Poltekita: Jurnal Ilmu Kesehatan
e-ISSN: 2527-7170 dan p-ISSN: 1907-459X
Volume 19 Issue 1, 2025, page 56-67
DOI: 10.33860/jik.v19i1.2026
Website:https://ojs.polkespalupress.id/index.php/JIK
Publisher: Poltekkes Kemenkes Palu

Original Article

Drug Utilization Study of Vancomycin in a Tertiary Hospital

Vitarani Dwi Ananda Ningrum[1]*, Nurul Ambariyah[2], Camelia D. Fortuna[3], Yulianto[1]
[1]Laboratory of Pharmacy Practice, Department of Pharmacy, Universitas Islam Indonesia, Yogyakarta, Indonesia
[2]Senior Clinical Pharmacist at Dr. Sardjito Hospital, Yogyakarta, Indonesia
[3]Department of Pharmacy, Universitas Islam Indonesia, Yogyakarta, Indonesia
*Corresponding author: vitarani.ningrum@uii.ac.id

ARTICLE INFO

Article History:
Received: 2024-04-01
Published: 2025-03-31

Keywords:
drug utilization study; vancomycin; tertiary hospital; Indonesia.

ABSTRACT

Vancomycin possesses not only a narrow therapeutic range but also nephrotoxic effects, thus requiring intensive monitoring. This study aims to analyze the vancomycin use among the inpatients of a referral in Indonesia. This retrospective cross-sectional research collected a two-year data from medical records. The research involved all the patients who met the inclusion criteria. The majority of the 90 patients receiving vancomycin were men with the most age range of 18-60 years. The dominant indication of vancomycin use was sepsis typically caused by methicillin-resistant Staphylococcus aureus (MRSA) and Staphylococcus haemolyticus. Meanwhile, the vancomycin dosing for the 1-<18 age range was mostly based on actual body weight, whereas that for other age categories took into account renal function. The effectiveness of vancomycin based on White Blood Cells and neutrophils was shown in 34.88% of patients examined for both parameters. In addition, 6.25% of the patients given a platelet count experienced suspected vancomycin-induced thrombocytopenia. No incidence of vancomycin-induced neutropenia and nephrotoxicity was found. Given that the risk of nephrotoxicity and the effectiveness of vancomycin are influenced by the steady-state concentrations and the area under the curve, this study recommends hospitals in Indonesia to provide Therapeutic Drug Monitoring (TDM) services.

INTRODUCTION

Methicillin-resistant Staphylococcus Aureus (MRSA) is a strain of *S. aureus* that is the main cause of bacteremia, endocarditis, skin and soft tissue infections, bone and joint infections, and hospital-acquired bacterial infections with consistently high levels of morbidity and mortality. Although the data on the prevalence of MRSA infection in Indonesia is not as complete as that in advanced countries, the mean prevalence recorded in hospitals ranges between 33% and 45.3%[1], and the highest reported prevalence has reached 52%[2] with an MRSA carrier rate of 4.3% among surgical patients when discharged.[3] This rapidly increasing incidence of MRSA infection has led to more prescriptions of vancomycin, which is the only antibiotic listed in the newest National Formulary of Indonesia as a third-line antibiotic (reserve antibiotic) and should be confirmed by culture test. Meanwhile, Vancomycin-resistant Enterococcus (VRE) issues have reached more than 20%,[4] especially among inpatients with at least 7 days of hospitalization, which then becomes another problem that should be prevented through the wise use of vancomycin.

In addition, caution should be exercised regarding the possibility of adverse drug reactions (ADRs) and clinically significant drug interactions between vancomycin and other drugs, possibly in the form of increased nephrotoxicity and ototoxicity. This can occur when such antibiotics are used concomitantly with amphotericin B, colistin, bacitracin, aminoglycosides, polymyxin B, and cisplatin, with a reported incidence rate of < 5% [5,6] and a very low prevalence of ototoxicity.[7]

Several studies on the use of vancomycin in Indonesia have been conducted, but the majority of them involved a limited number of patients, carried out less in-depth analyses of the dosage, and did not take into account the aspect of ADR.[8,9] In fact, until now TDM services using vancomycin are rarely found in Indonesian hospitals, only limited to research purposes conducted by academic institutions. Inadequate instruments and hospital human resources who are not yet proficient are challenges in implementing TDM in Indonesian hospitals. The hope is that this study will provide valuable advice for the government and hospital management who encourage the provision of TDM services. Therefore, this study analyzes retrospectively the use of vancomycin, which includes the diagnosis, dosage, duration of use, culture test, effectiveness, and incidence of ADR, to get broader data for all patient age categories as part of the recommendation for providing a safe, effective strategy toward TDM services.

METHODS

This retrospective cross-sectional study was conducted at Dr. Sardjito Hospital, which is one of the tertiary referral hospitals and teaching hospitals for prospective healthcare workers in Indonesia. This study analyzed the use of vancomycin injection for pediatric inpatients aged ≥ 1 year old, adult, and geriatric patients who have prescribed vancomycin for a minimum of 3 days. The research involved all the patients who met the research criteria including patients from pediatrics, ICU, surgical, and internal departments. The presentation of data at the medical record unit is based on disease, while data on drug use needs to be traced from data in the pharmacy department. Therefore, data collection began with data collection in the pharmacy department and was then explored further in the medical records. Patients who received vancomycin but died less than three days after it was prescribed were excluded from the study. The patients' demographic characteristics along with data on the diagnosis, dosage of vancomycin, duration of administration, and effectiveness of vancomycin based on the white blood cells (WBC) and neutrophil value, as well as ADRs such as nephrotoxicity, neutropenia, and thrombocytopenia, were obtained from the medical records. The use of vancomycin was considered effective if the patient experienced improvements in leukocyte and neutrophil values. Apart from that, if the blood sedimentation rate increased or was still high, then the use of vancomycin was categorized as ineffective. ADR events were assessed based on data recorded in the medical record. Nephrotoxicity is if the patient experiences a decrease in creatinine clearance, while neutropenia is if the patient's neutrophil levels decrease. In addition, thrombocytopenia if the patient experienced a decrease in platelets after using vancomycin. The univariate analysis was used to present the demographic characteristics, diagnosis, appropriateness of vancomycin dosing, effectiveness, and ADRs in percentages processed in the Excel program of Microsoft Office version 365. The achievement of effectiveness and incidence of ADRs due to vancomycin as assessed by the research team, was further confirmed by the pharmacist at Sardjito Hospital. The research has received ethical approval issued by the Faculty of Medicine of Universitas Gadjah Mada No. KE/FK/0149/EC.

