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Eight Unexpected Cases of Vancomycin Associated Acute Kidney Injury with Contemporary Dosing

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Abstract

Vancomycin is one of the most commonly utilized antibiotics in US hospitals. It remains the drug of choice for the treatment of methicillin-resistant *Staphylococcus aureus* infections in serious infections. For many of these deep-seated infections, guidelines recommend achieving troughs of 15–20 mg/L for treatment efficacy. At our institution we observed a number of cases of presumed vancomycin-induced acute tubular necrosis clinically diagnosed by the nephrology service. We report eight cases of presumed vancomycin-induced acute tubular necrosis, three of which required hemodialysis before resolution of nephrotoxicity. Only three of the eight patients received nephrotoxins prior to development of nephrotoxicity. All eight patients ultimately recovered renal function following discontinuation.

Keywords

kidney injury; vancomycin; acute tubular necrosis; hemodialysis

2. Introduction

Vancomycin is one of the most commonly utilized antibiotics in hospitals. [1–3] It remains the drug of choice for serious infections caused by methicillin-resistant *Staphylococcus*

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Conflicts of Interest

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aureus (MRSA) and is recommended as part of an empiric regimen in a number of common infections. [4] As resistant strains with rising minimum inhibitory concentrations (MICs) are increasingly common, aggressive dosing of vancomycin for the treatment of deep seated MRSA infections is becoming commonplace. Current guidelines for the treatment of MRSA recommend goal troughs of 15–20 mg/L for pneumonia, central nervous system infections and endocarditis. [5] These increasing vancomycin exposures have given rise to concerns of increased nephrotoxicity.

While nephrotoxicity was originally attributed to the impurities of the initial formulations, recent data have suggested that contemporary formulations of vancomycin may be nephrotoxic, even as monotherapy. [6–9] Now, with increasing daily doses being required for the optimal treatment of many infections, clinical studies have sought to describe those at highest risk for developing vancomycin-induced nephrotoxicity. [7, 8, 10–14] Meta-analyses and observational studies have identified a number of risk factors associated with developing vancomycin induced nephrotoxicity. Some of these risk factors include concurrent nephrotoxins, total daily doses > 4 grams, troughs > 15 mg/L and prolonged courses of therapy. [7, 8, 11, 13]

Despite over 60 years of experience in using this antibiotic, the mechanism of vancomycin-induced nephrotoxicity is not fully understood. Vancomycin-induced acute interstitial nephritis (AIN) has been described and is primarily attributed to allergic mechanisms. More controversy exists over whether vancomycin alone can cause acute tubular necrosis (ATN). It has been suggested that vancomycin causes direct injury to the proximal tubules in the kidney via oxidative stress. [15–18] Although the exact mechanism has not been defined, either maximal serum vancomycin concentrations or first 24- hour area under the concentration time curve appear to drive the severity of the injury. [19] Herein we describe eight cases of severe vancomycin-induced ATN clinically diagnosed by the nephrology consult service at our institution.

3. Case Reports

Cases were identified between July of 2009 and May of 2011 at Northwestern Memorial Hospital (NMH), an 897-bed tertiary hospital in Chicago, IL. Notably at our institution, only 1 or 2 gram aliquots of vancomycin were utilized during this time period. Vancomycin doses were determined by the primary team, with follow up concentration monitoring and dosage adjustment by pharmacists as appropriate. Cases were classified as having an acute kidney injury (AKI) event associated with vancomycin exposure if the individual in question had an increase in serum creatinine (SCr) > 0.5 mg/dL, > 50% increase in SCr over baseline, or a > 50% decrease in creatinine clearance (CrCl) from baseline while receiving intravenous vancomycin therapy in the absence of an alternative explanation.[20] Recovery of renal function was defined as a measure of SCr within 150% of baseline, a decrease of SCr to within 0.5 mg/dL of baseline or a recovery of CrCl to within 50% of baseline. The determination of ATN as the primary focus of nephrotoxicity was made by the nephrology consult service. Patient characteristics, infection sites and vancomycin dose and intervals were collected. Additionally, medication administration records were searched for any preceding or concurrent nephrotoxins. Clinical laboratory values from serum and urine

chemistries were also collected. This study was approved by the Institutional Review Board at Midwestern University and Northwestern University.

Patient specific vancomycin exposures were determined using BestDose version 1.126 (Laboratory of Applied Pharmacokinetics, Los Angeles, CA). This program utilized patient specific covariates (i.e. CrCl and weight), exact vancomycin doses and times delivered, and measured vancomycin concentrations to identify the most likely vancomycin exposure profile. The most likely exposure profile was defined as the weighted average concentrations based on the observed data and the Bayesian priors. Exposure metrics (i.e. AUC, $C_{\max}$ and $C_{\min}$) were calculated for each patient according to their first 24-hour exposure to vancomycin for the regimen that preceded acute kidney injury. The area under the curve (AUC) is presented as the AUC in the first 24 hours of exposure (as this exposure is the least likely in the causal pathway of kidney damage).[19, 21] $C_{\max}$ is the maximal predicted concentration, and $C_{\min}$ is the trough within the first 24 hours. For patients who were discharged on vancomycin and readmitted with AKI, only the first 24-hour inpatient exposure was estimated as relevant outpatient data were not available.

