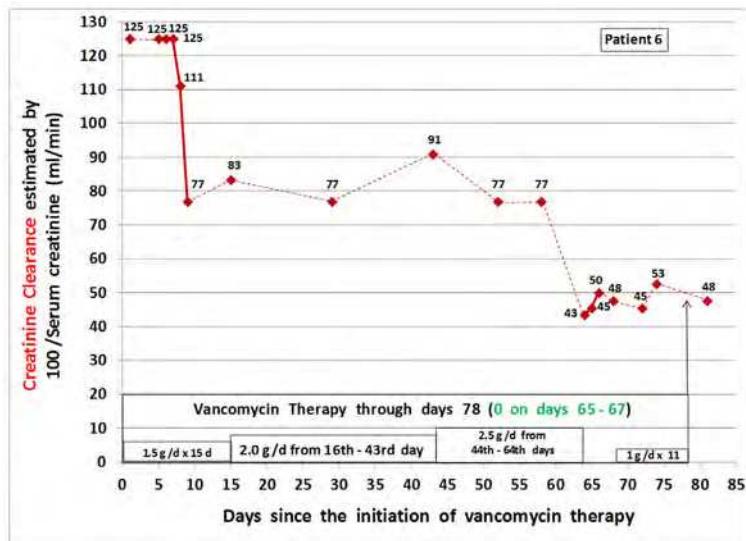


Fig. 6. B

The most informative was the marked drop in his creatinine clearance 2 weeks into vancomycin therapy (from ~ 125 to ~ 80 ml/min) (Fig 6B), which had easily escaped clinical

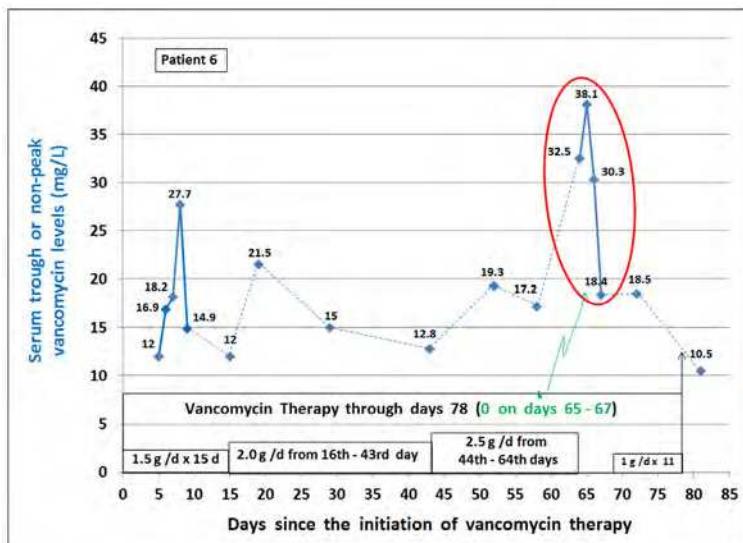


Fig. 6. C

detection by most physicians if evaluated simply based on examining the absolute values at one point in time or judged by the modest rise in creatinine from ~ 0.8 to 1.3 mg/dl (Fig 6A), the latter typically attributed to pre-renal or volume-related issues. Only when serum creatinine exceeded the rather arbitrary upper limit of normal of 1.2 mg/dl and only when it remained elevated was the concern of AKI raised in this patient. This issue of renal failure had finally become unequivocal and unmistakable when the entire course was reviewed longitudinally. After 10 weeks of vancomycin exposure, there was a 3-fold elevation in his serum creatinine (0.8 to 2.2 mg/dl) (Fig 6A), or more dramatically though more meaningfully in clinical nephrology, a corresponding 60 % decrease in creatinine clearance (from 125 to 50 ml/min).

Results on objective 2:

Lessons learned and insights deduced from the published literature and our case experience

To generate a typical profile of patients suffering from Van-AKI, we attempted to generalize from the group of our six patients on whom we have a complete set of clinical and laboratory data. When the serial renal function data and vancomycin levels for all 6 patients were plotted as group means on the same figure as a function of the time of vancomycin treatment, a clinical profile of Van-AKI and its recovery become apparent (Fig 7). Table 6 summarizes the group data as mean \pm SE on their demographic and hematologic data (Table 6A), serial renal function through the 60th and last day of follow-up (Table 6B), vancomycin dosages (cumulative and average daily dose), duration of treatment, and serial vancomycin levels (Table 6 C). The following statistical statements could thus be made, providing some insights and lessons on the issue of Van-AKI.

- For our cohort of 6 patients, the mean duration of vancomycin administration was 28.2 \pm 12.7 [SE] days (Table 6 C). Our group of patients, with more delayed diagnosis and

more severe renal failure, certainly confirmed the general impression from both prospective and retrospective studies that the chronicity of administration beyond 7 to 21 days posed independent risks for nephrotoxicity (Goetz & Sayer, 1993; Hidayat et al, 2006; Pritchard et al, 2008). The cumulative dose was 59.3 ± 23.6 g, yielding an average daily dose of 2.4 ± 0.6 g/day (Table 6 C). Since mean body weight (BW) was 85.5 ± 2.8 kg (Table 6A), the average dose was 28 mg/kg BW per day. The last dose given averaged 1.33 ± 0.17 g (Table 6 C), equivalent to 15.5 mg /kg body weight. In retrospect if not prospectively, this dose should be considered excessive and probably unnecessary because at the time of this last dose, both serum creatinine (4-6 fold of baseline) and vancomycin level (30 to 70 mg/L) for that day were known to have been significantly elevated (Table 6 B & C and Fig 7). We believe this last dose could have been much reduced or simply skipped (had greater restraints been exercised and more circumspection applied), considering the fore-knowledge of a significantly elevated serum creatinine (mean being 4.1 mg/dl, Fig 7) and high vancomycin levels of 65-70mg/L (Fig 7Fig 7). Existing literature suggests that both pre-existing renal insufficiency (as denoted by serum creatinine >1.7 mg/dl) (Pritchard et al, 2008) and elevated steady state serum vancomycin levels > 28 mg/ (Ingram et al, 2008) or elevated trough levels >14 mg/L (Rybäk et al 1990) are independent risk factors for ARF during vancomycin therapy (Hidayat et al, 2006; Pritchard et al, 2008; Lodise et al, 2008).