RESULTS

Ninety inpatients were prescribed vancomycin injections for different diagnoses with a variety of dosages and durations of administration. The dose of vancomycin takes into account age (and body weight for pediatric patients), and renal function. Coverage of subjects in all age categories resulted in variations in dose findings in this research. Meanwhile, in some hospitals in Indonesia, vancomycin is also known to be administered as eye drops, resulting from reconstituting the dry powder of vancomycin injection by adding aqua for injection and diluting

with 0.9% NaCl. In this study, the patients given such drops were excluded. The characteristics of the participants who fulfilled the inclusion criteria are presented in **Table 1**.

Table 1. Characteristics of the patients

Characteristics	Number of patients (%)
Gender	
Male	58 (64.5)
Female	32 (35.5)
Age (years)	
1-<18	9 (10)
18 – 60	56 (62.2)
> 60	25 (27.8)
Diagnosis	
Sepsis	25 (27.8)
Healthcare-associated pneumonia (HCAP)	24 (26.7)
Community-acquired pneumonia (CAP)	7 (7.8)
Sepsis shock	6 (6.7)
Diabetic ulcer	3 (3.3)
Neutropenic fever	3 (3.3)
Submandibular abscess	3 (3.3)
Endocarditis	2 (2.2)
Leukocytosis	2 (2.2)
Open segmental fracture	1 (1.1)
Crush injury with open segment	1 (1.1)
Staphylococcal UTI	1 (1.1)
Closed fracture of acetabulum	1 (1.1)
Pericarditis	1 (1.1)
Guillain-Barre syndrome	1 (1.1)
Stage V chronic kidney disease (CKD) on CAPD	1 (1.1)
Neglected open fracture of distal	1 (1.1)
Chronic obstructive pulmonary disease (COPD) with secondary infection	1 (1.1)
Wagner 3 MRSA diabetic ulcer	1 (1.1)
Peritonitis	1 (1.1)
Meningoencephalitis	1 (1.1)
Septic arthritis	1 (1.1)
Lung tumor with systemic infection	1 (1.1)
Non-hemorrhagic stroke with systemic infection	1 (1.1)
Bacterial culture test	
MRSA	3 (3.4)
MRSE	1 (1.1)
Streptococcus sanguinis	1 (1.1)
Streptococcus viridans	1 (1.1)
Staphylococcus lentus	1 (1.1)
Staphylococcus haemolyticus	3 (3.4)
Staphylococcus epidermidis	1 (1.1)
Streptococcus faecalis	1 (1.1)
Enterococcus faecalis	2 (2.2)
Gram-positive	8 (8.9)
No name of bacteria	2 (2.2)
No microbial growth	10 (11.1)
No culture	56 (62.2)
Vancomycin sensitivity test	
Sensitive	22 (24.5)
Intermediate	1 (1.1)
Resistant	2 (2.2)
No sensitivity test	65 (72.2)
Duration of use (days)	
< 7	32 (35.6)

Characteristics	Number of patients (%)
7	20 (22.2)
> 7	38 (42.2)

This study found that a large majority of patients who received vancomycin were men aged between 18-60 years old (62.2%). The two diseases most commonly treated with vancomycin are sepsis and HCAP (healthcare-associated pneumonia), respectively. The types of bacteria largely found in the blood culture tests were gram-positive bacteria, MRSA, and *Staphylococcus haemolyticus* with the longest seven (7) days' duration of vancomycin use (seven days) in this study.

To date, vancomycin administration in Indonesian hospitals has used a renal function approach based on creatinine clearance levels and/or body weight instead of the vancomycin pharmacokinetic AUC or Bayesian software program when only two vancomycin concentrations are available, as recommended by ASHP/The Infectious Diseases Society of America (IDSA)/PIDS/SIDP. The vancomycin dosing profiles used in this study are described in **Table 2**.

Table 2. Distribution and appropriateness of vancomycin dosing

Diagnosis	n	Age (years)			Creatinine clearance (mL/min)			Dosage appropriateness	
		1-<18	18-60	> 60	< 20	20-49	≥ 50	Yes (n=62)	No (n=28)
Sepsis [a]	25	1	14	10	1	7	13	17	subdose (3); overdose (5)
Healthcare-associated pneumonia (HCAP)[a]	24	3	15	6	2	7	11	15	subdose (5); overdose (4)
Community-acquired pneumonia (CAP)[a]	7	1	4	2	1		4	7	
Sepsis shock [a]	6	1	4	1	1		2	5	overdose (1)
Diabetic ulcer	3		2	1			3	1	subdose (2)
Neutropenic fever[a]	3	2	1			1	1		subdose (1); overdose (2)
Submandibular abscess[a]	3	1	2				2	1	subdose (1); overdose (1)
Endocarditis	2		2				2	1	subdose (1)
Leukocytosis	2		2				2	2	
Open segmental fracture	1		1				1	1	
Crush injury with open segment	1		1				1	1	
Staphylococcal UTI	1		1			1		1	
Closed fracture of acetabulum[a]	1		1		-	-	-	1	
Pericarditis	1		1				1	1	
Guillain-Barre syndrome	1			1			1	1	
Stage V chronic kidney disease (CKD) on CAPD	1		1		1				overdose (1)
Neglected open fracture of distal	1		1				1	1	
Chronic obstructive pulmonary disease (COPD) with secondary infection	1			1			1	1	

