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Review Article

Incidence, Risk Factors and Epidemiological Errors of Vancomycin Associated Acute Kidney Injury: A Systematic Review

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Abstract:

Changes in the incidence of Vancomycin Associated-Acute Kidney Injury (VA-AKI), risk factors and applicability of studies are questionable in recent times. This review aims to evaluate the incidence, risk factors and the epidemiological errors of findings on VA-AKI.

All studies related to vancomycin associated acute kidney injury in the past 20 years were identified from PubMed, MEDLINE, Google scholar and UWIlinC. During the past decade, the incidence of VA-AKI varied between 7.3% to 15.8%. The lowest incidence was found among the patients who received pharmacist intervention prior to the initiation of therapy, and the highest incidence was among elderly patients over 65-year-old. Notable risk factors were old age, high trough ≥15 µg/mL, AUC/MIC ratio > 650 mg × hour/L, concomitant use of aminoglycosides, broad-spectrum antibiotics, diuretics and vasopressor, using vancomycin without pharmacist intervention, hyperuricemia, respiratory failure, cardiac failure, chronic kidney disease, mechanical ventilation, obesity and black race. Common epidemiological errors in these studies were generalization and selection bias. The disparity of facilities among healthcare services is a concern.

Knowing modifiable risks, using vancomycin as monotherapy and advance consultation with pharmacists seem valuable preventive tools for VA-AKI regardless of resource settings.

Key words: VA-AKI; vancomycin associated AKI; vancomycin induced nephropathy; acute kidney injury; vancomycin toxicity

Introduction

A surge of reports on VA-AKI was noted after the infectious disease guidelines recommended to use sufficient initial and maintenance vancomycin doses to prevent treatment failure in in 2005 and in 2009 [1-4]. The nephrotoxicity related to a higher trough level from 1995 to 2012 was checked extensively and found out that the incidence of VA-AKI varied from 5-43% [1]. A longitudinal study from 2016 to 2019 stated that therapeutic drug monitoring was able to do on only 32.3% among the patients exposed to vancomycin [2]. The concerned on the recommended higher trough level in 2005 for the treatment of pneumonias associated with hospital, healthcare services and ventilators was expressed [3]. The most immediate response to the recommended higher trough level was produced based on the results between 2006 to 2008 which revealed an alarming outcome as 81.8% of patients with the trough level exceeded more than 35 mg/L developed VA-AKI [4]. Fortunately, a recent report in 2022, the incidence declined to 7.3% among patients who received pharmacist intervention prior to intravenous vancomycin therapy [5]. In the past decade, the incidence reached as high as 15.8% among the elderly hospitalized patients in 2016-2017 [6]. Despite being well-recognized as a nephrotoxin, the incidence of VA-AKI remained un-earthed in certain regions, probably due to lack of vancomycin level monitoring facilities. A complete picture can be seen when the incidence and risk factors are well-generalized. We aimed to identify the recent changes in incidence, reports on risk factors and to explore epidemiological errors related to the VA-AKI.

Renal affinity of vancomycin

The accumulation of vancomycin occurred two times higher in kidneys than in plasma and its toxicity was dose related. The vancomycin concentration in the kidney increased by 3.5-fold with high dose vancomycin (600 mg/Kg) [7]. Up to 90% of vancomycin unchanged form are filtered to the proximal convoluted tubules (PCT), resulting in accumulation in the PCT lining cells where it was metabolized [8]. Murphy E and Barreto E declared that vancomycin is a nephrotoxin and alternative therapy should be considered, for high-risk patients, if possible [9].

Pathophysiology of VA-AKI

The pathological manifestation of VA-AKI includes acute tubular necrosis (ATN), acute tubulointerstitial nephritis (ATIN) and intratubular crystal obstruction. A pooled renal biopsy reported that a combination of acute tubular necrosis (ATN) and acute tubulointerstitial nephritis (ATIN) were the most common findings. The ATIN was found to have a significantly higher risk of permanent renal dysfunction [HR: 5.08, 95% CI: 91.05–24.50)] [10]. The accumulation of vancomycin molecules in the PCT cells triggers inflammatory reactions, oxidative stress, and complement activation. Subsequent mitochondrial dysfunction, and apoptosis of the renal tubular epithelial cells led to acute tubular necrosis [11]. Htike, N. L et al stated that the pathophysiology of ATIN was thought to be mediated by a type IV delayed hypersensitivity reaction involving T-cells [12]. A smaller subset of patients developed VA-AKI due to intratubular crystal obstructions in the distal convoluted tubules, where casts are formed by uromodulin and vancomycin precipitates in a low urinary acidity (pH Less than 5.5) state [13].

