



Vancomycin-Induced Nephrotoxicity and Therapeutic Drug Monitoring: Current Insights and Clinical Management Strategies

Hafiza Sana Ur Rehman¹, Muhammad Zaeem Ahsan¹, Saliha Khalid²

¹Faculty of Pharmacy, Department of Pharmaceutical Sciences, The Superior University, Lahore

²Department of Molecular Biology and Genetics, School of Engineering and Natural Sciences, Kadir Has University 34083, Cibali Campus Fatih, Istanbul Turkey

 ***Corresponding Author:** Hafiza Sana Ur Rehman, Faculty of Pharmacy, Department of Pharmaceutical Sciences, The Superior University, Lahore
Email: sanaa8448@gmail.com

 CONFLICT OF INTEREST None declared.	 GRANT SUPPORT None declared.	 FINANCIAL SUPPORT None Declared.
--	--	--

 ABSTRACT
Background: Vancomycin remains a cornerstone antimicrobial for the treatment of serious methicillin-resistant <i>Staphylococcus aureus</i> (MRSA) infections; however, vancomycin-associated acute kidney injury (VA-AKI) remains an important treatment-related complication, particularly among critically ill patients, individuals with obesity or pre-existing renal impairment, and those receiving concomitant nephrotoxic medications. Objective: This narrative review synthesizes contemporary evidence on the epidemiology, pathophysiology, risk factors, diagnostic biomarkers, therapeutic drug monitoring (TDM), and clinical management of VA-AKI, with particular emphasis on developments in vancomycin exposure monitoring and individualized dosing. Methods: A structured literature search of PubMed, Embase, and the Cochrane Library was conducted for relevant studies published predominantly between 2020 and 2026. Seminal earlier studies and major clinical guidelines were also considered where necessary to describe established pharmacokinetic, pharmacodynamic, and toxicodynamic concepts. Key Findings: Current evidence supports a transition from trough-based monitoring toward area-under-the-concentration-time-curve (AUC)-guided dosing for serious MRSA infections. The 2020 ASHP/IDSA/PIDS/SIDP consensus guideline recommends targeting a 24-hour AUC to minimum inhibitory concentration ratio (AUC₂₄/MIC) of 400–600 when an MIC of 1 mg/L is assumed. AUC-guided monitoring has generally been associated with lower nephrotoxicity than traditional trough-targeted strategies while maintaining therapeutic efficacy. Concomitant administration of vancomycin and piperacillin-tazobactam has also been associated with a higher incidence of AKI than combinations involving vancomycin with cefepime or meropenem, although the contribution of true structural kidney injury versus changes in creatinine handling remains an area of investigation. Emerging biomarkers, including urinary kidney injury molecule-1 (KIM-1) and neutrophil gelatinase-associated lipocalin (NGAL), together with alternative renal function markers such as cystatin C, may permit earlier identification of kidney dysfunction than serum creatinine alone. Bayesian model-informed precision dosing provides an additional strategy for individualized AUC estimation using limited concentration sampling. Conclusion: Contemporary strategies for reducing VA-AKI emphasize AUC-guided TDM, individualized assessment of nephrotoxicity risk, minimization of avoidable concomitant nephrotoxins, appropriate renal function monitoring, and timely dose adjustment or antimicrobial modification when kidney injury develops. Bayesian precision-dosing approaches and emerging kidney injury biomarkers may further improve individualized vancomycin management, although additional prospective validation is required in several patient populations.

 Keywords	Vancomycin; Vancomycin-associated acute kidney injury; Nephrotoxicity; Therapeutic drug monitoring; Area under the curve; Bayesian dosing; Piperacillin-tazobactam; Kidney injury biomarkers
Acknowledgement	The authors acknowledge the contributions of their respective institutions and colleagues who provided academic and technical support during the preparation of this review
Rehman HSU et al. Short Title	Vancomycin Nephrotoxicity and Therapeutic Drug Monitoring





1. INTRODUCTION

Vancomycin is a glycopeptide antimicrobial that remains widely used for the treatment of serious infections caused by Gram-positive organisms, particularly methicillin-resistant *Staphylococcus aureus* (MRSA). Important clinical indications include bacteremia, infective endocarditis, osteomyelitis, and hospital-acquired pneumonia caused by susceptible Gram-positive pathogens [1,2,3]. Despite the availability of newer anti-MRSA agents, vancomycin continues to play a central role in clinical practice because of its established efficacy, widespread availability, extensive clinical experience, and relatively low acquisition cost. However, its narrow therapeutic index and potential for nephrotoxicity make appropriate dosing and therapeutic drug monitoring essential components of safe treatment [1,2]. Vancomycin-associated acute kidney injury (VA-AKI) is an important adverse event that may prolong hospitalization, increase healthcare utilization, necessitate modification or discontinuation of antimicrobial therapy, and, in severe cases, contribute to the need for renal replacement therapy [4,5]. Historically, vancomycin therapeutic drug monitoring relied predominantly on trough serum concentrations. The 2009 consensus recommendations advocated trough concentrations of 15–20 mg/L for serious MRSA infections as a practical surrogate for achieving the pharmacodynamic exposure target of an AUC₂₄/MIC of at least 400 [1,3]. Subsequent evidence demonstrated substantial variability in the relationship between trough concentration and total vancomycin exposure, with trough targets of 15–20 mg/L frequently producing unnecessarily high AUC values and an increased risk of nephrotoxicity without a corresponding improvement in clinical efficacy [1,3].

In response to these concerns, the American Society of Health-System Pharmacists (ASHP), Infectious Diseases Society of America (IDSA), Pediatric Infectious Diseases Society (PIDS), and Society of Infectious Diseases Pharmacists (SIDP) issued revised consensus recommendations in 2020 supporting AUC-guided vancomycin dosing for serious MRSA infections [1]. The guideline recommends an AUC₂₄/MIC target of 400–600, assuming an MIC of 1 mg/L as determined by broth microdilution. This approach is intended to achieve adequate antimicrobial exposure while reducing excessive vancomycin exposure and the associated risk of nephrotoxicity. Bayesian pharmacokinetic methods are particularly useful for AUC estimation because they combine population pharmacokinetic models with patient-specific characteristics and measured vancomycin concentrations, allowing individualized dose estimation with limited sampling and, in many circumstances, without waiting for pharmacokinetic steady state [1]. Beyond vancomycin exposure itself, the development of VA-AKI is influenced by multiple patient- and treatment-related factors, including pre-existing renal dysfunction, critical illness, obesity, hemodynamic instability, prolonged therapy, and concomitant exposure to other nephrotoxic agents. Particular attention has been directed toward the combination of vancomycin with piperacillin-tazobactam because observational studies and meta-analyses have repeatedly demonstrated higher creatinine-defined AKI rates with this regimen than with vancomycin combined with several alternative anti-pseudomonal β -lactams. At the same time, advances in kidney injury biomarkers and model-informed precision dosing have created opportunities for earlier detection of renal injury and more individualized vancomycin exposure management.

This narrative review provides an integrated synthesis of contemporary evidence on the epidemiology, pathophysiology, risk factors, diagnosis, prevention, and clinical management of VA-AKI. Particular emphasis is placed on the transition from trough-based to AUC-guided therapeutic drug monitoring, the association between vancomycin and piperacillin-tazobactam combination therapy and AKI, emerging biomarkers of kidney injury, Bayesian model-informed precision dosing, and practical considerations for vancomycin use in high-risk and special patient populations.

2. EPIDEMIOLOGY AND CLINICAL BURDEN OF VANCOMYCIN-ASSOCIATED NEPHROTOXICITY

The reported incidence of vancomycin-associated acute kidney injury (VA-AKI) varies considerably according to the characteristics of the study population, definition of AKI, vancomycin exposure, duration of treatment, and concomitant use of nephrotoxic medications. Reported rates range from approximately 5% in relatively low-risk populations to more than 40% among critically ill patients with multiple risk factors or concurrent exposure to nephrotoxic agents [4,6,7]. Estimates also vary geographically and across clinical cohorts. Reported incidences among hospitalized adults include approximately 11.4% in United States cohorts, 14.3% in mainland Chinese cohorts, 11.5% in Taiwanese cohorts, 15.4% in South Korean cohorts, and 11.2% in French cohorts [7]. In patients treated for infective endocarditis, an incidence of approximately 17% has been reported, potentially reflecting prolonged antimicrobial exposure, greater cumulative vancomycin exposure, underlying comorbidities, and the clinical severity of infection [7]. VA-AKI is clinically important because its consequences extend beyond transient elevations in serum creatinine. Observational analyses have associated VA-AKI with prolonged hospitalization, increased healthcare utilization, treatment modification, and adverse clinical outcomes [8,9]. Combined analyses of pharmacovigilance and electronic medical record databases have reported an association between VA-AKI and increased mortality, with an odds ratio of 1.30 (95% CI 1.17–1.46). Among patients who developed VA-AKI, failure to recover renal function was associated with substantially higher in-hospital mortality (HR 4.05, 95% CI 2.42–6.77) and increased 1-year mortality (HR 3.03) [9]. Because these findings arise primarily from observational data, however, they demonstrate association rather than establishing VA-AKI as an independent causal determinant of mortality.