[a]without creatinine clearance test (n = 27): sepsis (n = 4); HCAP (n = 4); CAP (n = 11); sepsis shock (n = 3); nephropenic fever(n = 1); submandibular abscess (n = 1); closed fracture of the acetabulum (1); Wagner 3 MRSA diabetic ulcer (1); septic arthritis (1)

Table 2 shows the distribution of the diagnosis and vancomycin dosing based on the patients' age category as well as the appropriateness according to the guidelines for recommended dosage. The study found a 31.1% inappropriateness of vancomycin dosing, mostly in patients with HCAP.

This study also found that 14 patients (15.6%) received a subtherapeutic dose of vancomycin, and a similar number of subjects were prescribed vancomycin at a dose that exceeded the standard. Meanwhile, several patients had subtherapeutic vancomycin doses because of longer administration intervals.

This study also showed that patients with impaired renal function were prescribed vancomycin based on creatinine clearance. Three patients with chronic renal disease who underwent hemodialysis were administered vancomycin. One patient with continuous ambulatory peritoneal dialysis (CAPD) received an excessive dose of vancomycin (500 mg/6 h).

Additionally, only 43 patients (47.8%) underwent white blood cell and neutrophil count tests to estimate the effectiveness of systemic vancomycin. The effectiveness of vancomycin and its adverse drug reactions are shown in **Table 3**.

Table 3. Effectiveness and ADR related with vancomycin use

Variables	Number of patients n=90 (%)			
	With test	Without test	Yes	No
Effectiveness				
WBCs and neutrophils	43 (47.8)	47 (52.2)	15 (16.7)	28 (31.1)
Adverse Drug Reaction				
Neutropenia	51 (56.7)	39 (43.3)	0 (0)	51 (56.7)
Thrombocytopenia	48 (53.3)	42 (46.7)*	3 (3.3)	45 (50.0)
Nephrotoxicity	39 (43.3)	51 (56.7)**	0 (0.0)	0 (0.0)

*17 patients underwent a platelet count test; 25 patients underwent a platelet count test only once.

** 23 patients were not given a renal function test; the remaining (n = 28) had a CrCl test once only

Table 3 shows that most of the vancomycin use is ineffective based on the WBC and neutrophil parameters. Vancomycin was assessed as effective in only 15 patients consisting of 9 adults and 6 elderly patients. Meanwhile, concerning ADRs, there was only thrombocytopenia in three patients (3.3%). Table 3 shows no incidence of neutropenia in patients who received vancomycin at Dr. Sardjito Hospital. The presence of a small number of patients who were categorized as effective in using vancomycin, and also the incidence of ADRs, meant that further analysis could not be carried out. The results of creatinine test in this study are presented in **Table 4**.

Table 4. Patients' creatinine level and use of combination drugs

Creatinine level	n (%)	Name of combination drugs potentially increasing the risk of nephrotoxicity	n (%)
No creatinine test	23 (25.6)	Furosemide	14 (15.6)
1x creatinine test	28 (31.1)	Ketorolac	10 (11.1)
Elevated creatinine	15 (16.7)	Gentamicin	6 (6.7)
1-10 %	4 (4.4)	Irbesartan	5 (5.6)
11-20%	6 (6.7)	Bisoprolol	5 (5.6)
21-30 %	0 (0.0)	Valsartan	5 (5.6)
31-40 %	5 (5.6)	Amikacin	5 (5.6)
Creatinine in normal range	24 (26.7)	Acyclovir	3 (3.3)

The highest frequency of creatinine tests for patients in the study location was only once during the use of vancomycin. In this study, there was no elevated creatinine level that reached 50% of the baseline, thereby indicating that no incidence of nephrotoxicity was found during the use of vancomycin. Meanwhile, the drugs in combination with vancomycin, which increase the

likelihood of nephrotoxicity, used by more than 10% of patients in this study were the loop diuretic furosemide and the analgesic ketorolac.

DISCUSSION

Several studies of vancomycin use in different countries also showed similar findings to those of this study regarding the majority of male patients being prescribed vancomycin regardless of the age categories.[10–13] In general, men are more susceptible to pathogenic infections, including bacterial infections, with a higher mortality rate, likely due to hormonal differences.[14,15]

Sepsis-septic shock cases dominated the diagnoses and were mostly treated with vancomycin. In general, the approach to selecting empiric antibiotics for sepsis and septic shock has yet to consider all variables and patient risk factors. However, vancomycin is the antibiotic of choice for sepsis or septic shock due to infection from the lungs, central nervous system (CNS), and soft tissue, but not from intra-abdominal or genitourinary infections [16]. In addition, it is recommended that serious nosocomial infections, such as HCAP, be treated with vancomycin [17]. A study involving 140 cases of vancomycin use in a tertiary hospital in China found that patients with MRSA infection were sensitive to vancomycin, with a minimum inhibitory concentration (MIC) range of 1-2 μg/mL.[13] Two meta-analyses concluded that the use of vancomycin is effective in patients infected with *S.aureus*, in critical condition, with renal impairment, sepsis, MRSA infection, and hospitalized patients for hemodialysis or in the emergency department as proven by achieving the therapeutic range in patients with a loading dose based on body weight with minimal ADR.[18,19]