Search strategy and selection criteria

PubMed, MEDLINE, Google Scholar and UWIlinC databases were selected as search databases. The initial search terms were “vancomycin”, “acute kidney injury” or “acute renal failure” or “aki” and “nephrot* and “vancomycin trough” or “vancomycin auc/*”. The search included both animal and human studies over the past 20 years. All the articles are centered on the incidence and/or risk factors of VA-AKI. The articles detailing acute kidney injury, drug pharmacodynamics, clinical outcomes, publications in English language, studies focused on adults and studies accessible in full-text form are included. The exclusion criteria are duplicate publications, AKI not related to vancomycin, studies lacking adequate data (abstracts with no full text available), publications older than 20 years, and non-intravenous use of vancomycin.

Records identified were 81 from PubMed, 57 from MEDLINE, 2610 from Google Scholar and 1401 from UWIlinC (total n= 4158). Records removed before the screening were those articles which did not include vancomycin (n= 4082) and duplicate articles (n= 44). Of the remaining 32 records, articles with no renal association (n=5), study with sample size Less than 400 (n=5), article based on vancomycin via intra-articular spacers use (n=1), articles on pediatric studies (n=6) and textbook article published beyond the past 20 years (n=1) were removed. The final selected studies in this review were 14 in which 7 articles focused on both incidence and risk and 7 articles mainly focused on risk of VA-AKI. The range of study designs were 7 systemic reviews with meta-analyses, 2 systematic reviews, 3 cross sectional studies, 1 cohort study, and 1 case-control study. Most studies used serum creatinine levels as the primary biomarker for diagnosing AKI according to AKIN, RIFLE or KDIGO criteria. (Figure 1)

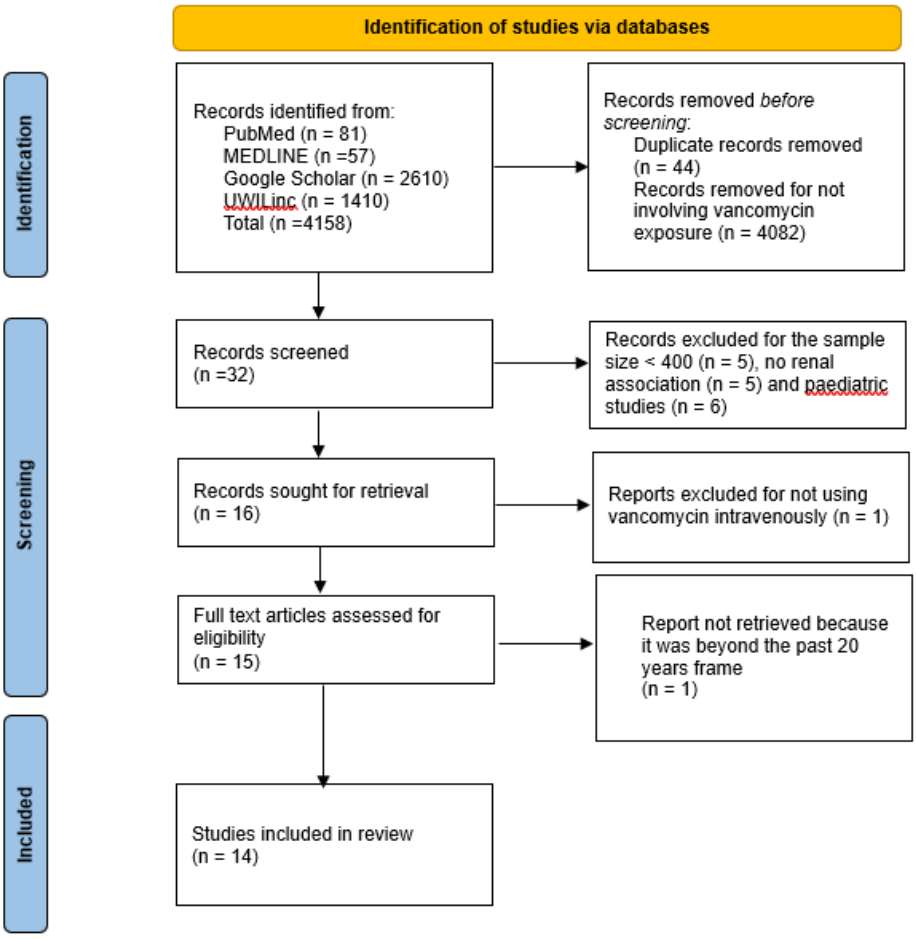

Figure 1: PRISMA flow diagram showing search strategy for literature review of VA-AKI

