Acute kidney injury associated with concomitant use of vancomycin with piperacillin-tazobactam: a focused review and meta-analysis

Hatice Duygu Bas MD, Kazim Baser MD, Shengping Yang PhD

ABSTRACT

Acute kidney injury (AKI) occurs frequently during the administration of certain medications in hospitalized patients and increases morbidity and mortality. The vancomycin and piperacillin/tazobactam combination is one of the most commonly used empiric antibiotic regimens in hospitalized patients to provide adequate coverage of drug-resistant pathogens. Recent studies suggest that this combination may be associated with more AKI than vancomycin monotherapy or vancomycin in combination with other antibiotics. We performed a literature review with a meta-analysis of published studies to evaluate the possible association between combination therapy with vancomycin and piperacillin/tazobactam and higher rates of AKI. Although the studies were heterogeneous, the meta-analysis suggests a higher rate of AKI with the concurrent use of piperacillin/tazobactam and vancomycin compared to vancomycin monotherapy or vancomycin combination with cefepime or meropenem. Prospective, randomized studies with larger sample sizes across multiple centers, controlling for potential confounding factors, are needed to validate this association.

Key words: vancomycin, piperacillin-tazobactam, nephrotoxicity, acute kidney injury, meta-analysis

INTRODUCTION

Combinations of vancomycin and anti-pseudomonal β-lactam antibiotics, such as piperacillin-tazobactam, are commonly prescribed empiric antibiotics in patients with sepsis due to a variety of infectious sources to cover drug-resistant pathogens. The combination of vancomycin and piperacillin-tazobactam is the most frequently used empiric antibiotic regimen in many institutions in the United States[1, 2], and there is increasing concern about its potential nephrotoxicity. In this focused review, the results and limitations of the published studies investigating the possible association between the concurrent use of vancomycin and piperacillin-tazobactam and higher rates of acute kidney injury (AKI) are summarized. We also performed a meta-analysis of published studies to evaluate the nephrotoxicity risk of this combination therapy.

Corresponding author: Hatice Duygu Bas MD
Contact Information: h.duygu.baser @ttuhsc.edu
DOI: 10.12746/swrccc 2016.0415.198

VANCOMYCIN AND VANCOMYCIN-INDUCED NEPHROTOXICITY

Vancomycin is a cornerstone antibiotic in the management of severe Gram-positive infections involving methicillin-resistant Staphylococcus aureus (MRSA). Despite the recent availability of alternative agents, vancomycin remains the first-line treatment for infections due to MRSA, and its usage has dra-

matically increased given the explosion of MRSA infections in both community and health care settings. [3-5]

Vancomycin-induced nephrotoxicity is well documented in the literature, and its incidence ranges from 5% to 35%, depending on the presence or absence of other risk factors, the population studied, and the definition of nephrotoxicity.[3-5] Risk factors for vancomycin-induced nephrotoxicity include high trough vancomycin levels (15 mg/L or higher, in particular 20 mg/L or higher), a daily vancomycin dose greater than 4 g, prolonged duration of therapy (particularly more than 7 days), a history of kidney disease, greater underlying severity of illness (e.g.,sepsis, major surgery, burns),and concomitant use of other nephrotoxic medications.[3-5] Although vancomycin-induced nephrotoxicity is generally reversible in most cases after discontinuation of vancomycin, nephrotoxicity is associated with longer hospital stays and poorer outcomes. [3, 4]

As the relationship between serum vancomycin concentration and treatment success or failure in *S. aureus* infection is well known, more intensive vancomycin dosing to maintain troughs between 15 mg/liter and 20 mg/liter for serious MRSA infections has been recommended by recent expert guidelines.[6] However, only limited data suggest that the maintenance of vancomycin trough values between 15 and 20 mg/liter improves outcomes.[3, 6, 7] Furthermore, there is a growing concern about higher rates of vancomycin-induced nephrotoxicity with the wide-spread use of these more-intensive vancomycin regimens. [3] In a recent meta-analysis of the fifteen studies evaluating vancomycin nephrotoxicity, higher troughs (>15 mg/liter) compared with lower trough levels (< 15 mg/liter) were associated with an increased odds of nephrotoxicity (odds ratio [OR], 2.67; 95% confidence interval [CI], 1.95 to 3.65).[3]