3.1 Case 1

A 49-year old female with a history of diabetes mellitus, peripheral artery disease and multiple amputations was transferred to our hospital from an inpatient rehabilitation center for the treatment of an MRSA peripherally inserted central catheter (PICC) line infection. She was started on 1 gram of vancomycin (10 mg/kg) every 8 hours (q8h). Her baseline SCr was 0.8–1.0 mg/dL. On hospital day 2, her dose was empirically increased to 2g (20 mg/kg) q8h for 2 doses, then decreased back to 1g q8h. Her predicted AUC, $C_{\max}$ and $C_{\min}$ for the first 24 hours of therapy were 1584.1 mg*h/L, 112.6 mg/L and 87.2 mg/L, respectively; however, these values indicate that she may have gone into acute kidney failure on day one and an estimate of her vancomycin profile prior to nephrotoxicity is unknown. On hospital day 4, it was noted that her SCr had increased to 1.74 mg/dL. She was not hypotensive at any point leading up to this increase in SCr. Of note, she had received lisinopril twice during this time. On this same day, a random vancomycin serum concentration was obtained revealing a concentration of 95.8 mg/L. The next day she received oral contrast for a chest CT due to concern for a developing pleural effusion. Urine chemistry studies were conducted on hospital day 6, showing a fractional excretion of sodium (FeNa) of 23%, a renal ultrasound this same day showed no evidence of obstruction. Hemodialysis (HD) was started on hospital day 8 per the nephrology service. Her SCr continued to increase and peaked at 4.17 mg/dL on hospital day 17, 13 days after stopping vancomycin. She continued to receive hemodialysis throughout her admission as well as in the outpatient setting. Her SCr continued to trend down, eventually returning to baseline 46 days after stopping vancomycin. Hemodialysis was stopped at this time.

3.2 Case 2

A 53-year-old male presented with C1-C2 osteomyelitis. His past medical history includes hypertension for which he was taking losartan. He was initiated on vancomycin 2g (15.75 mg/kg) every 12 hours (q12h) and piperacillin-tazobactam (TZP). At baseline, his SCr was 1.1 mg/dL. He received intravenous contrast for a head and neck CT on the second day of

his hospitalization. He was discharged after 5 days of therapy. In the first 24 hours of therapy, his estimated vancomycin exposure was an AUC of 299.5 mg*h/L, $C_{\max}$ 41.7 mg/L and $C_{\min}$ 1.7 mg/L. Before discharge, his SCr was 1.38 mg/dL, and a vancomycin trough returned a serum concentration of 14.9 mg/L. At discharge, he was transitioned from TZP to ertapenem and given ibuprofen for pain control.

Three days following discharge, the patient presented with new onset abdominal pain, fever and chills. At this time his SCr was noted to be 5.29 mg/dL and a random vancomycin serum concentration revealed concentrations of 93.8 mg/dL. His FeNa on admission was 4.6%, no eosinophils were detected in the urine. Vancomycin was discontinued on readmission. He was not oliguric or hypotensive at any point during the second admission. Upon his second discharge (6 days after stopping vancomycin) his SCr had decreased to 3.19. His abdominal pain and fevers had resolved by this time. Upon outpatient follow-up (46 days after stopping vancomycin) his SCr had returned to 1.48 md/dL.

3.3 Case 3

A 20-year-old female was admitted status post motor vehicle accident. At that time, she received contrast for CT imaging of her head, showing intracranial hemorrhage with midline shift, requiring craniotomy. On hospital day 8, she was started on vancomycin 1g (16.7 mg/kg) every 12 hours and piperacillin-tazobactam for the treatment of suspected ventilator associated pneumonia. She was not hypotensive at the time and was at her baseline SCr of 0.4–0.5 mg/dL. After 4 days of therapy, her vancomycin dose was increased to 1g every 6 hours in response to a vancomycin trough that was undetectable. Another serum concentration was taken after 5 doses on this new regimen, prompting an increase to 2g (33.3 mg/kg) every 8 hours. During the first 24 hours of therapy on this dosing scheme, her estimated vancomycin AUC, $C_{\max}$ and $C_{\min}$ were 644.7 mg*h/L, 90.4 mg/L and 4.6 mg/L, respectively. Of note she received contrast for a CT on day 5 of therapy. On day 9 of therapy (4 days after starting 2g every 8 hours), a vancomycin trough was obtained, showing a serum concentration of 54.9 mg/dL. At this point, her SCr was 2.12 mg/dL and urine chemistries suggested an intrinsic etiology (FeNa=3.7%) without eosinophiluria. Vancomycin was stopped at this time. Her SCr peaked at 4.19 mg/dL two days after stopping vancomycin. She was not oliguric at any point during her admission. Vancomycin was undetectable at discharge, 15 days following her last dose, additionally her SCr at this time was 1.43 mg/dL. Her SCr returned to baseline 17 days after discharge, 31 days after stopping vancomycin.