Results

A systematic review and meta-analysis by van Hal SJ et al., (2012) stated that the incidence of VA-AKI from 1995 to April 2012 was between 5 – 43% [1]. A longitudinal study by Kunming P et al., (2021), revealed that the incidence of VA-AKI was 14.3%. In addition, these patients had longer hospital stays (23 vs. 20 days, p Less than 0.001) and a higher 30-day mortality rate (8.8% vs. 1.5%, p Less than 0.001) [2]. Among ICU patients with pneumonia, VA-AKI was as high as 15.4% and the independent risk factors were initial vancomycin trough levels ≥15 mg/L (OR, 5.2, 95% CI, 1.9-13.9; P = 0.001), concomitant aminoglycoside use (OR, 2.67; 95% CI, 1.09-6.54; P = 0.03), and duration of vancomycin therapy (OR for each additional treatment day, 1.12; 95% CI, 1.02-1.23; P = 0.02) [3]. A study by Horey A et al., (2012) revealed that the prevalence of vancomycin associated nephrotoxicity was 12.6% with maximum trough concentrations (OR 1.14; 95% CI 1.09 to 1.20) and documented hypotension (OR 4.7; 95% CI 1.3 to 16.4) were with higher risk [4]. A systematic review and meta-analysis in 2022 revealed that the incidence of VA-AKI without pharmacist intervention was 9.6% and with pharmacist intervention was 7.3%. Hence, the incidence of VA-AKI was 2.3% less among the patients who received pharmacist intervention in advance (OR 0.52, 95% CI 0.41, 0.67, *P* Less than .001) [5]. In terms of age-related risk, a cross-sectional study by Pan K et al (2018) on elderly patients over 65-years-old revealed that the incidence of VA-AKI was 15.8% [6]. The studies which included incidence as well as risk ratios were summarized in the table (Table 1).

Author, year, [Ref #]	Aim	Study population	Study Design	Country (number of study)	Outcome Variables	Main Findings	Epidemiological errors
Van Hal et al 2012 [1]	To determine the nephrotoxicity potential of maintaining higher vancomycin troughs	15 studies with sample sizes ranging from 45 to 333 patients.	Systematic review and meta-analysis	USA (13) Korea (1) Slovakia (1)	Vancomycin associated Acute Kidney Injury (VA-AKI)	From 1995 to 2012, the incidence of VA-AKI ranges from 5% to 43%. Concomitant nephrotoxins use (OR, 3.30; 95% CI, 1.30 to 8.39; P = 0.01) and ICU patients (OR, 2.57; 95% CI, 1.44 to 4.58; P Less than0.01) were at risk.	It has selection and publication bias, as studies included a few countries, and only significant results were more likely to be published.
Kunming P et al 2021 [2]	To show the characteristics of VA-AKI	3719 hospitalized adult patients between January 1, 2016 and June 2019	Retrospective cohort	China (1)	VA-AKI	The incidence of VA-AKI was 14.3% among hospitalized patients. Concomitant piperacillin-tazobactam, cephalosporin and carbapenems therapy is at higher risk of AKI (OR 3.12, 95% CI 1.50-6.49, p = 0.002), (OR 1.55, 95% CI 1.08-2.21, p = 0.017), (OR 1.46, 95% CI 1.11-1.91, p = 0.006), respectively)	Large sample size increases the statistical power and reliability of the findings. The study excluded 998 patients due to missing serum creatinine measurements, which caused selection bias. As a single country-based study, generalization is low.
Cano, E et al 2012 [3]	To report the incidence of nephrotoxicity and associated risk factors in intensive care unit patients who received vancomycin	449 intensive care unit patients who received vancomycin for the treatment of HAP, VAP, and HCAP.	Retrospective multi-centre cross-sectional study	USA (1)	VA-AKI	The incidence of VA-AKI among ICU patients was 15.4%. Initial vancomycin trough levels ≥15 mg/L (OR, 5.2 [95% CI, 1.9-13.9]; P = 0.001), concomitant aminoglycoside use (OR, 2.67	The study acknowledges concomitant aminoglycoside use was the strongest risk factor for nephrotoxicity but does not sufficiently control for other potential nephrotoxic medications. The ICU setting of America
	for pneumonia					[95% CI, 1.09-6.54]; P = 0.03), and duration of vancomycin therapy (OR for each additional treatment day, 1.12 [95% CI, 1.02-1.23]; P = 0.02) were independent risk factors for VA-AKI.	would be different from other countries which decreased the generalization and external validity.

