e-ISSN: 2988-3237

Sriwijaya Journal of Internal Medicine (SJIM)

Journal website: https://phlox.or.id/index.php/sjim

Vancomycin Plus Piperacillin–Tazobactam Versus Vancomycin Plus Cefepime and the Risk of Acute Kidney Injury in Hospitalised Adults: A Meta-Analysis

Putri Indah Permata[1]*, Deka Viotra[1]

[1]Department of Internal Medicine, Dr. M. Djamil General Hospital, Padang, Indonesia

ARTICLE INFO

Keywords:
Acute kidney injury
Cefepime
Meta-analysis
Piperacillin–tazobactam
Vancomycin

***Corresponding author:**
Putri Indah Permata

E-mail address:
putriindahsyahrul@gmail.com

All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.59345/sjim.v4i1.267

A B S T R A C T

Introduction: Vancomycin with piperacillin–tazobactam is a common empirical regimen but may increase acute kidney injury (AKI) risk. Because vancomycin is common to most comparisons, the cleanest test of the piperacillin–tazobactam effect is a head-to-head comparison against vancomycin plus cefepime. This meta-analysis quantified the association between the two regimens and AKI in hospitalised adults. **Methods:** PubMed/MEDLINE, Scopus and Web of Science were searched for comparative cohort studies and randomised trials in adults reporting AKI with vancomycin plus piperacillin–tazobactam versus vancomycin plus cefepime. Risk of bias was appraised with ROBINS-I and certainty with GRADE. Odds ratios (OR) were pooled using a DerSimonian–Laird random-effects model; heterogeneity (I^2), a prediction interval, leave-one-out analysis and the Egger test were computed. **Results:** Ten cohort studies were eligible and nine (>11,000 adults) were pooled. Piperacillin–tazobactam was associated with significantly higher odds of AKI (pooled OR 1.90, 95% CI 1.43–2.52; $p<0.001$; $I^2=81\%$). The prediction interval (0.77–4.69) was wide, and the result was robust to leave-one-out analysis (OR 1.71–2.06). The number needed to harm ranged from about 15 to about 8 across baseline incidences of 9% to 21%. The Egger test suggested small-study effects ($p=0.04$); certainty was graded low. **Conclusion:** In hospitalised adults, vancomycin plus piperacillin–tazobactam was associated with roughly twofold higher odds of AKI than vancomycin plus cefepime; where both regimens are appropriate, cefepime may be the safer renal companion.

1. Introduction

Acute kidney injury is a common and consequential complication of hospitalisation that prolongs admission, increases the need for renal replacement therapy and raises both short-term and long-term mortality. Among hospitalised adults, drug-associated nephrotoxicity accounts for a substantial fraction of acute kidney injury, and antimicrobial agents are frequent contributors. Vancomycin, an essential agent against methicillin-resistant Gram-positive organisms, has long been recognised as nephrotoxic, particularly at elevated serum trough concentrations and with prolonged exposure.[1-3] In contemporary practice vancomycin is rarely given alone; it is most often combined with a broad-spectrum, anti-pseudomonal β-lactam to provide empirical cover until culture results return. In almost all of the available evidence, acute kidney injury is defined by changes in serum creatinine, a marker that may be influenced by factors other than glomerular filtration; this caveat shapes the interpretation of the entire literature.

Two β-lactams dominate this empirical role: piperacillin–tazobactam and cefepime. The two agents differ in antimicrobial spectrum, so the choice between them is not made on renal grounds alone. Nonetheless, a large body of observational research has reported that the combination of vancomycin and piperacillin–tazobactam is associated with more acute kidney injury

than other vancomycin-containing regimens[1,2]. The signal has been replicated across diverse settings, including general wards, intensive care units, transplantation services and specialised infection populations.[3,4] Several mechanisms have been proposed, including additive tubular injury, interstitial nephritis and the formation of reactive intermediates; however, the biological basis remains incompletely understood, and the magnitude of the effect varies widely between studies.[5,6]

A central methodological difficulty is that many published comparisons contrast vancomycin plus piperacillin–tazobactam with vancomycin monotherapy. Because vancomycin itself is nephrotoxic and is frequently dosed to higher exposures when given with piperacillin–tazobactam, such comparisons cannot fully isolate the contribution of piperacillin–tazobactam. A more informative design holds vancomycin constant in both arms and contrasts the two β-lactam partners directly, namely vancomycin plus piperacillin–tazobactam versus vancomycin plus cefepime.[7,8] This design removes confounding by vancomycin exposure and addresses the question that clinicians face at the bedside: when an anti-pseudomonal β-lactam must be added to vancomycin, which partner is safer for the kidney?