Piperacillin-tazobactam

Piperacillin-tazobactam is a beta-lactam antibiotic frequently used as empiric or targeted therapy for hospitalized patients who have risk factors for *Pseudomonas aeruginosa* or other multi-drug resistant Gram-negative organisms. In contrast to vancomycin, beta-lactam antibiotics are not usually associated with nephrotoxicity.[8, 9] Case reports and case-control studies in the literature have reported acute interstitial nephritis (AIN) with beta-lactam antibiotics, including piperacillin-tazobactam.[8, 9] Overall, it is associated with an incidence of AKI of less than 1% according to the piperacillin-tazobactam package insert lists.[10] However, higher rates of AKI have been recently reported when it is used in combination with vancomycin.[11-14]

AKI associated with concomitant use of vancomycin with piperacillin-tazobactam

To review the available data, a PubMed search was conducted using the following MeSH terms: vancomycin, piperacillin/tazobactam, acute kidney injury, nephrotoxicity. The reference lists from relevant articles were also reviewed to identify articles not indexed in PubMed. Only full, peer-reviewed articles were included since abstracts did not provide adequate details on methods and results. Using this search strategy, seven studies were found which investigated the association between combination therapy with vancomycin and piperacillin/tazobactam and the rates of acute kidney injury (Table).

Among the seven studies, five were retrospective, single-center cohort studies investigating the possible association mostly in non-critically ill hospitalized patients.[11-15] In four of these studies, a higher proportion of patients who received concomitant vancomycin and piperacillin-tazobactam developed AKI than those who received vancomycin alone or in combination with cefepime.[11-14] In the other study, 139 diabetic patients with osteomyelitis were included; the rate of nephrotoxicity was not significantly higher in patients receiving vancomycin-piperacillin/tazobactam than in those receiving vancomycin-cefepime.[15] In this study, the only significant predictors of AKI in a multiple logistic regression analysis were patient weight and average vancomycin trough levels. All these studies included patients who received antibiotic therapies for

Table *Details of studies investigating the occurrence of AKI associated with concurrent use of vancomycin and piperacillin/tazobactam*

Study	Number of patients	Design Patient groups (n)	AKI incidence (n, %)	AKI risk unadjusted OR (95% CI)	AKI adjusted OR (95% CI)
Burgess[11]	191	Retrospective, one center vancomycin/piperacillin-tazobactam (92) vs vancomycin (99)	Vancomycin/ piperacillin-tazobactam (15 out of 92, 16.3%) vs vancomycin (8 out of 99, 8.1%) (p=0.041)	2.22 (0.89-5.51)	2.48 (> 1.11)
Gomes [12]	224	Retrospective, one center vancomycin /piperacillin-tazobactam (112) vs vancomycin / cefepime (112)	Vancomycin/ piperacillin-tazobactam (39 out of 112, 34.8%) vs vancomycin /cefepime (14 out of 112, 12.5%) (p<0.0001)	3.74 (1.89–7.39)	5.67 (1.66–19.33)
Meaney[13]	125	Retrospective, one center vancomycin /piperacillin-tazobactam (58) vs vancomycin (67)	Vancomycin /piperacillin-tazobactam (13 out of 58, 22%) vs vancomycin (4 out of 67, 6%)	4.55 (1.39–14.9)	5.36 (1.41–20.5)
Kim[14]	228	Retrospective, one center vancomycin /piperacillin-tazobactam (101) vs vancomycin (101) vs piperacillin-tazobactam (26)	Vancomycin/ piperacillin-tazobactam (19 out of 101, 18.8%) vs vancomycin (4 out of 101, 4 %)	5.62 (1.84-17.2)	7.14(1.92-25)
Moenster[15]	139	Retrospective, one center vancomycin/piperacillin-tazobactam (109) vs vancomycin /cefepime (30)	Vancomycin/piperacillin-tazobactam (32 out of 109, 29%) vs vancomycin /cefepime (4 out of 30, 13%) (p= 0.099)	2.70 (0.87-8.37)	3.45 (0.96–12.40)
Hammond[16]	122	Retrospective, one center, in critically ill patients vancomycin/piperacillin-tazobactam(49)vs vancomycin / cefepime (73)	Vancomycin/piperacillin-tazobactam(16 out of 49, %32) vs vancomycin /cefepime (21 out of 73, %28)	1.20 (0.55-2.63)	NA
Peyko[17]	85	Prospective, one center vancomycin/piperacillin-tazobactam(59 vs vancomycin/ cefepime or meropenem (26)	Vancomycin/piperacillin-tazobactam (22 out of 59, %37) s vancomycin/ cefepime or meropenem (2 out of 26, 7.7%)	7.14 (1.54-33.15)	NA

