**Vancomycin-associated acute kidney injury epidemiology in children: A systematic review**

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**Declarations**

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**Abstract**

**Introduction:** Vancomycin is a recognised cause of drug-induced acute kidney injury.

**Objective:** The aim of this systematic review was to summarise the incidence of, and the risk factors for, vancomycin-associated acute kidney injury (v-AKI) in children.

**Design:** A systematic search was performed in November 2020 on the search engines PubMed, Web of Science and Medline, using predefined search terms. The inclusion criteria were primary paediatric studies, intervention with vancomycin, and studies that included AKI as an outcome. Study quality was assessed using the relevant Critical Appraisal Skills Programme checklist. The data are reported using descriptive statistics.

**Results:** 890 studies were identified and screened with twenty-five studies suitable for inclusion. A cohort of 12,730 patients with vancomycin-induced acute kidney injury (v-AKI) were included and the incidence of v-AKI in children was found to be 11.8% (1.6-27.2%). The median age of the cohort was 2.5 years (range 0-23) and 57% were male. Risk factors that increased the likelihood of v-AKI were; concomitant use of nephrotoxic medications, increased trough concentrations, and, to a lesser extent, increased dose, longer duration of treatment, impaired renal function and if the patient required paediatric intensive care.

**Conclusions:** The incidence of v-AKI in children is significant and methods to reduce this risk should be considered. Further prospective interventional studies to understand the mechanisms of nephrotoxicity from vancomycin are needed and targeting risk factors may make vancomycin administration safer.

**Funding and registration:** No financial support was received. The protocol was registered with PROSPERO [139459].

**Introduction**

Vancomycin is an important glycopeptide antibiotic that became available for clinical use over 60 years ago, however it was initially disregarded due to its toxicity profile (1). The advent of Clostridium difficile enterocoloitis and methicillin-resistant staphylococcus aureus (MRSA) led to a rise in the use of vancomycin and it remains one of the first line agents used to target gram-positive bacteria (2). It is known to have the potential for kidney toxicity, and current practice relies on monitoring therapeutic drug levels and kidney function. The increasing number of infections produced by beta-lactam-resistant Gram-positive bacteria is a concern with recent reports suggesting the rate of vancomycin resistance to be around 15% (3). The emergence of vancomycin treatment failures have led to speculation of the vancomycin minimum inhibitory concentration (MIC) creeping up (so-called “MIC-creep”) thus the potential use of increased doses, longer treatments and concomitant medications may continue (4).

Vancomycin is primarily excreted by the kidney and can cause toxicity to the proximal tubule epithelial cells (5). Despite having a narrow therapeutic window, the mechanisms of nephrotoxicity from vancomycin are poorly understood (6, 7). Vancomycin nephrotoxicity usually presents as acute kidney injury (AKI) in clinical practice through an elevation in serum creatinine values and rarely demands the need for acute renal replacement therapy (8). In a previous systematic review in adults, the typical onset of vancomycin-associated acute kidney injury (v-AKI) was 4.3-17 days after administration and usually improved within a week. It is a recognised cause of increased mortality and increased length of hospital stay (9-12).

To develop strategies to reduce v-AKI in children, we first require a better understanding of the scale of the problem and the risk factors involved. The primary aim of this systematic review is to describe the incidence and risk factors associated with the development of v-AKI in the paediatric population.

**Methodology**

The predefined protocol was registered with PROSPERO: International prospective register of systematic reviews [139459]. Three search engines were used: PubMed, Medline and Web of Science with the following search terms: [(AKI) OR (acute kidney injur\*) OR nephrotoxic\*) OR (renal injur\*) OR (kidney injur\*) OR (renal insufficiency) OR (kidney damage) OR (renal damage)] AND [(vancomycin) OR vancocin)] AND [(paediatric\*) OR (pediatric\*) OR (child\*) OR (infan\*) OR (adolescen\*) OR (neonat\*)]. Further eligible studies were not selected from reference lists as the initial search return was already extensive.

*Inclusion/exclusion criteria*

The inclusion criteria were: paediatric patient population, intervention with vancomycin, comparison with other patients receiving vancomycin, AKI as an outcome, and primary evidence only. The definition of AKI was using either the kidney disease improving global outcomes (KDIGO) and/or paediatric risk, injury, failure, loss, end-stage (pRIFLE) criteria (13, 14). Included studies were free full-text papers accessible through the University of Liverpool, published after the year 2010 and written in English. The exclusion criteria were: studies involving an adult population, papers not including vancomycin monotherapy, and secondary research.

*Selection process*

The initial search was conducted in November 2020 (CW), followed by a second independent search in December 2020 (CH). These same reviewers independently screened the titles and abstracts against the eligibility criteria. Any differences in allocation were resolved by a third reviewer (SM).

*Data collection, quality assessment and statistical analysis*

A data collection proforma was designed to collect the following information: year of publication, study design, study population, intervention, definition of AKI and outcomes. The quality of the data was assessed using the Critical Appraisal Skills Programme (CASP) checklist for cohort studies, providing a score out of 12 (15). The data were reported using descriptive statistics with study population data summarised using median value with range (age) and percentages (sex). Reported risk factors were defined as those found to be significantly associated with v-AKI in two or more studies. Those found to be significantly associated and reported only in one study, or insignificantly associated with v-AKI, were defined as “other risk factors” and reported in less detail. Individual study data was described as presented in the primary study. P-values of <0.05 and odds ratio (OR) or risk ratios (RR) with 95% confidence intervals (CI) that did not cross 1 were considered significant.