The clinical and economic burden of VA-AKI may include prolonged hospital stay, additional laboratory and therapeutic monitoring, interruption or modification of antimicrobial therapy, and, in severe cases, the need for renal replacement therapy [4,9]. Persistent impairment of kidney function after an AKI episode may further contribute to longer-term healthcare utilization. These concerns reinforce the importance of antimicrobial stewardship, appropriate therapeutic drug monitoring, avoidance of unnecessary concomitant nephrotoxins, and limiting the duration of vancomycin therapy to the shortest clinically appropriate course [4,10].



3. Pathophysiology and Mechanisms of Vancomycin-Induced Nephrotoxicity

The pathogenesis of VA-AKI is multifactorial and has not been completely elucidated. Current evidence, derived largely from preclinical, histopathological, and translational studies, supports proximal tubular injury as an important component of vancomycin-associated nephrotoxicity [4,11,12]. Vancomycin is predominantly eliminated by the kidneys with minimal metabolism. Following glomerular filtration, the drug may accumulate within proximal tubular epithelial cells through cellular uptake mechanisms involving receptor-mediated endocytosis and renal transport pathways. Excessive intracellular exposure may subsequently contribute to oxidative stress, mitochondrial dysfunction, inflammatory injury, apoptosis, and tubular obstruction [4,12,13].

3.1 Oxidative Stress and Mitochondrial Dysfunction

Oxidative stress is one of the most extensively investigated mechanisms of vancomycin-induced tubular injury. Experimental studies suggest that accumulation of vancomycin within proximal tubular epithelial cells promotes excessive production of reactive oxygen species (ROS), disrupts mitochondrial function, and activates pathways leading to cellular apoptosis and necrosis [4,12,14]. Preclinical studies evaluating antioxidant and free-radical-scavenging interventions provide additional support for the contribution of oxidative injury. Experimental superoxide dismutase-related interventions have been associated with attenuation of increases in blood urea nitrogen and serum creatinine and with reductions in histological evidence of proximal tubular injury in animal models [14]. Similarly, both in vivo and in vitro studies have reported that N-acetylcysteine, a glutathione precursor with antioxidant properties, can attenuate vancomycin-induced oxidative stress and apoptosis in renal tubular cells [15]. Although these findings strengthen the biological plausibility of oxidative stress as an important mechanism of VA-AKI, they are predominantly preclinical and should not be interpreted as evidence supporting routine antioxidant therapy in patients receiving vancomycin.

More recent experimental work has identified additional molecular pathways that may contribute to vancomycin-induced renal injury. Phosphoproteomic analyses of murine kidney tissue have demonstrated alterations in pathways involved in oxidoreductase activity, peroxisomal function, and peroxisome proliferator-activated receptor- α (PPAR α) signaling [16]. Because PPAR α contributes to fatty-acid oxidation and energy metabolism in proximal tubular cells, disruption of these pathways may further promote mitochondrial dysfunction and oxidative injury during vancomycin exposure.

3.2 Inflammation and Acute Tubulointerstitial Nephritis

Inflammatory and immune-mediated mechanisms may also contribute to vancomycin-associated kidney injury. Histopathological findings reported in patients with suspected vancomycin nephrotoxicity include acute tubular injury as well as acute tubulointerstitial nephritis [4]. Experimental evidence also suggests activation of inflammatory pathways and complement-associated mechanisms during vancomycin-induced renal injury. Acute tubulointerstitial nephritis represents a potentially distinct immune-mediated pattern of injury that may coexist with direct tubular toxicity. This mechanism may help explain some cases in which kidney dysfunction develops after a temporal delay following vancomycin exposure rather than in direct relation to cumulative drug exposure alone [4]. However, the relative contribution of direct tubular toxicity and immune-mediated injury is likely to vary among individual patients.

3.3 Intratubular Cast Formation

Another recognized histopathological feature of vancomycin-associated nephrotoxicity is the formation of intratubular casts containing vancomycin together with uromodulin (Tamm-Horsfall protein) [4,16]. These casts may obstruct tubular lumina and contribute to impaired tubular flow and additional epithelial injury. Cast formation has been described particularly in the setting of high vancomycin exposure and conditions that increase urinary concentration, including volume depletion. This mechanism may occur alongside oxidative and inflammatory tubular injury rather than representing an entirely separate pathological process. Accordingly, VA-AKI is increasingly viewed as the result of several interacting mechanisms rather than a single uniform form of nephrotoxicity.

3.4 Interaction With Concomitant Beta-Lactam Therapy

The higher incidence of creatinine-defined AKI reported with concomitant vancomycin and piperacillin-tazobactam has generated considerable interest in potential pharmacokinetic and cellular mechanisms underlying this association. One proposed mechanism involves renal organic anion transporters, particularly organic anion transporter-3 (OAT-3), which participates in proximal tubular handling of several beta-lactam antibiotics and creatinine [13]. Competition for tubular transport may reduce creatinine secretion and produce an increase in serum creatinine without an equivalent reduction in glomerular filtration, raising the possibility that at least part of the observed AKI signal with vancomycin plus piperacillin-tazobactam may represent pseudo-nephrotoxicity rather than structural kidney damage. Other mechanistic hypotheses suggest that concomitant beta-lactam exposure may modify vancomycin-associated tubular toxicity through transporter-mediated effects, oxidative stress, or altered mitochondrial function [13,17]. However, the extent to which piperacillin-tazobactam causes genuine synergistic structural kidney injury remains uncertain. Experimental and translational studies evaluating kidney injury biomarkers have produced findings that continue to support investigation of both true tubular injury and altered creatinine handling as possible explanations for the clinical association.

Overall, current evidence suggests that vancomycin-associated nephrotoxicity is multifactorial, involving interacting pathways of intracellular drug accumulation, oxidative and mitochondrial injury, inflammation, immune-mediated tubulointerstitial injury, and intratubular cast formation. These mechanisms may be further influenced by patient-specific susceptibility, systemic illness, vancomycin exposure, hydration status, and concomitant medications. The proposed integrated pathway is summarized in Figure 1.



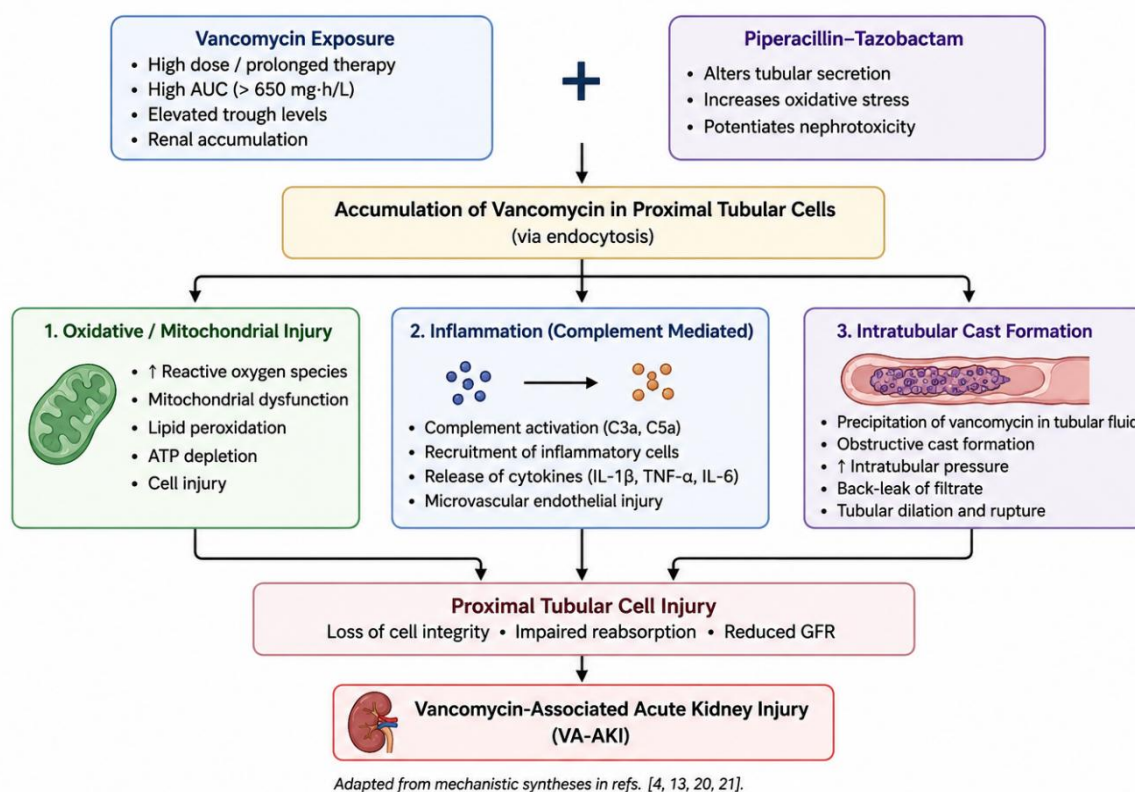


Figure 1. Proposed integrated mechanistic pathway of vancomycin-induced proximal tubular injury, incorporating oxidative/mitochondrial injury, complement-mediated inflammation, and obstructive intratubular cast formation, with potentiation by concomitant piperacillin-tazobactam. Adapted from mechanistic syntheses in refs. [4,13,20,21].