The use of vancomycin remains maintainable while efforts to prevent its resistance are being made, and to date, no other antibiotics are superior to vancomycin.[20] In addition, some guidelines and studies support the use of vancomycin as the antibiotic of choice for patients with HCAP. However, if there is no lower respiratory culture, it is recommended to stop administering empiric vancomycin to patients with MRSA-negative nasal and throat cultures and a clinical pulmonary infection score of < 6.[21] In addition to vancomycin, the IDSA has recommended the use of antibiotics such as daptomycin, telavancin, clindamycin, linezolid, or cefazolin for MRSA-infected inpatients with non-purulent cellulitis. The first three antibiotics are not yet available in the Indonesian market. Although a retrospective cohort study of more than 1000 non-critically ill patients with HCAP showed that linezolid is more effective than vancomycin,[22] it has not been listed in Indonesia's National Formulary to date, thus precluding it from being covered by the National Health Insurance or BPJS Kesehatan.[23]

In this study, MRSA-infected patients were assessed using cefoxitin screen*ing.* Cefoxitin is a surrogate marker for methicillin resistance. Cefoxitin screening in agar media is considered accurate, easy to perform, and offering high specificity. There are similar findings related to the type of bacteria that infect pediatric patients treated with vancomycin. A study reveals that Vancomycin actively eradicates gram-positive bacteria, such as *Staphylococcus aureus, S. epidermidis, S. pyogenes, S*. *pneumoniae, streptococcus viridans, Bacillus sp., Actinomyces sp.*, *Clostridium sp.* and *Corynebacterium* sp., as well as gram-negative bacteria, such as *Enterococcus sp.* [24]. Therefore, in this study, the use of vancomycin based on the bacterial culture results was deemed appropriate. In addition, the majority of the patients were found to be vancomycin-sensitive, which is similar to the findings of research conducted in another tertiary hospital in Indonesia.[25]

Vancomycin is an empiric antibiotic for *S. aureus* infection owing to its bactericidal activity against methicillin-resistant and methicillin-sensitive strains. However, according to the Infectious Diseases Society of America, the recommended first-line antibiotics for *Staphylococcal* infections are those in the beta-lactam group. Vancomycin is used not only as an empiric therapy but also as a definitive therapy for patients with beta-lactam allergy. However, despite its use as a definitive therapy, vancomycin remains less effective than beta-lactam antibiotics in patients with MSSA bloodstream infections.[26] In this study, the use of vancomycin was still dominated by the lack of culture and sensitivity tests. A limitation of this retrospective study is that the data

were based on medical records, making it difficult to further explore the patients' clinical presentation and clinical considerations from the doctor in charge.

A literature study stated that, due to the increasing failure of vancomycin therapy in MRSA infection, there is a tendency to administer it at high doses, although this can even increase the risk of nephrotoxicity. In addition to high doses (> 4 g/day), other factors that increase the risk of vancomycin-induced nephrotoxicity are concomitant use of other nephrotoxic drugs, such as amphotericin B and aminoglycosides, duration of vancomycin use for longer than 7 days, and inpatients' length of stay, especially in the ICU.[27]

The determination of vancomycin doses considers the severity of bacterial infection, patients' overall clinical conditions, renal function, and actual body weight. Meanwhile, the frequency of vancomycin administration is approximately every 8–24 h in accordance with the renal function, age, and vancomycin AUC to ensure its safety. Therefore, as an antibiotic with a narrow therapeutic range, vancomycin should be administered based on an individual approach, such as physiological changes in body composition from pediatric to elderly, level of severity, and clinical presentation.[28]

Pharmacokinetically, vancomycin is an antibiotic primarily eliminated through the kidneys and has the potential to cause nephrotoxicity, thus requiring consideration of patients' renal function when determining the dosage. The data obtained from the medical records of pediatric patients indicate that vancomycin dosage is determined based only on actual body weight without considering renal function (CrCl). However, pediatric patients clinically showed no renal function deterioration, thus allowing the absence of renal function tests. A pediatric population-based study involving nearly 2000 patients found primacy of renal function, in addition to actual body weight, to be a major consideration in the determination of vancomycin safe dosage for patients aged 1-18 years.[29] A meta-analysis concluded that pediatric patients with obesity have the potential to experience higher vancomycin concentrations and toxicity due to vancomycin use when the dose is determined solely based on actual body weight.[30] Therefore, it is necessary to examine renal function prior to vancomycin administration. Meanwhile, according to a study conducted at a children's hospital involving almost 300 patients over 3 years, vancomycin-induced nephrotoxicity is relatively rare in children, is reversible, and occurs in 6.5% of children, with the average serum creatinine level returning to normal within five days after vancomycin discontinuation.[31] On the other hand, it is recommended to consider actual body weight, eGFR, and age in the administration of vancomycin to patients because higher vancomycin levels are found in the elderly.[32] Further pharmacokinetic studies are necessary for other factors in Indonesian patients to provide a more accurate model of vancomycin dosing.

With regard to the highest use of vancomycin for sepsis-septic shock patients in this study (total n = 31 or 34.4%), a number of studies emphasize specific amounts of vancomycin dose, which comprise the need for a higher loading dose and maintenance dose for critically ill patients to achieve a therapeutic level of vancomycin more rapidly. The administration of a loading dose of 25 mg/kg followed by a maintenance dose based on the vancomycin serum showed significantly higher trough and peak concentrations, as well as AUC when compared to the use of an empiric dose of 15 mg/kg every 8 hours[33] despite a higher risk of acute renal injury.[34] Meanwhile, an updated consensus guideline suggests a dose of 15–20 mg/kg followed by daily maintenance infusions at doses of 30–40 mg/kg (up to 60 mg/kg) to achieve a target steady-state concentration of 20–25 mg/L for critically ill administrating continuous infusion.[28].