*Ethical approval*

This study was a systematic review of existing literature and therefore did not meet the criteria for needing ethical approval according to NHS Health Research Authority guidance.

**Results**

*Data retrieved*

The process of identifying suitable studies is summarised in the PRISMA diagram (Figure 1). The primary literature search returned 890 potential studies. The second independent screen identified 2 additional papers producing a total of 25 papers for inclusion.

The papers were published between 2011 and 2020. The study design included 23 retrospective cohort studies, and 2 case-control studies (16, 17). They were mostly single-centre studies (20/25) and took place in secondary and tertiary care hospital settings.

*Participants*

This study includes a total of 12,730 paediatric patients with a median age of 2.5 years (range 0-23), and 57% were male. There was missing age (17, 18) and gender data (19, 20) in two studies each. The median dose of vancomycin was 43.3mg/kg/day (range 14.9-60.0). Three papers did not report a dose (18, 19, 21). The main findings of the data are summarised in Table 1.

*Study quality*

The median CASP score for the 23 selected cohort studies was 10/12 (range 7-11/12), and for the 2 case-control studies the median score was 10/12 (range 9-11/12). The biggest variable was the application of the results to the local population as many of the papers looked at children belonging to specific populations, decreasing the generalizability of the results.

**Incidence of v-AKI and identified risk factors**

The systematic review demonstrated that the median incidence of v-AKI was 11.8% (16-40) (range 1.6-27.2) (22, 34). Six specific risk factors were reported by two or more papers to be statistically significantly associated with v-AKI and are described as follows. A summary can be found in Table 2.

*Dose of vancomycin*

Ten studies had evaluated the dose of vancomycin. Two studies (20%), including 7,270 patients, found an association between the dose of vancomycin and v-AKI (16, 36). Eight studies (80% of papers retrieved; 1,136 patients) did not find an association (20, 25, 26, 28, 29, 31, 37, 38). In the study by Sinclair et al. (33), the odds of nephrotoxicity increased by 16% for every additional 5 mg/kg of vancomycin (OR = 1.11; 95% CI = 1.01-1.22) and patients who received ≥80mg/kg/day were 3.3 times more likely to develop AKI (36).

*Duration of treatment*

A total of 13 studies evaluated the duration of vancomycin treatment. Three studies (23% of relevant studies; 455 patients) found the duration of treatment to be a statistically significant risk factor for v-AKI (24, 28, 36). Ten studies (77% of relevant studies retrieved; 2,610 children) showed no association (18, 25, 29-31, 34, 35, 37-39). Cies et al. found the duration of vancomycin therapy to be an independent risk factor for AKI in the paediatric intensive care setting (OR = 1.19; 95% CI = 1.04-1.37) and therapy ≥7 days was associated with an increased risk of v-AKI (OR = 1.21; 95% CI = 1.001-1.21) (24). Similar findings were reported by Knoderer et al. (2015) with a v-AKI incidence of 12.6% in children who received vancomycin for ≥8 days; increasing to 52.4% in those with a treatment duration of ≥15 days (28). Sinclair et al. found that the odds of developing v-AKI increased with each additional day of treatment (OR = 1.11; 95% CI = 1.01-1.22) (36).

*Vancomycin therapeutic levels*

Twenty studies included this factor in their analysis. Nine studies, (45% of relevant studies; 1,940 children), found an association between vancomycin levels and v-AKI (17, 19, 21, 25, 29, 31, 32, 35, 38). Eleven studies (55% of relevant studies; 3,234 children) showed no association (16, 18, 20, 26, 28, 30, 32, 34, 36, 37, 39). A final vancomycin trough concentration above the local threshold of ≥15 mg/L was reported to be an independent risk factor for v-AKI in children in several studies (19, 25, 29, 31, 38) and this was confirmed by Zhang et al in multivariate analysis (17). This finding was also described in patients on additional medications such as piperacillin-tazobactam (32) and in different subgroups of patients including children with cancer (OR = 17.83; 95% CI = 3.28-96.6) (35) and neonates on intensive care (21).

*Co-administration of a nephrotoxic medication*

Twenty papers studied the use of concomitant nephrotoxic medications, mostly aminoglycosides, piperacillin-tazobactam (TZP), furosemide, amphotericin, acyclovir, and meropenem, and twelve (60% of relevant studies; 11,439 children) found an association with the incidence of v-AKI for at least one drug (18, 19, 24, 25, 27, 30, 31, 33, 34, 36-38). Eight studies (40% of relevant studies; 2,278 children) found no association for any drug (16, 17, 22, 28, 29, 32, 35, 39). Five papers (25% of all relevant studies; 8,077 children) found both positive and negative associations with different concomitant medications (25, 30, 33, 34, 38). In the study by Sinclair et al., receiving any concomitant nephrotoxic medication increased the risk of AKI (OR = 5.02; 95% CI = 1.09-23.19) (36). Totapally et al. found concomitant nephrotoxins to be a significant risk factor in the PICU setting (OR = 2.23; 95% CI = 1.27-3.93; p-value <0.01) (37).

The drugs that were most commonly associated with AKI when co-administered with vancomycin were loop diuretics (specifically furosemide reported OR range 2.6-24.8, (17, 18, 25, 31) or general loop diuretics reported OR 42.8, (30)), TZP (reported OR range 1.46-3.14, (33, 38)), and vasopressors (reported OR range 11.1-18.4, (19, 24, 30)) (Table 3). Drugs found to be not associated with v-AKI in this systematic review included: contrast media (28-30), cyclosporine (17, 25, 34, 35, 38), tacrolimus (34, 35, 38), methotrexate (30, 33, 38) and vasoactive medications (16, 25, 30, 33).