2. Peak vancomycin levels (group mean 70 ± 10 mg/L), which we defined here as the individual patient's highest value at any time during therapy and irrespective of when it was last given, was observed 26.2 ± 11.1 days after the first dose and 9.5 ± 4.9 hours after the last dose (Fig 7, Table 6 C). Some patients received their last dose, despite in retrospect already exhibiting a very high peak vancomycin level a few hours earlier (Table 6 C). At the point when vancomycin was discontinued, drug level was 65.1 ± 12.5 mg/L (Table 6 C). We would therefore propose that vancomycin orders be written daily (if not every 12 h), similar to coumadin orders in the titration phase of trying to achieve certain target levels or attaining a steady-state concentration, instead of one generic scheduled order for several days at a time. Needless to say, in retrospect, both the peak vancomycin levels for individual patients and the level on the day of stopping vancomycin (65.1 mg/L; Fig 7) were substantially higher than the recommended steady-state cut-off level of 28 mg/L (Ingram et al, 2008) or the trough cut-off level of 14 mg/L (Pritchard et al, 2008).
3. On the day of peak vancomycin level (day 26.2 of therapy), average serum creatinine had already risen to 4.1 ± 0.78 mg/dl ($\Delta = 3.14 \pm 0.67$ mg/dl, $p < 0.005$ vs. baseline; Table 6 B) and the corresponding creatinine clearance (CrCl) had fallen to 29.5 ± 5.5 ml/min, ($\Delta = -84.7 \pm 11.2$ ml/min, $p < 0.001$ vs. baseline; Table 6 B).
4. Prior to the actual peak serum vancomycin levels documented on day 26, an earlier serum vancomycin had also been obtained, on ~ day 22 (± 10) or ~ 4.2 ± 2 days earlier. This "pre-peak" vancomycin level (30 ± 9.8 mg/L) was already significantly elevated (Table 6 C & Fig 7). On that day, serum creatinine (1.85 ± 0.48 mg/dl) was numerically higher than baseline ($\Delta = 0.89 \pm 0.4$, n.s.). This corresponded to an estimated CrCl of 79.2 ± 21.1 ml/min, or a drop of 35 ± 14 ml/min from baseline, though just shy of significance ($p=0.06$) (Table 6 B). It is noteworthy that in retrospect, three independent forewarning signs for nephrotoxicity had already emerged on this 22nd day of therapy: (a) duration of administration $>$ the 3rd week previously suggested as a risk factor

- (Goetz & Sayer, 1993); (b) mean serum creatinine > the 1.7 mg/dl postulated as a risk thresh-hold (Pritchard et al, 2008); and (c) mean steady state vancomycin levels > 28 mg/L as a risk threshold (Ingram et al, 2008).
5. Indeed, over these interim 4.2 days, serum creatinine had increased further from 1.85 to 4.1mg/dl ($\Delta = 2.24 \pm 0.74$ mg/dl, $p < 0.04$; Table 6 B and fig 7). There was also an additional loss of CrCl of 49.7 ± 19.3 ml/min, $p < 0.05$; Table 6 B and Fig 7).
 6. Serum creatinine peaked on the average 28.8 ± 9.9 days into vancomycin treatment, which occurred ~ 2 to 3 days after serum vancomycin level had reached its peak. Over this interval, there was a further increase in serum creatinine, climbing from 4.1 to 5.93 ± 1.23 mg/dl ($\Delta = 1.83 \pm 0.73$ mg/dl, $p < 0.05$; Table 6 B), associated with a further drop in CrCl from the 29.5 to 21.7 ± 5.1 ml/min ($\Delta = -7.9 \pm 3.0$ ml/min, $p < 0.05$; Table 6 B).
 7. Estimated CrCl fell from the mean baseline of 114.2 ± 15.3 to a nadir value of 21.7 ± 5.1 ml/min, $p < 0.005$ (Fig 7; Table 6 B). This was accompanied by a significant and marked increase in serum creatinine from the baseline of 0.96 ± 0.13 mg/dl to 5.93 mg/dl, a 6-fold increase ($\Delta = 4.97 \pm 1.12$ mg/dl, $p < 0.01$). Accordingly, there was a total loss of CrCl of 92.6 ± 13.6 ml/min, $p < 0.005$ at the time of the worst (or peak) serum creatinine. Serum creatinine peaked 28.8 days after initiating vancomycin therapy, which was temporally 2.9 ± 1.4 days after the last dose. It is noteworthy that although vancomycin level reached the highest value 9.5 ± 4.9 hours after the last dose, serum creatinine did not reach its peak until 68.7 ± 32.4 hours after the last dose, indicating a delay of ~ 60 hours between reaching peak drug level and the full impact of functional impairment.
 8. After vancomycin was stopped, serum creatinine returned towards the baseline, falling to a nadir value of 1.57 ± 0.22 mg/dl ($p < 0.02$ vs. peak creatinine of 5.93 mg/dl, $\Delta = 4.36 \pm 1.21$ mg/dl; Table 6 B). This was associated with an estimated CrCl of 72.3 ± 12.4 ml/min at the point of maximal functional recovery ($\Delta = 50.7 \pm 13$ ml/min, $p < 0.01$ compared to the lowest value at the worst time of the ARF; Table 6 B). The maximal functional improvement was noted 30.8 ± 10.4 days after the last dose, or 59.0 ± 15.7 days after the first dose of vancomycin (Table 6 C).
 9. Despite 2 months since vancomycin had been initiated and 1 month after the last dose of vancomycin, once AKI had developed, the functional recovery was unfortunately incomplete even at the time of maximal improvement in the serum creatinine. In the short-term follow-up of ~ 31 days after the last dose or after the onset of ARF, there remained a residual elevation of serum creatinine ($\Delta = 0.61 \pm 0.2$ mg/dl, $p < 0.04$), associated with what appeared to be an irreversible decline of CrCl of 41.9 ± 12.9 ml/min, $p < 0.03$ (Table 6 B & Fig 7). Compared to the baseline CrCl of 114.2 ml/min, this represented a 37 % residual loss of renal function. It is possible that with longer period of follow up further return of renal function may ensue.
 10. Vancomycin level was ordered and monitored in the recovery period based on decisions by the individual clinicians without any discernible or uniform pattern. In this cohort of 6 patients, the lowest drug level (17.5 ± 7.5 mg/L) was observed 8.0 ± 2.5 days after the last dose (Table 6 C). It is noteworthy that this concentration of vancomycin, 8 days after stopping vancomycin, still fell into if not exceeded most recommended therapeutic ranges.
 11. Compared to the duration of vancomycin administration of 28.2 days, the average recovery time for maximal return of renal function was 3.2 ± 1.7 fold longer, indicating significant clinical morbidities (and associated financial burdens) posed by a preventable medication complication.

Results on objective 3:**Practical guidelines for the safe and effective long-term vancomycin administration**

The financial and health burden for managing ARF due to Van-AKI is currently unknown and clearly cannot be determined by our retrospective studies, especially with such a small series and observed over such a short time window. Furthermore, we have no good information on the true incidence of Van-AKI. However, it suffices to note that for our first 5 patients, it took between 20 and 70 days of inpatient care and management (a mean of 35 ± 9.6 days after the diagnosis of ARF) before regaining partial renal function for discharge to outpatient follow-up. The clinical impact of Van-AKI was also substantial to affected patients since we found significant residual losses of renal function ~ 37 % (by CrCl) even 31 days after diagnosing ARF or after stopping the drug, using the lowest serum creatinine in the recovery. For these two and other additional reasons, the prevention and amelioration of Van-AKI should be a top priority. Drawing upon our own experience and analyses plus that published in the literature, we would like to turn the lessons and insights (from results on Objective II) into the following guidelines.

