CASE REPORT

Subtherapeutic Target Attainment of Intermittent Vancomycin in a Paediatric Burn Patient: A Case Report.

Sakina Nur Najah Abdul Jabar[1*], Suzana Mustafa[2]

[1] Pharmacy Department, Hospital Tengku Ampuan Afzan, Ministry of Health, Malaysia.
[2] Pharmacy Department, Hospital Raja Perempuan Zainab II, Ministry of Health, Malaysia.

Corresponding Author
Sakina Nur Najah Abdul Jabar
Pharmacy Department, Hospital Tengku Ampuan Afzan
Ministry of Health, Malaysia
Email: sakinajabar@gmail.com

Submitted: 10/07/2025. Revised edition: 08/10/2025. Accepted: 16/10/2025. Published online: 01/11/2025.

Abstract
Vancomycin pharmacokinetics in pediatric burn patients can be significantly altered compared to non-burned children due to the physiological changes caused by burn injuries, especially in the hypermetabolic and hyperdynamic phases. Subtherapeutic serum vancomycin concentrations and the consequent need for drastic modification of vancomycin dosage regimen has been reported. This is a case report of a paediatric patient with a Total Body Surface Area (TBSA) of 50 percent with subtherapeutic vancomycin target attainment even with a total daily dose of more than 80 mg/kg/day and the use of prolonged vancomycin infusion.

Keywords: *Burn, paediatric, pharmacokinetics, therapeutic drug monitoring, vancomycin.*

Introduction

Burns constitute a major global public health concern. The World Health Organization (WHO) estimated that burn injury has led to 180,000 deaths yearly, and two-thirds of the occurrence were in the African and South-East Asia regions. Children are more vulnerable to burn injury, and it is the fifth most common cause of non-fatal childhood injuries [1]. A study done by Collier Z. J. et.al. (2022) concluded that Asian children aged below five years old were the most impacted by disability-adjusted life years (DALYs); 314 years/100,000 people. Other findings reported that children aged between 5 and 14 years old had the highest burn rate (219 cases/100,000) [2].

In Malaysia, a cohort of 255 paediatric patients was admitted between 2016 to 2018 to a paediatric burn referral centre in Peninsular Malaysia. The study reported that blood and wound cultures showed growth of methicillin-resistant *Staphylococcus aureus* (MRSA), *Staphylococcus aureus*, *Enterococcus* sp., *Pseudomonas* sp., *Streptococcus* sp., *Escherichia coli*, *Acinetobacter baumannii*, and *Enterobacter* sp. [3]. Similar pathogens have also been isolated in paediatric burn patients from other regions [4,5].

Vancomycin is a glycopeptide antibiotic widely used in paediatric patients to treat serious Gram-positive infections, including those caused by MRSA. The area under the concentration-time curve over 24 hours relative to the minimum inhibitory concentration (AUC_{24}/MIC) of 400 - 600 mg.h/L is the best predictor of vancomycin efficacy and toxicity. Trough concentration is commonly used as an alternative measure of obtaining the AUC_{24}/MIC [6]. In paediatric burn patients, physiological changes including increased cardiac output, capillary leak, and altered renal clearance significantly affect vancomycin pharmacokinetics. The body's physiological reaction to a major burn injury can be divided into two main stages: an acute phase lasting about 48 hours, followed by a hypermetabolic phase that can continue for several weeks [7,8].

The acute phase begins immediately after the burn, characterized by a state of shock. During this period, small blood vessels in both affected and unaffected tissues become increasingly permeable, allowing fluids and proteins to leak out of the circulatory system, resulting in extensive tissue swelling. This fluid shift, along with circulating mediators, leads to decreased cardiac output, increased vascular resistance, and reduced blood flow to organs. These physiologic changes will lead to slower absorption of oral drugs, larger drug volume of distribution (Vd), changes in the amount of free drug, and reduction of drug clearance. The hypermetabolic phase begins around 48 hours post-injury. In this phase, inflammatory and circulating factors trigger a heightened metabolic response, cardiac output rises, vascular resistance decreases, and blood flow to various organs improves. Better absorption of oral drugs, changes in drug distribution patterns, and an increase in drug clearance, as well as drug loss via burn wounds, are expected [8].