*Critically ill children*

Four studies evaluated critically ill children and all four papers (100% of relevant studies; 1,709 children) found this population of patients to be at a statistically significantly increased risk of v-AKI (16, 29, 31, 34). Two papers found PICU was an independent risk factor for nephrotoxicity during vancomycin treatment ((OR = 2.91; 95% CI = 1.70-8.61; p-value <0.03; (34)) and (OR = 2.18; 95% CI = 1.20-2.94, (29))). McKamy et al. reported 99 children admitted to PICU and 22 (22.2%) developed nephrotoxic AKI (p-value <0.01) suggesting the incidence of v-AKI is increased in this population when compared to the overall incidence (31).

*Impaired renal function*

Three papers assessed v-AKI in patients with impaired renal function. All three studies (100% of relevant studies; 425 children) found prior impaired renal function to be a risk factor for v-AKI (OR 1.9-8.8; p-value <0.05) (17, 37, 40). One paper found the opposite with a decreased risk of nephrotoxicity in cardiac intensive care patients who had an elevated baseline serum creatinine (OR = 0.009, 95% CI = 0.0002-0.29; p-value <0.01), however the authors concluded that this may have been due to inaccuracies in the baseline creatinine values of some patients due to fluid overload or poor nutritional status (16).

**Other factors**

Two papers considered v-AKI in post-operative paediatric cardiothoracic patients. One study (50% of relevant studies; 54 patients) found an increased incidence of v-AKI when compared to controls (23) and the other study (including 418 children) found no difference (16).

With regards to neonates and infants, two studies evaluated the incidence and risk factors of v-AKI in this population. One study found a trough concentration of vancomycin >15 mg/L as a risk factor for v-AKI in a cohort of 110 neonates with a mean gestational age of 29 weeks. Interestingly the reported incidence of v-AKI in this group was low (2.7%) (21). The other study evaluated 182 neonates with a similar mean gestational age of 30 weeks and found no associated risk factors and a reported incidence of 8% (20). Another paper focused on children reported that age <1 year was found to be an independent risk factor for the development of late onset v-AKI (OR = 4.4; 95% CI = 1.3-15.4, p-value = 0.02) (28).

Lastly, two papers considered extracorporeal membrane oxygenation (ECMO) as a risk factor for v-AKI. One study (50% of relevant studies; 418 children) found it was a statistically significant risk factor for the development of nephrotoxicity (OR 14.4, 95% CI = 1.02–203; p-value = 0.048) (16). However, another study in 113 children found no significant effect of ECMO upon the incidence of v-AKI (24).

**Discussion**

This systematic review investigated the incidence, and risk factors involved in the development of v-AKI in the paediatric population. Following a robust search of the literature, 25 studies, including a total cohort of >12,000 children, were included. These studies report a median incidence of v-AKI of 11.8% (range 1.6-27.2%), an incidence comparable to studies performed in adult populations (6, 41, 42). Overall rates of AKI in non-critically ill children are reported to be >5% and in critically ill children the incidence is approximately 27% (43, 44). This systematic review suggests that vancomycin contributes to AKI in children, although the strength of the contribution may be modest. The epidemiology of AKI has changed over time with nephrotoxic agents becoming a leading cause, especially in hospitalised patients. Long term follow up data suggest that repeated episodes of AKI may lead to an increased risk of later chronic kidney disease (CKD) (45). It is especially important to consider v-AKI in children as it may result in a lifetime of increased CKD risk for them, and they have distinct differences in terms of drug handling when compared to adults (2).

Despite the heterogenous nature of the studies included, this systematic review has identified risk factors believed to be associated with the onset of v-AKI in children. These can be summarised into two key themes, factors associated with drug administration and those relating to the patient population. Potential drug administration factors associated with v-AKI include increased serum trough vancomycin concentrations and the use of concomitant nephrotoxic medications, with less evidence to support an independent effect of increased dose and duration of treatment. Population factors include critically ill children (those admitted to PICU, NICU and/or patients undergoing cardiothoracic surgery) and those with prior impaired renal function.

Studies in the adult population report similar vancomycin administration factors (46-48) and patient population factors (48). This study can be used to guide practical solutions that may reduce the incidence of v-AKI in the paediatric setting. These include regular monitoring of renal function, therapeutic drug level monitoring with dose adjustment to maintain these within an acceptable therapeutic range, avoiding the use of additional nephrotoxic agents such as diuretics and/or amphotericin (when possible), and awareness of high risk populations (PICU, NICU, post cardiac surgery or prior renal impairment). It may be appropriate to consider the use of alternatives antibiotic agents if there are additional risk factors. Previous single centre studies have demonstrated success in using a targeted preventative approach, such as the Nephrotoxic Injury Negated by Just in Time Action (NINJA) program where early intervention resulted in a 38% reduction of nephrotoxic medication exposure and a 62% reduction in nephrotoxin-associated AKI (49). Due to the cost of v-AKI to the patient and the healthcare system, improved awareness and recognition of v-AKI in the paediatric population are needed and there is an urgent need to actively incorporate multi-centre, multi-targeted prevention programmes into clinical care.

