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Vancomycin should be considered a nephrotoxic antimicrobial agent: CON

Subtitle: Bystander or Culprit: Vancomycin and AKI

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Many clinicians are convinced of the nephrotoxicity of vancomycin; however, the current supporting data is weak, and we should consider this debate still open. The concept of vancomycin nephrotoxicity has clear parallels to the evolving discussion about the nephrotoxicity of intravenous contrast with which I am sure the reader is familiar. The current evidence for vancomycin-induced acute kidney injury (VIAKI) are woefully inadequate to prove causation underlies the correlation; the construct of VIAKI is founded on historical impurity-filled compounding processes which are no longer relevant, build of a large volume of retrospective studies and a few randomized controlled trials where the finding of VIAKI was not a pre-specified outcome, and now capped by newer biopsy reports that suffer from selection and process bias.

Every episode of acute kidney injury (AKI) in the setting of vancomycin use is not VIAKI; unfortunately, our current diagnostic tools do not allow us to identify a clear cause of AKI in many cases we see, and frequently clinicians then default to VIAKI, hence the reported rates of VIAKI in the literature vary widely (5 – 40%). (1,2) The similarities to the diagnosis of contrast-induced nephropathy are obvious. I will endeavor over the next few paragraphs to convince the reader that we do not yet have the evidence needed to confidently identify vancomycin as a significant nephrotoxin (table 1).

To begin we first must address the clinical sine qua non of VIAKI, the elevated vancomycin trough. (3,4) There is growing evidence that monitoring of vancomycin AUC is a more appropriate measure of antibacterial effect with a target of AUC/MIC > 400 however most non-infectious disease specialists are likely more familiar with monitoring trough levels. (5) The target trough varies between 10 – 15 mcg/ml and 15 – 20 mcg/ml depending on the location and severity of infection, however recent evidence suggests that elevated trough levels do not improve infection cure rates raising questions about their utility. (5,6) Unfortunately, an elevated vancomycin trough in the setting of AKI does not prove causation, only highlights our inability to accurately assess kidney function during an AKI event.

Vancomycin clearance occurs primarily via glomerular filtration as unmetabolized drug. When compared to inulin clearance in healthy normal subjects, the gold standard of glomerular filtration rate (GFR), vancomycin clearance provides a better estimate of GFR than creatinine clearance (0.89 vs 0.79 respectively). (7) Consequently, anything that causes a reduction in GFR will, for the same vancomycin dose, result in less clearance and higher blood levels. When a patient develops AKI, for any reason, we know the creatinine measured today does not represent a steady-state value, nor likely will tomorrows, they are only camps through which the serum creatinine climbs as it accumulates to an eventual future peak concentration. Basing medication dosing – amount or interval – on a creatinine as an estimate of actual GFR will likely result in overdosing for that patient (the corollary holds true for patients recovering from an AKI event, where underdosing therapeutics may occur). Medication dosing predicated on the serum creatinine as an estimate of GFR requires a steady-state creatinine and GFR, a condition clearly not met during AKI. Therefore, during an AKI event, if vancomycin dosing is adjusted for an estimated GFR based on a creatinine value that is found to be higher tomorrow the next trough level will be greater than anticipated. The elevated vancomycin trough is an effect of the AKI but does not establish a causative relationship. The use of kinetic-GFR modeling could be utilized to reduce the impact of misestimation of GFR on single creatinine values. A study of 946 patients reported that in those with AKI kinetic-GFR modeling resulted in change of eGFR classification compared to Cockcroft-Gault and CKD-EPI estimates in 33.5% and 37.9% of patients respectively. (8) The use of kinetic GFR estimate could result in a change to medication dosing which would impact trough levels.
When reviewing the available literature on VIAKI we encounter the next limitation of our understanding, most available data arises from retrospective observational studies, or studies where VIAKI was not a preset outcome. A large meta-analysis of the literature identifying vancomycin pharmacokinetic markers associated with the risk of VIAKI found a consistent association between AKI and vancomycin with higher first and maximum vancomycin trough. (9) One of the most exhaustive reviews, they included 60 studies with over 13,000 adult participants; however, 52 of the studies were retrospective and one a post-hoc analysis. Additionally, 42 of the studies were judged to have moderate or high risk for bias. The association between the first vancomycin trough and AKI is interesting as a clear explanation for an elevated first trough level is an AKI event occurring over the first 1-2 days of vancomycin use and no literature has yet argued for significant first pass nephrotoxicity. More often a prolonged vancomycin course is suggested to be a risk factor for VIAKI. Another risk factor commonly identified for VIAKI is obesity. (10) Again, we must look at the dosing of vancomycin which is most frequently actual body weight-based (not ideal body weight-based). Thus, in obese patients with medications dosed on actual weight, the vancomycin dose will be higher than if dosed on ideal weight; resulting in elevated trough levels as GFR is not proportionately increased with excess adipose tissue.