AKI- acute kidney injury, vanco- vancomycin, OR- odds ratio, Cl- confidence interval, NA- not available

at least 48 or 72 hours, and most of the cases were non-critically ill hospitalized patients. The presence of renal impairment was an exclusion criterion in most of the studies, but the exact criteria differed with each study.[11-13, 15] The definition of nephrotoxicity was similar among the studies, which was an increase in serum creatinine by 0.5 mg/dL or ≥ 1.5 times baseline.

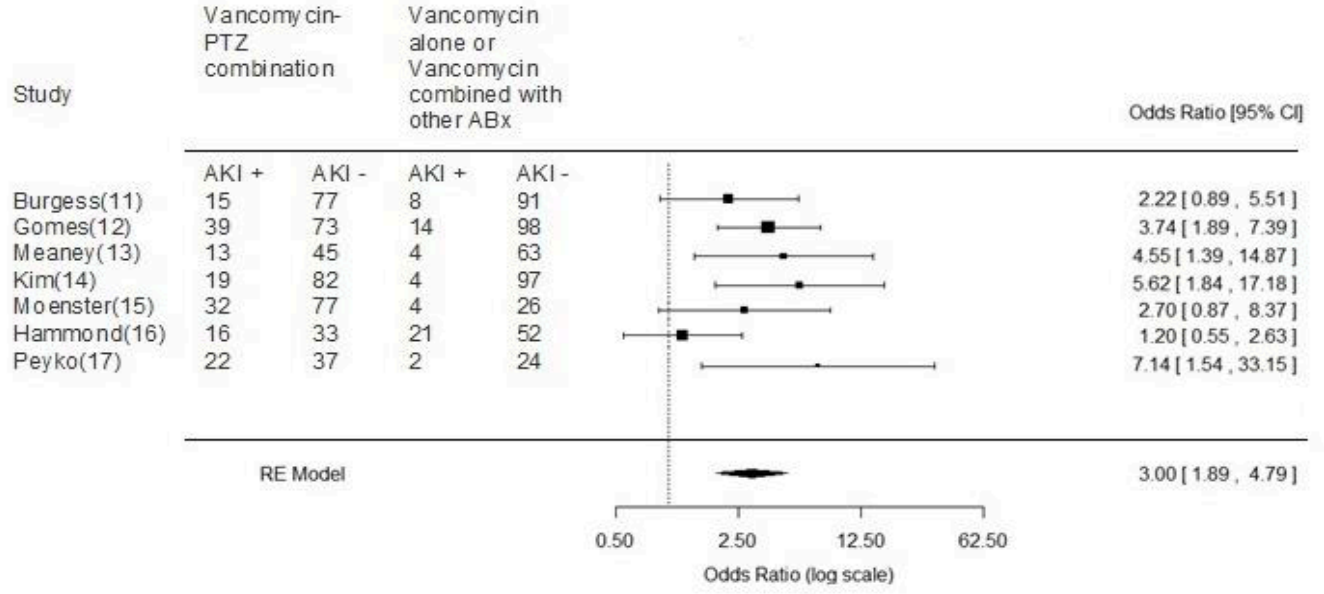
The possible association between the combination therapy and AKI was also evaluated in critically ill patients in a retrospective, single center study. [16] A total of 122 critically ill patients without baseline renal dysfunction who received at least 48 hours of combination therapy with vancomycin and piperacillin-tazobactam (49 patients) or vancomycin and cefepime (73 patients) were included in this study. There was no statistically significant difference in the incidence of AKI between patients given vancomycin in combination with piperacillin-tazobactam and those given vancomycin with cefepime.[16] Secondary outcomes, including the length of stay in the intensive care unit, the length of hospital stay, AKI duration, and the need for renal replacement therapy, did not differ according the choice of β-lactam antibiotic combined with vancomycin.[16] Patients who were receiving renal replacement therapy at the initiation of the antibiotic therapy, who had an estimated creatinine clearance of less than 60 ml/minute according to the Cockcroft- Gault equation at hospital admission or at the initiation of antibiotics, and who had structural kidney disease were excluded from the study. Therefore, the potential nephrotoxicity of these combinations remains to be evaluated in critically ill patients with all degrees of stable renal function in prospective studies.

