Piperacillin-tazobactam plus Vancomycin and Acute Kidney Injury

Introduction

1. Vancomycin and piperacillin-tazobactam are combined for broad-spectrum antibiotic coverage including MRSA and Pseudomonas in hospitalized patients.
2. AKI, often as acute tubular necrosis, is a known complication of vancomycin, especially with higher doses and co-administration of nephrotoxic drugs.
3. Piperacillin-tazobactam alone has minimal nephrotoxicity (<1%); its nephrotoxicity is usually due to acute interstitial nephritis.
4. Reported AKI rates vary in literature based on AKI definition and target population.
5. Both drugs affect OAT1/3 transporters in the kidney, which are crucial for creatinine clearance and are especially significant in patients with CKD.

Pharmacology		
	Vancomycin	**Piperacillin-tazobactam**[4]
Dose	• Depends on infection and PK/PD target • General dosing for systemic infections: IV 15-20 mg/kg IV Q8-12H for systemic infections	• Standard infusion: 3.375 g IV Q6H over 30 min • Antipseudomonal: 4.5 g IV Q6H over 30 min • Extended infusion: 4.5 g IV then 3.375 g over 4 hours Q8H
Administration	Administer IV over ≥60 minutes at concentrations ≤5 mg/mL to reduce the risk of vancomycin infusion reaction	Standard infusion: Infuse over 30 min Extended infusion: Infuse loading dose over 30 min, start maintenance dose four hours later infused over 4 hours
PK/PD	Negligible oral bioavailability T1/2 = 4-6 hours Renally eliminated (40-100% unchanged) AUC:MIC dependent kinetics, PK/PD target AUC/MIC ≥400 µg/mL; surrogate serum trough concentrations often used	T1/2 = 0.7-1.2 hours Renally eliminated (80% unchanged) Dose adjust at CrCl<40 T>MIC dependent kinetics, prolonged infusions enhance efficacy
Adverse Effects	Nephrotoxicity Ototoxicity Vancomycin-infusion reaction (flushing, hypotension, tachycardia)	GI upset (diarrhea, nausea, constipation) Headache Rash, pruritis
Drug Interactions and warnings	Substrate of OAT1/3 +/- Inducer of OAT1/3 ↑ nephrotoxicity: aminoglycosides, aspirin	Piperacillin: substrate and inhibitor of OAT1/3$^{\Delta}$, Tazobactam: substrate of OAT1/3 Interactions: Probenecid (↑ piperacillin-tazobactam), Methotrexate (↑ methotrexate)
Compatibility	Compatible with dextrose, NS, LR Incompatible with lipid emulsion	LR: only the formulation containing EDTA is compatible for Y-site administration Not chemically stable in solutions containing sodium bicarbonate or solutions that significantly alter pH Cannot be added to blood products or albumin hydrolysates
Comments	Serum troughs are a poor proxy of 24-hour AUC, trough-guided regimens have been shown to exceed the target AUC in 60% of adults[10]	Useful in the ED for anaerobic coverage in Grade III open fractures, pneumonia with lung abscess or empyema, and empiric antipseudomonal coverage in patients with risk factors