3.4 Case 4

A 46-year-old female with a history of metastatic breast cancer, presents with symptoms of a wound infection following a ventriculoperitoneal shunt revision. At baseline, her SCr was 0.5–0.6 mg/dL. Upon admission she was started on vancomycin 1g (12.33 mg/kg) q8h. Cultures grew *Klebsiella pneumoniae* (for which ciprofloxacin was added) and methicillin-resistant *Staphylococcus epidermidis*. Her estimated vancomycin exposure during the first 24 hours of therapy was an AUC of 310.5 mg*h/L, $C_{\max}$ 25.9 mg/L and $C_{\min}$ 8.2 mg/L. On day 4 of treatment her vancomycin dose was increased to 1g q6h in response to a trough of 12.6 mg/L. The dose was subsequently reduced back to 1g q8h on day 6 of treatment, following a trough of 25 mg/L. On day 8 of therapy, she was discharged on vancomycin 1g

q8h and ciprofloxacin. At this time her SCr was 0.58 and a vancomycin serum concentration before discharge was 16.8.

On day 16 of therapy, she re-presented to our emergency department following an supratherapeutic vancomycin serum concentration. At this time, she also had some new onset nausea. Upon readmission her SCr was 2.48 mg/dL and a random vancomycin serum concentration returned concentrations of 90.8 mg/L. Vancomycin was stopped at this time. On this same day a FeNa was calculated to be 0.8% and no eosinophils were detected in her urine. It was determined by the nephrology consult service that this was likely a mixed etiology of ATN from vancomycin as well as some pre-renal dysfunction. Her renal function continued to improve over her second admission. Twenty-seven days following discontinuation of vancomycin, her SCr had returned to baseline.

3.5 Case 5

A 23-year-old male with a history of acute lymphocytic leukemia in remission, presents with nausea, vomiting, chills, and fevers. His SCr on admission was 0.97 mg/dL, which was near his baseline. He was started on TZP and vancomycin for empiric treatment of a PICC line infection. Vancomycin was given as a 1g (10.26 mg/kg) dose of vancomycin on admission, a 2g (20.5 mg/kg) dose 2 hours later, and a 2g dose that evening. The next day he received a 2g dose in the morning. His predicted exposure (AUC, C_{max} and C_{min}) during the first 24 hours was 1774.6 mg*h/L, 109.3 mg/L and 55.7 mg/L, respectively. These values also are consistent with AKI within the first 24 hours. That morning (hospital day 2) his SCr was found to have increased to 3.62 mg/L. Vancomycin was stopped at this time. A random vancomycin serum concentration was drawn the next morning revealing a serum concentration of 64.7 mg/dL. A calculated FeNa on this day was 2.9% suggesting an intrinsic etiology. No eosinophils were seen on urinalysis and kidney imaging show no evidence of obstruction. On day 3 of hospitalization a renal biopsy was performed, suggesting drug induced ATN, presumably caused by vancomycin. He was not hypotensive leading up to this point. On day 4, he was started on intermittent hemodialysis. After his SCr peaked at 9.96 mg/dL on day 5 of hospitalization, his renal function continued to improve with intermittent HD, which was continued until hospital day 12 (10 days after discontinuing vancomycin). His renal function recovered 26 days after his last dose of vancomycin. This case has been previously published [22].

3.6 Case 6

A 24-year-old female presented for treatment of a MRSA labial abscess. Her past medical history was significant for HIV (CD4: 400 cells/mm³; not on treatment) and was 10 weeks pregnant. She was empirically started on vancomycin, ciprofloxacin and metronidazole. Vancomycin was dosed at 2g (15.6 mg/kg) every 8 hours following incision and drainage of the abscess. At that time, she was at her baseline SCr of 0.68 mg/dL. She received 3 doses of vancomycin before discontinuation, in response to a rapid increase in SCr to 2.07 mg/dL. During the first 24 hours of therapy her predicted AUC, C_{max} and C_{min} were 968.5 mg*h/L, 64.2 mg/L and 15.3 mg/L, respectively.

Overnight she received a single dose of ibuprofen for post-operative pain. Urine studies on hospital day 2 showed a FeNa of 4.1% with no eosinophiluria. She was not hypotensive at any point during her admission. Her SCr peaked on hospital day 3 at 3.23 mg/dL and she was discharged the next day on trimethoprim/sulfamethoxazole for the treatment of her MRSA abscess. At an outpatient follow up 13 days after stopping vancomycin, her SCr had returned to baseline.

3.7 Case 7

A 59-year-old male with a history of aortic stenosis post aortic valve replacement, coronary artery disease and hip replacement complicated by left hip wound infection admitted to our institution for total hip revision and debridement. On his initial admission, he received vancomycin and TZP for presumed osteomyelitis. Deep tissue cultures from revision did not grow any organisms. He was started on 1g (11.3 mg/kg) q12h, and increased to 1g q8h to achieve a trough of 15–20 mg/L. His predicted exposure during the first 24 hours of 1g q8h dosing was an AUC of 507.6 mg*h/L, C_{max} of 35.0 mg/L and a C_{min} of 13.4 mg/L. Upon discharge he was prescribed vancomycin 1.5g (16.9 mg/kg) twice daily and oral ciprofloxacin for presumed osteomyelitis. His SCr was close to his baseline at discharge, with vancomycin troughs of 15–16 mg/L.