*Limitations and future direction*

This systematic literature review has many limitations. Firstly, the papers included in the review were heterogenous, with differing populations of children who received differing doses of treatment. The papers included also used two different definitions to classify AKI (KDIGO and pRIFLE) and it was difficult to determine the severity of AKI within the individual cohorts and whether they stuck to the predetermined definitions. These factors also made it impossible to conduct a meta-analysis of the data. The included studies were mostly retrospective cohort studies and therefore contained many potential confounding factors. This may explain why some findings like the association with vasopressor agents but not vasoactive drugs were identified. Many of the studies had no control group and they looked at specific populations so the results may be less generalizable to all children receiving vancomycin. Finally, it was noted that many of the studies excluded participants with previous AKI or established CKD or death during treatment and these may have been important subgroups to study.

**Conclusion**

The incidence of v-AKI in children is high, especially considering it is iatrogenic. Identification of high-risk patients and defining safer ways to administer vancomycin is vital to reduce the incidence of v-AKI (50). Drug regimens should be personalised according to the presence of individual risk factors, concomitant nephrotoxins and continually assessed throughout treatment. Well-conducted, multi-centre, prospective studies are required to assess the impact of interventions to reduce the incidence of v-AKI and to better understand its long-term impact. **What is already known on this topic?**

* Vancomycin is a recognised cause of acute kidney injury (AKI).
* Mechanisms of vancomycin-associated AKI are poorly understood.
* Increasing bacterial resistance to vancomycin is potentially leading to the use of increased doses, longer treatment, and more frequent use of concomitant medications.

**What this study adds**

* The median reported incidence of vancomycin-induced nephrotoxicity in children is 11.8% and similar to adult studies.
* Vancomycin should be administered with caution and according to patient risk factors.
* Identification of patients at increased risk of v-AKI and discovering safer ways to administer vancomycin may reduce the incidence of v-AKI.

**References**

1. Levine DP. Vancomycin: a history. Clin Infect Dis. 2006;42 Suppl 1:S5-12.

2. BNFC. VANCOMYCIN: BNFC; [Available from: <https://bnfc.nice.org.uk/drug/vancomycin.html>.

3. Lopes SRM, Gormezano NWS, Gomes RC, Aikawa NE, Pereira RMR, Terreri MT, et al. Outcomes of 847 childhood-onset systemic lupus erythematosus patients in three age groups. Lupus. 2017;26(9):996-1001.

4. Diaz R, Ramalheira E, Afreixo V, Gago B. Evaluation of vancomycin MIC creep in Staphylococcus aureus. Journal of Global Antimicrobial Resistance. 2017;10:281-4.

5. King DW, Smith MA. Proliferative responses observed following vancomycin treatment in renal proximal tubule epithelial cells. Toxicol In Vitro. 2004;18(6):797-803.

6. Filippone EJ, Kraft WK, Farber JL. The Nephrotoxicity of Vancomycin. Clinical Pharmacology and Therapeutics. 2017;102(3):459-69.

7. Begg EJ, Barclay ML, Kirkpatrick CM. The therapeutic monitoring of antimicrobial agents. Br J Clin Pharmacol. 2001;52 Suppl 1(Suppl 1):35S-43S.

8. Matzke GR, Zhanel GG, Guay DRP. Clinical Pharmacokinetics of Vancomycin. Clinical Pharmacokinetics. 1986;11(4):257-82.

9. 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. Antimicrob Agents Chemother. 2013;57(2):734-44.

10. Minejima E, Choi J, Beringer P, Lou M, Tse E, Wong-Beringer A. Applying new diagnostic criteria for acute kidney injury to facilitate early identification of nephrotoxicity in vancomycin-treated patients. Antimicrobial agents and chemotherapy. 2011;55(7):3278-83.

11. Cano EL, Haque NZ, Welch VL, Cely CM, Peyrani P, Scerpella EG, et al. Incidence of nephrotoxicity and association with vancomycin use in intensive care unit patients with pneumonia: retrospective analysis of the IMPACT-HAP Database. Clin Ther. 2012;34(1):149-57.

12. Kullar R, Davis SL, Levine DP, Rybak MJ. Impact of vancomycin exposure on outcomes in patients with methicillin-resistant Staphylococcus aureus bacteremia: support for consensus guidelines suggested targets. Clin Infect Dis. 2011;52(8):975-81.

13. Kellum JA, Lameire, N. KDIGO Clinical Practice Guideline for Acute Kidney Injury. International Society of Nephrology. 2012;2(1):138.

14. Akcan-Arikan A, Zappitelli M, Loftis LL, Washburn KK, Jefferson LS, Goldstein SL. Modified RIFLE criteria in critically ill children with acute kidney injury. Kidney Int. 2007;71(10):1028-35.

15. Critical Appraisal Skills Programme (2019). CASP (Systematic Review) Checklist. [online] Critical Appraisal Skills Programme; 2019 [Available from: <https://casp-uk.net>.

16. Moffett BS, Hilvers PS, Dinh K, Arikan AA, Checchia P, Bronicki R. Vancomycin-associated acute kidney injury in pediatric cardiac intensive care patients. Congenit Heart Dis. 2015;10(1):E6-10.

17. Zhang H, Gao P, Wang Y, Chen J, Jia G, Zhang F, et al. Baseline kidney function is associated with vancomycin-induced acute kidney injury in children: a prospective nested case-control study. Pediatr Nephrol. 2020.

18. Bonazza S, Bresee LC, Kraft T, Ross BC, Dersch-Mills D. Frequency of and Risk Factors for Acute Kidney Injury Associated With Vancomycin Use in the Pediatric Intensive Care Unit. J Pediatr Pharmacol Ther. 2016;21(6):486-93.

