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REVIEW

Acute Kidney Injury Associated with the Concomitant Use of Vancomycin and Piperacillin-Tazobactam

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Abstract: In recent years, the increased use of vancomycin (VAN) in combination with piperacillin-tazobactam (TZP) has raised significant concerns in clinical practice regarding the heightened risk of acute kidney injury (AKI). This topic has become a focal point in clinical therapeutics due to the widespread application of VAN alongside TZP. The specific mechanisms underlying vancomycin and piperacillin-tazobactam (VPT) associated AKI remain unclear. In this review, we discuss several controversial or underexplored aspects of current research. While the majority of literature links VPT to an elevated risk of AKI, numerous studies present conflicting outcomes. Mechanisms proposed for the increased risk of AKI associated with VPT, based on clinical observations and animal studies, include additive toxic effects, increased VAN exposure due to concomitant use with TZP, exacerbated VAN-induced oxidative stress injury in proximal renal tubule by TZP, pseudo-nephrotoxicity mediated by VPT-induced impaired creatinine secretion, or a combination of the aforementioned mechanisms. Additionally, this review outlines potential strategies that might effectively mitigate the risk of VPT-induced AKI, offering insights and future implications in the realm of pharmacovigilance.

Keywords: vancomycin, piperacillin-tazobactam, acute kidney injury, nephrotoxicity, concomitant therapy

Introduction

Vancomycin (VAN) is a glycopeptide antibiotic and is primarily utilized in the treatment of infections including bacteremia, infective endocarditis, osteomyelitis, pneumonia and intra-abdominal infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) and other Gram-positive bacteria.[1] Piperacillin-tazobactam (TZP) exhibits broad-spectrum bactericidal activity against gram-negative bacteria and is indicated for moderate to severe infections such as community-acquired pneumonia, hospital-acquired pneumonia, urinary tract infections, skin and soft tissue infections, but it is ineffective against MRSA. Hence, the combination of both antibiotics covers a wide range of pathogens and empirical concomitant antimicrobial therapy of VAN and TZP (VPT) is recommended for most hospital-acquired infections, in order to cover *Pseudomonas aeruginosa* and MRSA. Clinically, this combination is also used in patients with febrile neutropenia[2] as febrile neutropenic patients are at a high risk of life-threating bacterial infections.[3] After decades of clinical use, it is well-recognized that VAN is related with an increasing risk of acute kidney injury (AKI). AKI stands as a significant healthcare challenge in contemporary medicine, with reported incidences ranging from 1% to 32% among hospitalized patients and 10% to 90% in intensive care unit (ICU) patients. The occurrence of AKI in hospitalized patients is associated with increased costs, prolonged hospital stays, and elevated rates of mortality and morbidity. TGF-β1[4] and interleukin-10 (IL-10) are key regulators of immune homeostasis.[5] IL-10 plays a role in AKI

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caused by different aetiologies.[6] Macrophage provide a role in TGF-β signalling in fibrosis after AKI.[7] In addition, numerous factors influence the development and occurrence of AKI.

A summary of clinical studies included in the review were listed in Table 1. Since Hellwig T et al and Min E et al[8,9] reported in 2011 that the co-administration of VPT leads to an increased risk of AKI, which was based on increases in serum creatinine, a plethora of studies on the subject of AKI due to concomitant of VPT therapy has emerged in recent years. While the initial reports faced scrutiny owing to potential biases in the study design, a consensus has emerged indicating a plausible elevation in the risk of AKI associated with the combined administration of VPT therapy. This consensus is grounded in a substantial body of evidence, although many of them were not high-quality, underscoring instances wherein patients undergoing VPT treatment exhibited heightened serum creatinine levels. As a result of these findings, certain clinicians may have opted to refrain from employing the combined therapeutic approach. Multiple clinical studies[10–12] have reported that the risk of AKI can escalate to 31.7%~35% when VPT were administered in combination.[13,14] This heightened risk persists with the prolonged co-administration of VPT over an extended duration (median duration approximately 1 month).[15] As demonstrated in Figure 1, a forest plot was generated. The forest plot demonstrates the ascending order of odds ratios (OR) or hazard ratios (HR) for AKI associated with VPT regimens, revealing considerable variability in the risk conferred by VPT regimens across different studies.

Currently, the mechanisms underlying co-administration of VPT induced AKI remain unclear. Some studies suggest a potential pseudo-nephrotoxicity mediated by impaired renal tubular creatinine secretion,[31] casting doubt on whether the observed relationship between co-administration of VPT and AKI truly reflects genuine renal toxicity. Referring to all above, the objective of this review is to consolidate the latest research findings from recent years, delineate the influencing factors contributing to AKI arising from the concurrent administration of VPT, and succinctly summarize the currently proposed potential nephrotoxic mechanisms.

We performed a comprehensive PubMed, Ovid-EMBASE, Biosis, Web of Science and Cochrane search up until December 2023, utilizing the terms “vancomycin” and “piperacillin-tazobactam” in conjunction with the terms “combination”, “concomitant”, “acute kidney injury”, “nephrotoxicity”. Our investigation focused on studies that explored the clinical outcomes and mechanisms of nephrotoxicity. This article relies on data from previously conducted studies and does not involve any new research with human participants or animals by the authors.

Risk Factors of AKI in Concomitant Therapy of Vancomycin and Piperacillin-Tazobactam

Severity of Illness

It is known to all that the severity of illness is a significant risk factor of AKI. In critically ill patients, the current research findings regarding the incidence of AKI in the VPT group, compared to the control group receiving VAN plus other β-lactams or VAN alone, are inconsistent. Some studies suggest an elevated risk of AKI with VPT compared to VAN combined with other β-lactams or VAN alone.[18,20–22,24,29,32] However, other studies indicate no significant difference in AKI incidence when comparing VPT with VAN combined with other β-lactams or VAN alone.[23,33] Discrepancies in the proportions of critically ill patients included in the studies contribute to varying outcomes. In an analysis including less than 50% ICU patients, a higher AKI risk was observed in the VPT group (adjusted Odds Ratio, aOR=3.04; 95% Confidence Interval, 95% CI: 1.49 to 6.22). Conversely, when over 50% ICU patients were included in the analysis, no increased AKI risk was observed in the VPT group (aOR=2.83; 95% CI: 0.74 to 10.85).[34] If the combination of two drugs significantly increase the risk of AKI in non-critical patients, it is plausible that this risk may be magnified rather than diminished in critically ill patients. Consequently, this contradictory observation has sparked debates: does the VPT concomitant therapy truly elevate the risk of AKI?

Dosing Strategy of Vancomycin

The nephrotoxicity of VAN has long been a focal point of scholarly inquiry, with a wealth of research endeavors dedicated to optimizing its dosing regimens through the analysis of its pharmacokinetics and variations in blood drug concentrations. The elevated trough concentrations may be associated with the nephrotoxicity of VAN. A consensus guideline focusing on VAN

Table 1 A Summary of Clinical Studies Investigating the Risk of AKI Induced by VTP Included in the Review

