How to Cite this article: M. Stokes and Jacob Stevens, Vancomycin-Associated Cast Nephropathy: Reality or fantasy, Kidney360, Publish Ahead of Print, 10.34067/KID.0007282021

Article Type: Perspective

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DOI: 10.34067/KID.0007282021

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Key Points:
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Abstract:

Disclosures: The authors have nothing to disclose.

Funding:

Author Contributions: M. Stokes: Conceptualization; Writing - original draft; Writing - review and editing Jacob Stevens: Conceptualization; Writing - original draft; Writing - review and editing

Data Sharing Statement:

Clinical Trials Registration:

Registration Number:

Registration Date:

The information on this cover page is based on the most recent submission data from the authors. It may vary from the final published article. Any fields remaining blank are not applicable for this manuscript.
Vancomycin-Associated Cast Nephropathy: Reality or Fantasy?

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Vancomycin is a glycopeptide antibiotic commonly used for severe gram-positive bacterial infections, notably methicillin-resistant Staphylococcus aureus. Acute kidney injury (AKI) occurs in 5-43% of vancomycin-treated patients\textsuperscript{1-3} and is commonly (59%) attributable to vancomycin nephrotoxicity (VANT).\textsuperscript{4} The true incidence of VANT is unknown, given the absence of randomized controlled trials and the high prevalence of confounding causes of AKI. However, a meta-analysis comparing vancomycin to a non-glycopeptide antibiotic suggests this risk is low (relative risk 2.45) with standard vancomycin doses (<4 g/day).\textsuperscript{4} The risk of nephrotoxicity with higher doses used for severe infections is undoubtedly higher. Fortunately, AKI usually resolves after drug discontinuation.\textsuperscript{4} Because kidney biopsy is rarely performed, the pathologic features of VANT are poorly characterized but both acute tubular injury and acute interstitial nephritis have been described. More recently, a novel “cast nephropathy” containing vancomycin intermingled with uromodulin has been described in VANT.\textsuperscript{6-8} However, the relationship of these casts to AKI (i.e., cause or effect) remains unclear.

**Vancomycin nephrotoxicity: Clinical features**

VANT is defined clinically as AKI that improves following discontinuation of the drug. Risk factors fall into three major categories: pharmacokinetics, patient factors, and concomitant nephrotoxin exposures.\textsuperscript{9} The frequency of AKI correlates with trough levels of vancomycin (82% if >35mg/L, versus 5% if <10mg/L), consistent with dose-dependent toxicity.\textsuperscript{9} In one meta-analysis, the incidence of AKI was 29.6% with trough levels >15mg/L versus 8.9% with levels <15mg/L (OR 2.67 (95% CI 1.95-3.65)).\textsuperscript{10} This highlights the risk for nephrotoxicity with higher targeted trough levels (15-20 mg/L) employed for resistant strains of S. aureus.\textsuperscript{11} Longer duration of therapy (>7 days) is also a risk factor, while the relationship to mode of administration (intermittent bolus vs. continuous infusion) is less consistent.\textsuperscript{9} Patient risk factors include obesity, chronic kidney disease, and critical illness.\textsuperscript{9} Lastly, co-administration of aminoglycosides and piperacillin-tazobactam compound the risk of AKI, possibly by altered
pharmacokinetics. The timing of AKI with VANT varies from 4-17 days after initiation of vancomycin, reflecting infrequent therapeutic drug monitoring and the poor performance of creatinine rise as a biomarker of injury (i.e., 2-3 days lag from injury to rise). Importantly, vancomycin is excreted predominantly (>90%) by glomerular filtration and its clearance is inversely proportional to creatinine clearance. Thus, a major challenge in diagnosing VANT is avoiding reverse causality bias by attributing AKI to high vancomycin levels when elevated levels may be consequent to AKI from other causes. Nonetheless, increased trough levels (or area under concentration time curve-to-minimum inhibitory concentration ratio) are important clues to the presence of VANT.