The patient was re-admitted four days later for acute renal failure and hypotension requiring vasopressors. His SCr at this time was 6.82 mg/dL. Urine studies revealed a FeNa of 1% and casts in the urine. Imaging of the kidneys did not show any evidence of obstruction. A vancomycin serum concentration drawn on presentation was 88.9 mg/L. He was anuric at this time and was started on intermittent hemodialysis, though he was quickly transitioned to continuous venovenous hemodiafiltration (CVVH). The nephrology team diagnosed a mixed etiology of prerenal disease with subsequent vancomycin-induced ATN as doses were not adjusted for worsening renal function. He was managed on CVVH for 16 days before being transitioned to intermittent hemodialysis. The patient was discharged 39 days after stopping vancomycin, with HD continuing for an additional 3 weeks. His SCr returned to baseline six months following discontinuation of vancomycin.

3.8 Case 8

A 23-year-old male patient with muscular dystrophy was admitted to our institution for increased work of breathing and mucous plugging. Of note the patient had a history of cardiomyopathy for which he was taking lisinopril. After initially not improving on 3 days of moxifloxacin monotherapy, he was escalated to vancomycin and piperacillin-tazobactam. His SCr was at his baseline (0.13–0.18 mg/dL) at the start of therapy. Vancomycin was ordered as 1g (9.7 mg/kg) every 8 hours, however the patient received 4 grams during the first 24 hours of therapy. His predicted exposure for the first 24 hours of therapy was 440.6 mg*h/L, 44.9 mg/L and 23.3 mg/L for AUC, C_{max} and C_{min} , respectively. The patient's serum creatinine increased to 0.65 mg/dL on day 2 of therapy. As his SCr continued to rise, vancomycin and lisinopril were discontinued on day 4 of therapy. Two days following discontinuation, the patient's vancomycin serum concentration was found to be 76.4 mg/L, prompting further workup of his AKI. A FeNa was found to be 3.3% without eosinophils in his urine or blood. Kidney ultrasound did not suggest any obstruction. The patient's SCr

continued to rise and he became oliguric, requiring initiation of intermittent hemodialysis for volume overload six days after discontinuation of vancomycin. Hemodialysis was continued throughout admission and briefly as an outpatient. His SCr had returned to baseline at his follow up visit to our clinic, 26 days after stopping vancomycin.

4 Discussion

We observed eight severe cases of AKI temporally associated with vancomycin exposure of highly variable degrees. Vancomycin consumption around this time period (i.e. 2012–2013) ranged between 79.9 and 86.7 days of therapy per 1,000 patient days at our 897-bed hospital. Thus, the 8 cases that were passively identified represent rare events relative to vancomycin administration; however, we do not believe that incidence can be calculated with these data since passive reports can underestimate the incidence of toxicity in a population. Active surveillance strategies may identify a higher incidence of vancomycin induced ATN.

In each case presented, vancomycin was dosed in a manner consistent with contemporary dosing guidelines. For patients who did not develop AKI within the first 24 hours, vancomycin AUC, Cmax, and Cmin ranged between 299.5 and 968.5 mg*h/L, 25.9 and 90.4 mg/L, and 1.7 and 23.3 mg/L. Thus highly variable exposures were observed in our patients experiencing acute tubular necrosis. This is, to our knowledge, the largest case series of presumed vancomycin induced acute tubular necrosis. All patients recovered within 150% of their pre-treatment renal function following discontinuation of vancomycin, though three patients required hemodialysis before recovery. Of the eight cases, three received concomitant angiotensin receptor blocker or angiotensin converting enzyme inhibitors and one received a single dose of ibuprofen. Four were receiving piperacillin-tazobactam during vancomycin therapy, which has been linked with increased rates of AKI. [23] No other nephrotoxins were administered prior to injury for six of the eight patients. Two patients (cases two and three) received intravenous contrast prior to the AKI event. Generally, contrast induced nephropathy is defined by SCr increases seen within 48–72 hours following administration.[24, 25] Neither patient had changes in SCr consistent with AKI during this time frame.

The mechanism of vancomycin induced nephrotoxicity has been widely studied in animal models, but remains controversial. These models have revealed changes consistent with acute tubular injury, primarily within the proximal tubule. [15, 18, 26, 27] Oxidative stress appears to further the pathogenesis of vancomycin nephrotoxicity in animal models leading to ATN. [15, 18, 26] These data are supported by case number 5 (biopsy proven ATN) indicating that vancomycin alone in high doses may produce ATN. Other cases of biopsy-proven vancomycin induced ATN have been published, though they are limited. [22, 28–32]