	Combination Antimicrobial Agents	Definition of AKI	Rate of AKI (%)	Risk, Odds, or Hazard Ratio (95% CI)	Study Design	Numbers of Patients
Hellwig et al, 2011[8]	VAN+TZP vs VAN vs TZP	Increase in baseline SCr of 50% or 0.5 mg/dl	VAN+TZP = **18.6** vs VAN = 4.9 vs TZP = 11.1	NA	Retrospective, single center	735
Min et al, 2011[9]	VAN+TZP vs VAN	Increase in baseline SCr of 50% or 0.5 mg/dl	VAN+TZP = **40.5** vs VAN = 9.0	NA	Retrospective, single center	140;VAN+TZP = 73 vs VAN = 67
Gomes et al, 2014[16]	VAN+TZP vs VAN+FEP	**AKIN**	TZP = **34.8** vs FEP = 12.5 (p<0.001)	NA	Retrospective, single center	224; TZP = 112 vs FEP = 112
Burgess et al, 2014[17]	VAN+TZP vs VAN	Increase in baseline SCr of 50%	TZP = **16.3** vs non-TZP = 8.1	OR=2.48 (1-sided χ^2test, 95% CI > 1.11) (p = 0.032)	Retrospective, single center	191;TZP = 92 vs non-TZP = 99
Hammond et al, 2016[18]	VAN+TZP vs VAN+FEP	**AKIN**	TZP = **32.7** vs FEP = 28.8 (p = 0.761)	Propensity β=−0.004 (p = 0.958)	Retrospective, single center	122; TZP = 49 vs FEP = 73
McQueen et al, 2016[19]	VAN+TZP vs VAN	Increase in baseline SCr of 100% or 0.5 mg/dl	TZP = **23.6** vs non-TZP = 3.8 (p=0.0001)	NA	Retrospective, single center	285;TZP = 106 vs non-TZP = 79
Navalkele et al, 2017[12]	VAN+TZP vs VAN+FEP	**RIFLE (also looked at AKIN and VCG)**	TZP = **29.0** vs FEP = 11.0;	OR = 4.3 (2.7–6.7) (p<0.001)	Retrospective, single center	558; TZP = 279 vs FEP = 279
Carreno et al, 2018[10]	VAN+TZP vs VAN vs TZP	**AKIN**	VAN+TZP = **26.8** vs VAN = 7.0 vs TZP = 8.5	NA	Retrospective, single center	213; VAN+TZP = 71 vs VAN = 71 vs TZP = 71
Buckley et al, 2018[20]	VAN+TZP vs VAN+FEP	**RIFLE**	TZP = **19.5** vs FEP = 17.3	NA	Retrospective, multicenter	333; TZP = 200 vs FEP = 133
Molina et al, 2019[21]	VAN+TZP vs VAN+FEP	**AKIN**	TZP = **28.7** vs FEP = 21.3	OR = 1.009 (1.003–1.015)	Retrospective, multicenter	394; TZP = 258 vs FEP=136
Schreier et al, 2019[22]	VAN+TZP vs VAN+FEP vs VAN+MEM	**AKIN**	Stage 1 of AKI: TZP = **62** vs FEP = 51 vs MEM = 50	Adjusted OR for VAN+TZP vs VAN+FEP = 1.11 (0.85–1.45); VAN+TZP vs VAN+MEM = 1.04 (0.71–1.42)	Retrospective, single center	3299; TZP = 1540 vs FEP = 1373 vs MEM = 386
Blevins et al, 2019[23]	VAN+TZP vs VAN+FEP vs VAN+MEM	**KDIGO**	TZP = **39.3** vs FEP = 24.2 vs MEM=23.5 (p<0.001)	NA	Retrospective, single center	2492; TZP = 366 vs FEP = 1734 vs MEM = 392
Inage et al, 2020[24]	VAN+TZP vs VAN	**RIFLE**	TZP = **19.8** vs non-TZP = 8	OR = 2.81 (1.52–5.17)	Retrospective, single center	539;TZP = 131 vs non-TZP = 462
Okada et al, 2021[25]	VAN+TZP vs VAN+FEP	**KDIGO**	TZP = **29.5** vs FEP = 7.1 (p<0.001)	OR = 4.59 (1.08–19.6) (*p* = 0.039)	Retrospective, single center	103; TZP = 61 vs FEP = 42
Lee et al, 2021[26]	VAN+TZP vs VAN+FEP vs VAN+MEM	**KDIGO**	TZP = **12.3** vs FEP = 9.5 vs MEM=9.1	TZP: aHR = 2.56 (2.49–2.63)	Retrospective, single center	789200; TZP = 56396 vs FEP = 18316 vs MEM = 5133
Elliott et al, 2022[27]	VAN+TZP vs VAN+FEP	**KDIGO**	TZP = **15** vs FEP = 12	NA	Retrospective, single center	348; TZP = 256 vs FEP = 92
Miano et al, 2022[28]	VAN+TZP vs VAN+FEP	Kidney function biomarker concentrations (creatinine and Cys-C)	**Creatinine increase 8.04% (1.21 to 15.34)** **Cystain C: decrease 5.63% (−18.19 to 8.86)**	NA	Prospective,single center	739; TZP = 297 vs FEP = 442
Dolly et al, 2023[15]	VAN+TZP vs VAN+CT (FEP or ETP or MEM)	Increase in SCr ⩾ 2 times higher than the baseline value	TZP = **14.4** vs CT = 5.5	NA	Retrospective, multicenter	826; TZP = 104 vs CT = 722
Chen et al, 2023[29]	VAN+TZP vs VAN+FEP vs VAN+MEM	**KDIGO**	TZP = **26.9** vs FEP = 21.8 vs MEM = 21.1	VAN+TZP vs VAN+FEP: OR = 1.37 (1.25–1.49) VAN+TZP vs VAN+MEM: OR = 1.27 (1.06–1.52)	Retrospective, multicenter	35654; TZP = 27459 vs FEP = 6371 vs MEM = 1824
Qian et al, 2023[30]	VAN+TZP vs VAN+FEP	**KDIGO**	TZP = **30.6** vs FEP = 27.3	OR = 0.89 (0.73 to 1.08)	Prospective, single center, randomized controlled trial	1939; TZP = 997 vs FEP = 942

Notes: Definitions and incidence of AKI in different studies were shown in bold text.

Abbreviations: AKI, acute kidney injury; VAN, vancomycin. TZP, piperacillin-tazobactam; ARF, acute renal failure; NA, not applicable; AKIN, Acute Kidney Injury Network; FEP, cefepime; SCr, serum creatine; OR, odds ratio; RIFLE, Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease classification; CT, combination therapy consistent of vancomycin and β-lactam; ETP, ertapenem; MEM, meropenem; ICU, intensive care unit; KDIGO, Kidney Disease Improving Global Outcomes; VCG, vancomycin consensus guideline definition.

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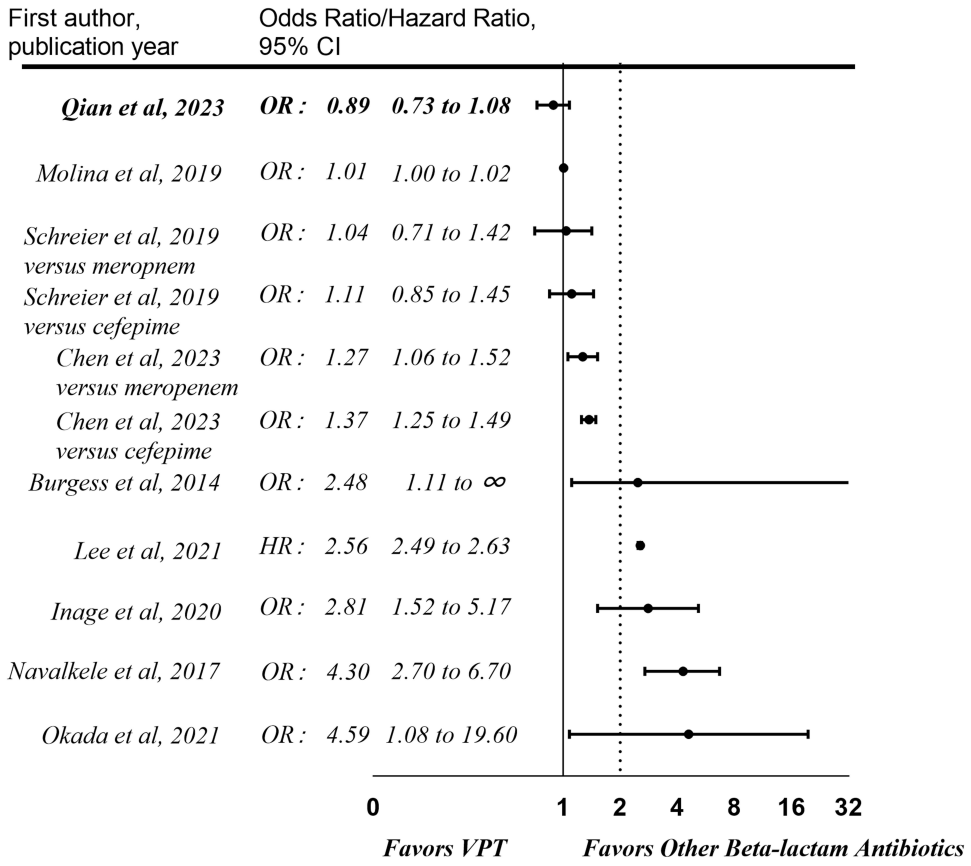

Figure 1 Forest plot of ORs and HRs of AKI induced by VPT concomitant therapy. The forest plot demonstrates the ascending order of ORs or HRs with 95% CI for AKI associated with VPT regimens, revealing considerable variability in the risk conferred by VPT regimens across different studies. The study by Qian et al,[30] presented in bold text, is the only large - scale RCT to date.

therapy (name as "consensus guideline") published by American Society of Health-System Pharmacists (ASHP), the Infectious Diseases Society of America (IDSA), the Pediatric Infectious Diseases Society (PIDS), and the Society of Infectious Diseases Pharmacists (SIDP) advocate for VAN dosing based on a daily area under the curve (AUC) target exposure of 400 to 600 mg × h/L, superseding the previous target trough concentration of 15–20 mg/L.[1] Analysis of VAN trough concentrations in patients guided by trough levels revealed a significantly higher trough level in the acute kidney injury (AKI) group compared to the non-AKI group (25.79±7.8 vs 15.7±6.9 μg/mL).[35] Other studies also indicate a significant association between drug exposure exceeding 15 mg/L and nephrotoxicity.[19,36–39] Given that most patients can achieve AUC24 > 400 mg × h/L with trough levels < 15 mg/L, considering VAN's nephrotoxicity as dose-dependent, perhaps AUC-guided dosing could be a modifiable risk factor for AKI.[40–42] The IDSA guidelines in 2020 shifted from recommending trough-guided dosing to AUC-guided dosing for VAN. A systematic review and meta-analysis have summarized the safety differences between AUC-guided and trough concentration-guided vancomycin dosing strategies.[43] Although most current studies are observational and lack randomized controlled trials, AUC-guided dosing strategies are associated with a lower incidence of vancomycin-induced AKI compared to trough-based strategies. Despite several limitations, the AUC-guided vancomycin dosing strategy remains a key approach for reducing vancomycin-induced nephrotoxicity.