4. RISK FACTORS FOR VANCOMYCIN-ASSOCIATED NEPHROTOXICITY

The development of vancomycin-associated acute kidney injury (VA-AKI) is influenced by a combination of patient-related, treatment-related, and pharmacokinetic factors. Observational studies and meta-analyses have identified several characteristics associated with increased risk, although the magnitude of these associations varies according to the study population, definition of AKI, vancomycin dosing strategy, and presence of competing causes of kidney injury. A systematic review and meta-analysis encompassing 53 studies published between 1998 and 2021 identified several patient-related factors associated with VA-AKI [5]. Obesity was associated with increased odds of VA-AKI (OR 1.46, 95% CI 1.12–1.90), while pre-existing renal disease showed one of the strongest comorbidity-related associations (OR 2.19, 95% CI 1.51–3.17) [5]. Other clinical conditions associated with increased risk included critical illness or intensive care unit admission, hepatic disease, heart failure, sepsis, coronary heart disease, and diabetes mellitus [5]. The same meta-analysis also reported demographic differences in VA-AKI risk, including higher odds among Black patients (OR 1.47, 95% CI 1.16–1.87) [5]. Such demographic associations should be interpreted as observational risk markers rather than evidence of direct biological causation.

Vancomycin exposure is another important determinant of nephrotoxicity risk. Prolonged treatment and higher vancomycin concentrations have repeatedly been associated with VA-AKI. Treatment duration exceeding 14 days was associated with increased odds of AKI (OR 1.73, 95% CI 1.06–2.83), while trough concentrations greater than 15 mg/L and 20 mg/L were associated with progressively higher odds of nephrotoxicity (OR 2.10, 95% CI 1.43–3.07 and OR 2.91, 95% CI 1.64–5.15, respectively) [5]. Higher total vancomycin exposure, reflected by an elevated 24-hour area under the concentration-time curve (AUC₂₄), has likewise been associated with an increased risk of AKI, supporting contemporary efforts to avoid unnecessarily high systemic exposure. Concomitant exposure to other nephrotoxic medications further increases the likelihood of renal dysfunction during vancomycin therapy. Amphotericin B demonstrated one of the strongest reported associations with VA-AKI (OR 5.21, 95% CI 3.44–7.87) [5]. Other frequently implicated agents include aminoglycosides, acyclovir, loop diuretics, vasopressors, non-steroidal anti-inflammatory drugs, and piperacillin-tazobactam [5,18]. These associations may reflect direct nephrotoxicity, hemodynamic effects, severity of underlying illness, or combinations of these mechanisms.

Patients with obesity represent a clinically important subgroup because alterations in vancomycin volume of distribution and clearance may increase variability in systemic exposure and predispose some patients to drug accumulation [7]. For this reason, individualized dosing and early therapeutic drug monitoring are particularly important in patients with obesity and other characteristics associated with altered vancomycin pharmacokinetics. Overall, the risk of VA-AKI is best considered cumulative rather than attributable to a single factor. Patients with baseline renal impairment, critical illness, high vancomycin exposure,



prolonged treatment, volume depletion, or concomitant nephrotoxic medications warrant particularly careful monitoring. Table 1 summarizes the principal risk factors reported in the contemporary literature.

Table 1. Principal Risk Factors for Vancomycin-Associated Acute Kidney Injury

Category	Risk factor	Reported effect size/association	Reference
Patient-related	Black race	OR 1.47 (95% CI 1.16–1.87); observational association	[5]
	Obesity	OR 1.46 (95% CI 1.12–1.90)	[5,7]
	Pre-existing renal disease	OR 2.19 (95% CI 1.51–3.17)	[5]
	ICU admission/critical illness	Consistently associated with increased VA-AKI risk	[4,5]
	Sepsis, heart failure, hepatic disease, diabetes mellitus	Associated with increased risk; magnitude varies among studies	[5]
	Intravascular volume depletion	Potentially modifiable factor contributing to renal vulnerability	[4]
Vancomycin exposure	Trough concentration >15 mg/L	OR 2.10 (95% CI 1.43–3.07)	[5]
	Trough concentration >20 mg/L	OR 2.91 (95% CI 1.64–5.15)	[5]
	Treatment duration >14 days	OR 1.73 (95% CI 1.06–2.83)	[5]
	AUC ₂₄ >650 mg·h/L	Higher exposure associated with increased AKI risk	[1]
Concomitant medications	Amphotericin B	OR 5.21 (95% CI 3.44–7.87)	[5]
	Piperacillin-tazobactam	Increased creatinine-defined AKI risk; effect varies by comparator	[18,19,20,21]
	Aminoglycosides, loop diuretics, vasopressors, acyclovir, NSAIDs	Associated with additional nephrotoxicity risk	[5,10]

OR, odds ratio; CI, confidence interval; ICU, intensive care unit; AKI, acute kidney injury; AUC₂₄, 24-hour area under the concentration-time curve; NSAIDs, non-steroidal anti-inflammatory drugs.

5. COMBINATION THERAPY WITH VANCOMYCIN AND PIPERACILLIN-TAZOBACTAM

One of the most consistently reported associations in the recent vancomycin safety literature is the increased incidence of creatinine-defined AKI among patients receiving vancomycin in combination with piperacillin-tazobactam (VPT) compared with vancomycin combined with alternative anti-pseudomonal beta-lactams. However, because most available evidence is observational and serum creatinine is commonly used to define AKI, the extent to which this association represents true structural nephrotoxicity remains an area of ongoing investigation. A 2022 systematic review and meta-analysis of 12 observational studies found that VPT was associated with a significantly greater risk of AKI than vancomycin combined with meropenem [19]. Importantly, no significant differences were identified in several downstream clinical outcomes, including hospital length of stay, requirement for renal replacement therapy, and mortality [19]. Other pooled analyses have similarly reported a higher incidence of AKI among patients receiving VPT than among those receiving vancomycin alone or vancomycin with alternative beta-lactam agents.

More recent evidence comes from a 2025 network meta-analysis incorporating 70 studies and 76,638 patients [20]. VPT was associated with higher odds of AKI than vancomycin plus cefepime (OR 2.55, 95% CI 2.00–3.28), vancomycin plus meropenem (OR 2.26, 95% CI 1.71–3.02), and vancomycin combined with other anti-pseudomonal beta-lactams (OR 2.47, 95% CI 1.87–3.29) [20]. However, the analysis did not demonstrate significant differences between VPT and comparator regimens in dialysis requirement, mortality, hospital length of stay, or time to AKI onset [20]. These findings suggest that VPT is associated with a greater frequency of creatinine-defined AKI, while evidence for a corresponding increase in severe or clinically consequential kidney injury remains less definitive. The biological basis for the observed association remains debated. Piperacillin and other beta-lactams interact with renal organic anion transport pathways involved in tubular creatinine handling [13]. Inhibition of tubular creatinine secretion may increase serum creatinine without a proportional reduction in glomerular filtration, potentially producing an apparent or “pseudo” AKI signal. This mechanism is particularly relevant because most clinical studies define AKI primarily on the basis of changes in serum creatinine.

At the same time, altered creatinine handling may not fully explain the observed association. Experimental and translational hypotheses have proposed that transporter interactions, oxidative stress, mitochondrial dysfunction, and other tubular mechanisms could contribute to genuine renal injury during combined vancomycin and piperacillin-tazobactam exposure [13,17]. At present,





however, available evidence does not conclusively establish the relative contribution of true structural nephrotoxicity and creatinine-related pseudo-nephrotoxicity. Studies incorporating alternative filtration markers and structural kidney injury biomarkers are therefore important for clarifying this distinction. From a clinical perspective, the consistent association between VPT and higher rates of creatinine-defined AKI warrants additional caution in patients who already have substantial nephrotoxicity risk. Where microbiologically and clinically appropriate, alternative anti-pseudomonal agents such as ceftazidime or meropenem may be considered, particularly in patients with pre-existing renal dysfunction or multiple concurrent nephrotoxic exposures. Selection of an alternative agent should nevertheless take into account the suspected source of infection, local antimicrobial susceptibility patterns, individual patient factors, and antimicrobial stewardship principles rather than nephrotoxicity risk alone.

