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Pharmacovigilance procedure for off-label large doses of vancomycin in children with serious illnesses

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ABSTRACT

The goal is to examine risk-control measures and the safety of off-label high-dose vancomycin usage in critically unwell children.
Techniques: Analysis was done on a case of severe kidney damage in the Pediatric Intensive Care Unit (PICU) brought on by off-label high-dose vancomycin (more than 40 mg/kg/day). A retrospective case-control analysis of 39 PICU patients treated with vancomycin between January and June 2020 was carried out.

Results: Of the 39 patients, only 53.8% (21/39) had blood concentration tests done, and 20 (51.3%) were given off-label high-dose vancomycin treatment. Three incidences of severe vancomycin-associated adverse events were among the five patients (25%; 5/20) in the off-label usage group. We enhanced training, provided customized medication regimens, increased monitoring of vancomycin trough serum levels, officially documented off-label drug usage, and implemented improvement measures based on risk factor analysis. Following the implementation of these precautions between July 2020 and December 2022, vancomycin was administered to 86 children in the PICU, and no instances of acute renal damage linked to vancomycin were noted. The vancomycin blood concentration monitoring rate rose to 88.4% (76/86).
Implications: When administering large doses of vancomycin to critically sick children, there is a chance that renal function may be harmed; thus, medical professionals should be especially mindful of this in clinical pharmaceutical safety procedures.

KEYWORDS

vancomycin, off-label, acute kidney injury, child, pharmacovigilance

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1 Introduction

An essential medication for treating severe Gram-positive bacterial infections is vancomycin, a glycopeptide antibiotic that works by preventing the formation of bacterial cell walls (Scholar, 2007). Vancomycin has been used extensively in newborns and children due to the rising frequency of nosocomial infections brought on by coagulase-negative staphylococci and drug-resistant Staphylococcus aureus (Downes et al., 2017; Diorio et al., 2018; Jernigan et al., 2020). There is still disagreement over the best vancomycin dosage and blood drug concentration for premature infants, term newborns, critically ill children, and obese children, despite agreement on the therapeutic drug range and dosage for adult patients (Sosnin et al., 2019; Sridharan et al., 2019; Issaranggoon Na Ayuthaya et al., 2020; Oskarsdottir et al., 2021; Smit et al., 2021). At the same time, there is a growing interest in how vancomycin affects children's renal function. According to reports,

intravenous

Vancomycin and piperacillin/tazobactam given to critically unwell children may raise the risk of acute kidney damage (Downes et al., 2017), and vancomycin-induced acute kidney injury is more likely to occur in children with renal insufficiency (Zhang et al., 2021). Vancomycin concentrations in pediatric patients must therefore be monitored, particularly in children who are in severe condition. In 2019, Chengdu Women's and Children's Central Hospital and Chengdu Adverse Reaction Center established a pharmacovigilance office for women and children. Four vigilance pharmacists and one medication safety officer (MSO) make up the office, which is in charge of the hospital's overall pharmacovigilance efforts. In our institution, a mechanism has been put in place to apply clinical medication interventions and detect indications of adverse drug events from aberrant drug concentration monitoring findings. The hospital has successfully improved the safe pharmaceutical environment inside the hospital by lowering the frequency of adverse drug events and creating a reasonably extensive medication safety monitoring system for particular groups via ongoing research and development. The office personnel observed an acute renal injury linked to vancomycin. In response, our hospital carried out a focused intervention and a comprehensive research to address risk factors related to the delivery of vancomycin to critically sick children.