Presently, several studies have focused on the issues surrounding drug dosing regimens and the nephrotoxicity associated with VPT therapy. However, a retrospective cohort study subset analysis[44] (n=636) suggested that, compared to trough-guided dosing, AUC-guided dosing did not lower the risk of AKI with VPT (17.8% vs 13.6%), although the initially estimated sample size might have been insufficient to detect a decrease in AKI risk, and the AUC-guided dosing group had a higher proportion of obese patients. A meta-analysis[45] also yielded similar results, indicating that AUC-guided dosing did not reduce the incidence of AKI compared to trough-guided dosing (OR=0.715, 95% CI: 0.439 to

1.163) in patients receiving concomitant therapy of VAN and antipseudomonal beta-lactam antibiotics. Furthermore, the AKI incidence in the VPT group with AUC-guided dosing was higher than that in the control group (OR=3.861, 95% CI: 2.165 to 6.887, P < 0.05). Additionally, AUC-guided dosing did not appear to reduce blood drug concentrations; the median initial daily total dose per weight (mg/kg) was higher in the trough-guided group (26.6±8.2 vs 24.1±7.3).[44] The meta-analysis[45] also indicated that the total daily dose of VAN with AUC-guided dosing did not decrease (standard mean difference, SMD=−0.139, 95% CI −0.458 to 0.179) compared to trough-guided dosing.

Current research questions the recommended AUC guided dosing strategy in the guidelines, since the AKI risk was not decreased when following the AUC guided dosing strategy. Whether following trough concentration-guided dosing or AUC guided dosing strategies, the risk of AKI induced by the concomitant of VPT has not been reduced.[40] A prospective observational study found significant nephrotoxicity when treating MRSA bacteremia with an AUC level ≥ 515 mg × h/L.[46] The optimal level related to reducing nephrotoxicity with AUC-guided dosing remains to be determined. A single-institution study compared the AUC level of 103 patients demonstrated that a higher prevalence of AKI in the VPT group (29.5%) when comparing with the VAN group (7.1%), under the circumstance of an AUC level <600 mg × h/L, which means prevention of AKI may be difficult with AUC-guided VAN dosing in patients receiving VPT.[25] As depicted in Figure 2, insights gleaned from the aforementioned literature suggest that co-administration of VPT may potentially narrow the therapeutic window of vancomycin, thereby reducing the threshold of VAN exposure leading to nephrotoxicity.

Individual Susceptibility of Vancomycin-Induced AKI

One study explored the role of Osteopontin (OPN) and Apolipoprotein E (APOE) gene polymorphisms in influencing susceptibility to vancomycin-induced AKI in critically ill patients.[47] The research identified significant differences in OPN and APOE genotype distributions between patients who developed AKI and those who did not. Notably, individuals carrying the APOE e2e3 genotype exhibited a significantly increased risk of AKI. Moreover, pharmacokinetic parameters of vancomycin were correlated with AKI incidence. Parallel to these investigations of genetic risk factors and the study of OPN and APOE, research has sought therapeutic interventions. One such study examined the potential of dapagliflozin

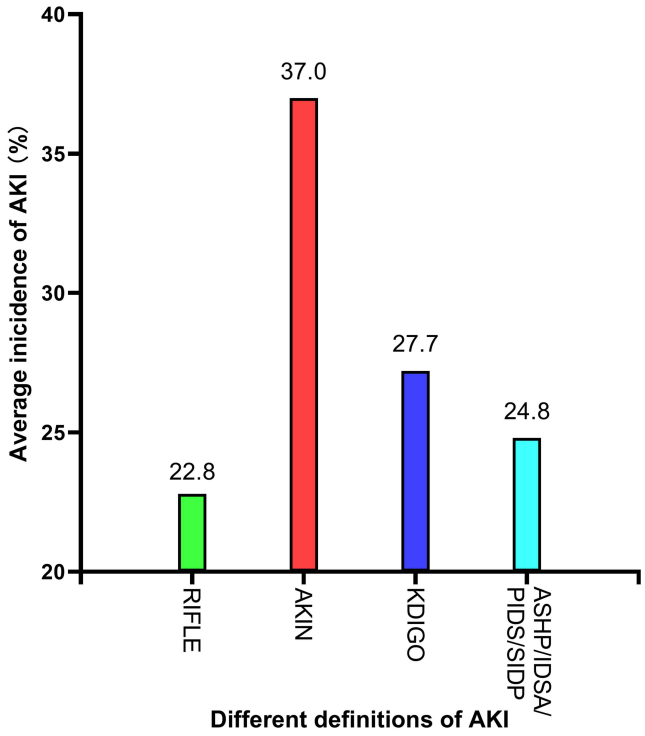

Figure 2 The average incidence of AKI under the concomitant VPT therapy defined by different criteria. The highest average AKI incidence rate is indicated by red, representing studies defined according to the AKIN standard (37.0%), followed by studies defined according to the KDIGO standard, indicated by blue (27.7%). The lowest average AKI incidence rate is found in studies defined according to the RIFLE standard, indicated by green (22.8%). The average AKI incidence rate of all definitions is above 20%.

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(DAPA), an oral antidiabetic agent, to mitigate vancomycin-induced AKI in a rat model.[48] VCM administration induced renal tubular damage, impaired renal function, and increased oxidative stress and apoptosis in the kidneys. DAPA pretreatment, particularly at a higher dose, attenuated these effects, reducing NADPH oxidase-4 (NOX4)-induced renal reactive oxygen species (ROS), inhibiting activin A activation, and modulating miRNA-21/PTEN/pAKT signaling. DAPA also improved antioxidant enzyme expression and alleviated kidney injury markers, leading to improved renal function and reduced apoptosis. Recent research has turned to the role of Klotho, a protein associated with kidney health, in mitigating vancomycin-AKI.[49] In vivo and in vitro studies demonstrated that vancomycin challenge reduced Klotho expression in renal tissue. Introduction of Klotho, either through recombinant Klotho administration or siRNA knockdown, modulated reactive oxygen species production, cell apoptosis, and expression of the JAK2/STAT3/GPx3 axis. Klotho enhances antioxidant capacity through the JAK2/STAT3/GPx3 axis, which in turn improves vancomycin-induced AKI. Taken together, these studies highlight the multi-faceted nature of vancomycin-induced AKI, involving patient-specific genetic factors, modifiable pathways amenable to therapeutic intervention, and the protective role of Klotho. The identification of OPN and APOE polymorphisms as potential risk factors may inform personalized risk assessment strategies. The demonstration of DAPA's protective effects and the identification of Klotho's protective mechanisms in preclinical models suggest potential therapeutic avenues for mitigating vancomycin-induced nephrotoxicity. Further research is needed to translate these findings into clinical practice and to explore the potential synergistic benefits of combining genetic risk stratification with targeted therapeutic interventions and Klotho augmentation strategies.

Different Definitions of AKI

Current Guidelines

As shown in Table 2, the definition of AKI varies among four established criteria, namely, Risk, Injury, Failure, Loss, End-stage renal disease (RIFLE), Acute Kidney Injury Network (AKIN), Kidney Disease: Improving Global Outcomes (KDIGO), and a consensus guideline focusing on VAN therapy published by ASHP, IDSA, PIDS, and SIDP.[1] These standards exhibit slight differences in the classification of AKI (Figure 2). AKIN and KDIGO criteria encompass a broader spectrum of AKI cases, incorporating smaller increases in serum creatinine (0.3 mg/dL) compared to the RIFLE criteria (at least a ≥50% increase). This distinction may impact the reported incidence of AKI. Indeed, research supports this conjecture, revealing alterations in AKI occurrence rates based on different AKI definition criteria. For instance, when compared to VAN combined with cefepime, the combined use of VPT is significantly associated with an increased risk of AKI.[12] Another analysis showed that the VPT primarily affects Stage I AKI incidence rates, with no significant impact on Stages II or III AKI rates.[16] In summary, the current determination of AKI predominantly relies upon the levels of serum creatinine.