A vancomycin dose of ≥ 2 g every 8 hours in adult patients with sepsis or septic shock and creatinine clearance of ≥ 80 mL/min/1.73 m^2 is required to achieve optimal therapeutic exposure [35]. In this study, however, the patients did not receive a loading dose, and even the dose of vancomycin for all patients with CrCl > 50 mL/minute was 1 gram/12 hours. Unfortunately, the administration of a vancomycin loading dose is an extremely rare occurrence in clinical practice in Indonesia, although it can become an important consideration as a strategy to achieve therapeutic levels faster and increase effectiveness, especially in cases of sepsis, due to increased vancomycin clearance.[36,37] However, several cohort studies on the benefits of loading doses have shown inconsistent findings.[38,39]

Vancomycin is a time-dependent antibiotic; therefore, with an appropriate daily dose, it is

recommended to administer vancomycin more frequently and pharmacokinetically through continuous infusion to minimize fluctuations in vancomycin levels [40,41]. Meanwhile, the guidelines recommend individualized vancomycin dosing for patients undergoing hemodialysis by setting a therapeutic target of vancomycin at a 24-hour AUC/MIC ratio of 400-600. Should there be limitations of such a service, it is recommended to conduct monitoring based on the pre-dialysis serum concentrations of vancomycin and extrapolate such values to estimate the AUC. Maintaining a pre-dialysis concentration between 15 and 20 mg/L is likely to result in a 24-hour AUC of < 600 mgh/L, which will reach the target of 400-600 AUC/MIC ratio, assuming an MIC of 1 mg/L. In general, a fixed vancomycin dose after hemodialysis (e.g., 750 mg or 1000 mg) is unlikely to reach the therapeutic target for patients, because it becomes more affected by obesity and/or excess fluid.[42] In addition, a study of the administration of 18 mg/kg vancomycin every 48-72 hours shows that 10 patients with CAPD can achieve the therapeutic level[43] although it also suggests that therapeutic drug monitoring (TDM) and pharmacodynamic effect (MIC) are important to provide an appropriate algorithm of vancomycin dosing for patients in such category.[44] The appropriateness of vancomycin dosing can also be based on the indications of its use in relation to the target for plasma steady-state concentrations of vancomycin.[11] The absence of TDM services or MIC examinations shows the limitations of a pharmacokinetic-pharmacodynamic analysis of vancomycin use, thus impeding the determination of the ideal vancomycin dosage.

In terms of ADR, vancomycin-induced thrombocytopenia occurred in two late-elderly patients and one older adult, of which two were male and one was female. The considerably low incidence of thrombocytopenia found in this study is in accordance with studies that analyzed comparable vancomycin-induced ADR designed as case reports or case series, since it is a relatively rare type of ADR found in the clinical domain.[45–50] A higher prevalence, reaching approximately 16.2%, was reported in a study involving 105 patients in a Vietnamese Hospital. [51] Thrombocytopenia indicates a decrease in platelet count to <100,000/mm^3. Vancomycin-induced thrombocytopenia typically occurs between the 5th and 10th day of vancomycin use and can be resolved by discontinuing vancomycin administration. Therefore, the platelet count will increase one–two days after discontinuation.

The thrombocytopenia case in the older adult in this study occurred on day 2 of vancomycin use and continued to decline until day 5. On the 7th day of vancomycin use, the platelet count increased to a normal range after the patient received platelet transfusions twice. A different result was observed in thrombocytopenia experienced by a late elderly patient. Vancomycin-induced thrombocytopenia occurred on the 6th day of treatment. Transfusion was administered on day 8 of vancomycin administration, but was not effective. The patient died dead on the 10th day of vancomycin use with septic shock. The incidence of thrombocytopenia in the third patient occurred on the 2nd day of vancomycin therapy. The patient received transfusion on day 4, which was effective in increasing the platelet count by >50%. The platelet count on day 6 was within the normal range. Similar studies have found that thrombocytopenia occurs with varied durations of vancomycin administration. Two patients experienced vancomycin-induced thrombocytopenia on the second day of administration.[52] However, the diagnosis of vancomycin-induced thrombocytopenia is often challenging due to the presence of other concomitant contributing factors, as well as because of the limitations of diagnostic test.[53] A limitation of this descriptive cross-sectional study is that it was difficult to confirm whether the incidence of thrombocytopenia in the three aforementioned patients was induced by vancomycin use.

In addition to thrombocytopenia, vancomycin has the potential to induce another ADR, neutropenia, a condition in which the number of neutrophils in the blood is reduced. A greater possibility of neutropenia occurs in patients who receive vancomycin therapy for >7 days, thus requiring weekly monitoring through a WBC count. Vancomycin-induced nephrotoxicity is an ADR associated with elevated trough concentrations of vancomycin.[54] To assess nephrotoxicity, it is necessary to examine serum creatinine levels at least twice, with a 50% increase from the initial creatinine level. Seven of 21 patients experienced reduced creatinine levels with a corresponding decrease in blood urea nitrogen (BUN) values. Meanwhile, other patients had elevated creatinine levels of approximately less than 0.5 Â mg/dL, and five of the 15 patients with elevated creatinine

had a history of chronic renal disease. However, the creatinine increase occurred inconsistently or within 48-72 hours. Two types of ADR associated with vancomycin use, neutropenia and nephrotoxicity, were not observed in this study.