Kunming P et al 2022 [5]	To quantify the relationship between pharmacist intervention and vancomycin-associated acute kidney injury (AKI).	34 studies with 19,298 participants	A systematic review and meta-analysis	USA (18) Japan (4) China (4) Australia (3) Spain (1) Netherland (1) Iran (1) South Africa (1)	VA-AKI	Compared with the preintervention group, the postintervention group patients had a significantly lower incidence of vancomycin-associated AKI: 7.3% for post- and 9.6% for preintervention (odds ratio [OR] 0.52, 95% confidence interval; 0.41, 0.67, *P* Less than .00001).	In this meta-analysis, 12 out of 34 included studies were conference abstracts, which may have limited methodological details, lacked peer review, or contained incomplete data, reducing the overall strength and generalizability of the evidence.
Pan K et al 2018 [6]	To investigate the current situation concerning, and risk factors for, vancomycin induced acute kidney injury (VI-AKI) in elderly Chinese patients	647 elderly in-patients over 65 years old	Cross sectional study	China	VA-AKI	The incidence of VA-AKI was 15.8%. Multiple logistic regression analysis revealed that hyperuricaemia [odds ratio (OR) = 3.045; *P* = 0.000)], mechanical ventilation (OR = 1.906; *P* = 0.022) and concomitant vasopressor therapy (OR = 1.919; *P* = 0.027) were independent risk factors for VI-AKI	The study is focused on elderly Chinese patients, meaning the findings may not be directly applicable to younger populations or non-Chinese ethnic groups and the generalization is poor.
Elyasi, S et al 2012 [17]	To find out the safety of high doses vancomycin	Sixty-five articles were retrieved	Systematic review	USA (33) France (6) Japan (4) England (3)	VA-AKI	The incidence of Vancomycin-induced renal toxicity was	The review systematically addresses key aspects of vancomycin-induced
		on vancomycin and nephrotoxicity		China (3) Italy (3) Taiwan (2) Belgium (2) Australia (2) Israel (2) Singapore (1) Czechoslovakia (1) Slovakia (1) Brazil (1) Canada (1)		reported in 10–20 % and 30–40 % of patients following conventional and high doses of vancomycin therapy, respectively.	nephrotoxicity, including incidence rates, mechanisms, predisposing factors, and vulnerable populations. However, confounding by co-medications of other nephrotoxin could lead to an overestimation of the true nephrotoxic potential of vancomycin.
Qin, X., at el 2020 [33]	To study the incidence of vancomycin-associated acute kidney injury (VA-AKI) in Hong Kong and identify risk factors for VA-AKI.	12,758 records with vancomycin prescription and measurement of serum drug level from January 2012 to December 2016 in Hong Kong	Systematic review	China (1)	VA-AKI	The incidence was respectively 10.6, 10.9, 11.3, 12.2, 11.2% from 2012 to 2016. Serum trough vancomycin level (OR of 15.1~20.0 level: 2.50 (95%CI [2.13, 2.93], OR of > 20.0 level: 3.89 (95%CI [3.34, 4.53], respectively), respiratory failure (OR 1.38; 95% CI 1.22, 1.58), chronic renal failure (OR 3.17; 95% CI 2.72, 3.70) and congestive heart failure (OR 1.56; 95% CI 1.37,1.79, concomitant diuretics (OR 1.71; 95% CI 1.51,1.94), PTZ (OR 1.39; 1.24, 1.57) and meropenem (OR 1.29; 95% CI 1.16,1.45), were	This large sample size enhances reliability and generalizability. As a retrospective study relying on medical records, the data may be prone to incomplete reporting or missing or inaccurately documented could introduce recall and reporting bias (Information biases).

						all associated with increased risk of VA-AKI.	

Table 1: Eligible Journal Articles on incidence and risk factors of Vancomycin Associated Acute Kidney Injury in adults.

VA-AKI, Vancomycin Associated Acute Kidney Injury; USA, United States of America; ICU, Intensive care unit; HAP, Hospital Acquired Pneumonia; VAP, Ventilator Associated Pneumonia; HCAP, Healthcare Associted Pneumonia; PTZ, Piparacillin-Tazoactam.