Other Biomarkers of AKI

During the acute phase of AKI, before a detectable increase in serum creatinine (SCr), the glomerular filtration rate (GFR) can decrease by up to 50%. Defining AKI based solely on SCr changes lacks clinical sensitivity, necessitating the incorporation of more sensitive and specific biomarkers. Biomarkers such as Kidney Injury Molecule 1 (KIM-1) and clusterin, which are sensitive to histopathological changes in renal parenchyma and show detectable increases within hours of mild tubular injury, along with Cystatin C (CysC), a biomarker enabling subclinical AKI detection, and tissue inhibitor of matrix metalloproteinase 2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP7), which have FDA approval for assessing moderate to severe AKI risk in laboratory settings. Notably, only two clinical studies investigating the nephrotoxicity of concomitant VPT have utilized renal biomarkers other than creatinine. In a prospective cohort study, a secondary analysis employing TIMP-2 and IGFBP7 demonstrated their efficacy in assessing renal stress in critically ill patients in different groups, with levels exceeding 0.3 on the first day correctly identifying progression to Stage 2/3 AKI. Moreover, in patients with high Acute Physiology and Chronic Health Evaluation II (APACHE II) scores, TIMP-2 and IGFBP7 levels in the concomitant administration of VPT group did not significantly differ from those in the VAN group.[50] In another prospective cohort study that aimed to validate the correlations of creatinine and Cystatin C changes in patients receiving combined VPT therapy,[28] the findings revealed a significant association between the co-administration of VPT and an 8.04% increase in creatinine (95% CI: 1.21% to 15.34%). This elevated creatinine level was further associated with a higher incidence of AKI defined by serum

Table 2 Different Definitions of AKI

	RIFLE	AKIN	KDIGO	ASHP/IDSA/PIDS/SIDP Consensus Guideline
Diagnostic criteria	–	Increase in serum creatinine of ≥0.3 mg/dL or ≥50% within 48 hours or Urine output of <0.5 mL/kg/hour for >6 hours	Increase in serum creatinine of ≥0.3 mg/dL within 48 hours or ≥50% within 7 days or urine output of <0.5 mL/kg/hour for >6 hours	Increase in SCr level of ≥0.5 mg/dL, or ≥50% or a decrease in calculated creatinine CL (CLcr) of 50% from baseline within 48 hours
Staging criteria				
Risk (RIFLE) or stage 1 (AKIN/KDIGO)	Increase in serum creatinine to 1.5 times baseline or urine output of <0.5 mL/kg/hour for 6 to 12 hours	Increase in serum creatinine of ≥0.3 mg/dL or to 150 to 200% baseline or urine output of <0.5 mL/kg/hour for 6 to 12 hours	Increase in serum creatinine of ≥0.3 mg/dL or 1.5 to 1.9 times baseline or urine output of <0.5 mL/kg/hour for 6 to 12 hours	
Injury (RIFLE) or stage 2 (AKIN/KDIGO)	Increase in serum creatinine to 2 times baseline or urine output of <0.5 mL/kg/hour for 12 to 24 hours	Increase in serum creatinine to 200 to 300% baseline or urine output of <0.5 mL/kg/hour for 12 to 24 hours	Increase in serum creatinine to 2 to 2.9 times baseline or urine output of <0.5 mL/kg/hour for 12 to 24 hours	
Failure (RIFLE) or stage 3 (AKIN/KDIGO)	Increase in serum creatinine to 3 times baseline or increase in serum creatinine by >0.5 mg/dL to >4 mg/dL or urine output of <0.3 mL/kg/hour for >24 hours or anuria for >12 hours or initiation of kidney replacement therapy	Increase in serum creatinine to >300% baseline or increase in serum creatinine by >0.5 mg/dL to ≥4 mg/dL or urine output of <0.3 mL/kg/hour for >24 hours or anuria for >12 hours or initiation of kidney replacement therapy	Increase in serum creatinine to ≥3 times baseline or increase in serum creatinine of ≥0.3 mg/dL to ≥4 mg/dL or urine output of <0.3 mL/kg/hour for ≥24 hours or anuria for ≥12 hours or initiation of kidney replacement therapy	
Loss (RIFLE)	Need for kidney replacement therapy for >4 weeks			
End stage (RIFLE)	Need for kidney replacement therapy for >3 months			

Abbreviations: RIFLE, Risk, Injury, Failure, Loss, End-stage renal disease, KDIGO, Kidney Disease: Improving Global Outcomes, AKIN, Acute Kidney Injury Network, ASHP, American Society of Health-System Pharmacists, IDSA, the Infectious Diseases Society of America, PIDS, the Pediatric Infectious Diseases Society, SIDP, the Society of Infectious Diseases Pharmacists.

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creatinine levels. However, there was no discernible correlation between this concomitant therapy and changes in Cystatin C (Cystatin C: −5.63%) or Blood Urea Nitrogen (BUN: −4.51%). In summary, while there is evidence suggesting an increased incidence of AKI defined by serum creatinine levels with the concomitant use of VPT, the conclusions drawn from comparisons with other kidney-related biomarker levels are contradictory. Therefore, the definition of AKI in the context of combined administration of VPT may warrant further exploration, necessitating comparisons with alternative AKI criteria beyond creatinine for a more comprehensive understanding.

Major Adverse Kidney Events

Although numerous studies have investigated AKI resulting from VPT regimens, most focus on AKI defined primarily by elevated serum creatinine levels. In terms of more clinically relevant kidney events, such as anuria, need for renal replacement therapy (RRT), AKI-related mortality, and progression to chronic kidney disease (CKD), it appears that VPT does not significantly affect their incidence. A meta-analysis summarizing observational studies found that the VPT regimen is most likely to cause severe AKI (stage 3 or failure) and the need for RRT. However, this tendency is not statistically significant.[51] Additionally, there were no significant differences in AKI recovery, length of hospital stay, or mortality rates. In a study analyzing renal recovery in septic patients with AKI, the recovery rates were 42.3% for those treated with VPT compared to 40.3% for those receiving vancomycin plus cefepime (p = 0.78).[27] This suggests that initial empiric therapy with VPT in sepsis does not increase the risk of AKI when appropriately de-escalated. In the only current randomized controlled trial (RCT), the incidence of Stage 3 AKI (85/997, 8.5%) and mortality (73/997, 7.3%) caused by the VPT regimen was not higher than that of the vancomycin combined with cefepime regimen (Stage 3 AKI: 70/942, 7.4%; mortality: 84/942, 8.9%). The length of hospital stay was similar between the two groups.[30] The aforementioned studies suggest that, although VPT may be associated with a higher incidence of AKI, this increased risk does not necessarily lead to more severe clinical events or extend hospitalization duration.

Potential Mechanisms of AKI in VPT

Synergistic Increase in the Risk of AKI

At the outset of the recognition of VPT-induced AKI, the prevailing hypothesis centered on the synergistically heightened risk of AKI. According to this hypothesis, TZP does not affect the metabolism of vancomycin but rather contributes to synergistic nephrotoxicity. As illustrated in Figure 3, the VPT concomitant regimen may potentially narrow the therapeutic window of vancomycin.

Nowadays, regarding the mechanism of nephrotoxicity associated with the concomitant of VPT, major perspectives have been proposed: interstitial nephritis caused by TZP, increased exposure of VAN, VAN-induced oxidative stress induced by VPT and elevated serum creatinine level caused by tubular secretion inhibition. Some studies suggest that the nephrotoxicity of VPT results from the additive effects of VAN-induced cell necrosis and acute interstitial nephritis caused by TZP.[52] Another study proposes that the nephrotoxicity of VPT is due to piperacillin-induced subclinical interstitial nephritis, which is exacerbated by VAN-induced oxidative stress.[53] Some case reports support this hypothesis.[54] It is known that TZP can induce interstitial nephritis, whereas VAN, when used with other antibiotics, may lead to acute tubular necrosis and tubulointerstitial nephritis. A reported case indicates that AKI reached stage 2 three days after VPT exposure, with renal biopsy revealing acute tubular necrosis and interstitial nephritis, suggesting that interstitial nephritis may be a potential cause of the rapid decline in renal function. It is noteworthy that, although there are rare case reports of interstitial nephritis in patients receiving VPT treatment, it is extremely uncommon in routine practice.However, a retrospective cohort study[26] presents a contrasting view, indicating a synergistic increase in the risk of AKI with VPT. The adjusted Hazard Ratio (aHR) for AKI after VPT exposure is 2.56 (95% CI: 2.49–2.63). The adjusted model shows a significant interaction between VAN and TZP, with an estimated aHR of 2.28 in the independent additive model. This cumulative toxicity was also not replicated in preclinical rat models.[55] Other mechanisms included increased exposure of VAN, pseudo-renal-toxicity, and increased VPT-induced tubular toxicity due to OAT-3 and piperacillin interaction.