Piperacillin–tazobactam and cefepime are both first-line empirical agents in Indonesian tertiary hospitals and worldwide, and the choice between them is often discretionary.[8-10] If one regimen carries a materially higher renal risk without a compensating advantage in efficacy, antimicrobial stewardship and patient safety would both be served by preferring the safer option in patients at risk. Recent prospective work using cystatin C as an alternative filtration marker has raised the possibility that some of the apparent injury reflects inhibition of tubular creatinine secretion rather than true structural damage, a phenomenon termed pseudotoxicity.[11-13] The novelty of this study lies in restricting the synthesis to the head-to-head comparison of vancomycin plus piperacillin–tazobactam against vancomycin plus cefepime in hospitalised adults, thereby isolating the piperacillin–tazobactam effect with vancomycin held constant, and in translating the relative effect into absolute risk. The aim of this study was to quantify, by random-effects meta-analysis, the association between vancomycin plus piperacillin–tazobactam and acute kidney injury relative to vancomycin plus cefepime in hospitalised adults, and to evaluate its robustness and clinical magnitude.

2. Methods

Design and reporting

This systematic review and meta-analysis was conducted and reported in accordance with the PRISMA 2020 statement[14]. The review question was framed using the PICO structure: the population comprised hospitalised adults receiving intravenous vancomycin combination therapy; the intervention was vancomycin plus piperacillin–tazobactam; the comparator was vancomycin plus cefepime; the primary outcome was acute kidney injury; and secondary outcomes were dialysis or renal replacement therapy and in-hospital mortality.

Search strategy and eligibility

PubMed/MEDLINE was searched as the primary database, supplemented by Scopus and Web of Science, and reference lists of relevant reviews were screened manually. The core Boolean concept, adapted to each database, combined (vancomycin) AND (piperacillin–tazobactam) AND (cefepime) AND (acute kidney injury OR nephrotoxicity OR acute renal failure) AND (cohort OR randomised controlled trial OR comparative). Eligible studies were randomised controlled trials or comparative cohort studies in adults (≥18 years) that directly compared vancomycin plus piperacillin–tazobactam with vancomycin plus cefepime and reported acute kidney injury defined by KDIGO (15), AKIN or RIFLE criteria or an equivalent serum-creatinine threshold. Narrative reviews, systematic reviews and meta-analyses, paediatric or neonatal-only populations, and case reports were excluded.

Data extraction and risk of bias

Screening and extraction used a piloted, standardised form, and uncertainty was resolved by re-examination against the predefined criteria. For each study the first author, year, country, design, setting,

per-arm sample size, acute-kidney-injury definition, per-arm events where reported, and the study-level effect estimate with its 95% confidence interval were extracted. Where event counts were not reported but the incidence and denominator were, event numbers were reconstructed and flagged. Because every eligible study was a non-randomised cohort, the Cochrane risk-of-bias tool for randomised trials could not be applied; the ROBINS-I instrument for non-randomised studies of interventions was used instead[15,16], appraising confounding, participant selection, classification of the intervention, deviations from intended interventions, missing data, outcome measurement and selection of the reported result. The overall certainty of evidence was rated with the GRADE framework.