VA-AKI risk factors

A pooled results of 7 RCTs and 7 cohort studies on 4033 patients by Ray AS et al., (2016) concluded that the risk of nephrotoxicity was 2.5-fold higher in patients who received intravenous vancomycin [14]. Kim J.Y et al. (included 53 studies in a meta-analysis (n = 50-3719), revealed a higher risk of Vancomycin Associated AKI (VA-AKI) among black and obese population. (OR 1.47, 95% CI: 1.16–1.87 and OR 1.46, 95% CI: 1.12–1.90, respectively) [15]. Pan K et al expressed independent associations between VA-AKI and hyperuricemia (OR 3.045; 95% CI 1.834, 5.057; *P* = Less than0.001), mechanical ventilation (OR 1.906; 95% CI 1.098; 3.310, *P* = 0.022) and concomitant vasopressor therapy (OR 1.919; 95% CI 1.078, 3.418; *P* = 0.027) [6]. A prospective cohort by Lodise, T (2008), found that the prevalence of AKI among patients who received vancomycin >4 G/day, Less than4/day and linezolid was noted as 34.6%, 10.9%, and 6.7%, respectively (P = 0.001) [16]. A systematic review by Elyasi et al., reported that high dose vancomycin >4 G/day, trough level >20 mg/dL and longer duration of therapy > 7 days were associated with higher prevalence of VA-AKI compared to the conventional dose (30-40% vs 10-20%) [17].

Among the critically ill patients, backwards logistic regression analysis by Hanrahan T.P (2015) revealed serum vancomycin concentration and APACHE II score as independent positive predictors (OR= 1.174, P= 0.024 and OR= 1.141, P= 0.012, respectively) [18]. A meta-analysis done in 2022 focused on the first 24 hours (0-24 hours) and second 24 hours (24-48 hours) vancomycin troughs. AKI was significantly less when trough level area under curve (AUC) was less than 650 mg×h/L [19]. Abdelmessih, E et al (2022) augmented another meta-analysis which showed that the VA-AKI was significantly lower in the AUC-guided dosing strategies than trough-guided dosing strategies (OR 0.625, 95% CI (0.469–0.834), p = 0.001) [20]. In 2021, Tsutsuura M et al found a significantly lower rate of treatment failure in patients with the trough level ≥ 15 µg/mL ((OR 0.63, 95% CI 0.47–0.85) but when trough concentrations ≥20 µg/mL, the rate of AKI was two times higher than trough concentrations between 15-20 µg/mL (OR 2.39, 95% CI 1.78–3.20) and target cut-off 600 ± 15% was associated with a higher risk of VA-AKI (OR 2.10, 95% CI 1.13–3.89) [21]. A retrospective cohort by Pitcock CT et al (2023) on prolonged vancomycin therapy (> 14 days) demonstrated a higher incidence of AKI (45.6% vs 28.4%, p Less than 0.001) with higher mortality (12.9% vs 8.3%, p = 0.078) in the trough level monitoring group compared to the AUG guided group and the latter had 54% less incidence of AKI (OR 0.46, 95% CI [0.31–0.69) [22]. Retrospective cohort by Ishigo T et al., (2024) supported with a comparison analysis which showed that high-AUC group, intermediate-AUC group and low-AUC group had different AKI rates (42.9%, 28.0%, 6.5%, respectively) [23]. A meta-analysis by Yang W et al (2024) revealed that vancomycin trough concentration (Ctrough) were indicators for nephrotoxicity (OR 2.193; 95% CI 1.582–3.442, p Less than 0.001) and C_{trough} 10–20 mg/L was equivalent with a mean AUC_{24} within 400–600 mg·h/L in most patients (92.3%). The conclusion was that the observed trough level, $C_{trough,}$ should remain a beneficial tool of monitoring for VA-AKI [24].

Kim T et al (2015) reassured with their findings that vancomycin monotherapy in hemodynamically stable non-critically ill patients had significantly lower nephrotoxicity (OR 0.14, 95 % CI 0.04–0.52, p = 0.004) compared to the combined Vancomycin/Piperacillin-Tazobactam group and the overall incidence was 11.8% [25]. In 2018, Luther MK et al declared that Piperacillin-Tazobactam and vancomycin combined therapy. had a significantly higher risk of VA-AKI than vancomycin monotherapy (OR 3.40; 95% CI, 2.57–4.50 [26]. A comprehensive review by Blair M et al., (2021) proposed the potential pathogenesis of Vancomycin Piperacillin-Tazobactam (VPT) induced AKI as multifactorial including tubular toxicity, oxidative stress, cast formation, acute interstitial nephritis and inhibition of tubular creatinine secretion [27]. Apart from Piperacillin-Tazobactam, concomitant use of cephalosporin (OR 1.55, 95% CI 1.08-2.21, *p* = 0.017), carbapenems (OR 1.46, 95% CI 1.11-1.91, *p* = 0.006) with vancomycin also had an increased risk of VA-AKI, according to a longitudinal study [2]. Documented factors with their odds for VA-AKI are demonstrated collectively in the Forest plot [Fig. 2]. A matched case-control study by Gyamlani G et al (2019) (n=33,527) revealed similar or even less odds ratio in the vancomycin group with trough level ≤20 mg/L compared to the linezolid/daptomycin group. However, when vancomycin levels > 20 mg/L, a 4-fold higher risk of AKI was observed, compared to vancomycin levels 2Less than 10 mg/L [28]. The studies which mainly focused on the risk of VA-AKI are collectively shown in the table (Table 2) and epidemiologic errors of the selected studies are summarized in table 1 & 2.