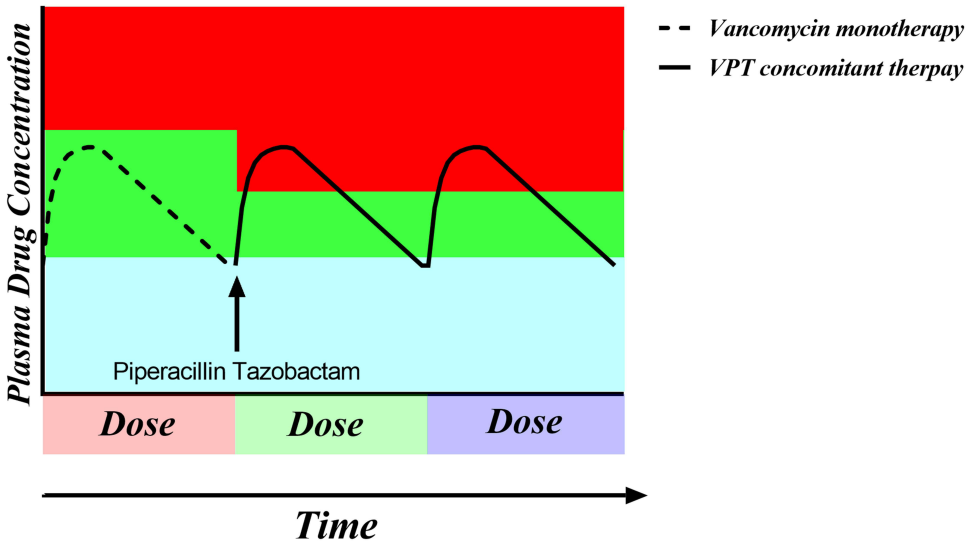

Figure 3 A hypothesis suggests that concomitant TZP therapy narrows the VAN therapeutic window and increases AKI risk. The blue area indicates suboptimal antimicrobial effect, the green shows the therapeutic window, and the red signifies higher nephrotoxicity risk. The dashed line represents vancomycin exposure in monotherapy; the solid line shows exposure with VPT co-administration. VPT may cause synergistic nephrotoxicity, lowering the VAN exposure threshold for AKI.

Increased Exposure of Vancomycin

As shown in Figure 4, one of the major hypotheses is the increased risk of VPT induced nephrotoxicity may be attributed to piperacillin reducing the clearance of VAN, leading to its accumulation in the renal unit.[17] This accumulation may cause oxidative stress and mitochondrial damage to the proximal renal tubules.[56] As discussed earlier, numerous studies have found a substantial increase in VAN exposure in patients experiencing VPT-induced AKI, whether based on trough concentrations or AUC guided dosing strategy.[25,38–46] However, there is currently a lack of high-quality pharmacokinetic investigations analyzing this phenomenon. Most studies predominantly compare VAN exposure metrics (AUC or trough concentrations) and other clinical indicators between AKI and non-AKI patients, without delving into pharmacokinetic alterations, particularly in terms of changes in VAN clearance rates.

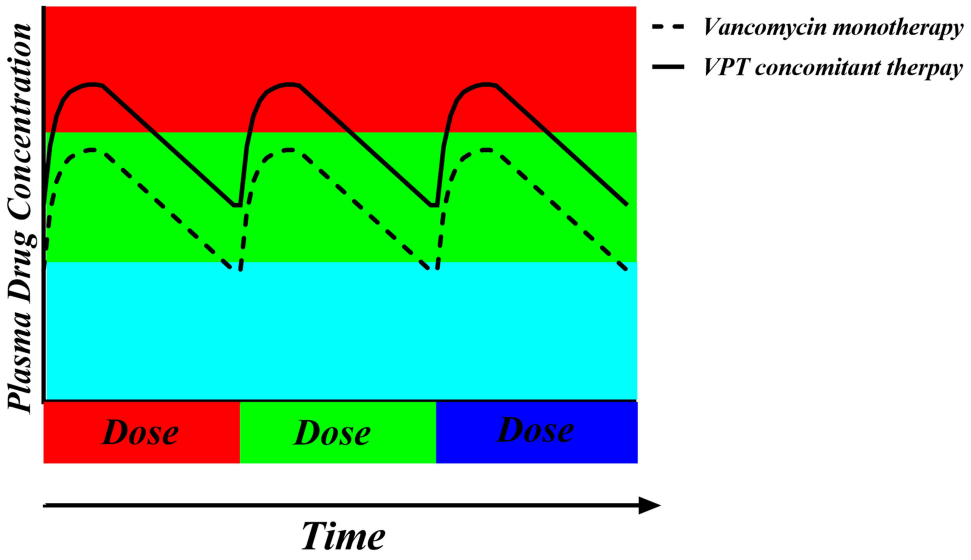

Figure 4 A hypothesis suggests that increased nephrotoxicity risk during VPT combination therapy is due to TZP reducing VAN clearance, leading to accumulation in the kidneys. The blue area indicates suboptimal antimicrobial effectiveness, the green area shows the therapeutic window, and the red zone represents the risk of nephrotoxicity. The dashed line shows vancomycin exposure over time in monotherapy, while the solid line depicts exposure with VPT co-administration.

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OAT-3, Piperacillin and Vancomycin: Nephrotoxicity or Pseudo-Nephrotoxicity?

TZP is a substrate for organic anion transporter-1 (OAT-1) and organic anion transporter-3 (OAT-3) on the basolateral side of proximal renal tubule cell membranes,[57] with competitive inhibition effects on creatinine. VAN may also partially inhibit messenger RNA and protein expression of OAT-1 and OAT-3.[58] The combined use of VAN and TZP leads to impaired creatinine secretion and increased serum creatinine (SCr). Therefore, the joint use of VPT sodium often exhibits a phenomenon of increased SCr with evident AKI, possibly mediated by pseudo-renal toxicity involving impaired tubular secretion, without actual tubular or renal function damage, as seen in trimethoprim-sulfamethoxazole and cimetidine.[31] This theory is supported by studies that show an increased risk of AKI with VPT but no significant increase in severe clinical outcomes such as the need for RRT or mortality, compared to the control group.[51,59] A clinical study by Jensen et al[60] found that patients taking TZP sodium had faster recovery of GFR calculated by SCr after discontinuation compared to patients receiving meropenem or cefepime. However, a secondary analysis of a prospective multicenter randomized clinical trial[50] studying urinary renal biomarkers TIMP-2 and IGFBP7 suggests renal stress with VPT; the levels of urinary TIMP-2 and IGFBP7 increased on the first day after VPT exposure. Moreover, if the nephrotoxicity of VPT is mediated by pseudo-renal toxicity due to impaired creatinine secretion, there should not be a concurrent increase in BUN and cystatin C, and the BUN/Cr ratio should be at normal level or lower than normal level. A prospective cohort study exploring the correlation between VPT-induced AKI and creatinine and cystatin C[28] showed that VPT was associated with a higher percentage increase in creatinine on the second day, 8.04% (95% CI 1.21 to 15.34), and a higher rate of AKI defined by creatinine (RR=1.34, 95% CI 1.01 to 1.78). In contrast, VPT showed no association with changes in alternative biomarkers (cystatin C: −5.63%, 95% CI −18.19 to 8.86; urea nitrogen: −4.51%, 95% CI −12.83 to 4.59). This provides support for the creatinine secretion hypothesis of VPT, but considering the single-center nature of the study, the limited data on cystatin C, and the susceptibility of BUN to extrarenal factors, further research is needed to confirm the pseudo-renal toxicity of VPT.