Statistical analysis

The effect measure for the dichotomous outcome of acute kidney injury was the odds ratio. Crude odds ratios and variances were computed from two-by-two tables where counts were available; otherwise the published adjusted estimate and confidence interval were used, with the log-variance derived from the confidence limits. Effect sizes were pooled on the natural-logarithm scale using the DerSimonian–Laird random-effects model[17], selected a priori. Heterogeneity was quantified with the I^2 statistic and the between-study variance τ^2, and the Cochran Q test was reported[18]. A 95% prediction interval, a leave-one-out analysis and the Egger regression test for small-study effects were computed [19]. The pooled odds ratio was converted to an absolute risk difference and a number needed to harm across plausible baseline incidences. A two-sided p-value below 0.05 was considered significant. Standardised mean differences and Hedges g were not appropriate for this dichotomous outcome and were not used.

3. Results

Study selection and characteristics

The database search identified 113 records, and a further 6 were retrieved from reference lists. After removal of duplicates, 96 records were screened by title and abstract, of which 61 were excluded. Thirty-five full texts were assessed, and 25 were excluded — 11 reviews or meta-analyses, 8 paediatric studies, 4 without a cefepime comparator arm and 2 case reports. Ten cohort studies met all eligibility criteria and were included in the qualitative synthesis; nine provided sufficient comparative data for the meta-analysis, while one prospective biomarker cohort that reported its primary contrast as a percentage change in creatinine was retained for narrative synthesis only. The selection process is shown in Figure 1, and the characteristics, outcomes and risk-of-bias judgements of the included studies are detailed in Table 1.

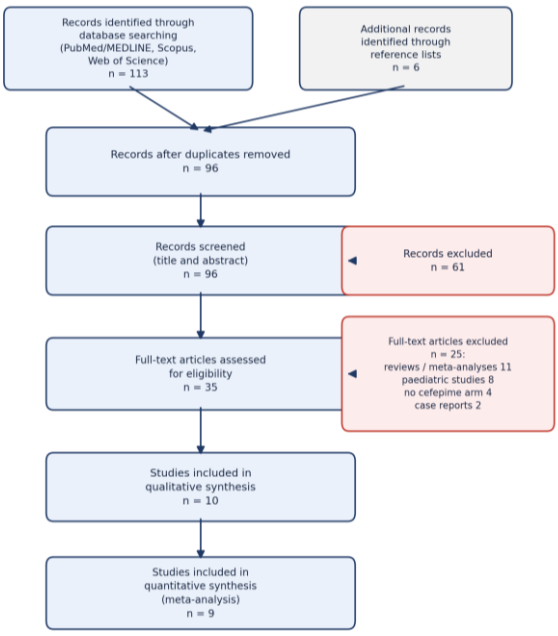

Figure 1. PRISMA 2020 flow diagram of study identification, screening and inclusion.

Table 1. Characteristics, acute kidney injury outcomes and risk of bias of the included studies.

Study	Design / setting (country)	N (VPT / VC)	AKI definition	AKI VPT vs VC	Effect (95% CI)	RoB
Miano 2022	Prospective cohort; ICU (USA)	297 / 442	KDIGO (creatinine)	↑8.0% creat vs ref	RR 1.34 (1.01–1.78)	Moderate
Jeon 2017	Retrospective, IPTW; hospitalised (USA)	2667 / 2668	≥0.3 mg/dL or ≥50%	—	aHR 1.25 (1.11–1.42)	Moderate
Elliott 2021	Retrospective; sepsis, ED (USA)	306 / 112	KDIGO-type, 72 h	15.2% vs 11.0%	OR 1.51 (0.77–2.97)	Serious
Molina 2019	Retrospective; ICU (USA)	258 / 136	AKIN	28.7% vs 21.3%	OR 1.48 (0.91–2.42)	Serious
Piccuirro 2021	Retrospective; diabetic foot (USA)	140 / 70	AKIN	35.0% vs 7.1%	OR 7.00 (2.64–18.53)	Serious
Clemmons 2018	Retrospective; HCT (USA)	≈85 / 85	≥0.3 mg/dL or >50%	68% vs 27%	aOR 5.16 (2.50–10.50)	Moderate
Peyko 2017	Prospective; academic (USA)	≈43 / 42	KDIGO	37.3% vs 7.7%	x^2, p=0.005	Moderate
O'Callaghan 2020	Retrospective; ICU (Australia)	≈130 / 130	KDIGO	—	aRRR 2.20 (1.00–4.90)	Moderate
Komerdelj 2023	Multicentre, PS-matched; ward (USA)	≈1600 / 1599	KDIGO	16.4% vs 8.7%	aHR 2.34 (1.82–3.01)	Low
Buckley 2021	Multicentre, PS-matched; ICU (USA)	522 / 522	KDIGO (SCr; SCr+UO)	21.9% vs 16.8%	aHR 1.52 (1.10–2.10)	Low