Data derived from recent studies suggest that vancomycin has minimal potential for nephrotoxicity, unless used at high doses or concurrently with nephrotoxic agents. [8] Lodise and colleagues conducted a retrospective study comparing the rates of nephrotoxicity among patients with suspected Gram-positive infections treated with vancomycin or linezolid. [7] Patients treated with vancomycin were split into two groups, those who

received 4 grams per day and those that received < 4 grams per day. After adjusting for ICU residence, CrCl 86.6 ml/min and weight of 101.4kg, receiving vancomycin doses of 4 grams per day was associated with an increased risk of nephrotoxicity (OR 4.4, 95%CI 1.7–11.8, $p=0.003$). In a meta-analysis conducted by van Hal et al, initial vancomycin troughs of 15 mg/L were also associated with a significant increase in risk of nephrotoxicity (OR 3.12, 95%CI 1.81–5.37, $p<0.0001$). [8] Our cases suggest that vancomycin associated nephrotoxicity can occur with high exposures and lesser exposures. The latter may be due to contributing nephrotoxins; thus, a better understanding of the exposure toxicity relationship is needed with and without concomitant nephrotoxins. In the only carefully controlled prospective trial, vancomycin associated nephrotoxicity occurred in 7.3% of patients compared 3.7% of patients treated with linezolid. [14]

Duration of therapy has also been identified as a potential risk factor associated with vancomycin-induced nephrotoxicity. In studies of nosocomial pneumonia and MRSA health-care associated pneumonia, treatment course length was significantly associated with increased risk of nephrotoxicity in multivariate analyses. [33, 34] In addition, a retrospective study conducted by Bosch and colleagues found that the probability of developing AKI increased as the number of administered vancomycin doses increased. [13] This association is not consistent across all studies, however, with some data suggesting no association between treatment duration with development of nephrotoxicity. [35].

Often, the diagnosis of vancomycin-induced nephrotoxicity has been confounded by whether the observed concentrations are the cause or result of the index AKI event. In our case series, measured vancomycin concentrations did not correlate with the degree of AKI or dialysis initiation. While vancomycin exposures were defined in the first 24 hours of therapy for each patient this case series was descriptive in nature thus conclusive exposure/toxicity relationships could not be defined. Additionally, patient specific factors such as severity of illness may affect the threshold for vancomycin induced nephrotoxicity. Further investigations are required to determine the vancomycin exposure that predicts the development of nephrotoxicity.

In our series, we identified 8 patients with severe AKI associated with vancomycin therapy. Vancomycin associated kidney injury is modified by many variables, and the optimal dosing for vancomycin in order to prevent kidney injury is highly debated. Risk factors identified from previous studies for vancomycin induced kidney injury include daily vancomycin doses exceeding 4 grams per day, extended duration of vancomycin therapy, high APACHE II score, intensive care unit residence, and concomitant vasopressor therapy [6–13, 23, 33–36]. Although it was previously rare for vancomycin alone to be nephrotoxic, this case series provides data to support a relationship between vancomycin use and the onset of ATN. Based on our findings, ATN should be considered as a possible etiology of AKI in patients on vancomycin without other nephrotoxins. These cases may serve as a warning signal for a deleterious and preventable adverse effect that requires further study. Investigations into the exposure profiles that predict vancomycin induced kidney injury are ongoing [19].

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References

1. Pakyz AL, MacDougall C, Oinonen M, Polk RE. Trends in antibacterial use in us academic health centers: 2002 to 2006. *Archives of internal medicine*. 2008; 168:2254–2260. [PubMed: 19001203]
2. Magill SS, Edwards JR, Beldavs ZG, Dumyati G, Janelle SJ, Kainer MA, et al. Prevalence of antimicrobial use in us acute care hospitals, may-september 2011. *Jama*. 2014; 312:1438–1446. [PubMed: 25291579]
3. Kelesidis T, Braykov N, Uslan DZ, Morgan DJ, Gandra S, Johannsson B, et al. Indications and types of antibiotic agents used in 6 acute care hospitals, 2009–2010: A pragmatic retrospective observational study. *Infect Control Hosp Epidemiol*. 2016; 37:70–79. [PubMed: 26456803]
4. America IDSo. Standards, practice guidelines, and statements developed and/or endorsed by idsa. 2016
5. Rybak MJ, Lomaestro BM, Rotschaher JC, Moellering RC, Craig WA, Billeter M, et al. Vancomycin therapeutic guidelines: A summary of consensus recommendations from the infectious diseases society of america, the american society of health-system pharmacists, and the society of infectious diseases pharmacists. *Clin Infect Dis*. 2009; 49:325–327. [PubMed: 19569969]
6. Moellering RC Jr. Vancomycin: A 50-year reassessment. *Clinical infectious diseases : an official publication of the Infectious Diseases Society of America*. 2006; 42(Suppl 1):S3–S4. [PubMed: 16323117]
7. Lodise TP, Lomaestro B, Graves J, Drusano GL. Larger vancomycin doses (at least four grams per day) are associated with an increased incidence of nephrotoxicity. *Antimicrobial agents and chemotherapy*. 2008; 52:1330–1336. [PubMed: 18227177]
8. van Hal SJ, Paterson DL, Lodise TP. Systematic review and meta-analysis of vancomycin-induced nephrotoxicity associated with dosing schedules that maintain troughs between 15 and 20 milligrams per liter. *Antimicrobial agents and chemotherapy*. 2013; 57:734–744. [PubMed: 23165462]
9. Norton K, Ingram PR, Heath CH, Manning L. Risk factors for nephrotoxicity in patients receiving outpatient continuous infusions of vancomycin in an australian tertiary hospital. *J Antimicrob Chemother*. 2014; 69:805–808. [PubMed: 24107387]
10. Hanrahan T, Whitehouse T, Lipman J, Roberts JA. Vancomycin-associated nephrotoxicity: A meta-analysis of administration by continuous versus intermittent infusion. *International journal of antimicrobial agents*. 2015; 46:249–253. [PubMed: 26141230]
11. Hanrahan TP, Harlow G, Hutchinson J, Dulhunty JM, Lipman J, Whitehouse T, et al. Vancomycin-associated nephrotoxicity in the critically ill: A retrospective multivariate regression analysis*. *Crit Care Med*. 2014; 42:2527–2536. [PubMed: 25083977]
12. Rostas SE, Kubiak DW, Calderwood MS. High-dose intravenous vancomycin therapy and the risk of nephrotoxicity. *Clin Ther*. 2014; 36:1098–1101. [PubMed: 24931573]
13. Bosch K, McLaughlin MM, Esterly JS, Rhodes NJ, Postelnick MJ, Scheetz MH. Impact of vancomycin treatment duration and dose on kidney injury. *International journal of antimicrobial agents*. 2014; 43:297–298. [PubMed: 24388114]
14. Wunderink RG, Niederman MS, Kollef MH, Shorr AF, Kunkel MJ, Baruch A, et al. Linezolid in methicillin-resistant staphylococcus aureus nosocomial pneumonia: A randomized, controlled study. *Clin Infect Dis*. 2012; 54:621–629. [PubMed: 22247123]
15. Ahmida MH. Protective role of curcumin in nephrotoxic oxidative damage induced by vancomycin in rats. *Experimental and toxicologic pathology : official journal of the Gesellschaft fur Toxikologische Pathologie*. 2012; 64:149–153. [PubMed: 20832269]

