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ORIGINAL ARTICLE

THERAPEUTIC DRUG MONITORING: VANCOMYCIN DOSING AND PRACTICES IN PEDIATRIC POPULATION IN ERBIL

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ABSTRACT

Background: Vancomycin is an essential antimicrobial used in pediatric healthcare, but achieving therapeutic serum concentrations is complex due to variable pharmacokinetics in different pediatric age groups. This study aimed to evaluate the effectiveness of empirical vancomycin dosing in achieving target trough concentrations in pediatric patients.

Materials & Methods: This prospective, observational study at Raparin Teaching Hospital for Children conducted over four months from June 2023 to October 2023, in Iraq. In this study, 75 pediatric patients who needed vancomycin treatment were included in the study, and 60 pediatric patients remained in the study after the inclusion and exclusion criteria. Sampling method was hospital record, patients receiving vancomycin. Included pediatric patients aged one day to 18 years receiving intravenous vancomycin. Intravenous vancomycin (Pfizer, United States) was administered as an infusion over 30 minutes. The dosage was determined by the treating physician based on age and renal function. Blood samples were collected at specified intervals after vancomycin infusion, including peak (end of infusion) and trough (just before the next scheduled dose) levels.

Results: Of the 60 pediatric patients who received vancomycin therapy for less than 5 days, 23 (38.3%) achieved target trough concentrations with the initial dose. Among them, neonates (21.1%), infants (27.3%), children (50%), and adolescents (60%) demonstrated varied success rates of target trough level attainment. The study also found 67.7% of vancomycin courses resulted in subtherapeutic levels (<10 mg/L). Nephrotoxicity occurred in 10% of treatment courses. The median time to achieve therapeutic levels was 3 days, often requiring dose adjustments.

Conclusion: Achieving target vancomycin trough concentrations in pediatric patients is challenging, with a significant trend towards subtherapeutic levels. This suggests the necessity for age-specific dosing regimens and close therapeutic monitoring to optimize vancomycin therapy in pediatric settings, especially in neonates and infants.

KEY WORDS: Pediatric; Vancomycin; Empirical Dosing; Therapeutic Drug Monitoring; Therapeutic Trough Levels; Target Attainment.

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INTRODUCTION

Improved medical technology and innovations have significantly increased the survival rates of the pediatric population in the Middle Eastern region particularly in Iraq. Yet, the risks of bacterial sepsis among children in the region remain an enigmatic concern in the healthcare sector. Stoll et al. bacterial sepsis is one of the primary causes of mortality in the pediatric patient population. [1]

In the face of rising antibiotic resistance, particularly the spectra of methicillin-resistant Staphylococcus aureus (MRSA), vancomycin remains a crucial weapon in the pediatric arsenal. Indeed, vancomycin is used frequently as a first-line antibiotic for children in managing infections caused by Gram-positive susceptible bacteria and other methicillin-resistant

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variants. [2] most effective pharmacodynamics (PD) or pharmacokinetic (PK) outcome for predicting vancomycin efficacy is the ratio between the area under the curve and the minimal inhibitory concentration (AUC/MIC). [3] PK data of vancomycin among patients suggests that the volume of distribution (Vd) tends to increase but is accompanied by decreased clearance (CL). [4]

In the fight against childhood infections in Iraq, vancomycin stands as a powerful antibiotic, often the last line of defense against resistant bacterial strains. Yet, wielding this weapon effectively demands precision, and that's where therapeutic drug monitoring (TDM) emerges as a critical ally. [6] Further, in Iraq National Committee for Drug Selection (NCDS) under the Ministry of Health borrows substantially from IDA's guidelines. Other factors in achieving the recommended levels include serum creatinine levels (SCR), weight, neutropenia count, pre-menstrual age (PMA), and the onset of infection as well as the clinical status of the neonates, infants or children. [7]

Therapeutic drug monitoring of vancomycin and the study of its PK and PD parameters has been explored in several populations. [8] However, most Asian studies are inconsistent concerning their analysis models and the population being examined. Lo et al., A Malaysian study, investigated therapeutic drug monitoring and PK of vancomycin in neonates.[8] Other studies explored the phenomenon in adults[9,10], while another study examined serum concentration levels of vancomycin in a subgroup of Saudi adults undergoing oncological medications. [11]peak and trough vancomycin serum concentration were determined after the third dose or at steady state as per standard of care. Vancomycin data were analyzed according to a one-compartment open model. Pharmacokinetic parameters such as clearance (CL

Vancomycin is a commonly used antibiotic in pediatric patients in Iraq, especially for serious infections caused by methicillin-resistant Staphylococcus aureus (MRSA). Therapeutic drug monitoring (TDM) is important for optimizing vancomycin therapy in this population to ensure efficacy and minimize toxicity. [12] Vancomycin's effectiveness hinges on achieving optimal blood concentrations.