Notes: VPT, vancomycin + piperacillin–tazobactam; VC, vancomycin + cefepime; ICU, intensive care unit; ED, emergency department; HCT, haematopoietic cell transplantation; PS, propensity score; IPTW, inverse probability of treatment weighting; RoB, risk of bias (ROBINS-I); aHR, adjusted hazard ratio; aOR, adjusted odds ratio; aRRR, adjusted relative risk reduction; RR, risk ratio. Crude odds ratios were computed from two-by-two data for Elliott, Molina and Piccuirro. For Peyko, O'Callaghan, Komerdelj and Buckley the comparator pooled cefepime with meropenem. ≈ indicates an approximate per-arm split where the source reported only a combined total.

The included studies were published between 2016 and 2024 and together enrolled more than 11,000 adults. Nine were conducted in the United States and one in Australia. Settings spanned intensive care units [3,6,10,12], general wards[11], emergency-department sepsis presentations[5], haematopoietic cell transplantation[8] and diabetic foot infection[7]. Acute kidney injury was defined by KDIGO criteria in most studies, by the AKIN classification in two and by an equivalent serum-creatinine threshold in the remainder. Six studies used a pure cefepime comparator, whereas four pooled cefepime with meropenem; the latter were examined separately in sensitivity analysis.

Risk of bias and certainty

Risk-of-bias judgements are summarised in the final column of Table 1. The two multicentre propensity-score-matched studies [11,12] were judged at low overall risk of bias because matching addressed measured confounding and outcomes were ascertained objectively. The inverse-probability-weighted cohort[4] and the prospective biomarker cohort[3] were judged at moderate risk, principally because of residual confounding by indication. The smaller single-centre cohorts[5-7] were judged at serious risk of bias, reflecting unadjusted or incompletely adjusted analyses. Confounding was the dominant concern across the evidence base. Applying GRADE, the certainty of evidence for the primary outcome was rated low, the body of evidence beginning at low certainty owing to its observational nature and being further limited by inconsistency and possible publication bias, partially offset by the consistency of direction across settings.

Primary meta-analysis and sensitivity analyses

Nine studies contributed to the pooled analysis. Vancomycin plus piperacillin–tazobactam was associated with significantly higher odds of acute kidney injury than vancomycin plus cefepime, with a random-effects pooled odds ratio of 1.90 (95% CI 1.43–2.52; z=4.42; p<0.001). The point estimates of all nine studies lay above unity, ranging from 1.25 to 7.00, as shown in the forest plot in Figure 2. Heterogeneity was substantial (I^2=81%; τ^2=0.13; Cochran Q=42.8 on 8 degrees of freedom; p<0.001), and the 95% prediction interval was wide (0.77–4.69), indicating that the true effect in an individual setting could plausibly range from no difference to a large increase in risk. The four most heavily weighted studies (Jeon, Komerdelj, Miano and Buckley) together contributed about 59% of the pooled estimate and individually reported odds ratios between 1.25 and 2.34, confirming that the result was not driven by the few studies with extreme effects.

