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Vancomycin should be considered a nephrotoxic antimicrobial agent:

Commentary

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Vancomycin is a glycopeptide antibiotic that was discovered more than 6 decades ago (1958) to treat serious gram-positive infections and other resistant organisms (1,2). Rapid FDA approval was based on both its bactericidal activity against penicillin-resistant *Staphylococcus aureus* and the dearth of alternative agents effective against these resistant organisms (1,2). Following its release into clinical practice, vancomycin earned the label of ‘Mississippi mud’ based on the brown color caused by particulate matter in early preparations. Despite its efficacy, this impure preparation suffered from a number of adverse drug effects including nephrotoxicity and ototoxicity (1,2). These toxicities created a challenge for clinicians treating resistant gram-positive infections as they were now faced with weighing vancomycin’s efficacy against its apparent toxicity. A potential solution to the resistant organism problem soon arrived as Beecham Pharmaceuticals developed methicillin, which was FDA-approved for clinical use and provided an effective alternative for many penicillin-resistant organisms (3). The clinical availability of methicillin combined with vancomycin's toxicity relegated this glycopeptide to a second line drug primarily employed for patients with beta-lactam allergies and other drug resistant organisms. Before long, however, vancomycin was resuscitated and pulled back off the shelf for clinical use based on 2 major developments. First, methicillin-resistant *Staphylococcus aureus* infections emerged in 1961 (3) and other organisms such as coagulase negative staphylococcus species similarly posed resistance problems not amenable to treatment with the available antibiotic armamentarium. Second, newer vancomycin formulations with improved purity were developed and were now available (1). In addition, oral vancomycin was noted to be very effective for pseudomembranous colitis (2). As a result, the next several decades witnessed a significant increase in vancomycin administration for the treatment of several otherwise potentially lethal infections (1,4). So, while the new vancomycin preparations were practice changing, the story continued to evolve. Despite the availability of these pure vancomycin formulations, acute kidney injury (AKI) was observed to complicate vancomycin therapy raising suspicion that vancomycin still maintained nephrotoxic potential. However, the actual nephrotoxicity of vancomycin monotherapy is a complicated and somewhat
controversial area. In fact, many clinicians find the nephrotoxicity issue as murky as the original vancomycin preparations. This lack of clarity forms the basis for this debate in *Kidney360*.

What do we know about the potential nephrotoxicity of vancomycin? Animal investigations of vancomycin support the notion that the drug is potentially nephrotoxic and kidney injury develops through various mechanisms. Induction of reactive oxygen species, which may affect cell metabolism and various enzymatic activities, plays a role in kidney injury (5,6). Escalating doses of this drug also appears to increase mitochondrial stress, releasing cytochrome-c and activating the caspase pathway, resulting in cellular stress and apoptosis (5,6). This bespeaks a dose-related nephrotoxicity. But do these nephrotoxic findings observed in preclinical animal models translate into similar toxicity in humans exposed to vancomycin? There is no definitive answer as we know that the results of preclinical drug efficacy and toxicity studies do not always translate into clinical effects in humans. In the published literature, the histology observed in cases of vancomycin-associated AKI consists primarily of 2 types of kidney lesions: acute tubular injury/necrosis and acute interstitial nephritis (7). A third lesion, called “vancomycin-associated cast nephropathy” was described in 2017 and replicated in a 2021 publication (8,9). Thus, the presence of these 3 kidney lesions (*Figure 1*) suggests that vancomycin has nephrotoxic potential.

In clinical practice, AKI incidence rates associated with vancomycin are highly variable with observed rates widely ranging from 0 to as high as 40% (5,10-12). In assessing the potential nephrotoxicity of vancomycin, the characteristics of the host, the illness requiring antibiotic therapy, and the clinical context must be considered. In fact, one must recognize that the higher numbers observed are exaggerated by factors that include but are not limited to the use of various AKI definitions, concomitant nephrotoxin exposure, and lack of control groups. Important potential confounders include inadequate control of factors that independently increase risk for AKI such as underlying infection/sepsis, underlying hemodynamics such as
hypotension, diagnostic and interventional procedures, and patient comorbidities such as preexisting CKD. In fact, more rigorous data temper these incidence rates by controlling for possible confounding factors and showed lower, albeit persistent nephrotoxicity (13). A meta-analysis comprised of cohort studies and randomized clinical trials comparing vancomycin to non-nephrotoxic antibiotics described that vancomycin had a modest relative risk of AKI of 2.45 (95% CI, 1.69 to 3.55) with an attributable risk percentage (percent of an outcome that could possibly be prevented if the risk factor was removed from the population) of 59% (13).