1. We propose that vancomycin be viewed as nephrotoxic till proven otherwise, just like aminoglycosides, cis-platinum, amphotericin B, and radio-contrast dyes. If there are no compelling indications, as was the case for 4 of our 6 patients (cases 1, 2, 3, and 5; Table 6 A), vancomycin should not be used, in deference to other safer suitable alternatives (see suggestions under Discussion).
2. If it must be used, the index of suspicion for Van-AKI should be high because even the slightest degree of renal injury (generally undetected by the meager increase in serum creatinine from its normal baseline) will impair excretion, predispose to drug accumulation and excess levels, which in turn inflicts more tissue damage and further compromises elimination, setting up a vicious cycle. Such a rapid buildup of vancomycin with steeply rising serum creatinine was amply illustrated by our patients 4 and 6, the former precipitously over 48 h and the latter in 13 days, but both were mediated by the same mechanism. There had been case reports of similarly steep functional decline caused by sharply increasing vancomycin levels (Shah-Khan et al, 2011).
3. Drug levels and serial renal function should be closely monitored continually throughout treatment, daily the first week, preferably thrice weekly but no fewer than twice weekly thereafter. For example, three of our 6 patients did not have drug levels and/or creatinine measured for 8-21 days immediately prior to their ARF and/or development of excessive vancomycin levels (cases 2, 5 and 6). In at least six subsets of patients who are particularly vulnerable to AKI, these preventive measures should be mandatory.
 - a. Those treated in the outpatient setting, nursing homes, or long-term care facilities where physician involvement and supervision are inherently minimal, indirect, and less than immediate, like our patients 2, 5 and 6. Lab results must be received, reviewed and acted upon in a timely fashion (within 23 h if dosed daily or within 11 h if dosed every 12 h) by professionals trained to monitor for nephrotoxicity and supervised by physicians experienced in this issue. Timely dose adjustments or stoppage must be feasible and reliable to prevent AKI.
 - b. Critically ill and complicated patients, like those in the ICU, who are at increased risks for ARF due to other potential nephrotoxic insults or hemodynamic instability (Colomo et al (2010)).

- c. Patients infected by MRSA requiring a high vancomycin MIC and therefore high trough levels of ~ 15-20 mg/L and urgent attainment of such high levels by rapid escalation. Only daily vancomycin and daily creatinine level would allow achievement of such target levels without undue risks for unrecognized renal toxicity (also see point # 4 below).
- d. Protracted infusion (>2 weeks).
- e. Pre-existing CKD.
- f. ARF or those with fluctuating serum creatinine.

Pre-emptive renal consultation at the earliest signs of potential nephrotoxicity may prevent costly AKI and y hospitalization.

- 4. Scheduled vancomycin dosing should be discouraged, and if necessary, written no longer than every 2 to 3 consecutive days because of the known narrow therapeutic window of vancomycin. The duration should be further limited to one day at a time in three particularly susceptible patient cohorts.
 - a. Elevated serum creatinine, whether before or during vancomycin therapy (e.g. cases 3, 4 and 6), since vancomycin excretion is already impaired,
 - b. Those in the early non-steady state of initiating therapy (e.g. cases 3 and 5), and
 - c. Those requiring rapid dose escalations to meet certain target levels (cases 1, 4, and 6).

In cases 1, 4, and 6, for instance, toxic trough vancomycin levels were created and found because of the rapid escalation without attaining a relative steady state at each incremental step. Our experience amply confirmed the virtually identical experience reported in the one case by Barraclough et al in 2007. We would support and re-emphasize their caution regarding the need not only to monitor very tightly and frequently during rapid dose escalation but also ordering one dose at a time.

By routinely refraining from a multi-day scheduled order, physicians could use the latest serum creatinine and vancomycin data to adjust the next dose to avoid further damage which otherwise could easily happen with a standing order. The danger of the latter approach was statistically and pictorially shown in our six patients by the delayed stoppage despite theoretically prior knowledge of vancomycin levels of 70 mg/L and creatinine elevation to 4-fold of the baseline 2 days earlier (Fig 7, Tables 6 B & C). The rationale and justification are identical to writing daily coumadin orders in similar non-steady states like dose titration or escalation. The trade off for the inconvenience and extra though manageable work load would be a far lower incidence of AKI [(and perhaps fewer cases of chronic kidney disease (CKD)] and reduced health care expenses.

- 5. Based on inferences from our statistical analyses, we recommend three simple practicable thresholds for drastic dose reduction or complete stoppage of vancomycin.
 - a. A doubling of baseline serum creatinine,
 - b. A serum creatinine ≥ 1.5 mg/dl for any adult patients,
 - c. 10- to 12-h trough levels $\geq 20-25$ mg/L (Table 6 C, Fig 7) (Ingram et al, 2008).

We urge serious considerations for an immediate stoppage if any 2 of these 3 criteria are present, at least temporarily withholding vancomycin until additional tests show stable or improved renal function and significant decline in vancomycin levels.

- 6. We would re-emphasize the observation from classical renal physiology that serum creatinine is a very insensitive index of renal function in terms of detecting early decline in GFR. It is also grossly inaccurate in quantifying the loss of renal function, especially when the absolute values are below 1.5 mg/dl or when the changes occur between 0.5 and 2 mg/dl. Sole reliance on the increases of serum creatinine or the absolute values as

indicator of ARF will delay detection and recognition of AKI. Decline in GFR is not linearly related to the rise in serum creatinine. An initial small rise in serum creatinine from a perfectly normal baseline actually represents a marked fall in GFR whereas a marked rise in advanced CKD represents only modest drops. Thus, even small increments from the normal should raise concerns of AKI, especially in the early phase. The 500 ml of IV fluids typically used to deliver the vancomycin q 12 h could easily mask a genuine increase in serum creatinine, making detection of AKI in the early phase even harder unless the index of suspicion is high.

The emaciated 40-kg patient described by Barracough et al (2007) illustrated this point well because his baseline serum creatinine was only 0.3 mg/dl. Although it went up precipitously to 0.5 mg/dl by day 4 day (already 40% loss of GFR) and then to 1.4 mg/dl (already 79 % loss of GFR) by day 8 day of therapy and with a vancomycin level 66 mg/L, the standing order of 1 g twice daily was not reduced until day 9, when creatinine finally peaked at 1.9 mg/dl (84% loss of GFR).

We thus recommend using the reciprocal (times a convenient constant like 100) as a simple, reliable and accurate estimate of CrCl and its changes reflect *relative changes* in GFR for a given patient. This approach will enhance the sensitivity and detection of early kidney injury, at a time when timely and appropriate dosage reduction or cessation should be made to prevent further nephrotoxicity.

The contrast between using serum creatinine and using 100/serum creatinine is best illustrated in 4 of our patients (cases 1, 3, 4, and 6). Two of them (cases 1 & 3) lost 62 to 76 % of their CrCl or GFR in 1 day (from 132 to 43 ml/min in case 1 and from 106 to 39 ml/min in case 3) if renal function is evaluated by using CrCl (Fig 1 B and Fig 3 B). In contrast, superficially there appeared to be quite "minimal" or "manageable" loss by serum creatinine over the same one day [(0.8 to 2.3 mg/dl in case 1 (Fig 1A) and 0.9 to 2.6 mg/dl in case 3 (Fig 3A)]. Similarly, case 4 lost 62 % of the GFR in 2 days when judged by CrCl (Fig 4 B), contrary to the "modest" rise in serum creatinine from 0.9 to 2.6 mg/dl (Fig 4 A). Likewise, patient # 6 suffered 36% loss of CrCl in 2 days (Fig 6B) as the corresponding serum creatinine went up by a "meager" delta of 0.5 mg/dl (from 0.8 to 1.3; Fig 6A) over the same 2 days.

We therefore recommend quantifying relative GFR loss by the decrements in CrCl, as estimated by 100 /serum creatinine. Specifically, we suggest that 20-30 % drop in GFR estimated by this serum creatinine reciprocal method would provide a better and earlier warning signal for possible nephrotoxicity than the thresholds of doubling of serum creatinine or values ≥ 1.5 mg/dl. As recommended later, a renal consult can be requested to assist with such a less conventional approach of evaluating GFR.