Vancomycin pharmacokinetics in paediatric burn patients are significantly altered from those in non-burned children due to the physiological changes caused by burn injuries, especially in the hypermetabolic and hyperdynamic phases [8]. Shorter vancomycin elimination half-life ($t_{1/2}$) was reported in burn patients, which resulted in a one-third increment in vancomycin clearance (CL_v). This will subsequently lead to subtherapeutic serum vancomycin concentrations and drastic modification of vancomycin dosage regimen [9,10]

To our knowledge, few reports have described the use of vancomycin in Malaysian paediatrics; nevertheless, no published data comprehensively address the optimization of initial dosing and therapeutic drug monitoring outcomes in burn cases. Studies done in the Malaysian indigenous

population mainly focus on pharmacogenetics variation and pharmacokinetics of other drugs such as clopidogrel [11,12]. Therefore, this case report aims to offer insights into optimizing vancomycin dosing in pediatric burn patients.

Case report

A 9-year-old indigenous Malaysian boy, weighing 21 kilograms (kg), was admitted to the Burn Unit on 21st September 2024 (Day 1) with scalds burns caused by hot water around 5 pm. He suffered burns on bilateral upper limbs, anterior and posterior trunk, bilateral thighs, buttocks, and genital area with a Total Body Surface Area (TBSA) of 50 percent. The burn injury involved varying depths of skin damage, ranging from superficial dermal to deep dermal layers.

Despite being treated with appropriate antibiotics following reported culture and sensitivity reports, there were still episodes of temperature spikes (ranging between 37.8 to 38.1 °C) and increasing C-reactive protein values (105 mg/L to 143.9 mg/L). Intravenous (IV) vancomycin 15 milligram per kilogram (mg/kg) every 8 hours was initiated on Day 20 post-burn as empirical coverage against MRSA infection. Nevertheless, no positive culture for Gram-positive organisms was obtained during the hospital stay. Patient was stable during the hospital stay with no desaturation episodes. Glomerular filtration rate (GFR) was estimated by using the Bedside Schwartz formula, ranging between 155 and 466 mL/min/1.73 m^2, with a urine output of 3 to 5 mL/kg/hour, during the vancomycin course. Augmented renal clearance (ARC), defined as GFR greater than or equal to 130 ml/min/1.73 m^2, was seen in this case [13].

Table 1 shows a summary of vancomycin regimes, obtained vancomycin concentrations, and computed pharmacokinetic profiles. The patient's Vd was approximately twice the normal reference range for paediatric patients (0.63 ± 0.16 L/kg), and a shorter vancomycin $t_{1/2}$ was observed in this patient compared to the normal paediatric range of 5.6 ± 2.1 hours [6]. Only a single therapeutic AUC_{24}/MIC measurement was obtained during treatment, even though the dose had been adjusted. The obtained trough concentrations were predominantly below 10 mg/L. A total daily dose of 86 mg/kg/day was recommended, representing an estimated 91% increase from the initial dose. However, no concentration monitoring was performed following this dose adjustment.

Discussion

Limited studies have been done in paediatric burn populations. Most studies focused on adult burn patients with variations in the degree of burns, and some included all age ranges in the study design. Several studies reported subtherapeutic trough vancomycin concentration following the standard initiation dose of vancomycin. Gomez D.S. et al. (2013) found that only 15% of pediatric burn patients receiving vancomycin at 10–15 mg/kg per dose every 6 hours, infused over one hour, achieved a trough concentration above 10 mg/L [10]. In a previous report, an average initial vancomycin dose of 31.5 ± 9.3 mg/kg/day, administered every six to eight hours, resulted in subtherapeutic trough concentrations averaging 1.4 ± 1.2 mg/L [14]. This was observed in a case report of an 8-year-old male patient with burns covering 20% of his total body surface area, including 8% third-degree burns on the lower limbs, who was started on intravenous vancomycin at 37 mg/kg/day every 6 hours and achieved a subtherapeutic trough concentration of 1.7 mg/L [15].