Management of VANT consists of reducing ongoing nephrotoxic exposures and monitoring for the development of severe AKI requiring renal replacement therapy. Identifying patients with risk factors for the development of VANT should prompt early and frequent therapeutic drug monitoring, to prevent unnecessarily high trough concentrations. If VANT is suspected clinically, should be discontinued until blood levels return to a therapeutic range.

Pathogenesis and pathology

The role of acute tubular injury in VANT is supported by morphologic findings in kidney biopsies and experimental models. Vancomycin can enter proximal tubular epithelium via the organic acid transport system at the basolateral membrane, and possibly also via megalin receptor-mediated transport at the apical surface, where it induces oxidative stress, mitochondrial damage, and activation of inflammatory and complement pathways. Distal tubular injury also occurs, as evidenced by increased urinary excretion of the distal tubule marker dimethylamine. Tubular toxicity is likely triggered by conditions that promote increased intratubular vancomycin concentration, including low urinary flow rates and tubular obstruction. Of note, acute interstitial nephritis due to vancomycin reflects an idiosyncratic allergic response. This is usually accompanied by signs of acute tubular injury.
and skin findings. Rare severe allergic reactions include toxic epidermal necrolysis and drug rash with eosinophilia and systemic symptoms (DRESS)\textsuperscript{5,9}. 

In 2017, Luque et al.\textsuperscript{6} described the first case of AKI with vancomycin-containing casts demonstrated by immunohistochemistry, immunoelectron microscopy, and infrared spectroscopy. These casts appeared granular by light microscopy and contained uromodulin (Tamm Horsfall protein) which was also detected in Bowman space. Transmission electron microscopy disclosed non-crystalline spherical vancomycin aggregates (100-900 nm). Similar pathologic findings were demonstrated in 8 other patients and in mice exposed to vancomycin. Uromodulin is synthesized by the thick ascending loop of Henle and uromodulin casts are a common finding in AKI of diverse causes\textsuperscript{18} but particularly prominent in outflow obstruction, where retrograde extension to proximal tubules and Bowman space may be seen, sometimes accompanied by tubular rupture, extrusion, and a localized inflammatory cell reaction. Tubular dilatation, casts, sloughed epithelium, and Bowman space expansion were noted in previous experimental models of VANT\textsuperscript{14,15}, providing additional indirect evidence for tubular obstruction in VANT. 

Subsequently, Tantranont et al.\textsuperscript{7} identified vancomycin and uromodulin-containing casts in most (25 of 28) patients with VANT (i.e., whose kidney function improved after vancomycin was discontinued), versus 1 of 9 patients without clinical nephrotoxicity. Casts localized to the distal tubule and had a variable appearance, ranging from periodic acid Schiff (PAS) red, granular aggregates to variegated spherules intermingled with uromodulin and necrotic epithelial cells, accompanied by acute tubular injury and/or interstitial nephritis\textsuperscript{7}. In mild cases, casts consisted predominantly of uromodulin and vancomycin was only detected by immunohistochemistry. By electron microscopy, some casts formed globular aggregates with a concentric multi-lamellated appearance, suggestive of crystallization. Other investigators have shown the presence of calcium phosphate apatite in vancomycin-containing
casts\textsuperscript{19}. Tantranont et al. speculated that vancomycin and uromodulin containing casts developed after direct tubular toxicity or single nephron obstruction from sloughed epithelial cells, setting off a vicious cycle of tubular obstruction and increased local vancomycin concentration that promoted crystallization and further tubular injury\textsuperscript{7}. Of note, casts with a similar morphologic and ultrastructural appearance derived from the plasma membrane of degenerating epithelial cells have also been described in cast nephropathy with delayed graft function associated with use of tacrolimus plus sirolimus\textsuperscript{20}. This raises the possibility that vancomycin-containing casts may be derived from necrotic/apoptotic epithelial cells that are shed following severe acute tubular injury.