When VPT is required, renal function and vancomycin exposure should be monitored closely, unnecessary concomitant nephrotoxins should be minimized, and broad-spectrum empirical therapy should be reassessed promptly once microbiological results become available. Early de-escalation to the narrowest appropriate antimicrobial regimen remains an important strategy for limiting unnecessary exposure. Figure 2 summarizes the comparative odds ratios for creatinine-defined AKI reported for VPT relative to vancomycin combined with ceftazidime, meropenem, and other anti-pseudomonal beta-lactams.

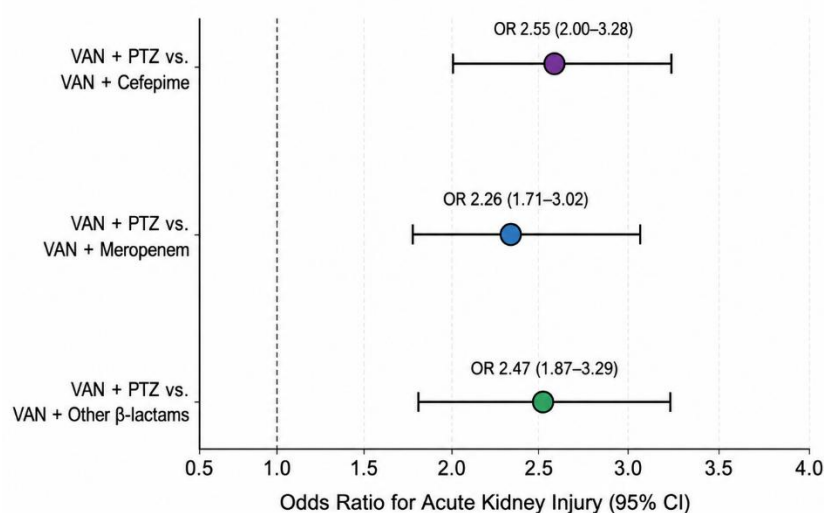


Figure 2. Comparative odds ratios for acute kidney injury with vancomycin plus piperacillin-tazobactam versus vancomycin combined with ceftazidime, meropenem, or other anti-pseudomonal β -lactams, from a 2025 network meta-analysis of 70 studies (n = 76,638) [16].

6. DIAGNOSIS: FROM SERUM CREATININE TO EMERGING KIDNEY BIOMARKERS

The clinical diagnosis of acute kidney injury during vancomycin therapy continues to rely primarily on conventional criteria based on changes in serum creatinine and urine output. According to Kidney Disease: Improving Global Outcomes (KDIGO) criteria, AKI is defined by an increase in serum creatinine of at least 0.3 mg/dL within 48 hours, an increase to at least 1.5 times baseline within the preceding 7 days, or a urine output of less than 0.5 mL/kg/h for at least 6 hours [22]. In patients receiving vancomycin, these criteria are commonly used to identify possible vancomycin-associated acute kidney injury (VA-AKI), although attribution of AKI specifically to vancomycin can be difficult in patients with other potential causes of renal dysfunction. Serum creatinine remains the most widely available marker of renal function, but it has important limitations for the early recognition of drug-associated kidney injury. Changes in serum creatinine generally reflect alterations in glomerular filtration rather than direct structural tubular damage and may become apparent only after renal injury has already occurred. Serum creatinine is also influenced by factors such as age, muscle mass, nutritional status, volume status, and tubular creatinine secretion [13,23]. The latter is particularly relevant in patients receiving certain beta-lactam antibiotics, including piperacillin-tazobactam, because inhibition of tubular creatinine secretion may increase serum creatinine without a proportionate reduction in glomerular filtration.

These limitations have stimulated interest in biomarkers that may identify tubular injury earlier than conventional creatinine-based measures. Kidney injury molecule-1 (KIM-1) is a transmembrane protein that is markedly upregulated in injured proximal tubular epithelial cells and can be detected in urine following tubular injury. Neutrophil gelatinase-associated lipocalin (NGAL) and clusterin have also been investigated as markers of renal tubular stress or injury. Studies evaluating patients exposed to vancomycin have suggested that urinary KIM-1 may increase earlier than serum creatinine and may have potential value for identifying vancomycin-associated tubular injury [24,25]. However, the relative performance of KIM-1, NGAL, clusterin, and other candidate biomarkers varies among studies and requires further prospective validation. Cystatin C represents a different category of renal biomarker. It is a low-molecular-weight protein produced relatively constantly by nucleated cells, freely filtered at the glomerulus, and subsequently reabsorbed and metabolized within the proximal tubule. Serum cystatin C can therefore provide an alternative estimate of glomerular filtration that is less dependent on skeletal muscle mass than serum creatinine. It has also been incorporated into some



pharmacokinetic and precision-dosing approaches. However, cystatin C should be distinguished from urinary structural injury biomarkers such as KIM-1 and NGAL rather than classified together with them as a single group of tubular injury markers.

Combinations of functional and structural biomarkers may ultimately provide greater diagnostic information than any single marker. In particular, concurrent assessment of changes in filtration markers and urinary tubular injury biomarkers could potentially help distinguish true structural kidney injury from isolated increases in serum creatinine caused by altered tubular secretion. This distinction may be especially relevant in patients receiving vancomycin together with piperacillin-tazobactam. Despite their potential, novel kidney injury biomarkers have not yet replaced serum creatinine and urine output in routine clinical assessment of VA-AKI. Important barriers include assay availability and cost, lack of universally validated diagnostic thresholds, variability among patient populations, and limited evidence that biomarker-guided interventions improve clinically meaningful outcomes. Consequently, conventional renal function monitoring remains the foundation of clinical surveillance, while emerging biomarkers currently have a more limited role in research and selected situations of diagnostic uncertainty.

7. THERAPEUTIC DRUG MONITORING: EVOLUTION FROM TROUGH- TO AUC-GUIDED DOSING

A major development in vancomycin therapeutic drug monitoring (TDM) has been the transition from trough concentration-based monitoring toward assessment of total drug exposure using the 24-hour area under the concentration-time curve (AUC₂₄). The 2020 ASHP/IDSA/PIDS/SIDP consensus guideline recommends AUC-guided monitoring for patients receiving vancomycin for serious MRSA infections [1]. Previous recommendations used trough serum concentrations of 15–20 mg/L as a practical surrogate for achieving an AUC₂₄/MIC ratio of at least 400 in serious MRSA infections. Subsequent pharmacokinetic and clinical evidence demonstrated substantial variability between trough concentrations and total vancomycin exposure. Targeting trough concentrations of 15–20 mg/L may therefore expose some patients to unnecessarily high AUC values and an increased risk of nephrotoxicity [1,3].

The revised guideline recommends an individualized AUC₂₄/MIC target of 400–600 for serious MRSA infections when the vancomycin MIC is assumed to be 1 mg/L using broth microdilution [1]. Expressed in terms of vancomycin exposure under this MIC assumption, the corresponding AUC₂₄ target is approximately 400–600 mg·h/L. The objective is to achieve adequate antimicrobial exposure while avoiding excessive systemic vancomycin concentrations and associated nephrotoxicity.

7.1 Evidence Supporting the AUC-Guided Approach

Clinical studies conducted before and after implementation of the revised monitoring recommendations have generally demonstrated lower rates of AKI with AUC-guided dosing than with traditional trough-targeted strategies. A prospective single-center cohort comparing trough-only Bayesian AUC-guided dosing with conventional trough-guided dosing reported an AKI incidence of 2.8% in the AUC-guided group compared with 17.4% in the trough-guided group ($P = 0.002$) [26]. Another institutional implementation study reported an AKI incidence of 14.0% (8/57 treatment courses) following implementation of model-informed AUC-based dosing compared with 27.8% (60/216 courses) during trough-guided monitoring [27]. AUC-based monitoring was also associated with improved attainment of the intended exposure range and reduced occurrence of excessive vancomycin exposure.

Other observational studies and pooled analyses have similarly reported lower nephrotoxicity with AUC-guided than with trough-guided monitoring [28,29,30,31]. Nevertheless, much of the available comparative evidence derives from observational, retrospective, or quasi-experimental studies rather than large randomized controlled trials. Consequently, the evidence most strongly supports AUC-guided monitoring as a strategy for reducing unnecessary vancomycin exposure and nephrotoxicity rather than establishing superiority for all clinical efficacy outcomes. The 2020 consensus guideline recommends AUC-guided monitoring in patients with suspected or confirmed serious MRSA infections and specifically advises against trough-only monitoring targeting 15–20 mg/L for these infections [1]. Evidence remains insufficient to extend the same recommendation unequivocally to all non-invasive MRSA infections or infections caused by other organisms [32].