Subtherapeutic target attainment was also found in several studies involving adult burn patients. Adult burn patients treated with the standard regimen of intravenous vancomycin 1 gram administered every 12 hours yielded lower trough concentration compared to control non-burned patients (6.4 versus 9.2 mg/L) [16]. Similar findings were reported in adult Chinese burn

patients, in which 83% of the subjects had with subtherapeutic trough vancomycin concentration of less than 10 mg/L [17].

A study reported a statistically significant increase averaging 108.2% from the initial standard vancomycin dose, resulting in a trough concentration of 7.3 ± 4.7 mg/L ($p < 0.001$). The mean adjusted dose was 58.3 $\pm$ 5.4 mg/kg/day administered every four to eight hours [14]. Similarly, another study found that burn patients had a shorter half-life and 33% faster vancomycin, requiring a dose of 46.6 ± 20 mg/kg/day compared to 26.1 ± 5.9 mg/kg/day in control patients to achieve nearly identical peak and trough serum concentrations. This study also found that a more frequent dosing interval was required in burn patients compared to controls to maintain the trough concentration within 5 to 10 mg/L. However, the study subjects consisted of burn patients aged between 5 and 47 years old [18]. A recent study by Gomez D.S. et al. (2013) involving paediatric burn patients aged one to eleven years suggested that a vancomycin dose of 90 to 100 mg/kg/day is necessary to achieve optimal pharmacokinetic and pharmacodynamic (PK/PD) target attainment in this population (AUC_{24}/MIC > 400 mg.h/L, trough concentration > 10 mg/L). This higher dose recommendation closely aligns with the vancomycin dosing given in this case report.

In this case, a strategy of prolonging the vancomycin infusion time to three hours was utilized. Though the vancomycin trough concentrations were subtherapeutic, the levels obtained in this case were promising, indicating progress toward target attainment. The effectiveness of using prolonged vancomycin infusion in order to obtain therapeutic targets was supported by a study done by Li J. et.al. (2024). This retrospective study found that prolonging vancomycin infusion to three hours (PI) leads to significantly higher trough concentrations compared to standard intermittent infusion of one hour (SI). The median trough concentration was statistically significant between these two groups (11.2 versus 7 mg/L, p-value: 0.02). The target concentration attainment rate in the PI group and SI group was 59.4% and 19.3%, respectively (p-value: 0.001). There were no significant differences between the groups regarding the safety profile [19].

Continuous vancomycin infusion (CI) has been practiced in hospital settings, even in paediatric patients. To date, no published data on paediatric burn patients with vancomycin CI. One study done in critically ill burn adult patients observed comparable overall clinical outcomes with CI Vancomycin dosing compared to intermittent infusion (II). Toxicity was minimal with both infusion methods, although patients receiving CI showed a higher frequency of Vancomycin levels exceeding 25 mg/L. Despite this increased incidence of elevated levels, no significant increase in adverse effects was noted, suggesting that both dosing strategies maintain a favourable safety profile. Additionally, CI resulted in more frequent attainment of therapeutic vancomycin concentrations and fewer instances of subtherapeutic concentrations compared to II [5]. Use of CI vancomycin was found beneficial in paediatrics practice in terms of time to therapeutic attainment [20,21]. However, evidence comparing CI to PI specifically is limited, with most research contrasting continuous versus standard intermittent strategies. Both prolonged and continuous infusions seem to provide similar safety profiles, with no significant difference in nephrotoxicity [5,19].