7. As shown in our patients individually and collectively, the current practice of ordering and measuring "random" vancomycin levels, without regard to the timing of the last administered dose, will continue to confuse and confound us. Random levels are essentially un-interpretable, often misleading and unreliable, generally inaccurate as an index of the area under the curve (AUC) relating drug concentration against time, and at times simply useless if not dangerous. For instance, to the best of our knowledge there is no published "normal" range to define what to expect for levels between 4 to 8 hours post-dosing. Such grey-zone times create unnecessary ambiguity and obligate extrapolation and speculation. In addition, there is a general tendency (and thus a common problem) for busy clinicians working as a team to assume a high value or "toxic levels" as "peak" previously ordered by a colleague without always checking

details of the last administration or verifying this assumption. Thus frequently if not invariably, high or "toxic" values are simply attributed to sampling within a few hours of the infusion when in fact they may actually be a 10-12 h trough level. A high peak value (if indeed verified to be peak) may not necessarily require dose reduction or discontinuation although even this assumption may not be correct or safe. But a true trough but high level should mandate immediate consideration of stopping vancomycin (or at least until nephrotoxicity is excluded). Reconstruction of the timing of a "random" level relative to the last infused dose is tedious, time-consuming and prohibitive. They render making sound clinical decisions on proper dosage adjustments very difficult.

On scientific ground, we would discourage if not deplore the practice of "random" vancomycin levels. It condones uncertainties and fosters the culture and attitude of making and accepting subjective arbitrary interpretations. We would therefore endorse getting only a true trough level like 10-12 h (after the last dose if given at q 12 h frequency), or 24- or 48-h troughs (if dosed at 24 to 48 h frequency for whatever reasons).

Parenthetically, though with undefined clinical impact, the AUC per unit time is smaller (thus the nephrotoxic risk lower) if dosed once q 12 h versus dosing q 24 or q 48 h even when the trough levels are identical, say, at 15 mg/L for all three regimens. This is because AUC (or the total drug exposure by time and concentration) has been shown to play a role in Van-AKI (Bailie et al 1988). We would therefore favor and recommend the q 12 h (or at the longest, < q 24 h) dosing schedule over the q 48 h regimen and accordingly suggest measuring the 12-h trough levels unless logically impossible. If q 24-h dosing is necessary, experience has shown comparable safety compared to q 12 h dosing if the 24-h rough levels were kept below 10 mg/L (Cohen, Dadashev et al. 2002).

8. We propose changing our default mode of ordering vancomycin "*to give the next dose only if the trough level falls below the therapeutic target*", as opposed to the current default mode of "*keep giving to sustain the trough level above the target range*". In practice, presently most physicians would re-dose even if the trough level was as high as 20-25 mg/L (or even 30), for fear that if we withhold, the level might drop precipitously below the therapeutic range regardless of the prevailing serum creatinine. Consequently, the actual trough levels are always substantially if not markedly higher than 20-25 mg/L.

Our recommendation of a conservative dosing is based on two considerations. First, by definition all levels prior to the trough would have exceeded 15-20 mg/L, which were shown to pose greater risks for nephrotoxicity (Hidayat et al (2006); Pritchard et al (2008); our series of six patients). Second, there is no published evidence that trough levels of 10-15 mg/L, for example, are necessarily associated with poorer clinical cure or response than levels of 15-20 mg/L if the MIC against a "sensitive" MRSA is supposed to be < 1 mg/L or at the worst < 2 mg/L (Hermsen, Hanson et al. 2010; Chan, Pham et al. 2011).

9. Although the initial loading dose of vancomycin (typically 15 mg/kg) is the same regardless of the level of renal function, the maintenance dose must be reduced in pre-existing renal insufficiency, newly developed ARF, and/or deteriorating function. This basic safety principle was forgotten or ignored in virtually all the reported cases including our 6 patients. We recommend using the nomogram (15 mg x GFR in ml/min) for daily maintenance dose (in mg per day) first suggested by Moellering et al (1981) for renal impairment. This rough guideline has stood the test of time and provides a good though crude first approximation, allowing us to make later and continual adjustments based on subsequent trough levels.

In practice, if serum creatinine is relatively stable, GFR can be estimated by the equation of Cockcroft-Gault for CrCl (in ml/min) [= (140 - age in years) x (lean body mass in kg) / (serum creatinine in mg/dl x 72)] (Cockcroft and Gault (1976)). For instance, the maintenance dose will be ~ 1.5 g / d (=15 mg/d x 100) for a CrCl of 100 ml/min. Likewise, it will be ~ 450 mg/d (=15 mg/d x 30) for a CrCl of 30 ml/min. We should note that even with a steady state creatinine, this equation is known to over-estimate CrCl in the (a) elderly, (b) emaciated, (c) edematous, (d) obese, and (e) paralysis or amputees. An even smaller dose must be considered in these situations.

For patients with changing serum creatinine, it is advisable not only to measure creatinine and vancomycin more frequently due to the non-steady state, but also obtain renal consultation. These patients are at increased risks created by the predictable positive feedback loop between falling GFR (as denoted by steadily rising serum creatinine) and increasing kidney vancomycin exposure (as reflected by rising vancomycin levels). For patients functionally anuric or anephric, 2 mg/kg/d is a reasonable initial dose. In these patients and those with established end-stage renal disease or dialysis dependency, nephrology should be consulted even though they fall outside of the scope of cohorts to be considered in this Chapter (Van-AKI).

10. Although unproven by randomized controlled trial, there are theoretical reasons and some anecdotal evidence to support the consideration of prompt and significant removal of vancomycin by hemodialysis in patients with Van-AKI and burdened with sustained toxic levels and severe renal failure. We would therefore recommend earliest possible referral to nephrology for assistance and support for such a therapeutic option.

Though without personal or literature data to address this issue, we would submit that it is an unresolved theory as to the scientific basis and/or the clinical superiority of targeting trough vancomycin levels between 15 and 20 mg/L for those MRSA with MIC > 1 but < 2 mg/L (Hermsen, Hanson et al. 2010; Chan, Pham et al. 2011).

We would urge exercising circumspection in accepting this recommendation and showing discretion and flexibility in applying the same if the goal is to achieve the bacterial killing without renal toxicity.

5. Discussion

For nearly half a century, vancomycin has been used successfully to treat infections caused by gram positive bacteria, notably MRSA, from various sources and in various organs. The issue of Van-AKI has been controversial due to the difficulty in establishing a cause-and-effect relationship between vancomycin and the alleged ARF. This is true among the affected patients reported in large epidemiologic surveys or drug toxicity monitoring studies because they generally provide little details on individual patients for an objective review or independent determination (Table 1). Similarly, among the two dozen or so reported cases of Van-AKI (Table 2), fewer than 10 had unequivocally excluded the usual confounding variables like sepsis, bacteremia, hemodynamic factors and concurrent nephrotoxins. Many also failed to provide serial vancomycin levels to show the temporal evolution with the ARF. Thus, to date, the existence of Van-AKI has been intensely debated and at times categorically dismissed.

Our first objective was to more firmly establish this clinical entity by performing a vigorous and comprehensive review of the existing literature and by reporting our own experience. We have obtained and presented three lines of evidence to argue for the entity of Van-AKI. First, the drug toxicity monitoring studies in the aggregate have offered a

substantial body of indirect evidence to support the existence of Van-AKI, mainly based on the close correlations between increased blood levels and/or increased dosage on the one hand and increased incidence on the other hand (Rybak et al, 2009) (Table 1). Typically, there was observed a very low incidence of Van-AKI with low trough vancomycin levels like < 10 mg/L (Sorrel et al, 1985), but increased incidence with higher trough levels like >14 (Pritchard et al, 2008) or >15-20 mg/L (Hidayat et al, 2006), or with a high steady-state level > 28 mg/L (Ingram et al, 2008), and a 3-fold higher incidence when daily dose >4 g (Lodise et al, 2008).