2 Participants and methods

2.1 Review an acute kidney injury case caused by off-label high-dose vancomycin

A 6.2-kg baby who had previously had a live-donor liver transplant for congenital biliary atresia and was on immunosuppression was brought to the intensive care unit (PICU) due to abrupt respiratory failure and severe pneumonia. The patient had a brief maculopapular rash, recurring fever (peaking at 39.4 °C), tachypnea, and sporadic coughing for one week. One day before admission, the patient's symptoms worsened, resulting in less oral intake and more respiratory effort. After using loratadine, the rash went away, and ibuprofen helped with the fever. There were no known medication allergies in the youngster. Immunosuppressants were used till admission without explanation; prior medical history includes liver transplants and newborn jaundice. Severe pneumonia, respiratory failure, moderate-to-severe dehydration, and moderate anemia were among the main admission diagnoses. During this presentation, there were no suspected adverse drug reactions (ADRs).

The baby had a temperature of 38.4 °C, a heart rate of 201 bpm, a respiratory rate of 52 breaths per minute, and a blood pressure of 111/69 mmHg when they were admitted. The patient had impaired skin turgor, slight perioral cyanosis, decreased salivation and tearing, and an irritated appearance. Lung auscultation revealed medium to moderate rales together with coarse breath sounds. There was also a surgical scar on the abdomen. The first range of serum creatinine values was within acceptable limits.

Along with supportive drugs, the patient received treatment with acetylcysteine (150 mg nebulized q8h), budesonide (1 mg nebulized q6h), and meropenem (120 mg IV q8h). On the third day in the hospital, voriconazole (25 mg PO every 12 hours) was started. After the addition of vancomycin (90 mg IV every 6 hours) on day 5, the baseline serum creatinine level was 45.4 μmol/L.

The trough serum concentration level was raised to 21.8 μg/mL two days after starting vancomycin (therapeutic range: 5–10 μg/mL; Clinical Pharmacology Group of Pediatric Branch of the Chinese Medical Association, 2015). In line with acute renal damage, serum creatinine simultaneously rose to 65.1 μmol/L (reference range: 17.3–54.6 μmol/L). After stopping vancomycin and switching to linezolid, creatinine returned to normal in two days, confirming the diagnosis of vancomycin-associated nephrotoxicity. To evaluate drug-induced renal impairment, a pharmacovigilance review was started.

2.2 Investigation of risk factors of vancomycin used in severely ill children

Our hospital's PICU is responsible for the transfer of critically ill children within the province and the city, as well as emergency rescue efforts for severe cases in the hospital. The most common adverse reaction to vancomycin in our hospital is various types of rashes, followed by red man syndrome, liver and kidney function damage, and fever. Although the number of cases of liver and kidney function damage is small, it has a significant impact on the growth and development of children, so attention should be paid to the safety of medication for children in clinical

practice.

To understand the vancomycin-associated adverse reactions in our hospital, we investigated the number of children who were administrated vancomycin. The schematic diagram of included patients was showed in Figure 1.

2.2.1 Patients and methods

Inclusion criteria: (1) Inpatient in our hospital from January 2020 to June 2020; (2) Received vancomycin treatment for ≥24 h; (3) Aged between 0 and 18 years, with no gender restriction.

Exclusion criteria: (1) Cases with incomplete clinical data (e.g., no clear records of weight, premature birth status, etc.); (2) History of abnormal renal function or kidney transplantation before vancomycin treatment; (3) Not hospitalized in PICU.

Included patients were divided into two groups according to the dosage of vancomycin. The dosage of vancomycin off-label use group was above 40 mg/kg/day, while on-label use group was below 40 mg/kg/day. The efficacy of each drug was assessed based on whether the expected effect of the drug was observed. To assess the safety, we evaluated not only the reported ADRs but also events that occurred during the administration of vancomycin. According to KDIGO Criteria, vancomycin-associated acute kidney injury were

defined an increase in serum creatinine by ≥ 0.3 mg/dL (≥26.5 μmol/L) within 48 h, or an increase in serum creatinine to ≥1.5 times baseline.

We obtained a list of patients' data including patient demographics, diagnoses, reasons for administration, weight, dosage and duration of vancomycin treatment, vancomycin trough serum concentration and details of ADRs. The age of the patients was categorized as follows: 0–1 year, 1–3 years, 4–7 years, 8–12 years and 12–18 years. The primary outcomes were the efficacy and safety of the drugs, including mortality.