Author, year, [Ref #]	Aim	Study population	Study Design	Country (number of study)	Outcome Variables	Main Findings	Epidemiological errors
Ray, A. S et al 2016 [14]	To determine the risk of AKI attributable to intravenous vancomycin	4033 from 7 RCTs and 7 cohort	Systematic review and meta-analysis	USA (7) Japan (2) Spain (2) Croatia (1) China (1) England (1)	VA-AKI	Vancomycin treatment is associated with a higher risk of AKI, with a relative risk of 2.45	Seven RCTs were included which minimized the bias. Combining RCTs and cohort studies in a meta-analysis introduced selection bias.

Kim, J.Y et al 2022 [15]	To evaluate the risk factors for vancomycin-associated acute k8idney injury (AKI) incidence	53 studies; 31 cohort & 22 case-control studies with sample size ranged from 50 to 3719	Systematic review and meta-analysis	USA (26) China (10) Japan (6) Australia (4) Korea (2) Belgium (1) Brazil (1) Canada (1) France (1) New Zealand (1)	Risk factors for VA-AKI	Black race (OR 1.47, 95% CI: 1.16–1.87), and Obesity (OR 1.46, 95% CI: 1.12–1.90) were significantly related to vancomycin-associated AKI	Meta-analysis provides a broad scope of evidence, making the findings more robust and generalizable. The association between race (Black vs. Caucasian) and AKI may reflect underlying disparities. Confounding bias related to socioeconomic factors or co-morbid conditions is there.
Hanrahan, T et al 2015 [18]	To evaluate the potential consequences of more aggressive vancomycin therapy	1430 critically ill-patients	Retrospective cross-sectional study	England (1)	VA-AKI	Higher serum vancomycin concentrations and greater duration of therapy are independently associated with increased odds of nephrotoxicity.	The study provides insights that are directly relevant to clinicians aiming to balance efficacy with safety in high-risk populations. The single-center study from an ICU in Birmingham, UK, limits generalization.
Aljefri, D.M et al 2019 [19]	To analyze the relationship between vancomycin area under the concentration -time curve (AUC) and acute kidney injury (AKI)	2491 from 8 Randomized cohort and case-control studies	Systematic review and meta-analysis	USA (5) USA-Singapore (1) Australia (1) Japan (1)	AKI	AUCs measured in the first or second 24 hours and lower than approximately 650 mg × hour/L may result in a decreased risk of AKI.	The study addresses a significant clinical question regarding the relationship between vancomycin's area under the concentration-time curve (AUC) and acute kidney injury (AKI). Many countries and institutions do not have facility for AUC monitoring severely limits the generalizability.
Tsutsuura M et al 2021 [21]	To explore the relationship between vancomycin (VCM) monitoring strategies and VCM effectiveness and safety	8 studies were included in the meta-analysis for effectiveness evaluation, 16 studies were included in the meta-analysis for safety evaluation, and one study was included in both analyses. All studies focused on adult patients with MRSA bacteraemia	Systematic review and meta-analysis	USA (11) Japan (4) Korea (2) Brazil (2) Australia (1) Taiwan (1) China (1)	Risk of VA-AKI	The incidence of acute kidney injury (AKI) was significantly higher for trough concentrations ≥20 μg/mL compared to those at 15-20 μg/mL (OR 2.39, 95% CI 1.78-3.20). Analysis of the target AUC/MIC showed significantly lower treatment failure rates for high AUC/MIC (cut-off 400 ± 15%) (OR 0.28, 95% CI 0.18-0.45). The safety analysis revealed that high AUC value (cut-off 600 ± 15%) significantly increased the risk of AKI (OR 2.10, 95% CI 1.13-3.89).	This systematic review analyzes the relationship between vancomycin monitoring strategies (trough and AUC/MIC) and clinical outcomes, providing valuable insights into both effectiveness and safety. The generalizability of these studies is limited for the countries which have lack of facilities for monitoring.