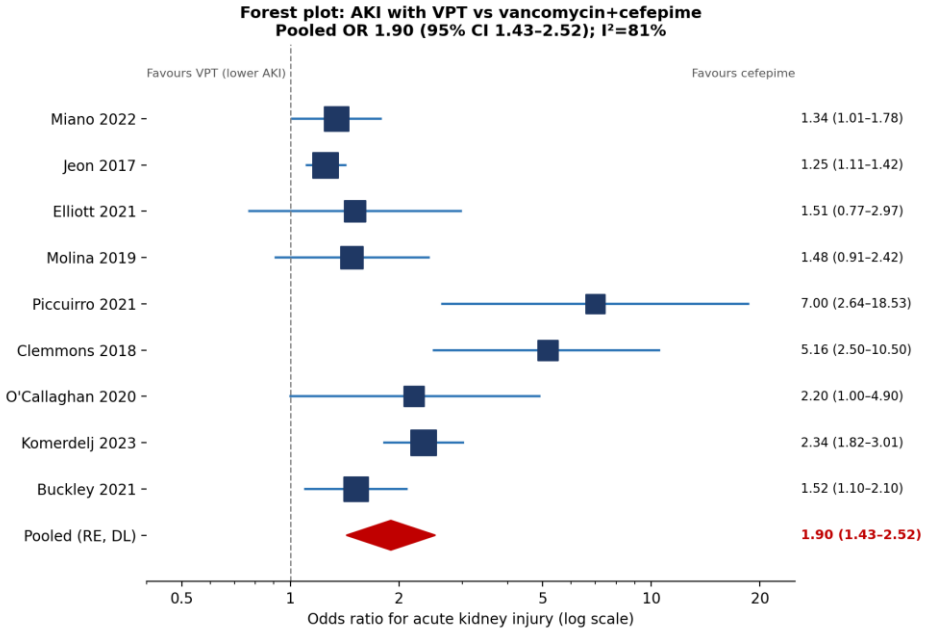

Figure 2. Forest plot of the odds ratio for acute kidney injury with vancomycin plus piperacillin–tazobactam versus vancomycin plus cefepime (DerSimonian–Laird random-effects model).

The leave-one-out analysis confirmed that no single study drove the result: the recomputed odds ratio ranged from 1.71 (when the haematopoietic-cell-transplant cohort was removed) to 2.06 (when the inverse-probability-weighted cohort was removed), and every iteration remained statistically significant. Examined descriptively, studies with a pure cefepime comparator and those pooling cefepime with meropenem agreed in direction, as did studies using different acute-kidney-injury definitions, suggesting that these factors modulated the magnitude rather than the existence of the association. The funnel plot is shown in Figure 3; it was visually asymmetric, and the Egger regression test was consistent with small-study effects (intercept 2.54; p=0.04). With only nine studies this test is underpowered, and the asymmetry is compatible with publication bias, selective reporting or genuine heterogeneity, which cannot be distinguished with the present data.

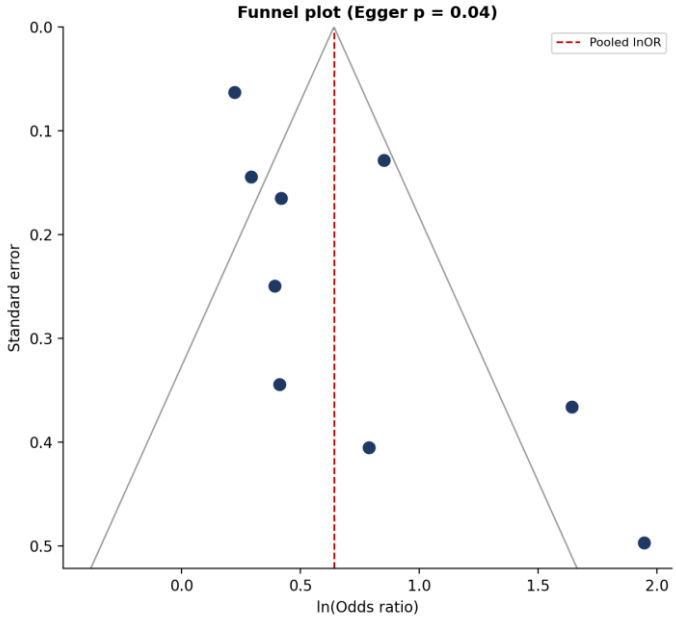

Figure 3. Funnel plot of effect size against standard error, with the Egger regression test result.