Exploring an effective vancomycin TDM model, dosing, and practices for developing an efficacious vancomycin dosing algorithm for the Kurdistan Iraq pediatric population. Furthermore, we aimed to evaluate the frequency of dose adjustments, the time required to reach therapeutic levels, and the rates of subtherapeutic and supratherapeutic trough concentrations.

MATERIALS AND METHODS

Study design

The study was a single-center, prospective, observational study that was conducted at Raparin Teaching Hospital for Children, a major pediatric care facility in Iraq. The study was conducted over four months from June 2023 to October 2023. The study protocol was reviewed and approved by the Ethical Committee of Hawler Medical University.

Patient selection

The study included pediatric patients aged one day to 18 years who were receiving intravenous vancomycin therapy or any indication as per the hospital's antibiotic stewardship program guidelines.

Patients were excluded if they had pre-existing acute or chronic kidney disease to avoid skewed pharmacokinetic data due to altered vancomycin clearance or if presented with an elevation in serum creatinine greater than 50% above age-adjusted normal values. Additionally, patients with known hypersensitivity to vancomycin, those receiving intermittent hemodialysis, those receiving concomitant nephrotoxic agent(s), or those with incomplete medical records were excluded.

Sample Size Justification

In the study period from June 2023 to October 2023, 75 pediatrics in the hospital where the study was conducted needed vancomycin treatment. Accordingly, all 75 pediatrics were included in the study and the sampling method was hospital record. This method was similar to other studies. [13]

A total of 75 pediatric patients who were administered IV vancomycin therapy were assessed for eligibility. Of these, 5 were excluded due to pre-existing or chronic kidney disease. The remaining 70 patients constituted the study cohort. Within this cohort, treatment duration stratified the patients into two groups: those who received vancomycin for a maximum of 5 days (n=60) and those treated for more than 5 days (n=10). The study flow chart is depicted in Figure 1.

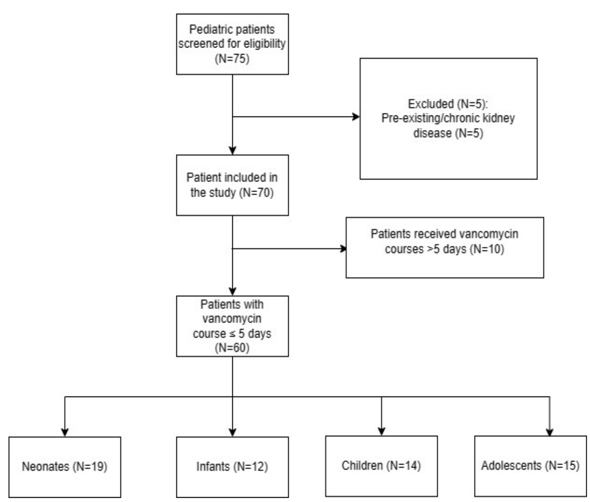

Figure 1: Study flowchart

Vancomycin Treatment

Intravenous vancomycin (Pfizer, United States) was administered as an infusion over 30 minutes. The dosage was determined by the treating physician based on age and renal function. The first dose was recorded along with the dosing interval selected. Vancomycin courses for more than 5 days included samples collected at least 72 hours after treatment initiation to evaluate steady-state levels.

Therapeutic Drug Monitoring

Blood samples were collected at specified intervals after vancomycin infusion, including peak (end of infusion) and trough (just before the next scheduled dose) levels. When possible, trough concentrations were drawn just before the fourth or fifth dose for steady-state measurement. Samples were collected by heel stick in neonates or direct venipuncture in older children. The serum was separated by centrifugation and frozen at -70°C until analysis.

Study outcomes

The primary outcome was the proportion of patients achieving target steady-state trough concentrations of 10-20 mcg/mL (neonates) or 15-20 mcg/mL (older children), based on current IDSA guidelines. Secondary outcomes included the daily vancomycin dose required to reach target troughs by age group, the number of dose adjustments needed, the time to achieve therapeutic levels, and the frequency of subtherapeutic and supratherapeutic trough concentrations.[14]

Statistical analysis

Baseline demographic and clinical characteristics were summarized using means and standard deviations (SDs) or medians and interquartile ranges (IQRs) for continuous data. Categorical data was summarized using count and percentages (n, %). For hypothesis testing, categorical variables were compared with the Chi-square or Fisher's exact test as appropriate, while continuous variables were analyzed using the t-test or Wilcoxon rank sum based on the normality check. Normality testing was performed using the Shapiro-Wilk test. Two-sided p-values <0.05 were considered statistically significant. All analyses were performed in R version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Baseline Characteristics

The study population ultimately comprised 60 pediatric patients receiving intravenous vancomycin therapy (Table 1). A summary of the baseline clinical and demographic characteristics is presented in Table 1.