Yang W et al 2024 [24]	The area under the curve over 24 h (AUC_{24}) and trough concentrations (C_{trough}), and their relationship with both nephrotoxicity and efficacy	100 publications on nephrotoxicity, 29 focused on AUC24 and 97 on C_{trough}, while 74 publications on efficacy, 27 reported AUC24/MIC and 68 reported C_{trough}.	Systematic review and meta-analysis	USA (46) Japan (20) China (12) Korea (4) Canada (3) France (2) Israel (2) Australia (2) Thailand (1) Qatar (1) Singapore (1) Poland (1) Saudi Arabia (1) Brazil (1) England (1) Spain (1) Iran (1)	Nephrotoxicity and efficacy of vancomycin in relationship with AUC_{24} and target C_{trough}	There was a significant association between nephrotoxicity and vancomycin C-trough (odds ratio = 2.193; 95% CI 1.582–3.442, p Less than0.001). 92.3% of the groups with a mean AUC_{24} within 400–600 mg·h/L showed a mean C_{trough} of 10–20 mg/L. Monitoring vancomycin C_{trough} remains a beneficial tool.	A very comprehensive meta-analysis which demonstrated the relationship between vancomycin pharmacokinetic indicators (AUC24 and C_{trough}). The un-matched comparison with much smaller number of studies on AUC_{24} to many studies on C_{trough} on nephrotoxicity, leading to less robust conclusions about the role of AUC24 in clinical practice. Lack of such facilities in many countries limits the generalization.
Gyamlani, G et al 2019 [28]	To determine the association of vancomycin with acute kidney injury (AKI) in relation to its serum concentration value and to examine the risk of AKI	33,527 US Veterans 33,527 patients who received either intravenous vancomycin (n = 22,057) or non-glycopeptide antibiotics (linezolid/daptomycin, n = 11,470)	Matched case-control study	USA (1)	AKI	The odds of AKI were similar or lower in patients receiving vancomycin compared to non-glycopeptide antibiotics when serum vancomycin levels were ≤20 mg/L. [OR, 1.1 (1.1–1.2), 1.2 (1–1.4) and 1.4 (1.1–1.7), respectively]	Being a matched cohort, the study offers a valuable comparison to assess the specific impact of vancomycin on AKI risk. However, the study uses data exclusively from U.S. veterans, limits generalizability and causes selection bias.

Table 2: Eligible Journal Articles which mainly focused on the risk of VA-AKI

VA-AKI, Vancomycin Associated Acute Kidney Injury; USA, United States of America, VCM, Vancomycin; AUC, Area Under Curve; MIC, Minimum Inhibitory Concentration, AUC_{24}, The area under the curve over 24 hours; C_{trough}, trough concentrations; MRSA, Methicillin Resistant Staphylococcus Aureus

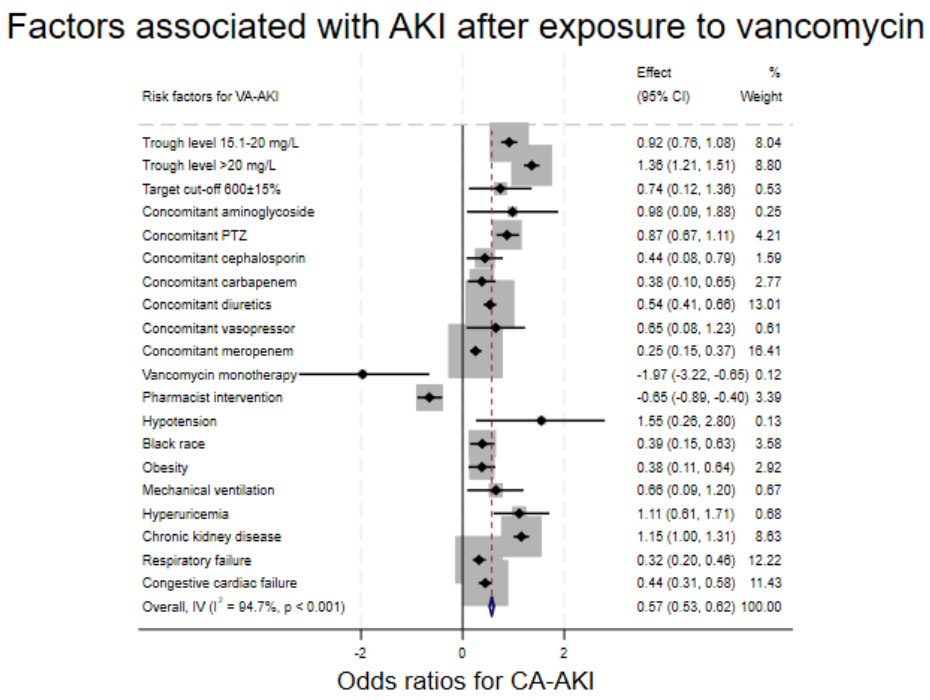

Figure 2: Forest plot demonstrating the odds ratio and factors associated with AKI after intravenous vancomycin usage