On the other hand, some studies focusing on the relationship between β-lactam antibiotics and the AKI suggest that the increased nephrotoxicity observed when β-lactam antibiotics are co-administered with VAN might occur through the augmentation of VAN-induced proximal tubular oxidative stress, coupled with intracellular accumulation of β-lactam antibiotics.[61] This phenomenon displays variations among different types of β-lactam antibiotics.[62,63] The toxicity of β-lactam antibiotics to proximal tubular cells is contingent upon their accumulation within these cells, a process dictated by the variations in drug uptake and excretion abilities. The accumulation of β-lactam antibiotics in proximal tubular cells depends on their affinity to the basolateral membrane transporters, constituting the first step of excretion, wherein OAT-3 plays a pivotal role. Some β-lactam antibiotics exhibit a higher affinity to OAT-3. For the majority of β-lactam antibiotics, the apical membrane passage through proximal tubular cells for urinary excretion mitigates their nephrotoxic potential. Notably observed differences in the inherent nephrotoxicity among cephalosporins and anti-staphylococcal β-lactam antibiotics during treatment of methicillin-sensitive Staphylococcus aureus bacteremia highlight this phenomenon.[64,65]

Upon entry into proximal tubular cells, β-lactam antibiotics induce oxidative damage by impeding mitochondrial function.[66] Co-administration of VAN with different β-lactam antibiotics accentuates the tendency for variations in proximal tubular injury induced by these antibiotics, surpassing the risk of AKI resulting from each antibiotic's individual use. This observation emerged unexpectedly from the CAMERA2 trial, a multicenter prospective randomized clinical trial aiming to investigate whether the addition of flucloxacillin to VAN in the treatment of methicillin-resistant Staphylococcus aureus bacteremia might confer benefits.[67] The CAMERA2 study showed a reduction in the duration of MRSA bacteremia by adding β-lactam antibiotics to VAN. However, due to a significant increase in AKI risk observed with the concomitant of VAN and β-lactam antibiotics compared to VAN alone, the study was prematurely terminated. Among 90 individuals treated with VAN and flucloxacillin, 25 cases (28%) experienced AKI risk, while among 21 individuals treated with VAN and cloxacillin, 5 cases (24%) were observed, and only 1 case (4%) occurred among 27 individuals treated with VAN and cefazolin. The discrepancy between the VAN and anti-Staphylococcus β-lactam antibiotic group versus the cefazolin group signifies the first direct comparison of different β-lactam antibiotics combined with VAN in terms of nephrotoxic risk, laying the foundation to understand why certain combinations lead to AKI risk while others do not.Studies analyzing the substrate affinity of various β-lactam antibiotics towards OAT-3 have revealed a strong correlation between the hydrophilicity of β-lactam antibiotics and their affinity for OAT-3 and subsequent

cellular uptake. Most β-lactam antibiotics that bind to OAT-3 also act as competitive inhibitors. Examination of the inhibitory activity of β-lactam antibiotics on OAT-3 indicates a close relationship between their binding propensity and the potential nephrotoxicity observed when co-administered with VAN. The high expression of OAT-3 on the basolateral membrane of the blood-brain barrier and the apical membrane of the choroid plexus suggests its role in aiding antibiotic penetration into the cerebrospinal fluid. This finding enhances our understanding of how hydrophobicity influences antibiotic entry into the central nervous system.

Based on the above discussion, the key mechanism underlying the risk of AKI induced by VPT is believed to be associated with the binding of piperacillin to OAT-3 (Figure 5). On one hand, this binding might competitively inhibit the secretion of creatinine after binding of piperacillin and OAT-3, potentially leading to elevated creatinine level and pseudo-nephrotoxicity. On the other hand, the binding of piperacillin to OAT-3 might exacerbate the intracellular accumulation of drugs in the proximal tubule cells, thereby intensifying the oxidative stress-induced injury induced by VAN.

How Can We Address the Risk of VTP-Related AKI?

Appropriate Dosing Strategy and Therapeutic Drug Monitoring

As the exposure levels of VAN are recognized as a risk factor contributing to AKI, it is imperative to employ strategies to mitigate the risk of AKI by controlling its exposure within the recommended ranges outlined in current guidelines. As previously discussed, VAN trough concentrations exceeding 20 mg/L significantly escalate the risk of AKI. Various studies have also indicated a significant increase in VAN-induced AKI risk with AUC24 values surpassing 515 mg × h/L,[46] 600 mg × h/L,[68] or 650 mg × h/L;[69] however, consensus on the optimal AUC cutoff values remains elusive. Considering the need to maintain a certain level of drug exposure for optimal therapeutic outcomes in antimicrobial treatment, defining an optimal AUC threshold becomes a nuanced task. There is no consistent conclusion regarding the AKI risk with different dosing regimens, and the recommendation persists to design VAN dosing based on the consensus guidelines' therapeutic drug monitoring scheme, ie, targeting AUC 400 to 600 mg × h/L or trough concentrations of 15–20 mg/L.[1] Although current research indicates that AUC-guided vancomycin dosing may not reduce nephrotoxicity in VPT regimens,[45] it still offers advantages over trough concentration-guided vancomycin in managing nephrotoxicity.[43] Therefore, we recommend using the AUC-guided vancomycin approach to minimize potential kidney toxicity. We recommend aligning AUC24 targets with guideline recommendations and, for patients with compromised renal function, contemplating a more strict AUC24 range to between 400 to 515 mg × h/L[46] to mitigate further renal impairment when AUC24 is utilized as a target parameter.

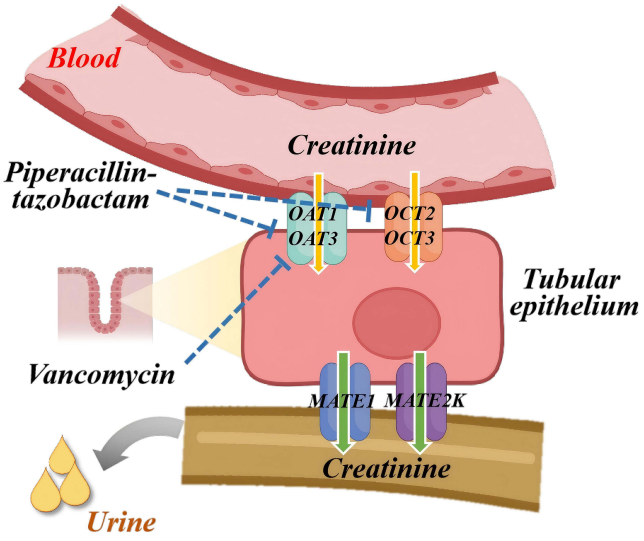

Figure 5 VPT may increase serum creatinine levels by affecting organic anion transporters (OAT-3). This effect can involve oxidative stress and the accumulation of proximal tubular cells. Additionally, interaction with VPT might inhibit creatinine secretion into the tubular lumen, causing pseudo-toxicity and elevated serum creatinine.
Abbreviations: MATE, multidrug and toxin extrusion; OAT, organic anion transporter; OCT, organic cation transporter.

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Continuous infusion protocols of VAN may also prove beneficial in reducing the risk of AKI when comparing with intermittent infusion protocols. Instances where continuous infusion might be warranted include critically ill patients, particularly those undergoing RRT, and individuals intolerant to intermittent infusion.[1] Pot disadvantages encompass the necessity for establishing a dedicated venous access route or compatibility considerations with other drugs administered through the same venous route. Data comparing intermittent and continuous administration of VAN are limited. Due to differences in study design, controls, and/or adjustments for confounding factors, as well as insufficient statistical power, it has not been definitively established whether continuous infusion is superior or inferior to intermittent infusion in terms of efficacy or safety to date. However, considering its potential to mitigate the risk of AKI, adopting a continuous infusion strategy during VPT concomitant therapy may contribute to reducing potential nephrotoxicity.[70]

In recent years, β-lactam antibiotics, particularly carbapenems, have been increasingly recommended for extended infusion protocols to reduce the incidence of adverse reactions and enhance therapeutic efficacy. Recent research has indicated that extending the infusion time of TZP may also contribute to more favorable clinical outcomes, especially in patients with sepsis and febrile neutropenia.[71,72] Although a meta-analysis conducted by Bellos et al observed a statistically non-significant trend in reducing the risk of nephrotoxicity with the co-administration of VAN and extended-infusion TZP, the renal protective effects of this strategy were not definitively confirmed.[51] Similarly, several retrospective cohort studies found no significant difference in the incidence of AKI between patients receiving extended-infusion TZP combined with VAN and those treated with standard-infusion TZP combined with VAN.[73,74] Nevertheless, considering the superior clinical efficacy associated with the extended-infusion regimen of TZP and until randomized controlled trials prove otherwise, it is suggested that adopting the extended-infusion protocol of TZP may be beneficial in reducing the occurrence of AKI.