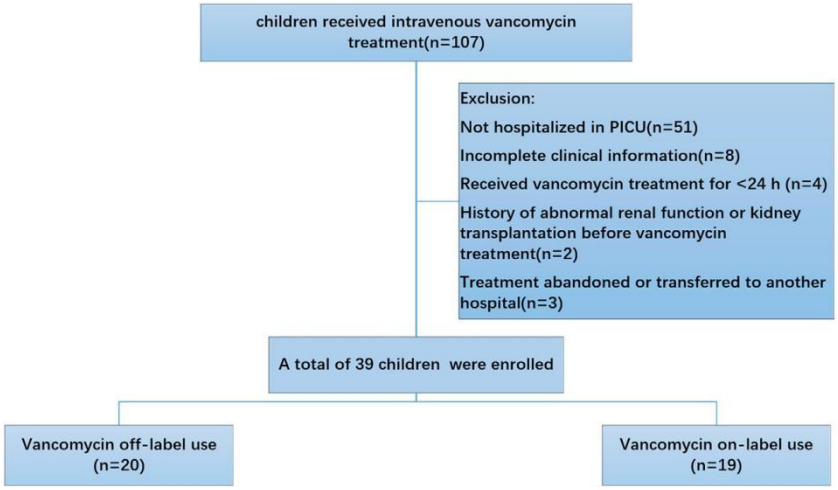

FIGURE 1
The schematic diagram of included patients.

2.2.2 Statistic methods

Descriptive analyses were performed to analyze the continuous variables. Categorical variables are expressed as numbers and percentages, and continuous variables as mean (standard deviation [SD]) or medians with the interquartile range. Student's t-test or Mann-Whitney rank-sum test was used to test the statistical significance of continuous data. Binary logistic regression analysis was performed to evaluate the association between parameters and adverse drug events. All analyses were performed using Excel 2019 for Windows and SPSS ver. 22 (IBM Corp., Armonk, NY, United States of America). A threshold of $P < 0.05$ was set to indicate statistical significance.

3 Results

3.1 Basic information of included patients

Based on the above inclusion and exclusion criteria, 39 pediatric patients were finally included in the analysis. Basic information, underlying diseases, vancomycin usage (dose, duration of treatment), detection results of vancomycin trough serum concentration, vancomycin-associated adverse reactions, and treatment outcomes were recorded. According to the vancomycin prescribing information, dose for pediatric and infant patients is 40 mg/kg per day, whereas newborns should receive 10–15 mg/kg per dose. In this survey, 6 patients (15.4%) received a lower dose than recommended, 13 patients (33.3%) received the recommended dose, and 20 patients (51.3%) received a higher dose than recommended. The maximum daily dose was 84.21 mg/kg, the minimum daily dose was 35.09 mg/kg, and the average dose was 46.30 ± 10.84 mg/kg. Table 1 shows the demographic and clinical characteristics of the included patients. The total number of cases was 39. Gender factor had no clinically significant difference between off-label use and on- label use of vancomycin. Some parameters in the studied table showed a significant difference when comparing off-label use with on-label use of vancomycin; these were steady-state dosage, mean

age, weight,

outcome and adverse reactions. Other parameters showed a non- significant difference when comparing off-label use with on-label use of vancomycin; these were gender, duration of vancomycin therapy and Infection types.

3.2 Vancomycin-associated adverse reactions in our hospital

39 pediatric patients in the PICU received vancomycin treatment, accounting for 43.32% of the total vancomycin usage in the hospital. Five cases of vancomycin-associated adverse reactions were reported, including three severe adverse reactions: one case each of liver function damage, kidney function damage, and red man syndrome. These accounted for 83.3% of the vancomycin-associated adverse reactions reported in the hospital in 2020. The basic information of the cases with severe adverse reactions is shown in Table 2.