19. McNeil JC, Kok EY, Forbes AR, Lamberth L, Hulten KG, Vallejo JG, et al. Healthcare-associated Staphylococcus aureus Bacteremia in Children: Evidence for Reverse Vancomycin Creep and Impact of Vancomycin Trough Values on Outcome. Pediatr Infect Dis J. 2016;35(3):263-8.

20. Reilly AM, Ding MX, Rower JE, Kiser TH. The Effectiveness of a Vancomycin Dosing Guideline in the Neonatal Intensive Care Unit for Achieving Goal Therapeutic Trough Concentrations. J Clin Pharmacol. 2019;59(7):997-1005.

21. Bhargava V, Malloy M, Fonseca R. The association between vancomycin trough concentrations and acute kidney injury in the neonatal intensive care unit. BMC Pediatr. 2017;17(1):50.

22. Al Nuhait M, Abu Esba LC, Al Harbi K, Al Meshary M, Bustami RT. Acute Kidney Injury in Pediatric Treated with Vancomycin and Piperacillin-Tazobactam in Tertiary Care Hospital. Int J Pediatr. 2018;2018:9256528.

23. Benefield EC, Hagemann TM, Allen HC, Farmer K, Burton ME, Chavez-Bueno S, et al. Vancomycin Dosing and Pharmacokinetics in Postoperative Pediatric Cardiothoracic Surgery Patients. J Pediatr Pharmacol Ther. 2016;21(1):66-74.

24. Cies JJ, Shankar V. Nephrotoxicity in patients with vancomycin trough concentrations of 15-20 μg/ml in a pediatric intensive care unit. Pharmacotherapy. 2013;33(4):392-400.

25. Feiten HDS, Okumura LM, Martinbiancho JK, Andreolio C, da Rocha TS, Antonacci Carvalho PR, et al. Vancomycin-associated Nephrotoxicity and Risk Factors in Critically Ill Children Without Preexisting Renal Injury. Pediatr Infect Dis J. 2019;38(9):934-8.

26. Geerlof LM, Boucher J. Evaluation of vancomycin dosing and corresponding drug concentrations in pediatric patients. Hosp Pediatr. 2014;4(6):342-7.

27. Hundeshagen G, Herndon DN, Capek KD, Branski LK, Voigt CD, Killion EA, et al. Co-administration of vancomycin and piperacillin-tazobactam is associated with increased renal dysfunction in adult and pediatric burn patients. Crit Care. 2017;21(1):318.

28. Knoderer CA, Gritzman AL, Nichols KR, Wilson AC. Late-Occurring Vancomycin-Associated Acute Kidney Injury in Children Receiving Prolonged Therapy. Ann Pharmacother. 2015;49(10):1113-9.

29. Knoderer CA, Nichols KR, Lyon KC, Veverka MM, Wilson AC. Are Elevated Vancomycin Serum Trough Concentrations Achieved Within the First 7 Days of Therapy Associated With Acute Kidney Injury in Children? J Pediatric Infect Dis Soc. 2014;3(2):127-31.

30. Matson KL, Shaffer CL, Beck GL, Simonsen KA. Assessment of initial serum vancomycin trough concentrations and their association with initial empirical weight-based vancomycin dosing and development of nephrotoxicity in children: a multicenter retrospective study. Pharmacotherapy. 2015;35(3):337-43.

31. McKamy S, Hernandez E, Jahng M, Moriwaki T, Deveikis A, Le J. Incidence and risk factors influencing the development of vancomycin nephrotoxicity in children. J Pediatr. 2011;158(3):422-6.

32. McQueen KE, Clark DW. Does Combination Therapy With Vancomycin and Piperacillin-Tazobactam Increase the Risk of Nephrotoxicity Versus Vancomycin Alone in Pediatric Patients? J Pediatr Pharmacol Ther. 2016;21(4):332-8.

33. Moffett BS, Morris J, Kam C, Galati M, Dutta A, Akcan-Arikan A. Vancomycin associated acute kidney injury in pediatric patients. Plos One. 2018;13(10).

34. Ragab AR, Al-Mazroua MK, Al-Harony MA. Incidence and predisposing factors of vancomycin-induced nephrotoxicity in children. Infect Dis Ther. 2013;2(1):37-46.

35. Seixas GT, Araujo OR, Silva DC, Arduini RG, Petrilli AS. Vancomycin Therapeutic Targets and Nephrotoxicity in Critically Ill Children With Cancer. J Pediatr Hematol Oncol. 2016;38(2):e56-62.

36. Sinclair EA, Yenokyan G, McMunn A, Fadrowski JJ, Milstone AM, Lee CK. Factors associated with acute kidney injury in children receiving vancomycin. Ann Pharmacother. 2014;48(12):1555-62.

37. Totapally BR, Machado J, Lee H, Paredes A, Raszynski A. Acute Kidney Injury During Vancomycin Therapy in Critically Ill Children. Pharmacotherapy. 2013;33(6):598-602.

38. Woldu H, Guglielmo BJ. Incidence and Risk Factors for Vancomycin Nephrotoxicity in Acutely Ill Pediatric Patients. Journal of Pharmacy Technology. 2018;34(1):9-16.

39. Zhang T, Cheng H, Li Y, Dong YZ, Zhang Y, Cheng XL, et al. Paediatric acute kidney injury induced by vancomycin monotherapy versus combined vancomycin and meropenem. J Clin Pharm Ther. 2019;44(3):440-6.