16. Cetin H, Olgar S, Oktem F, Ciris M, Uz E, Aslan C, et al. Novel evidence suggesting an anti-oxidant property for erythropoietin on vancomycin-induced nephrotoxicity in a rat model. *Clinical and Experimental Pharmacology and Physiology*. 2007; 34:1181–1185. [PubMed: 17880374]
17. Nishino Y, Takemura S, Minamiyama Y, Hirohashi K, Tanaka H, Inoue M, et al. Inhibition of vancomycin-induced nephrotoxicity by targeting superoxide dismutase to renal proximal tubule cells in the rat. *Redox report : communications in free radical research*. 2002; 7:317–319. [PubMed: 12688519]
18. Oktem F, Arslan MK, Ozguner F, Candir O, Yilmaz HR, Ciris M, et al. In vivo evidences suggesting the role of oxidative stress in pathogenesis of vancomycin-induced nephrotoxicity: Protection by erdosteine. *Toxicology*. 2005; 215:227–233. [PubMed: 16112787]
19. Rhodes NJ, Prozialeck WC, Lodise TP, Venkatesan N, O'Donnell JN, Pais G, et al. Evaluation of vancomycin exposures associated with elevations in novel urinary biomarkers of acute kidney injury in vancomycin-treated rats. *Antimicrob Agents Chemother*. 2016
20. Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute Dialysis Quality Initiative w. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: The second international consensus conference of the acute dialysis quality initiative (adqi) group. *Crit Care*. 2004; 8:R204–R212. [PubMed: 15312219]
21. Lodise TP, Patel N, Lomaestro BM, Rodvold KA, Drusano GL. Relationship between initial vancomycin concentration-time profile and nephrotoxicity among hospitalized patients. *Clin Infect Dis*. 2009; 49:507–514. [PubMed: 19586413]
22. Shah-Khan F, Scheetz MH, Ghossein C. Biopsy-proven acute tubular necrosis due to vancomycin toxicity. *Int J Nephrol*. 2011; 2011:436856. [PubMed: 21716699]
23. Gomes DM, Smotherman C, Birch A, Dupree L, Della Vecchia BJ, Kraemer DF, et al. Comparison of acute kidney injury during treatment with vancomycin in combination with piperacillin-tazobactam or cefepime. *Pharmacotherapy*. 2014; 34:662–669. [PubMed: 24753221]
24. Group KDIGOKAKIW. Section 4: Contrast-induced aki. *Kidney Int Suppl* (2011). 2012; 2:69–88. [PubMed: 25018920]
25. Thomsen HS. Guidelines for contrast media from the european society of urogenital radiology. *AJR Am J Roentgenol*. 2003; 181:1463–1471. [PubMed: 14627556]
26. Nishino Y, Takemura S, Minamiyama Y, Hirohashi K, Ogino T, Inoue M, et al. Targeting superoxide dismutase to renal proximal tubule cells attenuates vancomycin-induced nephrotoxicity in rats. *Free Radic Res*. 2003; 37:373–379. [PubMed: 12747731]
27. Vaidya VS, Ozer JS, Dieterle F, Collings FB, Ramirez V, Troth S, et al. Kidney injury molecule-1 outperforms traditional biomarkers of kidney injury in preclinical biomarker qualification studies. *Nature Biotechnology*. 2010; 28:478–485.
28. Sokol H, Vigneau C, Maury E, Guidet B, Offenstadt G. Biopsy-proven anuric acute tubular necrosis associated with vancomycin and one dose of aminoglycoside. *Nephrol Dial Transplant*. 2004; 19:1921–1922. [PubMed: 15199201]
29. Htike NL, Santoro J, Gilbert B, Elfenbein IB, Teehan G. Biopsy-proven vancomycin-associated interstitial nephritis and acute tubular necrosis. *Clin Exp Nephrol*. 2012; 16:320–324. [PubMed: 22086124]
30. Belen C, Budhiraja P, Bracamonte E, Popovtzer M. Biopsy-proven acute tubular necrosis associated with vancomycin in an adult patient. *Ren Fail*. 2012; 34:502–505. [PubMed: 22329801]
31. Wicklow BA, Ogborn MR, Gibson IW, Blydt-Hansen TD. Biopsy-proven acute tubular necrosis in a child attributed to vancomycin intoxication. *Pediatr Nephrol*. 2006; 21:1194–1196. [PubMed: 16721580]
32. Wu CY, Wang JS, Chiou YH, Chen CY, Su YT. Biopsy proven acute tubular necrosis associated with vancomycin in a child: Case report and literature review. *Ren Fail*. 2007; 29:1059–1061. [PubMed: 18067058]
33. Cano EL, Haque NZ, Welch VL, Cely CM, Peyrani P, Scerpella EG, et al. Incidence of nephrotoxicity and association with vancomycin use in intensive care unit patients with pneumonia: Retrospective analysis of the impact-hap database. *Clin Ther*. 2012; 34:149–157. [PubMed: 22284995]