3.3 Monitoring of vancomycin concentration in PICU

In this study, the duration of vancomycin treatment ranged from 2 to 36 days, with a median duration of 8 days. Thirty patients (76.9%) received treatment for more than 3 days. According to the "Expert Consensus on Therapeutic Drug Monitoring for Children" (2015) (11), blood concentration monitoring is recommended for children who have been on vancomycin for more than 3 days, have severe infections, unstable renal function, or are concomitantly using other nephrotoxic or ototoxic drugs. Actual therapeutic drug monitoring of vancomycin was performed on 21 cases (41 times), with a blood drug concentration submission rate of 53.8% (21/39). Adjustments of vancomycin dosage were made in 14 cases after monitoring. Table 3 presents the details of the 21 patients who underwent vancomycin concentration monitoring. The correlation between monitoring results and vancomycin dosage is illustrated in Figure 2, which shows that the vancomycin concentrations *in vivo* do not correlate with the dose administered.

TABLE 1 Demographic and clinical characteristics of the patients.

Group		Vancomycin off-label use (>40 mg/kg/day)	Vancomycin on-label use (≤40 mg/kg/day)	P
Sample size		20	19	
Steady-state dosage (mg/kg/d)		38.9 ± 1.8	53.3 ± 11.2	0.000[a]
Age (years)		1.8 ± 2.8	5.2 ± 4.5	0.007[a]
	<1, *n* (%)	13 (65.0%)	6 (31.6%)	
	1–3, *n* (%)	4 (20.0%)	4 (21.1%)	
	4–7, *n* (%)	2 (10.0%)	2 (10.5%)	
	8–12, *n* (%)	0 (0.0%)	2 (10.5%)	
	>12, *n* (%)	1 (5.0%)	5 (26.3%)	
Gender				
	Male, *n* (%)	13 (65%)	9 (47.4%)	0.267
	Female, *n* (%)	7 (35%)	10 (25.6%)	
Duration of vancomycin therapy (days)		9.1 ± 6.5	11.3 ± 8.3	0.267
Weight (kg), IQR		6.65 (3.3, 23.5)	15 (3,57)	0.010[a]
Outcome				
	Good outcome[a], *n* (%)	14 (70%)	18 (94.7%)	0.000[a]
	Poor outcome[a], *n* (%)	6 (30%)	1 (5.3%)	
Adverse reactions				
	Nephrotoxicity, *n* (%)	1 (5.0%)	0	0.047[a]
	Hepatotoxicity, *n* (%)	1 (5.0%)	0	
	Red man syndrome, *n* (%)	1 (5.0%)	0	
	Drug fever, *n* (%)	1 (5.0%)	0	
	Rash, *n* (%)	1 (5.0%)	0	

Infection type, *n* (%)				
	Septicopyemia, *n* (%)	9 (45.0%)	7 (36.8%)	0.605
	Pneumonia, *n* (%)	13 (65.0%)	11 (57.9%)	0.648
	Meningitis, *n* (%)	7 (35.0%)	2 (10.5%)	0.070
	Dermal infection, *n* (%)	2 (10.0%)	2 (10.5%)	0.957
	Urinary tract infection, *n* (%)	1 (5.0%)	1 (5.3%)	0.970
	Endocarditis, *n* (%)	1 (5.0%)	0 (0.0%)	0.323

[a]Good outcome: recovery or improvement; Poor outcome: AKI, or lack of improvement.

TABLE 2 Basic Information of Cases with severe Adverse Reactions.

ADRs	Age (days)	Weight (kg)	Single dose of vancomincy (mg)	Frequency	dosage (mg/kg/day)
Red man syndrome	49	4.36	50	q6h	45.87
Liver function lesion	46	3.6	50	q6h	55.56
vancomycin-associated nephrotoxicity	246	6.2	90	q6h	58.08

TABLE 3 Basic information of patients monitored for vancomycin drug concentration [*n*(%)].