Additional support was provided by the observations of synergism in nephrotoxicity between vancomycin and aminoglycoside (Farber et al, 1983; Sorrel et al, 1985; Rybak et al, 1990; Goetz & Sayer, 1993), the increased risks of Van-AKI with prolonged administration (Goetz & Sayer, 1993; Hidayat et al, 2006; Pritchard et al 2008), and the enhanced risks of nephrotoxicity (Lodise et al, 2008) or poorer renal outcome with vancomycin (Rodriguez Colomo et al, 2010) compared to linezolid in treating similar patient cohorts.

The second line of evidence was obtained from the 2 dozen cases of ARF associated with vancomycin administration (Table 2). Many were somewhat equivocal in terms of a clear cut etiology for the ARF, especially when no vancomycin levels were given and/or other common etiologies had been or could be vigorously excluded. There however remained about half a dozen well documented and unambiguous cases of Van-AKI, as evidenced by toxic drug levels and the absence of any other contributing factors or confounding variables for the ARF (Frimat et al, 1995; Barraclough et al, 2007; Ladino et al, 2008 [2 of 5 convincing cases]; Shah-Khan et al, 2011; Table 2).

The third and perhaps the strongest line of evidence is derived from our own experience, which includes 6 cases we have encountered and treated in the course of a month of renal consultation. There are probably two reasons for the relative ease with which these 6 patients with Van-AKI were discovered. One is the changing microbiology and characteristics of modern era patients and our obligated responses to these changes and adoption of current dosing practices. Two is the unique patient cohorts treated with vancomycin nowadays compared to the invariably septic or bacteremic patients with shock and pancytopenia in earlier decades. We shall elaborate on these two points.

First, there has been an apparent increase in the incidence of AKI during vancomycin therapy, largely due to three factors. One, the incidence of infections by documented MRSA and MRSE is growing rapidly. Two, there is an exponential increase in the use of vancomycin not only for sensitive and documented pathogens, but also for HCAP and osteomyelitis (especially in diabetics) in whom MRSA must be considered and/or covered, typically by vancomycin. After all, it is inexpensive, time-honored, tried, true, and proven to be effective against MSRA, the most prevalent and the deadliest bacteria. Three due to the widespread use (if not abuse) of vancomycin, there is a steady emergence of organisms sensitive only to rather high MIC, leading to the ID recommendation of trough levels > 15-20 mg/L (Rybak, Lomaestro et al. 2009). These three factors have combined to contribute to a significant upsurge of Van-AKI in our view.

Second, as opposed to the older cases where sepsis, bacteremia, hemodynamic instability, concurrently administered aminoglycosides, amphotericin B or contrast dyes could not be definitely excluded as etiologic factors for the ARF, none of these risk factors could have contributed to the AKI in our 6 patients (3 with HCAP and 3 with osteomyelitis, and none bacteremic or hypotensive) (Table 6 A). By providing and correlating serial vancomycin levels before, during, and after the ARF with the corresponding changes in renal function

during the evolution phase and recovery period of the AKI, we believe we have vigorously documented the existence of Van-AKI in these six patients in whom we have complete access to and full review of all their clinical and laboratory data (Fig 1-7).

Collectively, we believe these three independent lines of evidence firmly establish the fact that vancomycin is unquestionably nephrotoxic, no different than aminoglycoside, cisplatin, and radio-contrast dyes. The degree of renal failure was severe enough to initiate dialysis in one patient though he got less than one week of vancomycin. The other five patients had various degrees of residual renal impairment even a month after the last dose (Table 6 B, Fig 7). We therefore submit that the issue is no longer whether Van-AKI exists, but how to prevent or ameliorate it. To generate some practical guidelines towards this goal (our third objective), we took an intermediate step by pursuing the next objective. Our second objective was to statistically analyze our 6 patients to generate a clinical pattern and to define a typical profile of Van-AKI, with the intent to abstract some insights and derive some lessons which can eventually help us formulate preventive strategies. Generally speaking, we note that Van-AKI is a real and common complication of vancomycin treatment, especially during rapid dose escalation and/or prolonged infusion of fixed doses without frequent monitoring of drug levels and serum creatinine. Van-AKI could be costly both financially and clinically since significant irreversible functional loss can ensue (Table 6 B, Fig 7). In the detailed analysis of our 6 cases, we found that, in retrospect if not prospectively, most cases of Van-AKI could have been prevented or ameliorated if only the returned results on levels and serum creatinine were carefully examined and interpreted within the clinical context and if only timely and appropriate corrective responses were made.

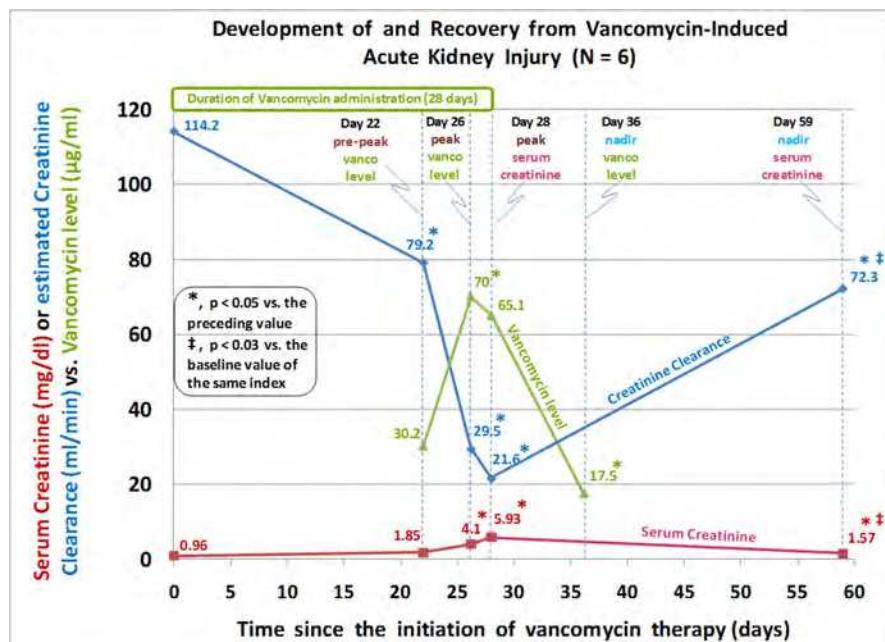


Fig. 7. Renal functional profile and changes in serum Vancomycin levels as averages of the 6 patients with AKI plotted against time since the initiation of vancomycin.