Although this study revealed that the dominant duration of administration was more than seven days, a previous study showed that there was no significant correlation between nephrotoxicity and duration of therapy. Nephrotoxicity occurs 6.7-fold more frequently in patients receiving vancomycin therapy concomitantly with aminoglycosides.[55] However, this did not occur in the 11 patients who received gentamicin (6 patients) or amikacin injection (the remaining) (Table 4). In addition, not all patients at Dr. Sardjito Hospital underwent a complete renal function test, thus leading to limited assessment of vancomycin-induced nephrotoxicity. Another limitation of this study was not including a control group, meaning that this study cannot prove either the effectiveness or the incidence of ADRs that were found to be caused by the use of vancomycin. Analytical studies involving a larger number of subjects, prospectively, and analyzing pharmacokinetics data to ensure effectiveness and ADR prevention of vancomycin are needed to provide a comprehensive perspective.

Frequent platelet, WBC, and neutrophil counts, and especially renal function tests for patients receiving vancomycin injection, are recommended to ensure safety and effectiveness, particularly for patients with high-risk factors such as patients administered a combination of aminoglycoside antibiotics. Similarly, for pediatric patients, actual body weight is insufficient to consider vancomycin dosing to avoid toxicity in pediatric patients with obesity.

CONCLUSION

Two diagnoses with the highest vancomycin use were sepsis and HCAP, mostly with appropriate dosing. Three (3.3%) patients experienced thrombocytopenia. Despite the low prevalence of vancomycin-induced ADR in the form of thrombocytopenia and neutropenia, frequent examinations are recommended to provide an early management strategy. In addition, it is necessary to monitor renal function to estimate the safe and effective amount of vancomycin dose for patients of various age categories, especially those with risk factors such as geriatric patients and combination therapy, including aminoglycosides. Therefore, this study recommends the importance of providing TDM services in Indonesian hospitals. In addition, prospective studies of vancomycin and the alternative antibiotics' pharmacokinetics and pharmacodynamics in patients with sepsis are recommended to provide an approach for accurate, effective, and safe antibiotic dosing.

Acknowledgments: This research was funded by the Pharmacy Department of Universitas Islam Indonesia through a 2022 Collaborative Research Grant.

Conflicts of Interest: The authors declare no conflict of interest.

REFERENCES

1. Erikawati D, Santosaningsih D, Santoso S. Tingginya Prevalensi MRSA pada Isolat Klinik Periode 2010- 2014 di RSUD Dr. Saiful Anwar Malang, Indonesia. Jurnal Kedokteran Brawijaya. 2016 Aug 29;149–56.
2. Syahniar R, Rayhana, Kharisma DS, Khatam M, Duarsa DBB. Methicillin-Resistant Staphylococcus aureus among Clinical Isolates in Indonesia: A Systematic Review. Biomedical and Pharmacology Journal. 2020 Dec 30;13(4):1871–8.
3. Santosaningsih D, Santoso S, Budayanti NS, Kuntaman K, Lestari ES, Farida H, et al. Epidemiology of Staphylococcus aureus Harboring the mecA or Panton-Valentine Leukocidin Genes in Hospitals in Java and Bali, Indonesia. The American Journal of Tropical Medicine and Hygiene. 2014 Apr 2;90(4):728–34.
4. Wilson HJ, Khokhar F, Enoch DA, Brown NM, Ahluwalia J, Dougan G, et al. Point-prevalence survey of carbapenemase-producing Enterobacteriaceae and vancomycin-resistant enterococci in adult inpatients in a university teaching hospital in the UK. Journal of Hospital Infection. 2018 Sep 1;100(1):35–9.