Discussion

The incidence of Vancomycin Associated Acute Kidney Injury varies according to age, race, pharmacokinetics of vancomycin and personal fitness. Reports on VA-AKI surged around the time of 2012 [1,3,4,17], which was thought to be due to higher target levels of Vancomycin. [29] The trend of the VA-AKI had apparently increased with recommended trough levels or AUC/MIC ratios. The incidence was as high as 15.8% among elderly hospitalized patients in China [6] and 15.4% among ICU patient in USA [3]. Based on these reports, the vancomycin consensus guidelines committee revised in 2020 with a recommendation of target AUC/MIC ratio of 400–600 mg*hour/L to prevent treatment failure and to ensure the safety for the treatment in severe MRSA [30]. However, countries with limited-resource settings were not able to adhere to these guidelines. Although Kim J.Y et al [15]. reported a higher risk of VA-AKI among blacks, reports from regions of black preponderance, such as Africa and the Caribbean, were scarce which indicates the study had a reduced external validity with possible selection bias and confounding by disparities in healthcare access or different baseline health conditions.

Many reports recognized initial trough level ≥15 mg/L or > 4 G/day as risk factors of VA-AKI. Further analysis revealed that the trough (>20 µg/mL) or target AUC/MIC ratio value cut-off > 600 mg·h/L were the strong risk factors for VA-AKI [2, 16-24]. On the other hand, lower trough level and AUC were associated with lower risk of VA-AKI. Suggestion by Bruniera, F. R et al (2015) to use adequate dosage for a shorter duration of therapy was quite agreeable to minimize treatment failure and toxicity [31]. The statement in 2019 by Gyamlani G et al, in which the risk of AKI with intravenous vancomycin monotherapy was not higher than other antimicrobial combined therapy unless vancomycin trough level reached beyond 20 µg/dL, reassured vancomycin prescribers [28]. Collectively, findings suggested that risk of VA-AKI could be minimized with lenient monotherapy.

It is important to be aware that more risk factors have been emerging. A retrospective study in 2014 mentioned that hypertension (74 vs. 51 %, p = 0.0009, OR 2.74, 95 % CI 1.5-5.0), furosemide use (65 vs. 39 %, p = 0.0009, OR 2.91, 95 % CI 1.64-5.15) and trough concentration ≥16.2 µg/mL (OR 2.33, 95 % CI 1.25-4.44) were associated with VA-AKI independently [32]. More risk factors were introduced by Qin, X et al (2020) in a retrospective cohort in which the different trough levels [OR of 15.1~20.0 level: 2.50 (95%CI 2.13, 2.93), OR of > 20.0 level: 3.89 (95%CI 3.34, 4.53, respectively), respiratory failure (OR 1.38; 95% CI 1.22, 1.58), chronic renal failure (OR 3.17; 95% CI 2.72, 3.70) and congestive heart failure (OR 1.56; 95% CI 1.37,1.79, concomitant diuretics (OR 1.71; 95% CI 1.51,1.94), PTZ (OR 1.39; 1.24, 1.57) and meropenem (OR 1.29; 95% CI 1.16,1.45), were found to have higher risk of VA-AKI [33]. Categorizing the risk factors into modifiable and non-modifiable factors by Kan WC et al in 2022 was also beneficial [34]. Focus on modifiable risk factors like intravascular volume depletion and acute severe illnesses should be maximized. Unfortunately, non-modifiable risks such as older age, female gender, black race, drug allergy, pre-existing comorbidities, end organ failures (cardiac, renal, liver), diabetes, immunocompromised state and obesity would remain untouchable.

Concerns should be raised for the countries with limited-resource settings where recommended trough levels or AUC/MIC ratios were not applicable and the vulnerability of those patients on conventional therapy remained questionable. The safety of vancomycin at these healthcare services should be explored more. To our knowledge, these institutions relied on the website calculator https://clincalc.com/Vancomycin/ [35], drug prescribing insert or infectious disease specialist guidance to use intravenous vancomycin. The suggestion made by Kunming P et al (2022) to seek pharmacist intervention prior to the intravenous vancomycin is quite reasonable for resource-limited countries.

Studies and systematic reviews have been reported mainly from resource-rich countries. Recommendations were impressive but the generalization was limited, and selection bias were there. We recommend the availability of Vancomycin trough levels for any users in clinical practice especially for high-risk patients.

Conclusion

The incidence of VA-AKI varies widely from 7.3% to 15.8%, according to the samples selected and associated risk factors. Some findings and recommendations had selection bias and decreased generalization. Reports were mainly from resource-rich countries. Correction of modifiable risks, vancomycin monotherapy, consulting infectious disease

specialists and pharmacists in advance seem useful tools to control VA-AKI regardless of resource settings.

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