There is only one prospective study evaluating the risk of AKI in adult patients receiving the combination of piperacillin-tazobactam and vancomycin versus the combination of cefepime or meropenem and vancomycin for greater than 72 hours.[17] Eighty-five patients in a single center receiving either antimicrobial combination were evaluated for AKI. The incidence of AKI was significantly higher in the piperacillin-tazobactam and vancomycin group (37.3%) compared with the cefepime or meropenem and vancomycin group (7.7%; χ^2 = 7.80, P = 0.005).[17]

Reasult of meta-analysis

The seven studies discussed above investigating the possible association between the combination therapy with vancomycin and piperacillin-tazobactam and higher rates of AKI were included in a meta-anal-

Figure Meta-analysis of the published studies



Abx- antibiotic, AKI- acute kidney injury, Cl- confidence interval, PTZ- piperacillin-tazobactam

ysis; the primary outcome was incidence of AKI (Figure). Although the studies were heterogeneous, the odds ratio for developing AKI with combination therapy with vancomycin and piperacillin-tazobactam was 3.00 (95% CI 1.89 to 4.79, I^2: 35.72%, with 95% CI 0.0-85.79%) in the meta-analysis.

Mechanisms for nephrotoxicity associated with vancomycin and piperacillin-tazobactam combination

The underlying mechanisms for increased AKI rates with the concurrent use of vancomycin and piperacillin-tazobactam are unclear. Vancomycin's nephrotoxic potential may be increased when it is combined with piperacillin- tazobactam similar to the addition of aminoglycosides to vancomycin. It has been previously shown that vancomycin combined with an aminoglycoside could be four times as nephrotoxic as vancomycin alone. [18] Animal and human studies suggest that vancomycin-induced nephrotoxicity occurs through destruction of glomeruli and accumulation of the drug in the proximal renal tubule leading to cellular necrosis via different mechanisms, including increased production of reactive oxygen species causing oxidative stress and complement mediated inflammation.[3-5, 19, 20] Semi-synthetic penicillins, including piperacillin/tazobactam, may cause AKI through AIN mediated mechanism. The nephrotoxicity mechanisms for these antibiotics, i.e., interstitial nephritis and direct cellular necrosis, may accelerate or potentiate one another, but more studies are needed to evaluate this possible interaction. [12,16]

Conclusions

Several studies suggest an increased risk of AKI with concurrent use of vancomycin and piperacillin/tazobactam. The research studies investigating this association have significant limitations. New prospective, randomized studies with larger sample sizes across multiple centers, controlling for potential confounding factors, are needed to validate this association. Until clear evidence becomes available, healthcare professionals should use caution before starting vancomycin- piperacillin/tazobactam combination as an empiric antibiotic therapy. All patients should be evaluated individually for the potential source of infection, comorbidities associated with a higher risk of AKI development, including the presence of DM, sepsis or preexisting renal disease, older age, being in a non-critical care or critical care unit, and concomitant use of nephrotoxic drugs. Early signs of renal impairment like oliguria, renal function, and vancomycin trough levels should be monitored in patients receiving this combination. The use of concomitant nephrotoxic agents should also be avoided if possible to reduce additive toxicities.