34. Jeffres MN, Isakow W, Doherty JA, Micek ST, Kollef MH. A retrospective analysis of possible renal toxicity associated with vancomycin in patients with health care-associated methicillin-resistant staphylococcus aureus pneumonia. *Clin Ther.* 2007; 29:1107–1115. [PubMed: 17692725]
35. Prabaker KK, Tran TP, Pratummas T, Goetz MB, Graber CJ. Elevated vancomycin trough is not associated with nephrotoxicity among inpatient veterans. *J Hosp Med.* 2012; 7:91–97. [PubMed: 22086511]
36. Kullar R, Davis SL, Taylor TN, Kaye KS, Rybak MJ. Effects of targeting higher vancomycin trough levels on clinical outcomes and costs in a matched patient cohort. *Pharmacotherapy.* 2012; 32:195–201. [PubMed: 22392452]

Table 1

Time course of vancomycin dosing and kidney injury for eight cases

Case 1														
	HD1	HD2	HD3	HD4	HD5	...	HD8	...	HD17	...	HD21			
VAN doses	1g @ 2038	2g @ 0100	1g @ 0100	1g @ 0100										
		2g @ 0940	1g @ 1005	1g @ 0900										
		1g @ 1700	1g @ 1800											
mg/kg/day	10	50	30	20										
SCr (mg/dL)	0.86	1.05	1.74	1.73	2.41	...		...	4.17	...	3.28			
VAN level				95.8 @ 8.06	105.3 @ 0400									
Notes							HD started				d/c			
Other NTs	lisinopril		lisinopril		PO contrast									
Case 2														
	HD1	HD2	HD3	HD4	HD5	(2 days at home)	RD1	RD2	RD3	RD4	RD5	RD6	RD7	
VAN doses	2g @ 0630	2g @ 0555	2g @ 0539	2g @ 0600	2g @ 0630									
	2g @ 1900	2g @ 1800	2g @ 1900	2g @ 1800	2g @ 1636									
mg/kg/day	31.5	31.5	31.5	31.5	31.5									
SCr (mg/dL)		1.12	1.34	1.29	1.38	...	5.29	5.47	5.21	4.8	3.68	4.09	3.79	
VAN level		14.9 @ 1758					93.8 @ 16.26		49.5 @ 0400	38.7 @ 0400	17.5 @ 0400	18.4 @ 0500	11.8 @ 0400	
Notes					d/c								d/c	
Other NTs	losartan/ TZP	losartan/ TZP	losartan/ TZP	losartan/ TZP	losartan/ TZP									
Case 3														
	HD1	...	HD8	HD9	HD10	HD11	HD12	HD13	HD14	HD15	HD16	HD17	...	HD29