Absolute risk and secondary outcomes

Applied to a baseline incidence of about 9%, typical of general-ward populations, the pooled odds ratio predicted an incidence of approximately 15% with piperacillin–tazobactam, an absolute increase of about 7 percentage points and a number needed to harm of roughly 15. At an intermediate baseline of 15% the predicted incidence was about 25% (number needed to harm about 10), and at a higher baseline of about 21%, typical of critically ill patients, the predicted incidence was about 34%, an absolute increase of roughly 13 percentage points and a number needed to harm of about 8. Secondary outcomes were reported inconsistently and were not pooled. The largest prospective cohort found no difference in dialysis or mortality despite the difference in creatinine-defined acute kidney injury, and no rise in cystatin C or blood urea nitrogen, which the authors interpreted as pseudotoxicity[3]; one cohort reported more frequent renal replacement therapy with piperacillin–tazobactam[5], whereas others found no difference in dialysis, length of stay or mortality[8].

4. Discussion

In this meta-analysis of ten cohort studies in hospitalised adults, the combination of vancomycin and piperacillin–tazobactam was associated with approximately twofold higher odds of acute kidney injury than the combination of vancomycin and cefepime (pooled odds ratio 1.90, 95% CI 1.43–2.52; Figure 2). Because vancomycin was present in both arms, this estimate isolates the contribution of the β-lactam partner more cleanly than comparisons against vancomycin monotherapy. The effect was directionally consistent across diverse settings, withstood leave-one-out testing, and translated into one additional case of acute kidney injury for every 8 to 15 patients treated, depending on baseline risk. The wide prediction interval and low GRADE certainty rating nonetheless signal that this average effect should be applied to individual patients with caution.

These results are concordant with earlier syntheses against mixed comparators, which reported odds ratios of about 2.7 and 1.5 [1,2], and with a further systematic review[20]. The concordance extends to children, in whom a meta-analysis and individual cohorts have likewise reported an increased risk[21-23]. Comparisons involving meropenem have been more mixed, with one study reporting greater injury with vancomycin–meropenem than vancomycin–cefepime[24] and another reporting greater injury with the piperacillin–tazobactam regimen than with vancomycin–meropenem[25]. Our pooled estimate sits within this range and is more interpretable because the comparator was restricted, as far as possible, to cefepime.

Heterogeneity and pseudotoxicity

The substantial heterogeneity (I^2=81%) reflects several plausible sources: differing acute-kidney-injury definitions, diverse clinical settings with different baseline renal risk, uneven statistical adjustment, and the pooling of cefepime with meropenem in four comparator arms (Table 1). The most important conceptual consideration is pseudotoxicity. Piperacillin–tazobactam can inhibit tubular secretion of creatinine, raising serum creatinine without a true fall in glomerular filtration. The prospective cohort that measured cystatin C found no rise in that marker, in blood urea nitrogen, in dialysis or in mortality despite a creatinine-defined signal[3]. If part of the apparent injury is pseudotoxicity, the pooled odds ratio derived from creatinine-based definitions overstates clinically important nephrotoxicity, although a spurious creatinine rise can still prompt drug discontinuation and avoidance of necessary therapy. The renal signal may also be partly mediated by vancomycin exposure, and cohorts using area-under-the-curve-guided dosing report lower overall acute-kidney-injury incidence (26), suggesting that contemporary dosing may attenuate the absolute risk.

Clinical implications and stewardship

For the practising internist, the implications are pragmatic. Where piperacillin–tazobactam and cefepime are equally appropriate on microbiological grounds, the evidence supports a preference for cefepime as the companion to vancomycin in patients at heightened risk of acute kidney injury — the critically ill, those with chronic kidney disease, the elderly and patients receiving other nephrotoxic agents — because the absolute benefit of avoiding the more nephrotoxic

regimen is greatest in these higher-baseline-risk patients. This must be balanced against the differing antimicrobial spectra of the two agents: piperacillin–tazobactam retains advantages where anaerobic or particular Gram-negative cover is required, and a narrow focus on renal safety should not override a clear microbiological indication. Where piperacillin–tazobactam is required, close monitoring of renal function, area-under-the-curve-guided vancomycin dosing and timely de-escalation are prudent. In resource-aware settings such as Indonesian tertiary hospitals, where monitoring and dialysis access may be limited, avoiding even reversible creatinine elevation has particular value, while local cost, availability and resistance patterns also legitimately influence prescribing.