Evaluaterenal Function Through Multiple Methodologies

Currently, among the predominant hypotheses regarding the mechanisms underlying AKI induced by VPT, there exists a theoretical concept of pseudo-nephrotoxicity supported by some clinical and basic research, primarily manifested through an elevation in creatinine levels. However, robust clinical evidence substantiating this notion is presently lacking. While it remains a plausible mechanism, studies have also indicated that the elevation of cystatin C levels, a potential biomarker, is not significantly pronounced in patients with VPT-induced AKI.[28] Consequently, we lean towards employing a comprehensive approach for the discrimination and diagnosis of AKI by incorporating various clinical indicators, such as cystatin C and BUN, as mentioned in the aforementioned studies. Numerous studies have suggested a substantial diagnostic and predictive value of neutrophil gelatinase-associated lipocalin (NGAL) in the context of AKI. However, despite its recognized potential, the clinical application of NGAL remains somewhat limited. Furthermore, there is currently a lack of research analyzing the effectiveness of AKI assessment utilizing NGAL specifically in patients receiving VPT therapy. Additional evidence is required to substantiate the predictive utility of NGAL in this particular clinical scenario. A study conducted in mice examined the alterations in NGAL levels and expression during TZP treatment.[56] The findings revealed an elevation of NGAL expression in the kidneys; however, serum NGAL levels did not exhibit a significant elevation comparable to that observed in creatinine or BUN. In summary, a judicious diagnostic approach for AKI is advocated, involving a holistic assessment of factors including urine output and other pertinent clinical signs. Diagnosing AKI in patients utilizing the VPT regimen should not solely rely on an elevation in creatinine but rather integrate a multifaceted evaluation.

Reducing the Duration of VPT Concomitant Therapy

According to a previous study, the highest risk of AKI occurs on the fifth day of VPT treatment.[75] In the latest RCT analyzing the nephrotoxicity risk of cefepime and TZP in acute infections, the AKI risk in patients co-administered VAN was found to be comparable.[30] However, it is noteworthy that the median treatment duration for included patients in this study was 3 days, shorter than the median treatment duration reported in prior studies on VPT-induced nephrotoxicity. Also, the TZP was administered 3.375g every 8 hours, lower than the standard dose of 3.375 to 4.5g every 6 hours. Consequently, we hypothesize that timely assessment of infection status and microbiological evaluation, coupled with prompt adjustment of antimicrobial therapy, facilitates rapid de-escalation of antibiotic treatment and reduces the duration of concomitant therapy involving VPT,

potentially mitigating the risk of AKI.[76] Nonetheless, there is limited evidence supporting the renal protective effects of early antibiotic regimen adjustments, as patients receiving treatment for <48 hours are typically excluded from the analysis in the majority of studies. In Figure 6, we provide a summary of the current research on the timeline of AKI onset and recovery. Despite this, Lorentz et al conducted a study restricting the course of VPT concomitant therapy to within 72 hours, significantly reducing the exposure time to the regimen and lowering the incidence of VPT-related AKI.[77] In line with this research, Schreier et al conducted a single-center retrospective cohort study involving 3,299 ICU patients to compare the risk of AKI associated with a short course of VPT (24–72 hours) against other antipseudomonal β-lactam plus VAN combinations.[22] The results indicated that short-term VPT therapy did not increase the risk of stage II or III AKI after adjusting for relevant confounders. The adjusted odds ratios were 1.11 (95% CI [0.85–1.45]) for VPT versus FEP-VAN, and 1.04 (95% CI [0.71–1.42]) for VPT versus MER-VAN. Additionally, a retrospective single-center cohort study found that a short-course VPT regimen (24–60 hours) was significantly associated with a lower risk of AKI compared to extended-course VPT therapy (>72 hours).[78] Therefore, based on the aforementioned studies and theoretical considerations, we posit that minimizing the duration of concomitant therapy involving VPT through timely infection assessment and microbiological examination may be a strategy to reduce the risk of AKI.

Based on current evidence, VPT regimens are unlikely to cause AKI within the short term (around three days). However, to improve stewardship decisions, we recommend implementing more frequent renal function monitoring and utilizing a panel of renal biomarkers. If signs of AKI or indications of renal impairment emerge during VPT therapy, clinicians should consider switching to alternative antibiotics such as cefepime or meropenem. Despite these

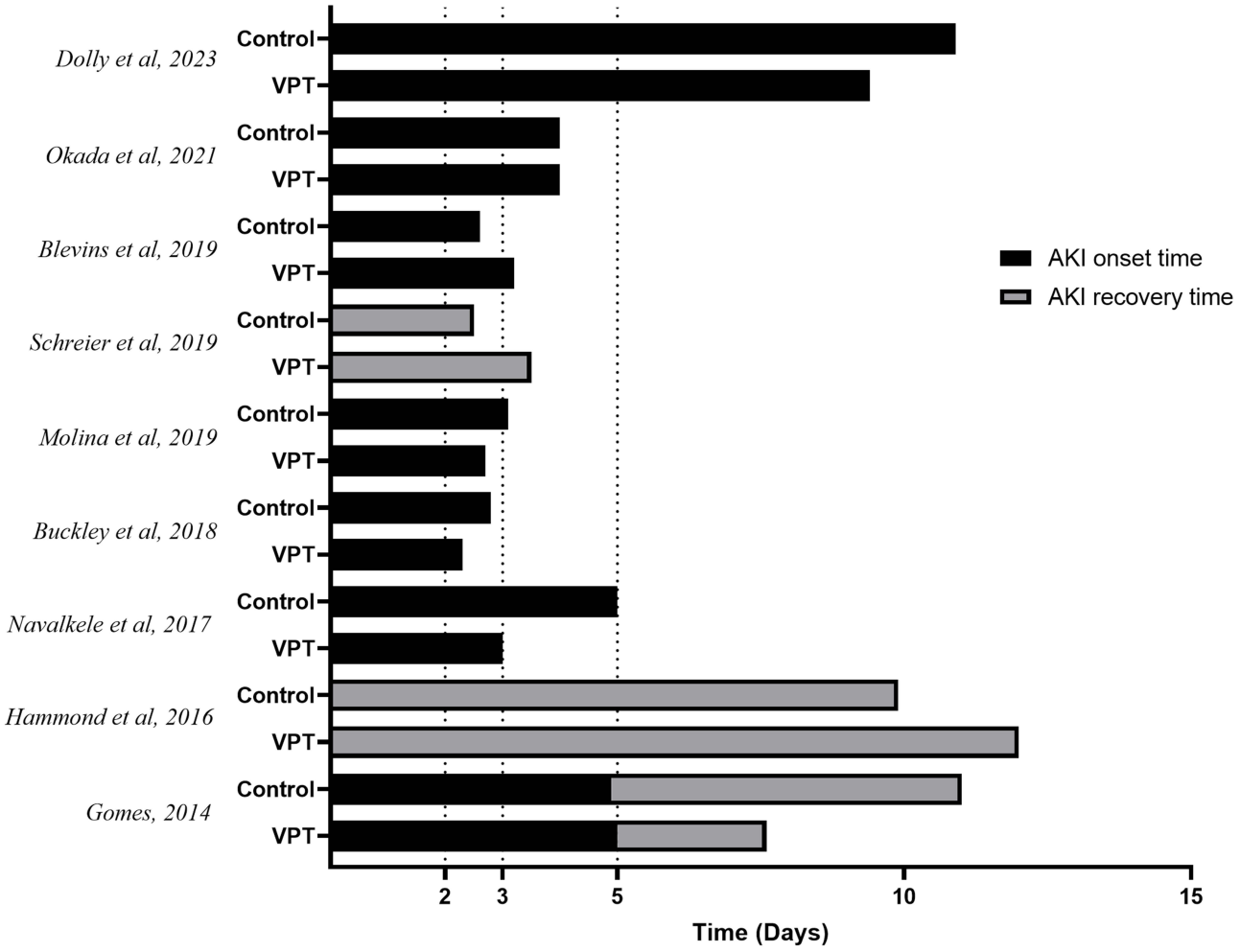

Figure 6 A summary of the current research on the timeline of AKI onset and recovery.

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recommendations, the optimal adjustment strategies remain unclear, highlighting the need for further research to establish evidence-based guidelines for timely and effective therapy modification.

Other Strategies

To navigate this complex clinical scenario, a meticulous risk assessment should be conducted, considering the intricate interplay between therapeutic benefits and potential nephrotoxicity inherent in VTP regimens. Renal function monitoring, utilizing established indicators such as serum creatinine levels and estimated glomerular filtration rate (eGFR), is imperative. Incorporating emerging biomarkers indicative of early renal damage may further refine the sensitivity of detection for incipient nephrotoxic effects.