Characteristics (N= 6 patients)	(Mean ± SE)	(Units)
Gender Male : Female	6 : 0	
Age (years)	55.7 ± 6.0	years
Body weights	85.5 ± 2.8	kg
Pre-existing chronic kidney disease	N=2 (33 %)	%
Hypertension	N=3 (50 %)	%
Diabetes mellitus	N=3 (50 %)	%
Congestive heart failure or coronary disease	0	%
History of liver disease or hepatic dysfunction	N=2 (33 %)	%
Signs of volume depletion	N=1 (16 %)	%
Positive blood or urine cultures	0	%
Exposure to radio-contrast agents (but both temporally unrelated to ARF)	N=2 (33 %)	%
Indication for vancomycin: - Pneumonia	N=3 (50%)	(1 MRSA)
Osteomyelitis	N=3 (50%)	(1 MRSA)
Hypotension (SBP <95 x >4 h) or signs of shock	0	%
Fever (temperature > 38 degrees C or 100.5 F)	N=2 (33%)	%
Baseline WBC	10.6 ± 1.9	v
Baseline absolute neutrophils	8.6 ± 1.8	K/mm3
Baseline absolute eosinophils	74 ± 32	per mm3
Urine eosinophils	0	%
Ultrasound evidence for obstructive uropathy	0	%
Overall assessment of the pathogenic role of vancomycin in the AKI	85 ± 1	%

Table 6. A. Demographics and baseline clinical characteristics (N= 6)

We therefore attempted to identify independent common risk factors resulting in Van-AKI. In this pursuit, we have confirmed but extended the three previously reported risk factors for Van-AKI (a) High blood vancomycin levels (Rybak et al, 1990; Hidayat et al, 2006; Pritchard et al, 2008; Ingram et al, 2008; Lodise et al, 2008). In all 6 of our patients, the clinical intent was to dose to achieve a target trough level >12-20 mg/L, but during the execution, toxic levels had developed. (b) Prolonged duration of administration (Goetz & Sayer, 1993; Hidayat et al, 2006; Pritchard et al 2008). Two of our patients (#2 & # 6) had received vancomycin for 56 and 78 days, primarily in the outpatient setting where the monitoring mechanism and dose adjustment and response time were suboptimal. (c) Rapid dose escalation without achieving steady state (Barracough et al, 2007). Three of our patients (#1, #4, and #6) suffered as a result of the desire to achieve the higher 15-20 mg/L target levels because of the apparent failure to await a steady state between dosage increments. In other two patients (# 3 & # 5), the intent to attain therapeutic levels within the first few days of administration resulted in excessive levels also due to non-steady state kinetics.

In our opinion, therefore, the most important but recurrent lesson to learn from all these cases and the literature would be meticulous avoidance of excess vancomycin levels since low levels were rarely reported to induce Van-AKI. Toxic levels typically develop during the non-steady state of either the initial days of a fixed dose schedule or the early phase of rapid dose escalation. While we have no data to base any proposed recommendation, it is

fair to state that the ID recommendation of targeting 15-20 mg/L represents the consensus opinion of a panel of experienced experts in this field. The primary goal of combating infections is of course complete bacterial eradication. Viewed from this perspective, it is understandable and reasonable that the default mode of ordering vancomycin is to *keep giving to sustain trough levels >15-20 mg/L*. In practice though, the empirically observed trough levels would almost always exceed 15-20 mg/L, sometimes even up to 25-30, due to lack of foolproof dosing formula and due to invariably changing renal functions. Thus these drug levels seemed to be constantly at the threshold of flirting with nephrotoxicity. This could occur not only at the time of the documented trough levels but also most certainly during all the preceding hours when levels (though typically not measured) could be expected to be significantly if not markedly elevated.

Renal Function by serum creatinine or Creatinine Clearance estimated by 100/serum creatinine (absolute values or changes)	Units	Mean	SE	P VALUES
Baseline serum creatinine	(mg/dl)	0.96	0.13	
Creatinine Clearance (CrCl)	(ml/min)	114	15	
Serum creatinine on the day just before vancomycin level reached the peak (day of "pre-peak" vancomycin)	(mg/dl)	1.85	0.48	n.s. vs. baseline
CrCl on the day of "pre-peak" vancomycin	(ml/min)	79.2	21.1	
Rise in serum creatinine on the day of "pre-peak" vancomycin vs. baseline	(mg/dl)	0.89	0.40	n.s. vs. baseline
Drop in CrCl on the day of "pre-peak" vancomycin	(ml/min)	- 35	14	p = 0.06
Serum creatinine on the day of peak vancomycin	(mg/dl)	4.10	0.78	
CrCl on the day of peak vancomycin	(ml/min)	29.5	5.5	
Rise in serum creatinine from baseline to the day of peak vancomycin	(mg/dl)	3.14	0.67	p < 0.005
Fall in CrCl from baseline to the day of peak vancomycin	(ml/min)	- 84.7	11.2	p < 0.001
Rise in serum creatinine from the day of "pre-peak" vancomycin to the day of peak vancomycin	(mg/dl)	2.24	0.74	p < 0.04
Drop in CrCl from "pre-peak" to peak vancomycin	(ml/min)	- 49.7	19.3	p < 0.05
Peak serum creatinine	(mg/dl)	5.93	1.23	
Increase in serum creatinine vs. baseline	(mg/dl)	4.97	1.12	p < 0.01
CrCl at peak serum creatinine (worst CrCl)	(ml/min)	21.6	5.1	
Fall in CrCl at peak serum creatinine (worst decline)	(ml/min)	- 92.6	13.6	p < 0.005
Interval between the first dose and peak serum creatinine	(days)	28.8	9.9	
Further rise in serum creatinine from the day of peak vancomycin level to the day of peak creatinine level	(mg/dl)	1.83	0.73	p < 0.05
Further fall in CrCl from the day of peak vancomycin level to the day of peak creatinine level	(ml/min)	- 7.9	3.0	p < 0.05
Nadir serum creatinine during recovery	(mg/dl)	1.57	0.22	
CrCl at the time of nadir serum creatinine (maximal recovery)	(ml/min)	72.3	12.4	
Time from the first dose to nadir serum creatinine (recovery time)	(days)	59	15.7	
Drop in serum creatinine between peak & nadir values	(mg/dl)	4.36	1.21	p < 0.02
Best CrCl recovery (maximal CrCl - worst CrCl)	(ml/min)	50.7	13	p < 0.01
Irreversible increase in serum creatinine vs. baseline	(mg/dl)	0.61	0.2	p < 0.04
Residual decline in CrCl despite maximal recovery	(ml/min)	- 41.9	12.9	p < 0.03

Table 6. B. Summary of Serial Renal Function data during the Evolution of AKI & during its Recovery (N=6) (Mean ± SE)

On the other hand, to pursue the other equally important goal of prevention of Van-AKI, a more appropriate default mode of ordering vancomycin, we propose, would be to *infuse only if trough levels fall below certain target ranges*, as long as the attained trough levels are sufficiently high to achieve bacterial killing. We submit that these two goals are not mutually exclusive but in fact achievable in the same patient at the same time. At least two retrospective studies could be cited to support this notion. In the treatment of deep-seated MRSA infections, a retrospective cohort study failed to find any difference in clinical outcome between those with measurably high ($>15\text{-}20 \text{ mg/L}$) and those with demonstrably lower trough levels (Hermesen, Hanson et al. 2010). In another retrospective study on vancomycin in the treatment of MRSA ventilator-associated pneumonia, the authors did not find any significant difference in survival or clinical cure in patients with trough level $< 15 \text{ mg/L}$ and those with trough levels $> 15 \text{ mg/L}$ (Chan, Pham et al. 2011).