40. Zhang H, Wang Y, Gao P, Hu J, Chen Y, Zhang L, et al. Pharmacokinetic Characteristics and Clinical Outcomes of Vancomycin in Young Children With Various Degrees of Renal Function. J Clin Pharmacol. 2016;56(6):740-8.

41. Jeffres MN IW, Doherty JA, Micek ST, Kollef MH. A retrospective analysis of possible renal toxicity associated with vancomycin in patients with health care-associated methicillin-resistant Staphylococcus aureus pneumonia. ScienceDirect Clinical Therapeutics. 2007;29(6).

42. 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.

43. Kaddourah A, Basu RK, Bagshaw SM, Goldstein SL, Investigators A. Epidemiology of Acute Kidney Injury in Critically Ill Children and Young Adults. N Engl J Med. 2017;376(1):11-20.

44. McGregor TL, Jones DP, Wang L, Danciu I, Bridges BC, Fleming GM, et al. Acute Kidney Injury Incidence in Noncritically Ill Hospitalized Children, Adolescents, and Young Adults: A Retrospective Observational Study. Am J Kidney Dis. 2016;67(3):384-90.

45. Goldstein SL. Acute kidney injury in children and its potential consequences in adulthood. Blood Purif. 2012;33(1-3):131-7.

46. Cano EL, Haque NZ, Welch VL, Cely CM, Peyrani P, Scerpella EG, et al. Incidence of Nephrotoxicity and Association With Vancomycin Use in Intensive Care Unit Patients With Pneumonia: Retrospective Analysis of the IMPACT-HAP Database. Clinical Therapeutics. 2012;34(1):149-57.

47. Contreiras C, Legal M, Lau TTY, Thalakada R, Shalansky S, Ensom MHH. Identification of risk factors for nephrotoxicity in patients receiving extended-duration, high-trough vancomycin therapy. The Canadian journal of hospital pharmacy. 2014;67(2):126-32.

48. Bamgbola O. Review of vancomycin-induced renal toxicity: an update. Therapeutic advances in endocrinology and metabolism. 2016;7(3):136-47.

49. Goldstein SL, Mottes T, Simpson K, Barclay C, Muething S, Haslam DB, et al. A sustained quality improvement program reduces nephrotoxic medication-associated acute kidney injury. Kidney Int. 2016;90(1):212-21.