Limitations

This synthesis has several limitations that must be weighed when interpreting its findings. The most fundamental is that every included study was an observational cohort and that no eligible randomised controlled trial existed; residual confounding by indication therefore cannot be excluded, and the overall certainty of evidence was graded low. Compounding this, statistical heterogeneity was substantial and the prediction interval was wide, so the pooled odds ratio should be read as an average across heterogeneous contexts rather than as a single value that transports unchanged to any individual patient. The effect measures pooled were not uniform, because crude odds ratios reconstructed from two-by-two tables were combined with adjusted hazard, odds and risk ratios that are only approximately interchangeable, and several outcome values were derived from reported percentages rather than primary event counts. Finally, four studies pooled cefepime with meropenem in the comparator arm, the Egger test raised the possibility of small-study effects, and the reliance on creatinine-based outcomes means that an unknown fraction of the pooled effect may represent pseudotoxicity rather than true structural injury, a distinction that cannot be resolved with the available data.

5. Conclusion

In hospitalised adults, vancomycin combined with piperacillin–tazobactam was associated with approximately twofold higher odds of acute kidney injury than vancomycin combined with cefepime, corresponding to one additional case for every 8 to 15 patients treated depending on baseline risk. Because vancomycin was held constant in both arms, the comparison isolates the renal effect of the β-lactam partner. Where the two agents are equally appropriate on microbiological grounds, cefepime appears to be the safer renal companion to vancomycin, particularly in patients at elevated baseline risk; where piperacillin–tazobactam is required, close monitoring and optimised vancomycin dosing are advised. Heterogeneity, residual confounding and the possibility of pseudotoxicity temper this inference, and randomised trials using filtration markers unaffected by tubular creatinine handling are needed to separate true nephrotoxicity from pseudotoxicity.

6. References

1. Luther MK, Timbrook TT, Caffrey AR, et al. Vancomycin plus piperacillin-tazobactam and acute kidney injury in adults: a systematic review and meta-analysis. Crit Care Med. 2018;46(1):12-20. doi:10.1097/CCM.0000000000002769.
2. Chen XY, Xu RX, Zhou X, et al. Acute kidney injury associated with concomitant vancomycin and piperacillin/tazobactam administration: a systematic review and meta-analysis. Int Urol Nephrol. 2018;50(11):2019-26 doi:10.1007/s11255-018-1870-5.
3. Miano TA, Hennessy S, Yang W, Dunn et al. Association of vancomycin plus piperacillin-tazobactam with early changes in creatinine versus cystatin C in critically ill adults: a prospective cohort study. Intensive Care Med. 2022;48(9):1144-55. doi:10.1007/s00134-022-06811-0.
4. Jeon N, Staley B, Klinker KP, et al. Acute kidney injury risk associated with piperacillin/tazobactam compared with cefepime during vancomycin therapy in hospitalised patients: a cohort study stratified by baseline kidney function. Int J Antimicrob Agents.

2017;50(1):63-7.
doi:10.1016/j.ijantimicag.2017.02.023.