Vancomycin Dosages and Serum Levels vs. the time course of changing serum creatinine	Units	Mean	S.E.
Cumulative dose	gram	59.3	23.6
Duration of vancomycin treatment	days	28.2	12.7
Average daily dose	g/day	2.4	0.6
Cumulative dose per unit body weight	mg/kg	679	260
Average daily dose per unit body weight	mg/kg/day	28	8
Vancomycin level on the day just before peak level ("pre-peak" day)	mg/L	30.2	9.8
Time from the first dose to the day of "pre-peak" vancomycin level	days	22	10
Time from the day of "pre-peak" level to the day of peak vancomycin	days	4.2	2.0
Peak vancomycin levels (defined as the highest value for a given patient during the entire course irrespective of when it was given)	mg/L	70.0	9.8
Time from the first dose to the day of peak vancomycin level	days	26.2	11.1
Time lag from the last dose to the appearance of peak vancomycin	hours	9.5	4.9
Vancomycin levels just before discontinuation	mg/L	65.1	12.5
Time when the last vancomycin dose given since the day of initiation	days	28.2	12.7
Amount of vancomycin given in the last dose	g	1.3	0.2
Nadir vancomycin level measured and recorded during recovery	mg/L	17.5	7.5
Time from the last dose to nadir vancomycin level in recovery	days	8.0	2.5
Time from the first dose to the day of peak serum creatinine	days	27.2	10.7
Interval between the last dose and the appearance of peak serum creatinine	hours	68.7	32.4
Time from the last dose to nadir serum creatinine (days to nadir)	days	30.8	10.4
Recovery time as a ratio of vancomycin exposure time	ratio	3.2	1.7

Table 6. C. Summary of Vancomycin dosage and serum levels during the course of AKI and its recovery (N=6)

Additionally, in the treatment of MRSA bacteremia, it has been shown that high trough vancomycin levels of 15 to 20 mg/L per se might not be a good determinant or predictor for therapeutic success, at least not in those with pneumonia or MRSA endocarditis (Walraven, North et al. 2011). Therefore, until prospective randomized control studies comparing certain trough vancomycin level ranges are done to provide hard evidence to prove the importance of trough levels in excess of $>15\text{-}20 \text{ mg/L}$, we propose physicians exercise appropriate caution, some circumspection, and some discretion in individual patients and

base final dosing decisions on the entire clinical contexts, including the prevailing renal function.

Statistical analyses of our group data have yielded some new perhaps noteworthy insights. One, in 4 of our 6 patients (#1, #2, # 3, and # 5), the indication for vancomycin was not compelling, at least in retrospect, since only two had documented MRSA. Thus similar to some of the reported cases, in 2/3 of our patients, Van-AKI could have been avoided. Two, the failure to closely monitor drug levels or renal function had definitely contributed to the unexpectedly toxic levels and to Van-AKI in 3 of our patients (#2, #5, and # 6). In them, levels had not been checked for 8 to 21 days. Two of them (#2 and # 6) were under a designed 10-weeks treatment plan as an outpatient.

Three, there was no appropriate response to the discovery of excessive vancomycin levels (e.g. 30 mg/L) on day 22 of therapy despite a doubling of serum creatinine from the normal baseline (1.85 vs. 0.96 mg/dl) (Tables 6 B and C). Four days had been allowed to elapse, letting the steady climb of vancomycin level to its highest value on day 26, when little to nothing was done to reduce or withhold the dose during this interim. The same concern could be stated for the last dose given on day 28 since it should have been stopped or drastically reduced, as opposed to the 1.3 g dose actually used despite a vancomycin level of 70 mg/L and a serum creatinine of 4.1 mg/dl already noted 1-2 days earlier.

Four, when this highest level of 70 mg/L was finally reported on day 26 of therapy, at a time when serum creatinine (4.1 mg/dl) was already increased 4 fold, there was a 1-2 day time delay before the drug was stopped (Fig 7). Five, there was no evidence for any systematic dose adjustments for the known renal impairment in 3 of our 6 patients (#3, # 4, and # 6), either because of the absence of renal consultation or the lack of familiarity with the nomogram by Moellering et al (1981) [$(15 \times \text{GFR in ml/min})$ for daily maintenance dose (in mg per day)]. This general equation has been found to be quite useful as it provides the first though crude approximation for dosages as a function of the residual renal function, permitting later finer adjustments based on subsequent trough levels. In practice, if serum creatinine is relatively stable, GFR can be estimated by using the equation of Cockcroft-Gault for CrCl (in ml/min) [= $(140 - \text{age in years}) \times (\text{lean body mass in kg}) / (\text{serum creatinine in mg/dl} \times 72)$] (Cockcroft and Gault, 1976).

The common basic issue among what appeared to have been judgment or logistic errors is either the lack of adequate monitoring or the lack of appropriate timely responses to typically already known warning signals for Van-AKI. Perhaps one additional source of problem or lesson to learn is the ordering, trusting, using and interpreting "random" vancomycin levels, here crudely defined any non-peak or non-trough levels, obtained at times totally without regard to the last administered dose. Such "random" levels are basically un-decipherable, generally misleading and unreliable, typically inaccurate as a surrogate of the AUC relating drug levels vs. time, and often simply useless if not hazardous. There is no published "normal" range statistically derived to define what one can expect for levels 4 to 8 hours post-dosing. This vacuum of information leaves plenty of doubts and much room for inaccurate extrapolations and erroneous speculations, making sound clinical decisions on proper dosage adjustments impossible.

We believe the practice of "random" levels should be abandoned, replaced by true 10-12 h trough levels. It should be noted that the AUC per unit time is smaller (thus nephrotoxic risk lower) if dosed once q 12 h vs. q 24 or q 48 h for identical trough levels for all three schedules. If a q 24-h dosing must be used, published experience would recommend aiming

at 24-h trough levels below 10 mg/L to achieve similar safety margins as q 12 h dosing without sacrificing efficacy (Cohen, Dadashev et al. 2002).

The cornerstone to avoiding Van-AKI is abstinence, if not absolutely indicated as for 4 of our 6 patients, and if suitable safer alternatives are available. Despite the vast and positive overall clinical experience with vancomycin as an anti-MRSA antibiotic, several newer, less nephrotoxic or non-nephrotoxic alternatives have emerged, some even proven in clinical trials to confer comparable efficacy in certain bacterial infections. A few of these studies merit our comments and considerations as alternative agents because they demonstrate non-inferiority or comparable efficacy to that of vancomycin, at least for certain organ infections. Thus, in MRSA ventilator-associated pneumonia, linezolid has been found in one retrospective study to produce similar survival rates but a trend towards higher cure rates than vancomycin (Chan, Pham et al. 2011). Clinical and microbiological outcomes in the treatment of nosocomial pneumonia were also found in one prospective randomized control trial to be comparable between linezolid and vancomycin (Rubinstein, Cammarata et al. 2001).

In patients with SA bacteremia and endocarditis, daptomycin has been shown to produce similar clinical responses as standard vancomycin therapy (Fowler, Boucher et al. 2006) and the reported success rates favored daptomycin over vancomycin among those patients infected with MRSA.

In skin and soft tissue infections, a prospective single-blinded multicenter study reported similar efficacy between daptomycin and vancomycin (Pertel et al, 2009). Similarly, teicoplanin (Van Laethem et al. 1988) and telavancin (Wilson et al. 2009) have been found to yield comparable cure rates as vancomycin for skin and soft tissue infections. It should be noted that teicoplanin is a glycopeptide with similar spectrum of anti-bacterial activities as vancomycin but with one third lower nephrotoxic risks, based on a recent Cochrane review of 24 studies involving 2,400 patients (Cavalcanti, Goncalves et al. 2010).

Finally, two 5th generation cephalosporin prodrugs (ceftaroline fosamil and ceftobiprole medocaril) have been found to possess anti-MRSA activities. Ceftaroline has been shown to produce similar clinical cure rates as vancomycin in complicated skin and skin structure infections (Iizawa, Nagai et al. 2004; Ge, Biek et al. 2008), whereas ceftobiprole was found to show similar efficacy as vancomycin in suspected gram positive infections, diabetic foot and mixed bacterial complicated skin and skin structure infections (Noel, Bush et al. 2008 a; Noel, Strauss et al. 2008; Noel, Strauss et al. 2008 b).