	Max Value	Min Value	Average Value
Age (days)	4,267	63	1179.46 ± 1513.42
Duration of medication (days)	35	2	14.76 ± 6.56
Daily dose (mg/kg)	77.42	28	46.57 ± 11.63
Vancomycin concentration (ug/mL)	39.3	3.3	14.04 ± 9.61

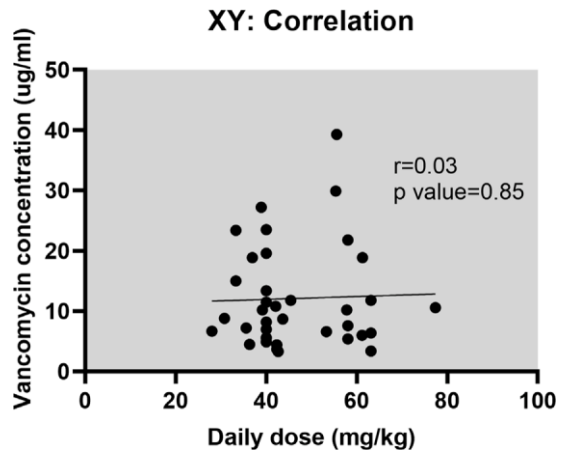

FIGURE 2
The correlation between vancomycin dosage and concentration (r = 0.03, p = 0.85).

3.4 Risk factor analysis of vancomycin therapy in severely ill children

3.4.1 Risks associated with characteristic of vancomycin

Vancomycin belongs to the category of high-alert medications for children in China, with the primary risk points being toxicity of vancomycin in the clinical setting, especially for severely ill children.

nephrotoxicity and ototoxicity. The recommended strategy involves its application under the guidance of infectious disease specialists, strictly adhering to its indications, and closely monitoring blood drug concentrations (Wang et al., 2017). In the early stages of vancomycin development, its severe toxicity was associated with contaminants in the drug preparation. However, with continuous improvements in preparation techniques, the toxicity related to drug impurities has been significantly reduced (Darko and Guharoy, 2003). Reports indicate that a vancomycin concentration of 10 mg/L is associated with increased risks of treatment failure and antibiotic resistance, while concentrations exceeding 20 mg/L may increase the likelihood of nephrotoxicity (Liu et al., 2011; Elyasi et al., 2012; Jung et al., 2014). This is particularly relevant in critically ill patients with dynamic pharmacokinetics, where trough serum concentrations may not reliably reflect AUC targets. Bayesian approaches enable AUC estimation with limited blood samples, facilitating individualized dosing in children where frequent sampling is challenging. Therefore, it is crucial to revisit the

3.4.2 Physiopathological risks in severely ill children

The pediatric population varies widely in age, body size, and developmental stage, which also affects changes in pharmacokinetics and pharmacodynamics (Thakkar et al.,

2017). Due to variations in renal clearance and distribution volume, it is more difficult for children to achieve and maintain the desired serum concentrations of vancomycin compared to adults, and this challenge is often exacerbated in severely ill pediatric patients. Changes such as capillary leakage, fluid shifts, alterations in renal clearance (both increases and decreases), variations in protein concentration and drug binding, and modifications in liver function can lead to significant variations in vancomycin serum concentrations in severely ill children, even at standard doses (Kloprogge et al., 2019). Therapeutic interventions like renal replacement therapy, extracorporeal membrane oxygenation, administration of blood products, use of vasoactive agents, and administration of multiple drugs may all result in notable pharmacodynamic changes. The existing standard dosing guidelines for vancomycin in children have not been specifically validated in critically ill patients. These patients likely exhibit different drug distribution and elimination patterns compared to the general population, affecting the calculation of crucial pharmacokinetic parameters such as AUC, which warrants further investigation (Mahmood, 2014). Consequently, achieving optimal therapeutic vancomycin levels may rely on continuous monitoring, corresponding dose adjustments, and clinical response to treatment.