Author Affiliations: Hatice Duygu Bas and Kazim Baser are residents in Internal Medicine at Texas Tech University Health Sciences Center in Lubbock, TX. Shengping Yang is biostatistician in the Department of Pathology at TTUHSC in Lubbock, TX.
Submitted: 5/9/2016
Accepted: 6/9/2016
Reviewers: Kristen Fuhrmann Pharm D, Richard Winn MD
Published electronically: 7/15/2016
Conflict of Interest Disclosures: None

References

1. MacDougall C, Polk RE. Variability in rates of use of antibacterials among 130 US hospitals and risk-adjustment models for interhospital comparison. Infection control and hospital epidemiology 2008; 29(3): 203-11.
2. Pakyz AL, MacDougall C, Oinonen M, Polk RE. Trends in antibacterial use in US academic health centers: 2002 to 2006. Archives of internal medicine 2008; 168(20): 2254-60.
3. van Hal SJ, Paterson DL, Lodise TP. Systematic review and meta-analysis of vancomycin-induced nephrotoxicity associated with dosing schedules that maintain troughs between 15 and 20 milligrams per liter. Antimicrobial agents and chemotherapy 2013; 57(2): 734-44.
4. Elyasi S, Khalili H, Dashti-Khavidaki S, Mohammadpour A. Vancomycin-induced nephrotoxicity: mechanism, incidence, risk factors and special populations. A literature review. European journal of clinical pharmacology 2012; 68(9): 1243-55.
5. Gupta A, Biyani M, Khaira A. Vancomycin nephrotoxicity: myths and facts. The Netherlands journal of medicine 2011; 69(9): 379-83.
6. Rybak M, Lomaestro B, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists 2009; 66(1): 82-98.
7. Kullar R, Davis SL, Taylor TN, Kaye KS, Rybak MJ. Effects of targeting higher vancomycin trough levels on clinical outcomes and costs in a matched patient cohort. Pharmacotherapy 2012; 32(3): 195-201.
8. McCormick H, Tomaka N, Baggett S, et al. Comparison of acute renal injury associated with intermittent and extended infusion piperacillin/tazobactam. American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists 2015; 72(11 Suppl 1): S25-30.
9. Pill MW, O'Neill CV, Chapman MM, Singh AK. Suspected acute interstitial nephritis induced by piperacillin-tazobactam. Pharmacotherapy 1997; 17(1): 166-9.
10. Zosyn (Piperacillin-tazobactam) package insert. Wyeth Pharma- ceuticals Inc. Philadelphia P.
11. Burgess LD, Drew RH. Comparison of the incidence of vancomycin-induced nephrotoxicity in hospitalized patients with and without concomitant piperacillin-tazobactam. Pharmacotherapy 2014; 34(7): 670-6.
12. Gomes DM, Smotherman C, Birch A, et al. Comparison of acute kidney injury during treatment with vancomycin in combination with piperacillin-tazobactam or cefepime. Pharmacotherapy 2014; 34(7): 662-9.
13. Meaney CJ, Hynicka LM, Tsoukleris MG. Vancomycin-associated nephrotoxicity in adult medicine patients: incidence, outcomes, and risk factors. Pharmacotherapy 2014; 34(7): 653-61.
14. Kim T, Kandiah S, Patel M, et al. Risk factors for kidney injury during vancomycin and piperacillin/tazobactam administration, including increased odds of injury with combination therapy. BMC research notes 2015; 8: 579.
15. Moenster RP, Linneman TW, Finnegan PM, Hand S, Thomas Z, McDonald JR. Acute renal failure associated with vancomycin and beta-lactams for the treatment of osteomyelitis in diabetics: piperacillin-tazobactam as compared with cefepime. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases 2014; 20(6): O384-9.
16. Hammond DA, Smith MN, Painter JT, Meena NK, Lusardi K. Comparative incidence of acute kidney injury in critically ill patients receiving vancomycin with concomitant piperacillin-tazobactam or cefepime: A Retrospective Cohort Study. Pharmacotherapy 2016.
17. 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 2016 Feb 23. pii: 0897190016628960. [Epub ahead of print]
18. Rybak MJ, Albrecht LM, Boike SC, Chandrasekar PH. Nephrotoxicity of vancomycin, alone and with an aminoglycoside. The Journal of antimicrobial chemotherapy 1990; 25(4): 679-87.
19. King DW, Smith MA. Proliferative responses observed following vancomycin treatment in renal proximal tubule epithelial cells. Toxicology in vitro : an international journal published in association with BIBRA 2004; 18(6): 797-803.
20. Nishino Y, Takemura S, Minamiyama Y, et al. Inhibition of vancomycin-induced nephrotoxicity by targeting superoxide dismutase to renal proximal tubule cells in the rat. Redox report : communications in free radical research 2002; 7(5): 317-9.