7.2 Practical Implementation Considerations

AUC₂₄ can be estimated using either conventional pharmacokinetic equations or Bayesian model-informed methods. One approach uses two appropriately timed serum vancomycin concentrations, typically a post-distribution concentration obtained approximately 1–2 hours after completion of the infusion and a trough concentration obtained near the end of the dosing interval, together with first-order pharmacokinetic equations [1]. The preferred approach described in the 2020 consensus guideline uses Bayesian software incorporating a validated population pharmacokinetic model and patient-specific data [1]. Bayesian methods can estimate vancomycin exposure using one or two measured concentrations. Two concentrations generally provide more information and are preferred when feasible, whereas a single appropriately obtained concentration may be sufficient in selected patients depending on the population pharmacokinetic model and clinical circumstances.

An important advantage of Bayesian AUC estimation is that assessment does not necessarily require achievement of pharmacokinetic steady state. This permits evaluation of target attainment earlier in therapy. For serious MRSA infections, the guideline recommends achieving the intended AUC exposure within the first 24–48 hours whenever possible [1]. Monitoring frequency should be individualized according to clinical stability and risk of nephrotoxicity. More frequent, including potentially daily, monitoring may be appropriate in patients who are hemodynamically unstable or have rapidly changing renal function. Patients with stable renal function receiving prolonged therapy may require substantially less frequent monitoring, with once-weekly assessment being reasonable in selected stable patients [1]. Vancomycin monitoring is also particularly important in patients at increased risk of



nephrotoxicity, those receiving concomitant nephrotoxic medications, patients with unstable renal function, and those receiving prolonged treatment.

Table 2. Comparison of Trough-Guided and AUC-Guided Vancomycin Monitoring

Parameter	Trough-Guided Monitoring	AUC-Guided Monitoring
Primary exposure target	Trough concentration of 15–20 mg/L historically used as a surrogate for adequate AUC exposure in serious MRSA infections	AUC ₂₄ /MIC target of 400–600 for serious MRSA infections; corresponds to AUC ₂₄ ≈ 400–600 mg·h/L when MIC = 1 mg/L
Monitoring approach	Serum trough concentration obtained near the end of the dosing interval and used to guide dose adjustment	AUC estimated using two concentrations with first-order PK equations or, preferably, Bayesian pharmacokinetic modeling
Sampling requirements	Usually one trough concentration	Bayesian methods may use 1–2 concentrations; two appropriately timed concentrations are preferred when feasible
Need for steady state	Conventionally performed near steady state	Bayesian estimation can be performed before steady state, allowing earlier assessment of exposure
Nephrotoxicity	Trough targets of 15–20 mg/L may produce excessive exposure and are associated with greater nephrotoxicity	Generally associated with lower nephrotoxicity and less excessive vancomycin exposure in comparative studies
Clinical efficacy	Historically effective but trough concentration correlates imperfectly with total drug exposure	Intended to maintain adequate antimicrobial exposure while reducing unnecessary toxicity; superiority for all efficacy outcomes has not been established
Guideline position	Trough-only targeting of 15–20 mg/L is no longer recommended for serious MRSA infections	Recommended approach for serious MRSA infections in the 2020 ASHP/IDSA/PIDS/SIDP consensus guideline
Major limitations	Poor and variable relationship between trough concentration and AUC; may expose some patients to excessive vancomycin	Requires appropriate sampling, pharmacokinetic expertise and/or validated software; performance depends on the population PK model and patient population

AKI, acute kidney injury; AUC₂₄, 24-hour area under the concentration-time curve; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant Staphylococcus aureus; PK, pharmacokinetic.

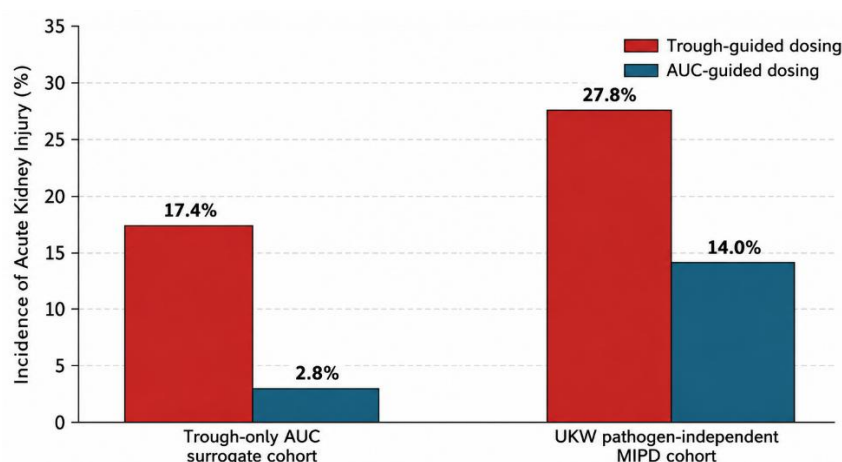


Figure 3. Incidence of vancomycin-associated acute kidney injury under trough-guided versus AUC-guided dosing in two independent implementation cohorts [25,33].

8. INFUSION STRATEGY: CONTINUOUS VERSUS INTERMITTENT INFUSION

In addition to the choice of therapeutic drug monitoring strategy, the method of vancomycin administration may influence pharmacokinetic target attainment and potentially affect nephrotoxicity. Continuous infusion maintains relatively stable serum concentrations and may reduce fluctuations in vancomycin exposure compared with conventional intermittent infusion. However, available evidence has not established continuous infusion as a consistently superior strategy for preventing vancomycin-associated acute kidney injury (VA-AKI) [33,34]. A meta-analysis comparing continuous and intermittent vancomycin administration reported a trend toward lower nephrotoxicity with continuous infusion, although the difference did not reach statistical significance (risk ratio





0.799) [33]. Clinical efficacy was generally comparable between the two administration strategies, and the available evidence was insufficient to establish a definitive nephroprotective advantage of continuous infusion. Comparative studies in critically ill populations have likewise suggested broadly similar clinical effectiveness between continuous and intermittent administration [34].

Evidence from pediatric critical care suggests that continuous infusion may improve pharmacokinetic target attainment. In a randomized clinical trial involving 68 critically ill pediatric patients, continuous infusion achieved the predefined AUC₂₄ target substantially more frequently than intermittent infusion (82% versus 23%) [35]. Mean AUC₂₄ was also higher in the continuous-infusion group (587.7 ± 184.4 versus 361.9 ± 113.2 mg·h/L). Nephrotoxicity was uncommon, with one event reported in each treatment group. These findings suggest that continuous infusion may facilitate target attainment in critically ill children, although the small sample size limits conclusions regarding comparative safety and clinical outcomes [35]. Evidence from outpatient parenteral antimicrobial therapy (OPAT) has not demonstrated a clear safety advantage. In a retrospective single-center study of 492 patients, continuous infusion was not associated with a statistically significant reduction in nephrotoxicity compared with intermittent infusion (adjusted HR 0.72, 95% CI 0.35–1.50), and no significant advantage was observed for other safety or readmission outcomes [36]. Similarly, pooled evidence evaluating prolonged or continuous administration in critically ill patients has not consistently demonstrated improvements in mortality or other major clinical outcomes compared with intermittent infusion [37].

Continuous infusion may have particular pharmacokinetic utility in patients receiving continuous kidney replacement therapy. In a prospective interventional study of critically ill patients undergoing continuous venovenous hemofiltration, continuous infusion was associated with greater attainment of predefined concentration and AUC₂₄/MIC targets than intermittent infusion [38]. However, clinical success, microbiological success, adverse events, and mortality did not differ significantly between the two approaches, indicating that improved pharmacokinetic target attainment does not necessarily translate into superior clinical outcomes. Overall, continuous infusion represents a reasonable alternative to intermittent vancomycin administration in selected patients, particularly when therapeutic exposure is difficult to achieve with conventional intermittent dosing or when continuous kidney replacement therapy produces substantial pharmacokinetic variability [1,38]. Nevertheless, current evidence does not support continuous infusion as a universally superior or consistently nephroprotective strategy. Regardless of the infusion method, appropriate AUC-guided exposure monitoring and avoidance of excessive vancomycin exposure remain central to minimizing nephrotoxicity.

9. MODEL-INFORMED PRECISION DOSING, BAYESIAN SOFTWARE, AND EMERGING COMPUTATIONAL APPROACHES

The transition toward AUC-guided vancomycin therapy has increased interest in model-informed precision dosing (MIPD). Bayesian MIPD platforms combine prior information from population pharmacokinetic models with patient-specific characteristics, such as age, body size, and renal function, and subsequently incorporate measured vancomycin concentrations when available to estimate individualized pharmacokinetic parameters and AUC exposure [1,39]. Compared with conventional first-order pharmacokinetic approaches, Bayesian estimation offers several practical advantages. It can accommodate flexible sampling schedules, may require fewer measured concentrations, and can estimate AUC before pharmacokinetic steady state is reached [1,39]. This allows earlier assessment of vancomycin exposure, which is particularly valuable when therapeutic targets are intended to be achieved within the first 24–48 hours of treatment. However, Bayesian dosing should be distinguished from true pre-dose prediction: conventional Bayesian updating generally becomes more patient-specific after measured drug concentrations are incorporated, whereas newer computational approaches aim to individualize the initial regimen before the first therapeutic drug monitoring sample is available.