In summary, several newer antibiotics have been shown to provide a potential equally effective but less nephrotoxic alternative to vancomycin for deep-seated MRSA infections. It is beyond the scope and our goal to comment on the advisability of deploying such alternatives other than updating their availabilities.

Our third and final objective was to use the lessons and insights from the literature and our case series to generate and recommend some simple practical guidelines targeted to the prevention and amelioration of Van-AKI. We will present these recommendations in a summary form in Table 7 below (Section VII).

6. Conclusions and recommendations

In conclusion, the era of vancomycin administration has spanned over half a century. Due to the widespread use of antibiotics whether indicated or not, there has been a growing emergence of microorganisms increasingly resistant to the existing antibiotics. MRSA has dictated the greater reliance on vancomycin. This in turn breeds the development of strains relatively insensitive to vancomycin, forces physicians to target higher drug levels and

1. Vancomycin is nephrotoxic and should be used only if truly indicated and in the absence of other safer suitable alternatives.
2. Close surveillance for Van-AKI must be performed throughout treatment by measuring drug levels and serial serum creatinine, once daily the first week, thrice weekly the second week, and no fewer than twice weekly thereafter. These preventive measures should be mandatory and in some cases done daily for the following cohorts at increased risks for AKI. (a) Those treated in the outpatient setting, nursing homes, or long-term care facilities; (b) Critically ill and complicated patients; (c) Patients needing high trough levels of ~15-20 mg/L and/or rapid dose escalation; (d) Protracted duration > 2 weeks; (e) Pre-existing CKD; (f) ARF or unstable/fluctuating serum creatinine.
3. Scheduled vancomycin dosing should be abandoned, and if absolutely necessary, written for less than 2 - 3 days at a time (like titrating Coumadin dosage in anticoagulation). To take advantage of the latest creatinine and vancomycin levels, daily orders should be written for (a) pre-existing elevated serum creatinine or changing levels, (b) the first week of initiating therapy due to the inherent non-steady state, and (c) rapid dose escalation.
4. Vancomycin should be stopped or drastically cut if any of the following thresholds emerges: (a) Doubling of normal baseline serum creatinine, (b) A serum creatinine ≥ 1.5 mg/dL for adults, (c) 10- to 12-h trough levels $> 20-25$ mg/L. Vancomycin must be stopped immediately if (a) or (b) plus (c) are present. A better safeguard will be a standard protocol by which the ordering MD &/or the RN executing the order is required to review, register, and document the latest trough level and the latest serum creatinine *before* administering the vancomycin (similar to blood sugar documentation before giving the next dose of insulin).
5. Since serum creatinine is an insensitive and inaccurate index of GFR, its reciprocal $\times 100$ (100/serum creatinine) should be used to better estimate CrCl (and GFR). For a given patient, the decrement in CrCl will yield a more accurate measure of relative GFR losses and if this exceeds 20-30 %, nephrotoxicity should be considered and vancomycin stopped or reduced.
6. Ordering "random" serum vancomycin levels should be discouraged because they are un-interpretable (without published data to extrapolate to or correlate with the AUC). Reconstruction of the timing of a "random" level relative to the last dose is tedious, time-consuming and prohibitive. Since they tend to confuse and mislead in clinical decisions on proper dosage adjustments, only true 10-12 h trough levels (or in some special necessary cases 24- or 48-h) should be obtained.
7. For safety reasons, the default mode should be to "*give the next dose only if the trough level falls below the therapeutic target*", as opposed to "*keep giving to sustain the trough level above the target range*".
8. After an initial loading dose (identical regardless of renal function), the daily maintenance dose must be reduced in CKD and/or ARF, using the published nomogram ($15 \times \text{CrCl}$ in ml/min) (in mg per day). If serum creatinine is stable, CrCl (in ml/min) can be estimated by the Cockcroft-Gault formula $[(140 - \text{age in years}) \times (\text{lean body mass in kg}) / (\text{serum creatinine in mg/dL} \times 72)]$. A smaller dose than calculated must be given in: (a) elderly, (b) emaciated, (c) edematous, (d) obese, and (e) paraparesis or amputees because the formula will over-estimate CrCl in these conditions.

9. Since it is unproven that achieving trough levels of 15-20 mg/L is necessarily and unequivocally associated with superior clinical response than 10-15 mg/L (Hermsen, Hanson et al. 2010, Chan, Pham et al. 2011), a balance must be struck for a given patient between the efficacy in combating infection and the avoidance of Van-AKI in the actual dosing to achieve certain recommended target ranges.
10. For patients with ARF, rapidly rising serum creatinine, and/or sustained vancomycin levels in the toxic range (>45 mg/L), renal consultation should be considered to assist with dosage adjustment and perhaps removal by hemodialysis, possibly to ameliorate nephrotoxicity and accelerate recovery.

Table 7. Recommendations for the Prevention of Vancomycin-induced Nephrotoxicity

consequently increasing the incidence of Van-AKI. The growing incidence of diagnosed diabetic foot ulcers and osteomyelitis and the mounting incidence of HCAP have further escalated the prescriptions of vancomycin, contributing to the increasing appearance of Van-AKI. Though unproven, it appears from personal and anecdotal experience of the senior author over the last 4 decades that the incidence of vancomycin-induced nephrotoxicity has been under-recognized, under-diagnosed, and under-reported.

Although vancomycin levels are typically monitored (albeit without any systematic or rational pattern) the primary goal is to ensure a relative drug excess and therefore adequacy of bacterial killing, not to prevent nephrotoxicity. Generally, renal safety almost appears to be an afterthought, only considered when serum creatinine is found to be very high or vancomycin level is in the blatantly toxic range. This is because to date Van-AKI as a real clinical entity of major concern has remained a debatable issue and eluded the attention of the most physicians except the ID experts and nephrologists. We believe and hope this chapter has firmly and fully established this as a serious and significant predictable adverse consequence of vancomycin administration, especially during dosage escalation, during prolonged therapy, used at rather high doses, and/or given without any following tight and close safety precautions.

There have been few if any published specific and pragmatic guidelines aimed at preventing and/or ameliorating AKI. Until large and prospective studies have been conducted to generate better alternatives, we would recommend the following interim and tentative guidelines.

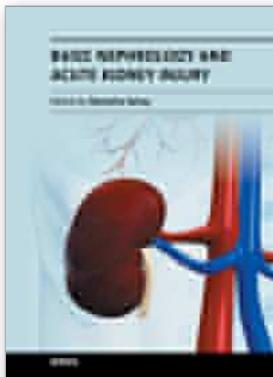
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Basic Nephrology and Acute Kidney Injury

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The first section of the book covers the basics of nephrology and second section focuses on acute kidney injury. This easy to reference text examines the physiological and biochemical aspects of renal diseases - all in one convenient resource. Experts in the field discuss topics of increasing concern in nephrology including newer methods of assessing renal function. The field of acute kidney injury in nephrology is a rapidly evolving one with research translating into clinical guidelines and standards. This text brings together experts to provide an authoritative reference for management of AKI in various clinical settings. Pregnancy related AKI is an important entity which has also been discussed in detail. The recent advances in the field of critical care AKI have been incorporated as well and help the reader to update their knowledge.

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University Campus STeP Ri
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