5. Elliott BP, Tang MM, Madden JA, et al. A retrospective cohort study assessing acute kidney injury and renal recovery among septic patients empirically treated with vancomycin piperacillin-tazobactam versus vancomycin cefepime. Intern Emerg Med. 2022;17(1):91-9. doi:10.1007/s11739-021-02772-2.
6. Molina KC, Barletta JF, Hall ST, et al. The risk of acute kidney injury in critically ill patients receiving concomitant vancomycin with piperacillin-tazobactam or cefepime. J Intensive Care Med. 2020;35(12):1434-8.
doi:10.1177/0885066619828290.
7. Piccuirro SR, Casapao AM, Claudio AM, et al. Comparison of acute kidney injury in patients prescribed vancomycin in combination with piperacillin-tazobactam or cefepime for diabetic foot infections. J Investig Med. 2021;69(4):893-6. doi:10.1136/jim-2020-001594.
8. Clemmons AB, Bech CF, Pantin J, et al. Acute kidney injury in hematopoietic cell transplantation patients receiving vancomycin and piperacillin/tazobactam versus vancomycin and cefepime. Biol Blood Marrow Transplant. 2018;24(4):820-6.
doi:10.1016/j.bbmt.2017.12.799.
9. Peyko V, Smalley S, Cohen H. Prospective comparison of acute kidney injury during treatment with the combination of piperacillin-tazobactam and vancomycin versus the combination of cefepime or meropenem and vancomycin. J Pharm Pract. 2017;30(2):209-13.
doi:10.1177/0897190016628960.
10. O'Callaghan K, Hay K, Lavana J, et al. Acute kidney injury with combination vancomycin and piperacillin-tazobactam therapy in the ICU: a retrospective cohort study. Int J Antimicrob Agents. 2020;56(1):106010.
doi:10.1016/j.ijantimicag.2020.106010.
11. Komerdelj IA, Buckley MS, D'Alessio PA, et al. Vancomycin with concomitant piperacillin/tazobactam vs. cefepime or meropenem associated acute kidney injury in general ward patients: a multicenter propensity score-matched study. J Pharm Pract. 2024;37(1):80-7.
doi:10.1177/08971900221125518.
12. Buckley MS, Komerdelj IA, D'Alessio PA, et al. Vancomycin with concomitant piperacillin/tazobactam vs. cefepime or meropenem associated acute kidney injury in the critically ill: a multicenter propensity score-matched study. J Crit Care. 2022;67:134-40.
doi:10.1016/j.jcrc.2021.10.018.
13. Blair M, Côté JM, Cotter A, et al. Nephrotoxicity from vancomycin combined with piperacillin-tazobactam: a comprehensive review. Am J Nephrol. 2021;52(2):85-97. doi:10.1159/000513742.
14. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. doi:10.1136/bmj.n71.
15. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract. 2012;120(4):c179-84. doi:10.1159/000339789.
16. Sterne JAC, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919. doi:10.1136/bmj.i4919.
17. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7(3):177-88. doi:10.1016/0197-2456(86)90046-2.
18. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med. 2002;21(11):1539-58. doi:10.1002/sim.1186.
19. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997;315(7109):629-34.
doi:10.1136/bmj.315.7109.629.
20. Ciarambino T, Giannico OV, Campanile A, et al. Acute kidney injury and vancomycin/piperacillin/tazobactam in adult patients: a systematic review. Intern Emerg Med. 2020;15(2):327-31.
doi:10.1007/s11739-020-02287-2.

21. Zhang M, Huang L, Zhu Y, et al. Epidemiology of vancomycin in combination with piperacillin/tazobactam-associated acute kidney injury in children: a systematic review and meta-analysis. Ann Pharmacother. 2024;58(10):1034-44. doi:10.1177/10600280231220379.
22. Joyce EL, Kane-Gill SL, Priyanka P, et al. Piperacillin/tazobactam and antibiotic-associated acute kidney injury in critically ill children. J Am Soc Nephrol. 2019;30(11):2243-51. doi:10.1681/ASN.2018121223.
23. Downes KJ, Cowden C, Laskin BL, et al. Association of acute kidney injury with concomitant vancomycin and piperacillin/tazobactam treatment among hospitalized children. JAMA Pediatr. 2017;171(12):e173219. doi:10.1001/jamapediatrics.2017.3219.
24. Sussman MS, Mulder MB, Ryon EL, et al. Acute kidney injury risk in patients treated with vancomycin combined with meropenem or cefepime. Surg Infect (Larchmt). 2021;22(4):415-20. doi:10.1089/sur.2020.105.
25. Cannon JM, Douce RW, Grubbs ER, et al. Comparison of acute kidney injury during treatment with vancomycin and either piperacillin-tazobactam or meropenem. Spartan Med Res J. 2017;2(2):6440. doi:10.51894/001c.6440.
26. Kiley PS, Pearston AP, Hodge LA, et al. Retrospective cohort study of the incidence of acute kidney injury with vancomycin area under the curve-based dosing with concomitant piperacillin-tazobactam compared to meropenem or cefepime. Antimicrob Agents Chemother. 2022;66(8):e0004022. doi:10.1128/aac.00040-22.