Δ = meropenem is also a substrate of OAT1/3 but not an inhibitor

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Overview of Evidence				
Author, year	**Design/ sample size**	**Intervention & Comparison**	**AKI definition**	**Outcome**
Sanz et al., 2002	Prospective, multi-center (n = 969)	Amikacin+cefepime vs. amikacin+piperacillin-tazobactam	• ↑ SCr ≥50% from baseline	• **No difference** in severe nephrotoxicity between amikacin+piperacillin-tazobactam vs. amikacin+cefepime
Karino et al., 2016	Retrospective cohort and nested case-control studies (n = 320)	Vancomycin+piperacillin-tazobactam standard infusion vs. Vancomycin+piperacillin-tazobactam extended-infusion	• RIFILE criteria • AKIN criteria • Vancomycin consensus guideline definition	• **AKI occurred in 33% of patients receiving** vancomycin+piperacillin-tazobactam • Use of extended infusion piperacillin-tazobactam did not increase risk of AKI • **Highest daily incidence of AKI occurred on day 5 of combination therapy**
Hammond et al., 2017	Meta-analysis of 14 observational studies (n = 3549)	Vancomycin+piperacillin-tazobactam vs. vancomycin+any β-lactam or vancomycin alone	All included studies used one of the following: • RIFLE criteria • AKIN criteria • ↑ SCr ≥100% or >0.5 mg/dL	• **Vancomycin+piperacillin-tazobactam greater association with AKI (aOR, 3.11; 95% CI, 1.77–5.47)** • Highest incidence of AKI in patients admitted to the ICU (OR 3.83 95% CI, 1.67-8.78)
Rutter et al., 2017	Retrospective matched cohort (n = 4103)	Vancomycin+piperacillin-tazobactam vs. vancomycin+cefepime	• RIFLE criteria	• **Vancomycin+piperacillin-tazobactam 2.18 times more likely to cause AKI** vs. vancomycin+cefepime (95% CI, 1.64–2.94) • Vancomycin doses between 3 and 4 g daily used,
Peyko et al., 2017	Prospective observational cohort (n = 85)	Vancomycin+piperacillin-tazobactam vs. vancomycin+cefepime or vancomycin+meropenem	• KDIGO	• **Incidence of AKI was higher in with vancomycin+piperacillin-tazobactam** vs. vancomycin+cefepime or meropenem (37.3% vs. 7.7% *P* = .005)
Rutter and Burgess et al., 2017	Retrospective matched cohort (n = 2448)	Vancomycin+piperacillin-tazobactam vs. Vancomycin+ampicillin-sulbactam	• RIFLE criteria	• **Increased risk of AKI with vancomycin+piperacillin-tazobactam (aOR, 1.77; 95% CI, 1.26–2.46), no increased rate of AKI with vancomycin+ampicillin-sulbactam** • Rates of AKI similar for piperacillin-tazobactam and ampicillin-sulbactam without vancomycin
Jeon et al., 2017	Retrospective matched cohort (n = 5335)	Vancomycin+piperacillin-tazobactam vs. vancomycin+cefepime	• ↑ SCr ≥0.3 mg/dL or ≥50% from baseline	• Vancomycin+piperacillin-tazobactam associated with a higher risk of AKI vs. vancomycin-cefepime (aHR, 1.25; 95% CI, 1.11–1.42.)
Mousavi et al., 2017	Retrospective matched cohort (n = 280)	Vancomycin+piperacillin-tazobactam standard infusion vs. Vancomycin+piperacillin-tazobactam extended-infusion	• RIFLE criteria • AKIN criteria	• **Similar rate of AKI between vancomycin+piperacillin-tazobactam standard infusion vs. vancomycin+piperacillin-tazobactam extended-infusion** • Higher vancomycin troughs were observed in the extended infusion group
Miano et al., 2022	Prospective, observational	Vancomycin+piperacillin-tazobactam vs. vancomycin+cefepime for ≥48 hours	↑ SCr vs. ↑ Cystatin C vs. ↑ BUN	• Vancomycin + piperacillin-tazobactam ➡ ↑ **serum creatinine-defined AKI, but no change in cystatin C, BUN, or AKI outcomes (dialysis/mortality).** • Indicates vancomycin + piperacillin-tazobactam AKI may be pseudotoxicity.
Qian et al, 2023 (ACORN Trial)	Randomized controlled Trial N=2511	Vancomycin+piperacillin-tazobactam vs. vancomycin+cefepime	KDIGO ↑ SCr ≥0.3 mg/dL or ≥50% from baseline	• The highest stage of acute kidney injury or death **was not significantly different** between the cefepime group and the piperacillin-tazobactam group • The incidence of major adverse kidney events at day 14 **did not differ between groups** (124 patients [10.2%] in the cefepime group vs 114 patients [8.8%] in the piperacillintazobactam group • ~77% of each concurrently received vancomycin

RIFLE, AKIN and KDIGO definitions of AKI are based upon ↑ in serum creatinine or ↓ in urine output

Conclusions

- Since 2011, evidence indicates combined vancomycin+ piperacillin-tazobactam may be nephrotoxic.
  - Most studies were retrospective, defining nephrotoxicity by creatinine-based AKI.
- Recent data show this AKI definition doesn't align with severe AKI outcomes (hemodialysis/mortality).
- Non-tubular secretion biomarkers (Cystatin C, BUN) didn't show the same AKI increase.
- **Despite >50 studies linking the drug combo with AKI, some expert report true renal risk is likely minimal.**
- In emergencies, timely antibiotic use is vital; nephrotoxicity concerns shouldn't delay this combo, especially for short use.

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