Epidemiologically, the incidence of vancomycin-associated AKI appears to increase when the upper limit for target trough levels for complicated infections was increased from 15mg/L to 20mg/L (14). This supports the observation that AKI is dose-related and most often associated with larger doses and supratherapeutic vancomycin levels (14,15), whereas therapy with conventional vancomycin doses that achieve levels within the lower therapeutic range (10-15mg/L) are rarely associated with nephrotoxicity. In fact, excessive vancomycin trough levels (>35mg/L) were associated with more AKI (82%) than trough levels <10mg/ml (5%) (16). Since the majority of vancomycin-associated AKI cases report supratherapeutic or “toxic” levels, a dose-related form of nephrotoxicity is supported. But, this interpretation is confounded by the following question: Did the supratherapeutic vancomycin levels cause nephrotoxic AKI or did AKI develop as a result of unrelated factors such as sepsis, hypotension, or other nephrotoxins and reduce vancomycin clearance?

Thus, based on the preceding discussion, the actual nephrotoxicity of vancomycin is not as clear-cut as one might think. In this issue of Kidney360, a debate is undertaken examine the conundrum of vancomycin nephrotoxicity. Our experts include Mark Murphy and Erin Barreto from the Mayo Clinic, who make the case that vancomycin is nephrotoxic and Scott Mullaney from UCSD, who argues that the AKI that develops in the setting of vancomycin therapy can be explained by other factors that promote kidney injury. Let’s analyze their arguments.
Murphy and Barreto’s PRO argument hinges upon experimental data that unequivocally demonstrate histopathological kidney damage with exposure to vancomycin. This is further bolstered by an acute elevation in biomarkers of kidney injury in the setting of vancomycin therapy. They note that renal excretion of vancomycin is the first step in the pathway to kidney injury as drug accumulates in tubular cells and promotes injury through a number of mechanisms. These include oxidative stress with injurious free radical production and mitochondrial damage as well as complement pathway activation. They allude to the possibility of vancomycin-associated cast nephropathy as yet another example of nephrotoxicity. The PRO authors then present their second argument to support vancomycin nephrotoxicity by citing human data. The authors admit up front that the data are not as powerful as the experimental evidence. They note the problem with studies and sorting out the ‘chicken or egg’ aspect of vancomycin nephrotoxicity (supratherapeutic vancomycin levels cause AKI or other AKI causes elevate vancomycin levels). Murphy and Barreto harken back to comparative trials and pooled data showing that the risk of AKI was higher with vancomycin as compared to linezolid. They discuss the higher quality Zephyr trial that supports vancomycin nephrotoxicity as compared to linezolid. The PROVIDE trials (multicenter prospective observational study) showed that higher vancomycin exposure was associated with a higher risk for AKI, bespeaking dose and duration-related nephrotoxicity.

On the CON side, Mullaney makes the point that the nephrotoxicity of vancomycin is based on weak, flawed data and draws parallels between the issue of contrast-associated AKI and vancomycin-associated AKI. He argues that the initial impure vancomycin formulation has colored the view of this drug and the label as a toxin has stuck. This led to confounded retrospective studies, RCTs weakened by the lack of AKI as a prespecified outcome, lack of baseline matching of AKI risk factors (kidney function, other risk factors, concurrent nephrotoxin use, etc.) and a myriad of case reports/series suffering from selection and process bias. Mullaney also notes
that since vancomycin is cleared by the kidneys, vancomycin trough levels rise from any impairment in GFR, thereby making the finding of excessive levels in this setting far from proof of causation. Dr. Mullaney argues that the entity of vancomycin-associated cast nephropathy is a far cry from proof of vancomycin nephrotoxicity. He notes that the renal excretion of vancomycin dictates that vancomycin will be present in the urine and the drug’s comingling with uromodulin and forming casts does not prove that nephrotoxicity. Overall, he favors the term “vancomycin-associated nephrotoxicity” as it is applied to contrast medium—suggesting it is not necessarily the “cause” of AKI.

So, who has won this debate? As reviewed, animal studies support a dose-related nephrotoxicity via the mechanisms previously discussed. Human data suggest that vancomycin is nephrotoxic primarily when supratherapeutic levels (>30 mg/L) develop. Except for an idiosyncratic reaction causing AIN, therapeutic levels of vancomycin appears, for the most part, relatively free of direct kidney toxicity. I believe that Dr. Mullaney provided a strong argument to question the idea that vancomycin monotherapy should be listed as a classical nephrotoxin. Drs. Murphy and Baretto provide equally strong arguments in support of vancomycin nephrotoxicity, in particular with high doses and supratherapeutic levels. As such, I will let the readers decide on their own after reading the debate series.
**Disclosures**
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**Author Contributions**
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**Figure Legends**

**Figure 1. Kidney histology observed with vancomycin-associated acute kidney injury.**

A. Acute tubular injury seen in a patient with vancomycin-associated acute kidney injury. Note the dilated tubules and flattened epithelium (Hematoxylin & eosin stain).

B. Acute interstitial nephritis observed in a patient with vancomycin-associated acute kidney injury. There is a diffuse inflammatory cell infiltrate within the interstitium (Hematoxylin & eosin stain).

C. Vancomycin-associated cast nephropathy noted in a patient with vancomycin-associated acute kidney injury. The cast is surrounded by a cellular reaction (Hematoxylin phloxine saffron stain).