**Vancomycin-associated Cast Nephropathy: Reality or Fantasy?**

There is little doubt that vancomycin-containing casts are real and not “fantastical” and are a reliable indicator of VANT\textsuperscript{6,7}. But whether these casts cause AKI (e.g., via tubular obstruction) or simply reflect reduced “wash-out” in the setting of AKI remains unclear (Figure 1). This question is probably impossible to answer since serial kidney biopsies are not ethical in human subjects or feasible in animal models. Moreover, because vancomycin encounters the proximal tubule before reaching the distal tubule, it is very difficult to prove a primary pathogenetic role for distal tubular obstruction, independent of proximal tubular injury. Similar uncertainty surrounds many other kidney diseases and drug toxicities characterized by cast formation and/or intratubular drug crystallization\textsuperscript{21}, in which the pathophysiology of AKI may involve both direct cytotoxic injury to tubular epithelium and outflow obstruction\textsuperscript{22}.

The formation of casts may involve interactions between cast constituents and uromodulin (as in myeloma cast nephropathy), in addition to altered conditions in the distal tubule microenvironment that enhance uromodulin gel formation\textsuperscript{23} and promote supersaturation and precipitation, such as increased concentration and urinary pH\textsuperscript{24}. In vancomycin-associated cast nephropathy it is notable that
kidney function recovered completely in most reported cases, even those requiring renal replacement therapy, indicating that these casts are reversible, or at least excretable. This contrasts with other forms of nephropathy associated with drug precipitates which typically have residual kidney dysfunction, presumably due to their insolubility. Further studies are needed to understand the nature of vancomycin-uromodulin interactions, and to determine if vancomycin undergoes crystallization in the kidney tubule in VANT. These findings might inform strategies to prevent or ameliorate this toxicity. The detection of vancomycin-containing casts in the urine, if reproducible, might eliminate the need for an invasive diagnostic biopsy in VANT and shed more light on the dynamics of cast formation and its relationship to AKI.

Should vancomycin immunostaining now be added to the renal pathologist’s diagnostic armamentarium? Given the rarity of this toxicity and the limited added value of identifying vancomycin-containing casts for managing patients with suspected VANT, this extra effort seems hard to justify. However, the findings of numerous uromodulin-containing casts should certainly raise the possibility of VANT in the appropriate clinical setting. Uromodulin casts have distinct tinctorial properties by light microscopy and a filamentous ultrastructural appearance that are easily recognizable. The ultrastructural finding of nanospherical casts of variable electron density, admixed with uromodulin filaments, may offer additional evidence of possible vancomycin-associated cast nephropathy. However, the latter will require increased attention to distal tubules, which are rarely targeted by routine kidney biopsy examination.

The Kidney Medicine Personalized Medicine Project has drawn renewed attention to the clinical impact of AKI and the need to identify differences in pathomechanisms that affect patient outcomes. The discovery of vancomycin-containing casts in patients with VANT suggests a potential novel form of
drug-related AKI. However, further study is needed to determine if this distinctive pathologic finding is the cause or consequence of VANT.

Disclosures: The authors have nothing to disclose.

Funding: None.

Acknowledgments: The content of this article reflects the personal experience and views of the author(s) and should not be considered medical advice or recommendation. The content does not reflect the views or opinions of the American Society of Nephrology (ASN) or Kidney360. Responsibility for the information and views expressed herein lies entirely with the author(s).

Author Contributions: Michael Stokes: Conceptualization; Writing - original draft; Writing - review and editing. Jacob Stevens: Conceptualization; Writing - original draft; Writing - review and editing.

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Figure 1: Vancomycin and uromodulin containing casts in the distal tubule are a common kidney biopsy finding in patients with acute kidney injury (AKI) attributed to vancomycin nephrotoxicity. Whether these casts are the cause or the result of AKI remains unknown.
Two possible roles of vancomycin-containing casts in vancomycin nephrotoxicity

AKI (e.g., from proximal tubular injury)
↓
Reduced urine flow
↓
Cast formation

Cast formation (e.g., from increased vancomycin concentration)
↓
Tubular obstruction
↓
AKI