Clinical evidence supporting MIPD is increasing. A retrospective cohort study evaluating AUC-guided vancomycin therapy using Bayesian MIPD with single-concentration monitoring reported improvement in a composite desirability-of-outcome measure incorporating treatment success, avoidance of VA-AKI, and survival compared with conventional trough-guided management [39]. The approach also permitted earlier assessment of AUC target attainment and greater flexibility in the timing of serum concentration measurement. Nevertheless, the observational design limits causal interpretation, and prospective comparative studies remain important. The choice of population pharmacokinetic model embedded within a Bayesian platform may also influence dose recommendations and exposure estimates. A large quasi-experimental analysis evaluating a change from the Goti to the Thomson pharmacokinetic model reported an increase in AUC₂₄ target attainment from 46.5% to 51.1% and a reduction in median time to target attainment from 47.8 to 28.2 hours [40]. A small increase in severe AKI was also observed (1.75% versus 2.03%). These findings suggest that the underlying pharmacokinetic model can influence target attainment and safety-related metrics. However, because these findings were reported from a quasi-experimental study published as a conference supplement, they should be interpreted cautiously and confirmed in independent prospective evaluations.

Machine-learning approaches represent an emerging extension of precision dosing. One potential application is individualized prediction of pharmacokinetic parameters before the first dose. A 2026 study involving critically ill children developed a hybrid machine-learning/population-pharmacokinetic model capable of predicting individual vancomycin clearance and volume of distribution using routinely available pre-dose clinical variables [41]. The model incorporated factors such as body weight, renal function, age-related characteristics, and clinical status and demonstrated promising performance in both test and external validation cohorts. Such approaches could potentially improve selection of the initial vancomycin regimen before conventional therapeutic drug monitoring data become available. Machine learning has also been investigated for early prediction of VA-AKI. A multicenter retrospective study comparing eight machine-learning algorithms identified AUC₂₄–48h, trough concentration, and concomitant administration of piperacillin-tazobactam, diuretics, and vasopressors as important predictors of VA-AKI [42]. Naïve Bayes and random forest models achieved an overall reported accuracy of 97.3%; however, the corresponding recall was 62.5% and the F1





score was 71.4%. These additional performance measures demonstrate why overall accuracy alone should not be interpreted as evidence of excellent clinical predictive performance, particularly when the outcome of interest is relatively uncommon. External validation, calibration assessment, and prospective evaluation of clinical utility are required before such models can be incorporated into routine therapeutic decision-making.

Despite their potential, both Bayesian and machine-learning approaches have important limitations. Performance depends on the quality and applicability of the underlying pharmacokinetic or predictive model, and a model developed in one population may not perform equally well in another. Evidence remains more limited in patients with extreme obesity, neonates and young children, patients with rapidly changing renal function, and those receiving different forms of kidney replacement therapy [1]. In addition, machine-learning models require careful evaluation for overfitting, calibration, transportability, interpretability, and clinically meaningful performance rather than reliance on accuracy alone. Therefore, Bayesian MIPD currently represents the more established computational approach for implementing AUC-guided vancomycin dosing, whereas machine-learning methods should be considered promising but investigational tools. Future research should emphasize prospective multicenter validation, comparison of competing pharmacokinetic models, evaluation in underrepresented patient populations, and demonstration that computationally guided dosing improves clinically meaningful outcomes rather than pharmacokinetic target attainment alone.

10. SPECIAL POPULATIONS

10.1 Obesity

Obesity introduces important challenges to vancomycin dosing because both the volume of distribution and clearance may differ from those observed in non-obese patients, resulting in substantial interindividual variability in drug exposure. Obesity has also been associated with increased odds of vancomycin-associated acute kidney injury (VA-AKI) [5]. Consequently, reliance on conventional trough-based dosing may increase the likelihood of either inadequate or excessive vancomycin exposure. For obese adults with serious infections, the 2020 consensus guideline recommends that loading doses, when indicated, be based on actual body weight, with a suggested dose of 20–25 mg/kg and a maximum of 3,000 mg [1]. Maintenance dosing should not simply be extrapolated from actual body weight alone; rather, it should account for renal function, estimated vancomycin clearance, and the desired AUC exposure. Early and frequent AUC monitoring is recommended, particularly when high empiric daily doses are required [1]. Accordingly, AUC-guided individualized dosing is particularly valuable in patients with obesity because it permits adjustment according to measured systemic exposure rather than relying exclusively on weight-based dose calculations.

10.2 Critically Ill Patients

Vancomycin pharmacokinetics are particularly variable in critically ill patients because of dynamic changes in volume status, organ perfusion, renal function, fluid resuscitation, augmented renal clearance, and the frequent use of vasoactive or potentially nephrotoxic medications [4]. These changes can result in both inadequate early exposure and subsequent drug accumulation as clinical and renal status evolve. For critically ill patients with suspected or confirmed serious MRSA infection in whom rapid attainment of therapeutic exposure is required, a loading dose may be appropriate, followed by individualized AUC-guided maintenance dosing [1]. Bayesian model-informed precision dosing is particularly attractive in this population because AUC estimation can be performed before pharmacokinetic steady state is reached, allowing earlier dose adjustment as patient physiology changes. Monitoring frequency should be guided by clinical stability rather than by a fixed schedule. Frequent or daily monitoring may be appropriate in hemodynamically unstable patients or those with rapidly changing renal function, whereas less frequent monitoring may be sufficient once renal function and vancomycin exposure have stabilized [1].

10.3 Pediatric and Neonatal Populations

AUC-guided vancomycin monitoring is also recommended for pediatric patients with serious MRSA infections, although the pediatric evidence base is less extensive than that available for adults and several exposure targets have been extrapolated from adult data [1]. The 2020 consensus guideline suggests targeting an AUC₂₄ of approximately 400 mg·h/L, potentially up to 600 mg·h/L when clinically appropriate and assuming an MIC of 1 mg/L, while emphasizing avoidance of unnecessarily high exposure [1]. Neonates require separate consideration because vancomycin clearance changes substantially with postmenstrual age, body weight, maturation of renal function, and serum creatinine. The consensus guideline therefore supports AUC-guided monitoring, preferably using Bayesian estimation, rather than applying adult or older-child dosing assumptions directly to neonates [1]. Emerging computational approaches may further assist initial dose individualization. A recent multicenter study in critically ill children developed and externally validated a machine-learning/population-pharmacokinetic model capable of estimating vancomycin clearance and volume of distribution before the first dose [41,43]. Although these findings are promising, prospective evaluation is required to determine whether improved pharmacokinetic prediction translates into better clinical outcomes.

10.4 Kidney Replacement Therapy

Patients receiving kidney replacement therapy constitute a particularly complex population because vancomycin clearance is influenced not only by residual renal function but also by dialysis modality, membrane characteristics, treatment duration, and, in continuous therapies, effluent flow rate. For patients receiving intermittent hemodialysis, direct AUC monitoring is operationally challenging and has not been as extensively validated as in patients with preserved renal function. The 2020 consensus guideline therefore considers predialysis vancomycin concentrations of approximately 15–20 mg/L a practical approach that is expected to correspond to an AUC₂₄ of approximately 400–600 mg·h/L in many patients [1].





Continuous kidney replacement therapy presents different pharmacokinetic considerations. The consensus guideline recommends weight-based loading followed by maintenance dosing that accounts for the intensity of extracorporeal clearance and emphasizes early therapeutic monitoring [1]. Prospective evidence in patients undergoing continuous venovenous hemofiltration has demonstrated greater PK/PD target attainment with continuous than with intermittent vancomycin infusion; however, significant improvements in clinical success, microbiological success, adverse events, or mortality were not demonstrated [38]. Thus, vancomycin dosing during kidney replacement therapy should be individualized according to the specific modality and intensity of extracorporeal clearance rather than managed according to a single universal dosing strategy.

11. PREVENTION AND CLINICAL MANAGEMENT STRATEGIES

Prevention and management of VA-AKI require integration of appropriate antimicrobial selection, individualized vancomycin exposure, renal function surveillance, and reduction of modifiable nephrotoxic risk factors.

Use AUC-guided dosing when indicated. For serious MRSA infections, an individualized AUC₂₄/MIC target of 400–600 is recommended when the MIC is assumed to be 1 mg/L. This corresponds to an AUC₂₄ exposure of approximately 400–600 mg·h/L. AUC-guided monitoring reduces unnecessary vancomycin exposure and has generally been associated with lower nephrotoxicity than conventional trough-targeted strategies [1,26,27,29].