In paediatric burn patients, physiological changes such as hyperdynamic circulation and increased cardiac output enhance renal blood flow, contributing to ARC. This leads to faster vancomycin clearance and often necessitates higher dosing regimens to achieve PK/PD targets. Studies have shown that standard vancomycin doses (60 mg/kg/day) often fail to reach optimal exposure in patients with ARC, while increased doses of 70-80 mg/kg/day or more may be

required. Modeling studies emphasize the importance of individualized dosing in this population to avoid underdosing and treatment failure [22]. Vancomycin treatment failure is associated with significantly increased 30-day mortality and can negatively impact long-term survival [23].

Conclusion

Interpatient variability and enhanced vancomycin clearance identified in burns patients will lead to subtherapeutic vancomycin target attainment. Standard initial dosing may not be sufficient for therapeutic attainment. Clinicians should anticipate increased vancomycin requirements in pediatric burn patients due to altered pharmacokinetics. Early therapeutic drug monitoring and individualized dosing strategies are essential to achieve optimal target concentrations and ensure treatment efficacy. Multicenter pharmacokinetic studies focusing on pediatric burn populations in Southeast Asia are warranted to address regional variations and improve evidence-based dosing guidelines.

Conflicts of interest

The authors have no funding or conflicts of interest to disclose. The first author is under the Malaysia Advanced Clinical Pharmacy Programme (MyACPP - Clinical Pharmacokinetic).

Acknowledgements

The authors would like to thank the Director General of Health Malaysia for his permission to publish this article. The authors express their gratitude to the Head of the Department of Pharmacy at Hospital Tengku Ampuan Afzan and Hospital Raja Perempuan Zainab II, Ministry of Health, who provided insight, advice, and expertise that greatly assisted in this article.

Authors' contribution

SNNAJ contributed to manuscript preparation, data collection, and revisions. SM contributed to manuscript review, editing, and approved the final version.

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Table 1. Summary of Vancomycin regimes, obtained Vancomycin concentrations and computed pharmacokinetic profiles.

Days post burn (Day)	Vancomycin regime	Infusion Duration (hour)	Vancomycin daily dose (mg/kg/day)	Vancomycin concentration (mg/L)		Computed pharmacokinetic profiles				Suggested regime
				Trough[a]	Peak[b]	Ke[c] (/hr)	$t_{1/2}$[c] (hr)	Vd[c] (L/kg)	AUC24/MIC[d] Target: 400-600 (mg.h/L)	
22	315 mg every 8 hours	1	45	< 2	8.4	Unable to be computed			Unable to be computed	315 mg every 6 hours
25	315 mg every 6 hours	1	60	2.5	7.8	0.38	1.83	1.55	**128 (Subtherapeutic target attainment)**	400 mg every 6 hours
28	400 mg every 6 hours	2	76	3.3	NM	0.26	2.67	1.55	**265 (Subtherapeutic target attainment)**	400 mg every 6 hours
31	400 mg every 6 hours	3	76	6.5	NM	0.18	3.91	1.55	425 (Therapeutic target attainment)	400 mg every 6 hours
34	400 mg every 6 hours	3	76	3.5	NM	0.25	2.77	1.55	**313 (Subtherapeutic target attainment)**	450 mg every 6 hours
35	450mg every 6 hours	3	86	NM	NM	Unable to be computed			Unable to be computed	OFF

Ke: Elimination rate constant; $t_{1/2}$: Elimination half-life; Vd: Volume of distribution; AUC_{24}/MIC: Area under the concentration-time curve over 24 hours relative to minimum inhibitory concentration; NM: not measured.

[a] Trough was measured concentration obtained within 0-60 minutes before dose served.

[b] Peak was measured concentration obtained 2 hours after dose served, alternatively, 1 hour after Vancomycin infusion completed.

[c] Estimated via the Sawchuk-Zaske calculation method.

[d] Estimated via the trapezoidal approach, assuming MIC of 1 mg/L.