5. Bamgbola O. Review of vancomycin-induced renal toxicity: an update. Ther Adv Endocrinol Metab. 2016 Jun;7(3):136–47.
6. Kan WC, Chen YC, Wu VC, Shiao CC. Vancomycin-Associated Acute Kidney Injury: A Narrative Review from Pathophysiology to Clinical Application. Int J Mol Sci. 2022 Feb 12;23(4):2052.
7. Humphrey C, Veve MP, Walker B, Shorman MA. Long-term vancomycin use had low risk of ototoxicity. PLOS ONE. 2019 Nov 6;14(11):e0224561.
8. Nuryah A, Yuniarti N, Puspitasari I. Prevalensi dan Evaluasi Kesesuaian Penggunaan Antibiotik pada Pasien dengan Infeksi Methicillin Resistant Staphylococcus Aureus di RSUP Dr. Soeradji Tirtonegoro Klaten. Majalah Farmaseutik. 2019 Sep 2;15(2):123–9.
9. Suardi M, Sofjan M, Raveinal R. Kesesuaian Dosis Vankomisin pada Pasien Penyakit Ginjal Kronik Stadium 3 dan 4 di Bangsal Penyakit Dalam RSUP Dr. M. Djamil Padang. Jurnal Sains Farmasi & Klinis. 2016 Dec 28;3(1):64–71.
10. Mahmoodian A, Abbasi S, Farsaei S. A new approach to Vancomycin utilization evaluation: A cross-sectional study in intensive care unit. J Res Pharm Pract. 2016;5(4):279–84.
11. Kabbara WK, El-Khoury G, Chamas NR. Prospective evaluation of vancomycin therapeutic usage and trough levels monitoring. The Journal of Infection in Developing Countries. 2018 Nov 30;12(11):978–84.
12. Salih TAM, Yousef BA, Salih MAM, Eltom KS. Drug Utilization Evaluation of Vancomycin among Patients in Jafar Ibn Auf Pediatric Hospital, 2018. F1000Res. 2021 Nov 12;8:1708.
13. Tang J, Hu J, Kang L, Deng Z, Wu J, Pan J. The use of vancomycin in the treatment of adult patients with methicillin-resistant Staphylococcus aureus (MRSA) infection: a survey in a tertiary hospital in China. Int J Clin Exp Med. 2015 Oct 15;8(10):19436–41.
14. Ruggieri A, Anticoli S, D'Ambrosio A, Giordani L, Viora M. The influence of sex and gender on immunity, infection and vaccination. Ann Ist Super Sanita. 2016 Jun;52(2):198–204.
15. Klein SL, Flanagan KL. Sex differences in immune responses. Nat Rev Immunol. 2016 Oct;16(10):626–38.
16. Strich JR, Heil EL, Masur H. Considerations for Empiric Antimicrobial Therapy in Sepsis and Septic Shock in an Era of Antimicrobial Resistance. The Journal of Infectious Diseases. 2020 Jul 21;222(Supplement_2):S119–31.
17. Choo EJ, Chambers HF. Treatment of Methicillin-Resistant Staphylococcus aureus Bacteremia. Infect Chemother. 2016 Dec;48(4):267–73.
18. Zhang G, Zhang N, Xu J, Yang T, Yin H, Cai Y. Efficacy and safety of vancomycin for the treatment of *Staphylococcus aureus* bacteraemia: a systematic review and meta-analysis. International Journal of Antimicrobial Agents. 2023 Oct 1;62(4):106946.
19. Haseeb A, Alqurashi MK, Althaqafi AS, Alsharif JM, Faidah HS, Bushyah M, et al. A Systematic Review on Clinical Safety and Efficacy of Vancomycin Loading Dose in Critically Ill Patients. Antibiotics. 2022 Mar 18;11(3):409.
20. Cong Y, Yang S, Rao X. Vancomycin resistant Staphylococcus aureus infections: A review of case updating and clinical features. Journal of Advanced Research. 2020 Jan 1;21:169–76.
21. Boyce JM, Pop OF, Abreu-Lanfranco O, Hung WY, Fisher A, Karjoo A, et al. A Trial of Discontinuation of Empiric Vancomycin Therapy in Patients with Suspected Methicillin-Resistant Staphylococcus aureus Health Care-Associated Pneumonia. Antimicrob Agents Chemother. 2013 Mar;57(3):1163–8.
22. Reveles KR, Mortensen EM, Attridge RT, Frei CR. Comparative-effectiveness of vancomycin and linezolid as part of guideline-recommended empiric therapy for healthcare-associated pneumonia. BMC Res Notes. 2015 Sep 17;8:450.
23. Ministry of Health of the Republic of Indonesia. Formularium Nasional (National Formulary) [Internet]. Ministry of Health of the Republic of Indonesia; 2021. Available from: http://farmalkes.kemkes.go.id/unduh/kmk-no-hk-01-07-menkes-350-2020-ttg-formularium-nasional/
24. F.R. Bruniera, F. M. Ferreira, L.R.M. SAVIOLLI, F.L.A. Fonseca, V.B. Campos Junqueira, Bacci MR, et al. The use of vancomycin with its therapeutic and adverse effects: a review [Internet]. European Review. 2015 [cited 2018 Feb 15]. Available from: http://www.europeanreview.org/article/8585

25. Budayanti NS, Aisyah DN, Fatmawati NND, Tarini NMA, Kozlakidis Z, Adisasmito W. Identification and Distribution of Pathogens in a Major Tertiary Hospital of Indonesia. Front Public Health. 2020 Jan 31;7:395.
26. McDanel JS, Perencevich EN, Diekema DJ, Herwaldt LA, Smith TC, Chrischilles EA, et al. Comparative Effectiveness of Beta-Lactams Versus Vancomycin for Treatment of Methicillin-Susceptible Staphylococcus aureus Bloodstream Infections Among 122 Hospitals. Clin Infect Dis. 2015 Aug 1;61(3):361–7.
27. Elyasi S, Khalili H, Dashti-Khavidaki S, Mohammadpour A. Vancomycin-induced nephrotoxicity: mechanism, incidence, risk factors and special populations. A literature review. Eur J Clin Pharmacol. 2012 Sep 1;68(9):1243–55.
28. Rybak MJ, Le J, Lodise TP, Levine DP, Bradley JS, Liu C, et al. Therapeutic monitoring of vancomycin for serious methicillin-resistant Staphylococcus aureus infections: A revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm. 2020 May 19;77(11):835–64.
29. Smit C, Goulooze SC, Brüggemann RJM, Sherwin CM, Knibbe CAJ. Dosing Recommendations for Vancomycin in Children and Adolescents with Varying Levels of Obesity and Renal Dysfunction: a Population Pharmacokinetic Study in 1892 Children Aged 1–18 Years. AAPS J. 2021 Apr 11;23(3):53.
30. Khare M, Azim A, Kneese G, Haag M, Weinstein K, Rhee KE, et al. Vancomycin Dosing in Children With Overweight or Obesity: A Systematic Review and Meta-analysis. Hosp Pediatr. 2020 Apr;10(4):359–68.
31. Woldu H, Guglielmo BJ. Incidence and Risk Factors for Vancomycin Nephrotoxicity in Acutely Ill Pediatric Patients: Journal of Pharmacy Technology [Internet]. 2017 Dec 10 [cited 2018 Sep 11]; Available from: http://journals.sagepub.com/doi/abs/10.1177/8755122517747088
32. Gu Q, Jones N, Drennan P, Peto TE, Walker AS, Eyre DW. Assessment of an institutional guideline for vancomycin dosing and identification of predictive factors associated with dose and drug trough levels. Journal of Infection. 2022 Oct 1;85(4):382–9.
33. Shahrami B, Najmeddin F, Mousavi S, Ahmadi A, Rouini MR, Sadeghi K, et al. Achievement of Vancomycin Therapeutic Goals in Critically Ill Patients: Early Individualization May Be Beneficial. Critical Care Research and Practice. 2016 Mar 17;2016:e1245815.
34. Hodiamont CJ, Juffermans NP, Berends SE, van Vessem DJ, Hakkens N, Mathôt RAA, et al. Impact of a vancomycin loading dose on the achievement of target vancomycin exposure in the first 24 h and on the accompanying risk of nephrotoxicity in critically ill patients. Journal of Antimicrobial Chemotherapy. 2021 Nov 1;76(11):2941–9.
35. Heffernan AJ, Germano A, Sime FB, Roberts JA, Kimura E. Vancomycin population pharmacokinetics for adult patients with sepsis or septic shock: are current dosing regimens sufficient? Eur J Clin Pharmacol. 2019 Sep 1;75(9):1219–26.
36. Katip W, Jaruratanasirikul S, Pattharachayakul S, Wongpoowarak W, Jitsurong A, Lucksiri A. The pharmacokinetics of vancomycin during the initial loading dose in patients with septic shock. IDR. 2016 Nov 22;9:253–60.
37. Matsumoto K, Oda K, Shoji K, Hanai Y, Takahashi Y, Fujii S, et al. Clinical Practice Guidelines for Therapeutic Drug Monitoring of Vancomycin in the Framework of Model-Informed Precision Dosing: A Consensus Review by the Japanese Society of Chemotherapy and the Japanese Society of Therapeutic Drug Monitoring. Pharmaceutics. 2022 Feb 23;14(3):489.
38. Flannery AH, Wallace KL, Rhudy CN, Olmsted AS, Minrath RC, Pope SM, et al. Efficacy and safety of vancomycin loading doses in critically ill patients with methicillin-resistant Staphylococcus aureus infection. Therapeutic Advances in Infection. 2021 Jan 1;8:20499361211005965.
39. Al Sulaiman K, Alshaya A, Aljuhani O, Alsaeed A, Alshehri N, Vishwakarma R, et al. The impact of early target attainment of vancomycin in critically ill patients with confirmed Gram-positive infection: A retrospective cohort study. BMC Infectious Diseases. 2021 Nov