50. Nephrology BAfP. BAPN AKI MANAGEMENT RECOMMENDATIONS. British Association for Paediatric Nephrology.

**Figure Legends and Tables**

**Figure 1 | A PRIMSA Flow Diagram summarising the process of screening and selection**

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| **Table 1 | A summary results table for the studies included in the systematic review** |
| **Author**  | **Year** | **Type of study** | **Study population & setting** | **Intervention details** | **Definition of kidney injury** | **Incidence of v-AKI** | **Result** |
| **Al Nuhait et al. (22)** | 2018 | Single centre retrospective cohort  | N=248, 54.0% male, median age of 5 years (IQR 2-7), paediatric tertiary care hospital. Neonates were excluded.  | Vancomycin monotherapy or concomitant therapy. Vancomycin duration of treatment ≥48 hours. Mean dose was 45.8mg/kg/day. | KDIGO | 1.6% | There was no increased risk of AKI in those receiving concomitant therapy versus vancomycin monotherapy.  |
| **Benefield et al.(23)**  | 2016 | Single centre retrospective cohort  | N=54, 55.6% male, mean age 1.1 years in a paediatric tertiary care hospital. Patients who had prior cardiothoracic surgery or not.  | Mean dose of vancomycin was 19.9mg/kg/day. | pRIFLE | 25.9% | All patients with v-AKI had prior cardiothoracic surgery. No other risk factors were identified.  |
| **Bhargava et al.(21)**  | 2017 | Single centre retrospective cohort | N=110 neonates, 52.7% male, mean gestational age (±SD) was 29 (±5) weeks, neonatal intensive care unit.  | Vancomycin duration of treatment ≥5 days.a | pRIFLE | 2.7% | A trough concentration of >15mg/L was a risk factor for v-AKI. |
| **Bonazza et al.(18)**  | 2016 | Single centre retrospective cohort | N=265 children on a paediatric intensive care unit, 58.5% male.b | n/aa | pRIFLE | 23.4% | Risk factors identified included treatment for >5 days, a trough concentration >20mg/L and use of >1 nephrotoxic medication. |
| **Cies et al.(24)**  | 2013 | Single centre retrospective cohort  | N=113 children on a paediatric intensive care unit, 60.2% male, median age of 2 years (range 0.08-23)  | Mean dose of vancomycin was 56.8mg/kg/day. | KDIGO | 7.1% | Duration of therapy and concomitant vasopressor use were risk factors for nephrotoxicity. |
| **Feiten et al.(25)** | 2019 | Single centre retrospective cohort  | N=110 children on a paediatric intensive care unit, 53.6% male, median age 15.5 months (IQR 6.00-70.25). | Median initial daily dose of vancomycin was 57.7mg/kg with a median treatment duration of 12 days. | pRIFLE | 11.8% | Identified risk factors included frequency of vancomycin dose, increased trough levels and use of furosemide or amphotericin. |
| **Geerlof et al.(26)**  | 2014 | Single centre observational retrospective cohort | N=102 children, 60.8% male, mean age 6.2 years (range 6 months-17 years) in a paediatric tertiary care hospital. | Mean daily dose of vancomycin was 54.9mg/kg. | KDIGO | 6.9% | Dose did not appear to be a risk factor for nephrotoxicity.  |
| **Hundeshagen et al.(27)**  | 2017 | Multicentre retrospective cohort | N=472 children, 62.7% male, mean age 7.3 years, paediatric burns unit. | Vancomycin alone (V), or with imipenem-cilastin (V/IC) or piperacillin-tazobactam (V/PT) for at least 48 hours. Initial starting dose was 15mg/kg every 6 hours. | KDIGO | 3.8% | The children receiving concomitant vancomycin and piperacillin-tazobactam made up all stage 3 paediatric AKI cases.  |
| **Knoderer et al.(29)**  | 2014 | Single centre retrospective cohort  | N=859 children, 54.1% male, median age 2.5 years (IQR 1-9).d | Mean vancomycin dose was 44.4mg/kg/day and treatment duration >72 hours. | pRIFLE | 19.4% | PICU admission and an initial trough concentration of ≥15µg/ml were associated with an increased risk of AKI.  |
| **Knoderer et al.(28)**  | 2015 | Single centre retrospective cohort | N=167 children, 56.3% male, median age 1.5 years (IQR 0.09-6.25), neonates excluded.d | Vancomycin duration >8 days, mean dose of vancomycin of 42.2mg/kg/day. | pRIFLE  | 12.6% | The only significant risk factor identified was age <1 year.  |
| **Matson et al.(30)**  | 2015 | Multicentre retrospective cohort | N=316 children, 50.9% male, mean age 6.8 years, two paediatric tertiary care hospitals. Neonates admitted to the neonatal intensive care unit were excluded. | Mean starting dose of vancomycin was 47.2mg/kg/day. | KDIGO | 22.7% | Concomitant loop diuretics, vasopressors, NSAIDs and ACE-inhibitors were all significant risk factors for nephrotoxicity. |
| **McKamy et al.(31)**  | 2011 | Multicentre retrospective cohort  | N=167 children including 6 term neonates, 53.9% male, mean age 6.7 years, community-based paediatric tertiary care hospital. Any premature infants and neonates admitted to the neonatal intensive care unit were excluded. | Mean vancomycin dose was 49.5mg/kg/day. | KDIGO | 14.4% | The main risk factors identified were high vancomycin trough concentration, concomitant treatment with furosemide and PICU admission. |
| **McNeil et al.(19)** | 2016 | Single centre retrospective cohort  | N=341 children including 82 with a history of prematurity, median age 20.4 months (IQR 1.2-115.7), paediatric tertiary care hospital.c  | n/aa | KDIGO | 14.9% | Risk factors independently associated with AKI were a trough concentration >15µg/mL and concomitant use of vasopressors or aminoglycosides.  |
| **McQueen et al.(32)**  | 2016 | Single centre retrospective cohort  | N=185 children, 59.5% male, mean age of 5.7 years, paediatric tertiary care hospital. | Patients were treated with vancomycin alone, or concomitant piperacillin-tazobactam for ≥48 hours. Mean vancomycin dose was 50kg/kg/day. | KDIGO | 3.8% (vancomycin alone), 23.6% (vancomycin and TZP) | The only other risk factor identified was for the combination group which was higher trough concentration of vancomycin.  |
| **Moffett et al.(16)**  | 2015 | Single centre case-control  | N=418 children on cardiac ICU including 83 neonates, 57.8% male, median age 181 days (range 2 days to 17.9 years), paediatric tertiary care hospital. | >1 dose of vancomycin, mean dose was 36.1mg/kg/day. | KDIGO | 7.2% | Extracorporeal membrane oxygenation was associated with an increased risk of v-AKI. |
| **Moffett et al.(33)**  | 2018 | Single centre retrospective cohort  | N=7,095 children including 674 neonates, 55.4% male, median age 4.1 years (IQR 0.67-11.2 years), paediatric tertiary care hospital. | Mean dose of vancomycin was 14.9mg/kg/day. Most (81.3%) received this for ≤72h. | KDIGO | 12.1% | Several risk factors were identified, including total dose, ICU admission, and concomitant medication (including nafcillin, clindamycin, and acetazolamide).  |
| **Ragab et al.(34)**  | 2013 | Single centre retrospective cohort  | N=265 children excluding neonates and infants, 49.1% male, mean age 1.9 years, community secondary care hospital. | Vancomycin treatment was for >48 hours with mean dose of 41.8mg/kg/day. | KDIGO | 27.2% | AKI was associated with concomitant aminoglycoside administration and admission to intensive care.  |
| **Reilly et al.(20)**  | 2019 | Single centre retrospective cohort | N=182 neonates with mean postmenstrual age (±SD) was 30.5 (±4.5) weeks, in the neonatal intensive care unit.c  | Mean dose of vancomycin was 37.5mg/kg/day. | KDIGO | 8.0% | No difference between vancomycin regimes.  |
| **Seixas et al.(35)**  | 2015 | Single centre observational cohort (mixed prospective and retrospective) | N=94 critically ill children with cancer, 61.7% male, median age 7.3 years (IQR 3.7-10.9), in a paediatric intensive care unit.  | Mean vancomycin dose was 59.2mg/kg/day. | KDIGO | 22.3% | A trough concentration of ≥20µg/mL was a significant risk factor for AKI. |
| **Sinclair et al.(36)**  | 2014 | Single centre retrospective cohort  | N=175 children, 57.1% male, median age 5.2 years (IQR 2.1-11.25), in a paediatric tertiary care hospital. | Mean dose was 60.0mg/kg/day and treatment duration >48 hours. | pRIFLE | 13.7% | AKI risk increased with every 5mg/kg increase in dose, each additional day of treatment and concomitant nephrotoxic medications.  |
| **Totapally et al.(37)**  | 2013 | Single centre retrospective chart  | N=284 children, 59.0% male, median age 2.2 years (IQR 0.24-7.57), in a paediatric tertiary care hospital. | Mean dose of vancomycin was 25.8mg/kg/day. | pRIFLE | 17.2% | Administration of other nephrotoxic drugs as well as a high BUN:SCr before therapy were both identified as risk factors for v-AKI. |
| **Woldu et al.(38)**  | 2017 | Single centre retrospective cohort  | N=291 children, 61.5% male, mean age 6.6 years, in a paediatric tertiary care hospital. | Mean dose of vancomycin was 16.8mg/kg/day. | KDIGO | 6.5% | The risk of developing AKI was increased by a final trough concentration of ≥15mg/dL and added piperacillin-tazobactam.  |
| **Zhang et al. (17)** | 2020 | Multicentre retrospective case-control | N= 124 children, 57.3% male, aged 0-14 years, in two tertiary care hospitals.b | Mean dose of vancomycin was 41.3mg/kg/day for >4 days. | pRIFLE | 8.0% | Nephrotoxicity was associated with furosemide use, moderate baseline kidney insufficiency and a trough concentration ≥15μg/ml.  |
| **Zhang et al.(40)**  | 2016 | Single centre retrospective cohort | N=110 children including 4 neonates, 67.3% male, median age 5.8 months (range 1.1-24.0 months), in a paediatric tertiary care hospital.  | Median dose of vancomycin was 39.5mg/kg/day, treatment duration ≥48 hours. | KDIGO | 4.5% | The risk was increased in children who had a moderately impaired baseline creatinine clearance.  |
| **Zhang et al.(39)** | 2018 | Multicentre retrospective cohort  | N=183 children, 61.2% male, median age 41.4 months (IQR 7.4-69.3 months), in two tertiary care hospitals.  | Median vancomycin dose was 40.0mg/kg/day with a median duration of 28 days. | KDIGO | 10.7% | Increased trough concentration was a risk factor for v-AKI in the group treated with concomitant meropenem.  |