Maintain adequate volume status and hemodynamic stability. Volume depletion, hypotension, and impaired renal perfusion may increase susceptibility to AKI. Appropriate fluid and hemodynamic management should therefore form part of general renal-protective care, while recognizing that direct clinical evidence demonstrating a vancomycin-specific protective effect of hydration alone remains limited.

Minimize avoidable nephrotoxic co-exposures. Concomitant administration of nephrotoxic medications should be reviewed regularly. Where clinically appropriate, exposure to agents such as aminoglycosides, amphotericin B, non-steroidal anti-inflammatory drugs, and other potentially nephrotoxic therapies should be minimized. The combination of vancomycin and piperacillin-tazobactam has repeatedly been associated with increased creatinine-defined AKI; however, the contribution of altered creatinine secretion versus structural kidney injury remains debated. A prospective cohort demonstrated increased creatinine-defined AKI with vancomycin plus piperacillin-tazobactam without corresponding changes in cystatin C, supporting the possibility of pseudo-nephrotoxicity in at least some patients. Consequently, cefepime, meropenem, or another alternative should not automatically replace piperacillin-tazobactam solely on the basis of nephrotoxicity concerns. Selection should also consider infection source, microbiological susceptibility, local resistance patterns, spectrum of activity, patient-specific adverse-effect risks, and antimicrobial stewardship principles.

Limit antimicrobial exposure to the clinically necessary duration. Vancomycin therapy should be reassessed when microbiological and clinical information becomes available. De-escalation, transition to a more appropriate targeted agent, or discontinuation of unnecessary combination therapy can reduce cumulative drug and nephrotoxin exposure [5,44].

Consider continuous infusion selectively. Continuous infusion may be useful when satisfactory exposure is difficult to achieve with intermittent administration or in selected critically ill patients. Current evidence does not establish continuous infusion as a universally superior nephroprotective strategy [1,33,36,38]. The consensus guideline considers it a reasonable alternative when AUC targets cannot readily be achieved using intermittent administration.

Individualize the intensity of monitoring. Patients with hemodynamic instability, rapidly changing renal function, high vancomycin exposure, prolonged treatment, or multiple nephrotoxic co-exposures may require frequent assessment. In clinically stable patients, monitoring intervals can be extended according to clinical judgment [1].

Do not currently rely on novel biomarkers for routine therapeutic decisions. Structural injury biomarkers such as KIM-1 and NGAL and alternative filtration markers such as cystatin C are promising tools for clarifying the nature and timing of kidney injury. However, validated thresholds and prospective evidence demonstrating improved outcomes from biomarker-guided vancomycin management remain insufficient. They should therefore be regarded primarily as research or adjunctive tools rather than routine determinants of whether vancomycin should be continued or discontinued.

Reassess therapy promptly when AKI develops. Development of AKI should prompt assessment of vancomycin exposure, volume and hemodynamic status, concomitant nephrotoxins, alternative causes of renal dysfunction, and the continuing need for vancomycin. Depending on infection severity and renal trajectory, management may include dose modification, temporary interruption, substitution with an appropriate alternative antimicrobial, or continued treatment with intensified monitoring. The response should therefore be individualized rather than assuming that every creatinine increase requires immediate discontinuation. Experimental strategies aimed at pharmacological nephroprotection, including N-acetylcysteine and other antioxidant approaches, have demonstrated protective signals predominantly in preclinical models [11,14,15]. These interventions have not been established as effective strategies for preventing VA-AKI in adequately powered clinical trials and should not currently be recommended for routine practice.

12. LIMITATIONS OF CURRENT EVIDENCE AND FUTURE DIRECTIONS

Despite substantial advances in vancomycin therapeutic monitoring, several important evidence gaps remain. First, much of the comparative evidence supporting AUC-guided monitoring is derived from observational, retrospective, or quasi-experimental studies





rather than large randomized controlled trials. Although these studies generally demonstrate lower vancomycin exposure and reduced nephrotoxicity with AUC-guided management, residual confounding and differences in institutional practice cannot be completely excluded. Second, the performance of Bayesian population pharmacokinetic models remains population dependent. Models developed in conventional adult populations may not perform equally well in patients with extreme obesity, rapidly changing renal function, neonates, pregnancy, or different modalities of kidney replacement therapy. The accuracy, transportability, and clinical consequences of model selection therefore require further prospective evaluation.

Third, the precise boundaries of the optimal vancomycin therapeutic window remain incompletely characterized. Current guidelines recommend an AUC₂₄/MIC of 400–600 for serious MRSA infections when MIC is assumed to be 1 mg/L [1]. Evidence supporting efficacy at exposures below an AUC₂₄ of 400 mg·h/L remains insufficient, whereas the probability of nephrotoxicity appears to increase progressively with higher exposure rather than at a single universally applicable toxicity threshold. Future research should determine whether narrower or population-specific exposure targets can preserve efficacy while further reducing toxicity. Fourth, the mechanism underlying the association between vancomycin plus piperacillin-tazobactam and creatinine-defined AKI remains unresolved. Evidence supporting altered tubular creatinine secretion has raised concern that some events classified as AKI may represent pseudo-nephrotoxicity, whereas other experimental and clinical findings remain compatible with genuine kidney injury. Studies incorporating creatinine-independent filtration markers, validated structural kidney injury biomarkers, and patient-centered renal outcomes are needed to clarify this relationship.

Fifth, although emerging urinary biomarkers may detect tubular injury earlier than conventional serum creatinine, their incremental clinical value remains uncertain. Future prospective studies should determine whether biomarker-guided interventions reduce progression to severe AKI, the need for kidney replacement therapy, persistent renal dysfunction, or other clinically meaningful outcomes. Finally, computational approaches to vancomycin dosing are evolving rapidly. Bayesian MIPD is increasingly established for AUC estimation, while machine-learning and hybrid pharmacokinetic approaches remain at an earlier stage of clinical translation. Notably, some newer machine-learning models have now undergone multicenter and external validation, including a 2026 pediatric ML-PPK model [41]; therefore, it is no longer accurate to characterize all such models as single-center internally validated studies. Nevertheless, prospective impact studies demonstrating improved clinical outcomes are still required before machine-learning-based dosing can be recommended for routine practice.

Future research should prioritize pragmatic prospective comparisons of dosing strategies, validation of pharmacokinetic models across underrepresented populations, biomarker-guided interventional studies, rigorous evaluation of computational dosing systems, and studies using clinically meaningful renal and infectious outcomes rather than pharmacokinetic target attainment alone.

CONCLUSION

Vancomycin-associated acute kidney injury remains an important limitation of an antimicrobial agent that continues to play a central role in the management of serious MRSA infections. Since the publication of the 2020 consensus guideline, vancomycin management has increasingly shifted from trough-based monitoring toward AUC-guided therapeutic drug monitoring, with an AUC₂₄/MIC target of 400–600 recommended for serious MRSA infections when the MIC is assumed to be 1 mg/L [1]. This approach aims to maintain adequate antimicrobial exposure while reducing unnecessary drug exposure and nephrotoxicity. At the same time, contemporary understanding of VA-AKI has expanded beyond vancomycin concentration alone. Patient susceptibility, critical illness, renal function, cumulative exposure, concomitant nephrotoxins, and potentially complex interactions with beta-lactam antibiotics all influence the observed risk of kidney dysfunction. Recognition of oxidative and mitochondrial injury, inflammatory mechanisms, and intratubular cast formation has further emphasized the multifactorial nature of vancomycin-associated renal injury. Bayesian model-informed precision dosing provides an increasingly practical means of individualizing vancomycin exposure, particularly in patients with variable pharmacokinetics, whereas novel kidney biomarkers and machine-learning approaches remain promising areas of investigation rather than established replacements for conventional clinical monitoring. Current best practice therefore centers on appropriate indication and duration of vancomycin therapy, AUC-guided dosing for serious MRSA infection, individualized monitoring according to renal and clinical stability, minimization of avoidable nephrotoxic exposures, and prompt reassessment when kidney dysfunction develops. Future prospective studies should focus on refining exposure targets, validating dosing models in underrepresented populations, determining the clinical value of emerging biomarkers, and establishing whether computational dosing strategies improve patient-centered outcomes.