24;21(1):1182.
40. Rybak MJ. The pharmacokinetic and pharmacodynamic properties of vancomycin. Clin Infect Dis. 2006 Jan 1;42 Suppl 1:S35-39.
41. Vandecasteele SJ, De Vriese AS, Tacconelli E. The pharmacokinetics and pharmacodynamics of vancomycin in clinical practice: evidence and uncertainties. Journal of Antimicrobial Chemotherapy. 2013 Apr 1;68(4):743–8.
42. Lewis SJ, Nolin TD. New Vancomycin Dosing Guidelines for Hemodialysis Patients: Rationale, Caveats, and Limitations. Kidney360. 2021 Aug 26;2(8):1313–5.
43. Ponce D, Zamoner W, Freitas FM, Balbi A, Awdishu L. Vancomycin Removal During High-Volume Peritoneal Dialysis in Acute Kidney Injury Patients: A Prospective Cohort Clinical Study. Kidney Int Rep. 2018 Sep 27;4(1):112–8.
44. Lam E, Lien YT (Kayla), Kraft WK, Piraino B, Vozmediano V, Schmidt S, et al. Vancomycin in peritoneal dialysis: Clinical pharmacology considerations in therapy. Perit Dial Int. 2020 Jul 1;40(4):384–93.
45. Yamanouchi J, Hato T, Shiraishi S, Takeuchi K, Yakushijin Y, Yasukawa M. Vancomycin-induced Immune Thrombocytopenia Proven by the Detection of Vancomycin-dependent Anti-platelet Antibody with Flow Cytometry. Intern Med. 2016 Oct 15;55(20):3035–8.
46. Abdalhadi H, Fahmawi Y, Das A, Fouty B. Life-Threatening Intrapulmonary Hemorrhage due to Vancomycin-Induced Thrombocytopenia: A Case Report. Case Reports in Critical Care. 2020 Sep 30;2020:e8890335.
47. Guleng SR, Wu RH, Guo XB. Vancomycin-induced thrombocytopenia in endocarditis: A case report and review of literature. World Journal of Clinical Cases. 2021 Mar 6;9(7):1696–704.
48. Kalra K, Mittal HG, Maria A. Vancomycin-induced thrombocytopenia in a newborn. Drug Metabolism and Personalized Therapy. 2016 Dec 1;31(4):235–7.
49. Savage-Elliott I, Wu VJ, Sanchez FL. Drug-Induced Thrombocytopenia Secondary to Commonly Used Antibiotics in Total Joint Arthroplasty. Arthroplasty Today. 2020 Jun 1;6(2):137–40.
50. Shah RA, Musthaq A, Khardori N. Vancomycin-induced thrombocytopenia in a 60-year-old man: a case report. J Med Case Reports. 2009 Dec;3(1):1–4.
51. HT. Nguyen, T. Pham, HT. Bui. Prevalence and related factors for injectable vancomycin or teicoplanin-associated thrombocytopenia in a Vietnamese hospital. 4. 2015;42:Mahidol University Journal of Pharmaceutical Sciences.
52. Danieletto CF, Ferreira GZ, Farah GJ, Cuman RKN. Vancomycin-induced thrombocytopenia: a rare adverse effect in a patient -submitted to bone graft in the jaw. Spec Care Dentist. 2017 Jan;37(1):38–42.
53. Mohammadi M, Jahangard-Rafsanjani Z, Sarayani A, Hadjibabaei M, Taghizadeh-Ghehi M. Vancomycin-Induced Thrombocytopenia: A Narrative Review. Drug Saf. 2017 Jan;40(1):49–59.
54. Tongsai S, Koomanachai P. The safety and efficacy of high versus low vancomycin trough levels in the treatment of patients with infections caused by methicillin-resistant Staphylococcus aureus: a meta-analysis. BMC Res Notes. 2016 Sep 29;9:455.
55. Filippone EJ, Kraft WK, Farber JL. The Nephrotoxicity of Vancomycin. Clinical Pharmacology and Therapeutics. 2017 Sep;102(3):459.