Case 1																
	HD1	HD2	HD3	HD4	HD5	...	HD8	...	HD17	...	HD21					
VAN doses			1g @ 2200	1g @ 1130	1g @ 1000	1g @ 1000	1g @ 1000	1g @ 0400	1g @ 0400	2g @ 0700						
				1g @ 2200	1g @ 2330	1g @ 2200	1g @ 2200	1g @ 1000	1g @ 1007	2g @ 1522						
								1g @ 1700	2g @ 1516	2g @ 2300						
								1g @ 2200	2g @ 2300							
mg/kg/day		...	16.7	33.3	33.3	33.3	33.3	66.6	100	100	...					
SCr (mg/dL)	0.7		0.42	0.48	0.45	0.46	0.39	0.43	0.43	0.46	2.56	4.19	1.43			
VAN level							<3.5 @ 2106		8.7 @ 0945		54.9 @ 1633	39.5 @ 1340				
Notes													d/c			
Other NTs	Contrast		TZP	TZP	TZP	TZP	TZP/ Contrast	TZP	TZP	TZP						
Case 4																
	HD1	HD2	HD3	HD4	HD5	HD6	HD7	HD8	HD9	HD10	(5 days at home)	RD1	RD2	RD3	RD4	RD5
VAN doses		1g @ 0145	1g @ 0200	1g @ 1000	1g @ 0300	1g @ 0300	1g @ 0630	1g @ 0630	1g @ 0630	1g @ 0630						
		1g @ 1000	1g @ 1000	1g @ 1700	1g @ 0945	1g @ 0830	1g @ 1430	1g @ 1530	1g @ 1430							
		1g @ 1800	1g @ 1800	1g @ 2300	1g @ 1500	1g @ 1430	1g @ 2230	1g @ 2230	1g @ 2230							
			1g @ 2330		1g @ 2100	1g @ 2230										
mg/kg/day		37	49.4	37	49.4	49.4	37	37	37	12.3						
SCr (mg/dL)	0.62	0.6	0.53		0.51				0.58		...	2.48	2.27	2.19	2.11	1.68
VAN level				12.6 @ 0700		25 @ 0800			16.8 @ 1512 ^a			90.8 @ 2138	71.4 @ 0613	49.6 @ 0400	29.6 @ 0614	15.6 @ 0400
Notes										d/c						
Other NTs																
Case 5																

Case 1														
	HD1	HD2	HD3	HD4	HD5	...	HD8	...	HD17	...	HD21			
	HD1	HD2	HD3	HD4	HD5	...	HD12	...	HD28	...	HD30			
VAN doses	1g @ 0700	2g @ 0800												
	2g @ 0900													
	2g @ 1956													
mg/kg/day	51.3	20.5												
SCr (mg/dL)	0.97	4.26	6.25	8.41	9.96	...	5.88	...	1.4	...	1.25			
VAN level				64.7 @ 0349										
Notes			Renal biopsy	HD started			HD stopped				d/c			
Other NTs	TZP	TZP	TZP											
Case 6														
	HD1	HD2	HD3	HD4										
VAN doses	2g @ 2230	2g @ 630												
		2g @ 1442												
mg/kg/day	15.6	31.2												
SCr (mg/dL)	0.68	2.07	3.23	3.05										
VAN level		56 @ 1515	40.5 @ 1805	28.6 @ 0605										
Notes				d/c										
Other NTs		ibuprofen 600mg x1												
Case 7														
	HD1	HD2	HD3	HD4	HD5	HD6	HD7	HD8	(4 days home)	RD1	RD2	RD3	RD4	...
VAN doses		1g @ 0300	1g @ 0300	1g @ 0700	1g @ 0142	1g @ 0630	1g @ 0700	1g @ 1930						RD39

Case 1															
	HD1	HD2	HD3	HD4	HD5	...	HD8	...	HD17	...	HD21				
		1g @ 1528	1g @ 1457	1g @ 1630	1g @ 1216	1g @ 1530	1g @ 1546								
			1g @ 2300		1g @ 2130	1g @ 2328	1g @ 2340								
mg/kg/day		22.5	33.8	22.5	33.8	33.8	33.8	11.3							
SCr (mg/dL)	0.82	1.14	-	-	-	0.8	0.78	1.16		6.82	6.82	7.5	8.27	...	1.52 ... 2.25
VAN level			10.3 @ 1330		15.3 @ 0930	16.2 @ 1435						90 @ 0400			
Notes											HD started		CVVH started	Received TZP x3 days and gent x1, may have delayed recovery	CVVH stopped/HD started d/c
Other NTs	TZP	TZP	TZP	TZP	TZP	TZP	TZP								
Case 8															
	HD1	...	HD4	HD5	HD6	HD7	HD8	HD9	HD10	...	HD14	HD20	HD21		
VAN doses			1g @ 1600	1g @ 0120	1g @ 1000	1g @ 1014	1g @ 1107								
				1g @ 0359	1g @ 2300	1g @ 2230									
				1g @ 1200											
				1g @ 2242											
mg/kg/day			9.7	38.8	19.4	19.4	9.7								
SCr (mg/dL)	0.19		0.13	0.18	0.65	1.11	1.5	1.77	2.27		2.87	0.89	1.03		
									76.4 @ 1725		47.6 @ 0547	10.8 @ 0555			
VAN level				19.8 @ 1155											
Notes											HD started		d/c		
Other NTs		lisinopril	TZP/ lisinopril	TZP/ lisinopril	TZP/ lisinopril	TZP/ lisinopril	TZP	TZP							

Abbreviations: HD#, Hospital day #; VAN, vancomycin; g, grams; mg/kg/day; milligram s per kilogram per day; SCr, serum creatinine; HD, hemodialysis; PO, oral; d/c, discharged; NTs, nephrotoxins; TZP, piperacillin/tazobactam; CVVH, continuous venovenous hemofiltration

This concentration may have been erroneous or incorrectly recorded in the computer system

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