3.4.3 Risks of off-label dosing

In this investigation, it was observed that off-label dosing of vancomycin is a relatively common practice in the clinical management of severely ill children, posing risks for both physicians and patients. The new "Medical Practitioners Law" stipulates that off-label drug use can only be initiated "under special circumstances where there are no effective or better treatment options available," and it should be accompanied by strict informed consent, monitoring of adverse reactions, and proactive treatment. The 2020 consensus guidelines for vancomycin therapeutic drug monitoring, updated by the American Society of Health-System Pharmacists (ASHP), the Infectious Diseases Society of America (IDSA), the Pediatric Infectious Diseases Society (PIDS), and the Society of Infectious Diseases Pharmacists (SIDP) (Rybak et al., 2020), also mention that "the safety of vancomycin doses exceeding 80 mg kg-1 d-1 in children has not been prospectively evaluated. It is advisable to avoid vancomycin doses ≥100 mg kg-1 d-1, as they may exceed exposure thresholds." The three cases of severe adverse reactions reported in the PICU all involved doses exceeding the recommended label, indicating that extra caution should be exercised when using off-label doses of vancomycin for anti-infective treatment in severely ill children. Monitoring serum creatinine concentrations and vancomycin trough serum concentration is recommended to ensure safety and efficacy.

4 Discussion

The following enhancements are suggested in light of the risk considerations linked to vancomycin therapy: (1) Boost the vancomycin blood concentration monitoring rate. Children receiving vancomycin must have their trough serum concentration monitored at least once during treatment; (2) pharmacists should use the Bayesian method in conjunction with monitoring results to determine individual pharmacokinetic parameters for dose adjustment, resulting in customized medication regimens; (3) PICU physicians and nurses must receive training on vancomycin pharmacokinetics, pharmacodynamics, dosage and usage for children, medication precautions, effects of concurrent medications, selection of compatible solvents, preparation concentration, dripping speed, the correlation between drug concentration monitoring results and dosage, severe adverse reactions, and the risks of off-label drug use; (4) Put in place an off-label drug use record system for vancomycin overdose in critically ill children. A permission form must be completed, express informed agreement from the patient or their family members must be acquired, and comprehensive disclosure requirements must be met if a patient does in fact need an off-label dosage. We examined the usage of vancomycin among hospitalized children in the PICU from July 2020 to December 2022 and contrasted it with data from January to June 2021 prior to the intervention in order to evaluate the efficacy of the initiatives. According to the findings, 86 children were treated with vancomycin, and none of them suffered from renal function impairment as a consequence of off-label vancomycin dosage. Following the intervention, the vancomycin blood concentration monitoring rate rose from 53.8% (21/39) to 88.4% (76/86), with a statistically significant change ($\chi 2 = 18.401$, $P < 0.01$).

A thorough analysis of the patient's medication regimen revealed that the acute kidney damage was caused by supratherapeutic vancomycin exposure from off-label use. Our results support earlier research in children that shows significant interindividual variability in vancomycin clearance, particularly in critically sick patients, underscoring the shortcomings of trough-only monitoring (Akunne et al., 2022). The single-center design, small sample size, and reliance on trough serum concentrations rather than AUC-guided dosage are limitations of this research that may compromise exposure accuracy and generalizability. To confirm safer dosage regimens in this susceptible group, model-informed Bayesian prediction for AUC targeting should be used in future multi-center prospective studies.

5 Conclusion

With its shown clinical effectiveness against hospital-acquired infections, penicillin-resistant Streptococcus pneumoniae, and methicillin-resistant Staphylococcus aureus, vancomycin is often used to treat critically unwell children. However, children may have irreparable damage from its nephrotoxicity and ototoxicity, particularly in cases of acute illness if dosage fluctuations are substantial. There are also off-label dosage procedures used in clinical settings, which, if improperly handled, might quickly result in negative side effects. As a result, pharmacists should focus especially on vancomycin's safe clinical usage.

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