Firstly, the engagement of a multidisciplinary team, comprising infectious disease physicians, nephrologists,and pharmacists, is pivotal for a comprehensive evaluation and decision-making process. Clear and precise communication, coupled with meticulous documentation of decisions, is essential for ensuring patient safety and adhering to evidence-based medical practice. This approach aligns with the tenets of precision medicine, recognizing the inherent variability in individual responses to drug therapy and aiming to optimize therapeutic outcomes while minimizing the risk of adverse effects, particularly within the context of AKI associated with VTP regimens. To address the risk of prolonged VPT exposure and promote standardized AUC-based vancomycin monitoring, our institution has implemented protocols guided by our antimicrobial stewardship team. These include regular therapeutic drug monitoring and automated alerts set up by the stewardship team to prompt timely dose adjustments and prevent unnecessarily extended therapy durations. This approach helps ensure that vancomycin use is optimized for each patient and reduces the risk of nephrotoxicity associated with prolonged exposure.

Secondly, in patients with a history of renal insufficiency or established AKI, the use of VPT should be avoided. While the specific mechanisms of VPT and its potential nephrotoxic effects remain subjects of ongoing investigation, it is prudent to minimize the administration of drug combinations that could exacerbate renal toxicity in individuals with confirmed pre-existing renal dysfunction or AKI. In instances where renal impairment is either detected or suspected, timely intervention involves the judicious discontinuation or modification of the implicated agents, with a preference for discontinuing the therapy exhibiting a higher potential for nephrotoxicity. Subsequent management strategies may encompass supportive measures, such as hydration, diuretics, or, in severe cases, renal replacement therapy.

Thirdly, utilizing prognostic indicators or predictive tools can help assess the risk of AKI in patients. Currently, there are no tools specifically designed to predict the AKI risk associated with VPT regimens. However, the development of AI tools or nomogram models could facilitate future management of VPT-related AKI risks. Due to the absence of dedicated predictive models, clinicians and pharmacists can turn to existing AKI prediction tools, such as risk prediction models and prognostic indicators. Hematological parameters are widely used for their simplicity and cost-effectiveness. Blood tests provide hematological indices that are inexpensive and reliable markers for AKI, allowing comparison with other risk factors. The neutrophil-to-lymphocyte ratio (NLR) is a reliable prognostic marker for predicting AKI development, especially in patients with severe sepsis.[79,80] Red cell distribution width is another easily accessible inflammatory biomarker, which also holds predictive value for mortality in patients with sepsis-induced AKI.[81] Mean platelet volume (MPV), measured in femtoliters (fL), indicates the average platelet size, with MPV $\geq$ 10.2 fL identified as a significant prognostic risk factor for AKI patients requiring RRT.[82–84] Utilizing these simple indicators may aid in managing patients with AKI. In addition, machine learning-based predictive models are emerging. A notable model published by Tomašev et al in *Nature* in 2019, involving data from 172 hospitals and 1,062 clinics, demonstrated excellent predictive capabilities, forecasting AKI up to 48 hours earlier than traditional clinical approaches.[85] Although this method has not been independently validated for the VPT cohort, it represents a potential strategy for managing AKI risks.

Summary

This review summaries the current evidence of AKI induced by the combination of VPT. VPT-induced AKI is a relatively common and high-risk adverse event in clinical practice, with occurrence rates varying across studies but often reaching 30% in critically ill patients. Its development significantly impacts patient morbidity, prolongs hospital stays, increases healthcare costs, and complicates treatment outcomes. Distinguishing true AKI from pseudo-AKI is

particularly urgent, as misclassification may lead to unnecessary treatment modifications or delays, potentially compromising patient recovery. The precise mechanism underlying VPT-induced AKI, whether attributed to heightened exposure to VAN, exacerbated vancomycin-induced oxidative stress injury by piperacillin, pseudo-nephrotoxicity mediated by VPT-induced impaired creatinine secretion, or a combination of the aforementioned mechanisms, remains elusive and warrants further investigation. Potential mechanisms and possible strategies to reduce the risk of VPT-associated AKI were summarized in Figure 7.

To address these challenges, further research is essential. Critical gaps include the need for validation of novel renal biomarkers such as NGAL, TIMP-2, and IGFBP7, which could enable earlier and more accurate detection of AKI. Additionally, more pharmacokinetic studies are required to understand vancomycin clearance when combined with TZP to optimize dosing and minimize toxicity. Finally, well-designed prospective trials comparing different β-lactam and vancomycin regimens are needed to determine the safest and most effective strategies, ultimately improving patient outcomes and reducing the incidence of VPT-induced AKI.

Based on current research, several strategies can help reduce the risk of VPT-associated AKI. First, while guidelines recommend an AUC range of 400 to 600 mg×h/L for vancomycin, it is advisable to pursue a more cautious target range of 400 to 515 mg×h/L when feasible. To support this, increasing the frequency of vancomycin TDM and incorporating additional renal function indicators can facilitate early detection of kidney injury. Additionally, minimizing the duration of combined VPT therapy may help decrease nephrotoxicity. Avoiding the concomitant use of other nephrotoxic medications whenever possible can further reduce AKI risk. Incorporating these measures into clinical practice can enhance the safety and efficacy of VPT therapy.

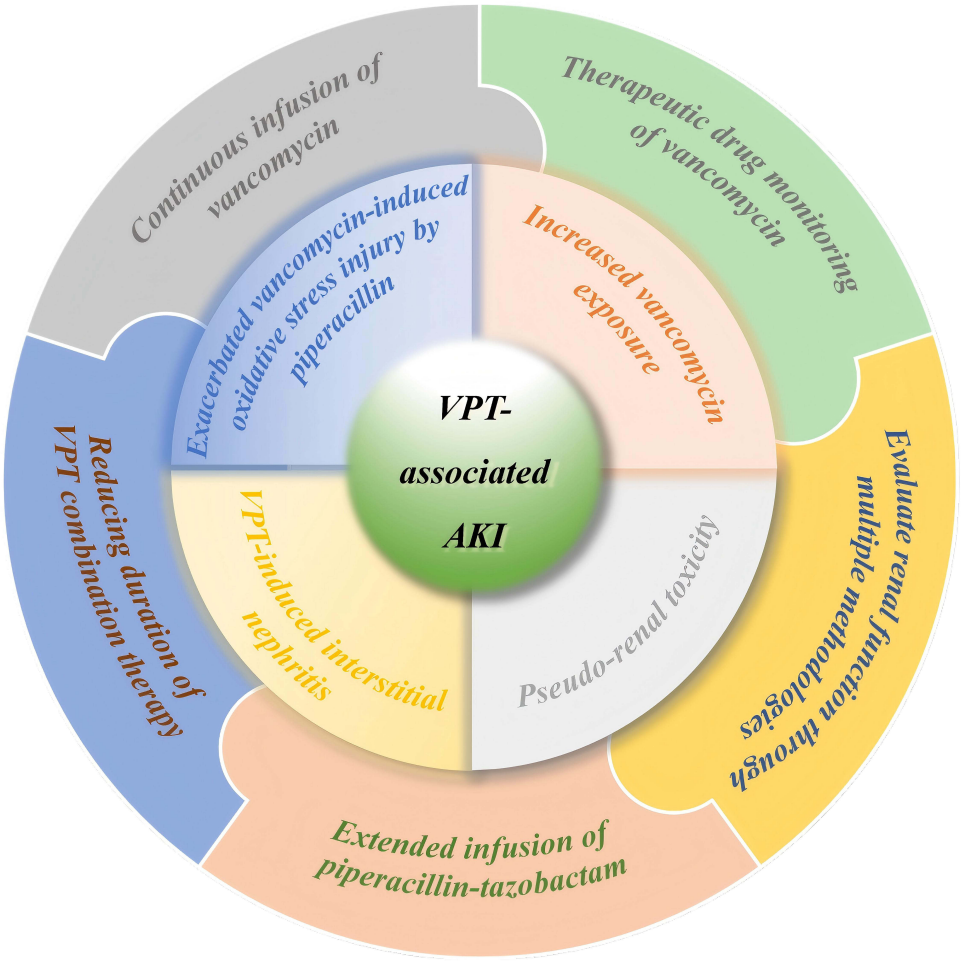

Figure 7 A summary of potential mechanisms and possible strategies to reduce the risk of VPT-associated AKI.

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Author Contributions

These authors contributed equally to this work and share first authorship (Dayu Chen, Jingjing Kan & Qiaoling Gu). All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. The funders had no role in the design of the study; in the collection, analyses, or interpretation of references; in the writing of the manuscript; or in the decision to publish the manuscript.

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