Not all data on the existence of VIAKI originates from retrospective studies and a review of the sparse randomized controlled trial (RCT) data was published in 2016. (11) The review of seven RCT concluded there is a small measurable risk of AKI associated with intravenous vancomycin, relative risk of 2.45. However, as the authors state “None of the included RCTs were designed to address the risk of kidney injury... Thus, in none of the studies were patients in the two arms matched for baseline renal function, other risk factors for AKI, or concurrent exposure to other nephrotoxins; additionally, in most cases, there was no confirmation that these parameters were evenly distributed between the arms. Also, renal end points were not prespecified and in some cases, were not strictly defined...”. The baseline matching described are absolute requirements to assess the nephrotoxicity of a single agent, as would be the clear definition of renal outcomes. These limitations are important when attempting to use these studies to assess the risk of AKI from vancomycin use rather than during vancomycin use. Vancomycin is not routinely given to otherwise healthy individuals with no other risk factors for AKI.

Although truly prospective randomized studies of VIAKI are rare, one of 103 patients with multiple risk factors for AKI examined the risk of VIAKI by switching from vancomycin to alternative antibiotics (AA) after the subjects received a single loading dose of vancomycin but before culture data returned to guide antibiotic selection. (12) As there is no strong evidence for first-pass nephrotoxicity, the investigators designed the study to investigate the risks of prolonged vancomycin use in well-matched groups. No significant difference in AKI was seen between those remaining on vancomycin and those switched to AA after a loading dose (31.4% vs 32.7%; p=0.89). In those remaining on vancomycin, initial trough levels were above 20 mcg/ml in 47.1% of subjects. As randomized control trials represent our best evidence, studies such as this should be performed and strongly weighed.

The newest contribution to our “understanding” of VIAKI comes from several recent studies of kidney biopsy in the setting of AKI while patients were receiving vancomycin. (13,14) The vancomycin-induced renal injury has previously been suggested to be acute tubular necrosis or acute tubulointerstitial nephritis, but these new studies suggest a novel pathology – the vancomycin tubular cast and obstruction. Both studies demonstrate intraluminal casts staining for vancomycin and uromodulin and suggest these casts cause the AKI in patients who were already diagnosed with VIAKI. However significant limitations prohibit arriving at that conclusion. First, uromodulin (previously known as Tamm-Horsfall protein) is the most abundant protein in the urine of healthy adults and is less a marker of tubular damage than a marker of tubular health. (15,16) As stated earlier, vancomycin is cleared by
glomerular filtration so its presence in the tubular fluid is expected in any patient receiving the antibiotic. The identification of two molecules that should be present in the tubular lumen is not enough to provide causation of AKI. The questions to be asked are what factors favor co-precipitation and the formation of the casts – pH, volume status, biochemical constituents... What happens during AKI to promote cast development and are these casts present with other etiologies of AKI? Are they the result of AKI rather than the cause? Finally, both studies only stained for vancomycin which likely was not the only therapeutic (or potentially nephrotoxic) agent these patients were receiving. Locating the one substance searched for, exactly where it should be, is not indicative of pathology.

I hope the reader will consider that the current evidence supporting the diagnosis of VIAKI, not AKI in a patient receiving vancomycin, is not convincing. The proof stands upon retrospective trials with concerns for significant bias, studies where reporting VIAKI was an afterthought, few randomized controlled trials (some which do not demonstrate VIAKI), and the suggestion of multiple pathologies. Patients who receive vancomycin frequently have multiple risk factors for AKI and require a thoughtful approach beyond “high vancomycin trough = VIAKI”. Until well-designed studies demonstrate vancomycin nephrotoxicity, we should not brand vancomycin a nephrotoxin.

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**Author Contributions**
Scott Mullaney: Writing - original draft
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| Evidence | Limitation |
|----------|------------|
| Historical Compounding with Impurities | Irrelevant given current manufacturing techniques |
| Elevated vancomycin trough level in AKI | Vancomycin troughs will increase due to AKI from any cause |
| Increased AKI with vancomycin in retrospective trials | Frequent bias in design, "evidence" mirrors much of the CIN literature Association with elevated first trough would require renal injury after only a few doses |
| Increased AKI with vancomycin in randomized controlled trials | Studies not performed to assess vancomycin nephrotoxicity Poor matching of groups and definition of renal endpoints for this outcome |
| Presence of vancomycin containing casts on biopsy | Vancomycin cleared via GFR, presence in tubule to be expected Selection bias in who undergoes biopsy |