a Dose of vancomycin was not specified.

b No mean or median age was available.

c Data on sex was not available.

dData on setting was not available.

**Table 2 | An overview of the potential risk factors identified in this systematic review.**

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| --- | --- | --- |
| **Risk factor** | Number of studies showing a positive association (% total studies identifying this potential risk factor) | Number of studies showing a negative/no association (% total studies identifying this potential risk factor) |
| Dose of vancomycin | 2 (20) | 8 (80) |
| Duration of treatment | 3 (23) | 10 (77) |
| Vancomycin therapeutic levels | 9 (45) | 11 (55) |
| Co-administration of a nephrotoxic medication | 12 (60) | 8 (40) |
| Critically ill children | 4 (100) | 0 (0) |
| Impaired renal function | 3 (100) | 0 (0) |
| Post cardiac surgery | 1 (50) | 1 (50) |
| Neonates and infants | 1 (50) | 1 (50) |
| Extracorporeal membrane oxygenation (ECMO) | 1 (50) | 1 (50) |

**Table 3 | Drugs found to be significantly associated with an increased risk of vancomycin-associated AKI by at least one study**

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| --- | --- | --- | --- |
| **Drug** | **Papers with significant findings** | **Result** | **Papers showing no association** |
| Furosemide | Zhang et al. (17) | OR = 24.8; CI = 6.4-98.2; p-value 0.000 | Moffett et al. (2015) (16)Moffett et al. (2018) (33)Ragab et al. (34)Seixas et al. (35)Woldu et al. (38)Zhang et al. (2019) (39) |
| McKamy et al. (31) | OR = 9.45; CI = 3.44-26.00; p-value < 0.01 |
| Bonazza et al. (18) | OR 3.52, 95% CI = 1.88-6.62; p-value <0.01 |
| Feiten et al. (25) | OR = 2.563; 95% CI = 1.377-4.769; p-value <0.01 |
| All Loop-diuretics | Matson et al. (30) | OR = 42.8; p-value <0.01 | n/a |
| Piperacillin-Tazobactam (TZP) | Woldu et al. (38) | OR = 3.14; 95% CI = 1.02-9.6; p-value = 0.046 | Al Nuhait et al. (22)Feiten et al. (25)Zhang et al. (2020) (17) |
| Hundeshagen et al. (27) | KDIGO stage 3 AKI was higher in the V/TZP group (2%) than in the V group (0%; p-value <0.05) |
| Moffett et al. (2018) (33) | OR = 1.46; 95% CI = 1.16–1.84; p-value = 0.001 |
| McQueen et al. (32) | Nephrotoxicity developed in 3/79 patients (3.8%) in the vancomycin group and in 25/106 patients (23.6%) on combination therapy with TZP (p-value = 0.0001) |
| Vasopressors | Cies et al. (24) | OR = 11.1; 95% CI = 1.4-85; p-value = 0.011 | n/a |
| Matson et al. (30) | OR = 18.4; p-value = 0.02 |
| McNeil et al. (19) | 4/13 (30.8%) of children with AKI had concomitant vasopressor use compared to 5/94 (5.3%) of children without AKI (p-value = 0.01) |