REFERENCES

1. Rybak MJ, Le J, Lodise TP, Levine DP, Bradley JS, Liu C, Mueller BA, Pai MP, Wong-Beringer A, Rotschafer JC, Rodvold KA, Maples HD, Lomaestro BM. Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: a revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm*. 2020;77(11):835-864. doi:10.1093/ajhp/zxaa036
2. Filippone EJ, Kraft WK, Farber JL. The nephrotoxicity of vancomycin. *Clin Pharmacol Ther*. 2017;102(3):459-469. doi:10.1002/cpt.726





3. 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. *Antimicrob Agents Chemother.* 2013;57(2):734-744. doi:10.1128/AAC.01568-12
4. Vancomycin-Associated Acute Kidney Injury: A Narrative Review from Pathophysiology to Clinical Application. *Int J Mol Sci.* 2022;23(4):2052. doi:10.3390/ijms23042052
5. Kim JY, Yee J, Yoon HY, Han JM, Gwak HS. Risk factors for vancomycin-associated acute kidney injury: a systematic review and meta-analysis. *Br J Clin Pharmacol.* 2022;88(9):3977-3989. doi:10.1111/bcp.15429
6. Incidence, Risk Factors and Epidemiological Errors of Vancomycin Associated Acute Kidney Injury: A Systematic Review. *J Clin Case Rep Med Images.* 2022.
7. Vancomycin associated acute kidney injury in patients with infectious endocarditis: a large retrospective cohort study. *Front Pharmacol.* 2023;14:1260802. doi:10.3389/fphar.2023.1260802
8. Risk factors for acute kidney injury associated with intravenous vancomycin in neurosurgical inpatients: a retrospective study. 2024.
9. Non-recovery of vancomycin-associated nephrotoxicity is related to worsening survival outcomes: combined retrospective analyses of two real-world databases. 2022. PMID:36169161
10. Overview of Antibiotic-Induced Nephrotoxicity. *Kidney Int Rep.* 2023;8(11):2211-2225.
11. Vancomycin-Induced Kidney Injury: Animal Models of Toxicodynamics, Mechanisms of Injury, Human Translation, and Potential Strategies for Prevention. *Pharmacotherapy.* 2020.
12. Nephrotoxicity of vancomycin in combination with beta-lactam agents: ceftolozane-tazobactam vs piperacillin-tazobactam. *Clin Infect Dis.* 2023. PMID:35982631
13. Understanding vancomycin nephrotoxicity augmented by β -lactams: a synthesis of endosymbiosis, proximal renal tubule mitochondrial metabolism, and β -lactam chemistry. *Lancet Infect Dis.* 2023.
14. Lowered risk of nephrotoxicity through intervention against the combined use of vancomycin and tazobactam/piperacillin: a retrospective cohort study. 2021.
15. Yu P, Luo J, Song H, Qian T, He X, Fang J, Dong W, Bian X. N-acetylcysteine ameliorates vancomycin-induced nephrotoxicity by inhibiting oxidative stress and apoptosis in the in vivo and in vitro models. *Int J Med Sci.* 2022;19(4):754-764. doi:10.7150/ijms.69807
16. Yang Q, Yin X, Li H, Ding L, Sun H, Yang L, Li Z. Analysis of kidney proteomes to identify biological pathways associated with vancomycin-induced nephrotoxicity in mice by tandem mass tag-labeled quantitative and parallel reaction monitoring phosphoproteomics. *J Appl Toxicol.* 2023. doi:10.1177/09603271231183885
17. Progression of kidney injury with the combination of vancomycin and piperacillin-tazobactam or cefepime in sepsis-associated acute kidney injury. *Front Nephrol.* 2022;2:995358. doi:10.3389/fneph.2022.995358
18. Munshi R, VanNatta M, Khan MH, Alam M, Malek AE. Factors affecting vancomycin and piperacillin/tazobactam-induced nephrotoxicity. *Open Forum Infect Dis.* 2025;12(Suppl1). doi:10.1093/ofid/ofae631.1820
19. Alshehri AM, Alzahrani MY, Abujamal MA, Abdalla MH, Alowais SA, Alfayez OM, Alyami MS, Almutairi AR, Almohammed OA. Comparative risk of acute kidney injury following concurrent administration of vancomycin with piperacillin/tazobactam or meropenem: a systematic review and meta-analysis of observational studies. *Antibiotics (Basel).* 2022;11(4):526. doi:10.3390/antibiotics11040526
20. Vancomycin combined with piperacillin/tazobactam increases the risk of acute kidney injury compared with vancomycin plus other anti-pseudomonal beta-lactams: a systematic review and network meta-analysis. *J Antimicrob Chemother.* 2025;80(1):47-59.
21. Evaluating the Nephrotoxicity of Area-under-the-Curve-Based Dosing of Vancomycin with Concomitant Antipseudomonal Beta-Lactam Antibiotics: A Systematic Review and Meta-Analysis. *Medicina (Kaunas).* 2023;59(4):691. doi:10.3390/medicina59040691
22. Kidney Disease: Improving Global Outcomes (KDIGO). 2026 Clinical Practice Guideline for Acute Kidney Injury and Acute Kidney Disease (Public Review Draft). KDIGO; 2026.
23. Biomarkers of drug-induced kidney toxicity. *Curr Opin Toxicol.*
24. Serum and urinary biomarkers of vancomycin-induced acute kidney injury: a prospective, observational analysis. *Medicine (Baltimore).* 2024.





25. Novel Kidney Biomarkers and Antibiotics-Induced Acute Kidney Injury: A Practical Assessment of Current and Future Applications. *Pharmacotherapy*. 2024.
26. Comparison of the incidence of vancomycin-associated nephrotoxicity following the change from trough-guided dosing to AUC-guided dosing using trough-only data. *J Antimicrob Chemother*. 2023. PMID:37889089
27. Gundlach LC, Surat G, Kunkel M, Scherf-Clavel O. Implementation of pathogen independent model informed precision AUC-based dosing of vancomycin at University Hospital Wuerzburg (UKW). *Open Forum Infect Dis*. 2025;12(Suppl1). doi:10.1093/ofid/ofae631.1952
28. Knight JM, Iso T, Perez KK, Swan JT, Janak CE, Ikwuagwu JO, Musick WL. Risk of acute kidney injury based on vancomycin target trough attainment strategy: area-under-the-curve-guided Bayesian software, nomogram, or trough-guided dosing. *Ann Pharmacother*. 2024;58(2):110-117. doi:10.1177/10600280231171373
29. Implementing AUC monitoring in a pharmacist-managed vancomycin dosing protocol: a retrospective cohort study. 2023.
30. Navigating vancomycin and acute kidney injury: AUC- vs trough-guided monitoring in initial and steady-state therapy. *Medicina*. 2025.
31. Evaluation of real-world vancomycin dosing and attainment of therapeutic drug monitoring targets. 2023.
32. Evaluation of vancomycin AUC/MIC ratio in Indian patients with enterococcal infections: impact on clinical outcomes and nephrotoxicity. *Open Forum Infect Dis*. 2025.
33. Vancomycin-associated nephrotoxicity: a meta-analysis of administration by continuous versus intermittent infusion. *Anaesth Intensive Care*. 2022.
34. Maluangnon C, Tongyoo S, Permpikul C. Continuous vancomycin infusion versus intermittent infusion in critically ill patients. 2023.
35. Baran Roshan NS, Mirrahimi B, Najmeddin F, Ahmadizadeh SN, Behzad A, Hashemi SM, Alemzadeh M, Taherpour N. Comparison of the areas under the curve of vancomycin continuous vs. intermittent infusion in critically ill pediatrics: a randomized clinical trial. *Iran J Pharm Res*. 2024;23(1):e145933. doi:10.5812/ijpr-145933
36. Benefield AJ, et al. Patient safety outcomes for continuous infusion vancomycin as outpatient parenteral antimicrobial therapy. *Pharmacotherapy*. 2023;43(9):894-903. doi:10.1002/phar.2833
37. Prolonged versus intermittent vancomycin infusion in critically ill patients with sepsis: a systematic review and meta-analysis. 2023.
38. Continuous infusion versus intermittent infusion of vancomycin in critically ill patients undergoing continuous venovenous hemofiltration: a prospective interventional study. 2022.
39. Model-informed precision dosing improves outcomes in patients receiving vancomycin for gram-positive infections. *Open Forum Infect Dis*. 2024.
40. Hughes MS, Tong DMH, Hughes J. Improved vancomycin target attainment following a quasi-experimental change in pharmacokinetic model for Bayesian precision dosing. *Open Forum Infect Dis*. 2025;12(Suppl1). doi:10.1093/ofid/ofae631.1436
41. Machine-learning prediction of pre-dose pharmacokinetics optimizes initial vancomycin dosing in critically ill children. *Front Pharmacol*. 2026.
42. Comparison of eight machine learning-based covariate risk prediction models for vancomycin-associated acute kidney injury during initial dosing. *Open Forum Infect Dis*. 2026.
43. Machine learning-assisted prediction of vancomycin area under the concentration-time curve and trough concentrations in initial dosing design. *Open Forum Infect Dis*. 2026.
44. Vancomycin nephrotoxicity relative to alternative antibiotic treatments: a systematic review and meta-analysis of randomized controlled trials. *Open Forum Infect Dis*. 2021.