Table 1: Baseline demographic and clinical characteristics and Initial Vancomycin Dosing of the Patients

Characteristic		Neonates (n=19)	Infants (n=12)	Children (n=14)	Adolescents (n=15)
Sex, male (n, %)		7 (36.8%)	5 (41.6%)	8 (57.1%)	7 (46.7%)
Settings, (n, %)	NICU	14 (73.7%)	6 (50%)	0.0	0.0
	PICU	4 (21.1%)	2 (16.7%)	8 (57.1%)	8 (53.3%)
	General pediatrics	1 (5.2%)	4 (33.3%)	6 (42.9%)	7 (46.7%)
Age (Year)	Median (range)	19d (8-61d)	117d (32-302d)	3.7y (1.8-12.1y)	15.1y (13-18.3y)
	IQR	27.5	146	7.6	3
	Mean(SD)	27.25±17.5	147.4± 93.5	6.2±4.1	15.4±1.6
Weight (kg)	Median (range)	3.7 (2.5-4.6)	5.8 (3.2-11.2)	20.6 (10.6-40.8)	56.7 (32.1-70.3)
	IQR	1.1	3	14.8	20.5
	Mean (SD)	3.5±0.63	6.2±2.3	23.7± 9.4	53.0±11.9
Allergy to penicillin, %		0.0	2 (16.7%)	1 (7.1%)	1 (6.7%)
Serum creatinine µmol/L, mean (SD)		22.5 (9.4)	13.9 (8.9)	17.5 (6.6)	32.4 (10.6)
Initial dosing mg/kg/day	Median (range)	20 (25)	45 (15.5)	52.5 (25)	55 (45)
	IQR	17.5	10	15	25.5
	Mean(SD)	23.3±9.3	46.3±6.8	50.6±10.2	50.9±15.6
Dosing interval, hours mean (SD)		12.8 (4.0)	6.1 (1.3)	6.1 (0.5)	6.2 (1.2)

Table 2: Clinical characteristics of the patients given vancomycin medications for more than 5 days.

Bacteria isolated and type of infection		N	Therapeutic duration days		
			Mean (SD)	Median	Range
MRSA (a)	SSTI (b)	2	21.5 (±9.9)	21.5	14.0
	Bacteremia	2	20 (±6.4)	20.0	9.0
Coagulase-negative staphylococcal species	Foreign body infections	1	6.9 (-)	-	-
	Line infections	2	17.0 (13.4)	17.0	19.0
Penicillin-I/R (c), alpha-hemolytic streptococcus,	Urinary tract infections	1	12.0 (-)	-	-
	Bacteremia	2	11.8 (±4.5)	11.8	6.5
Staphylococcus epidermis	Line infections	3	16.3 (±9.5)	15.0	19.0
Rothia mucilaginosa	Line infection	1	17.4 (-)	-	-
Enterococcus ampicillin-S	Bacteremia (penicillin allergy)	1	14.8 (-)	-	-
Total		**15**	**15.3 (±4.5)**	**16.3**	**14.6**
No Bacteria isolated	Febrile neutropenia therapy	2	8.0 (±0.7)	8.0	1.0
	Presumed neonatal infection (d)	2	10.5 (±1.4)	10.5	2.0
	Treatment for presumed infection	2	7.2 (±1.9)	7.2	2.7
Total		**6**			
a MRSA- methicillin-resistant Staphylococcus aureus b SSTI-skin or soft-tissue infections					
c Penicillin-I/R- resistance or intermediate susceptibility to penicillin					
d Presumed neonatal infection-meningitis, necrotizing enterocolitis					

Twenty one pediatric patients received vancomycin therapy for more than five days, of them, 15 were obtained for bacterial isolates (Table 2). Methicillin-resistant Staphylococcus aureus (MRSA) infections, including skin or soft-tissue infections (SSTI) and bacteremia, were treated in four patients, with the therapy duration of 21.5 ±9.9 and 20 ±6.4 days, respectively.

Coagulase-negative staphylococcal species were identified in 3 patients with foreign body and line infections. Notably, the treatment duration for line infections was notably longer (mean of 17± 13.4 days) compared to 12 days in a single case of foreign body infection. Infections due to penicillin-intermediate/resistant alpha-hemolytic streptococcus, which included urinary tract infections (N=1) and bacteremia (N=2), required a treatment duration of approximately 12 days. Staphylococcus epidermis was associated with line infections in three patients, with an average therapy duration of 16.3±9.5 days. Infections due to Rothia mucilaginosa and Enterococcus ampicillin-sensitive strains were least observed (one case for each) and presented with treatment durations of 17.4 and 14.8 days, respectively. Patients without bacterial isolates (N=6) were cases of febrile neutropenia, presumed neonatal infections, and presumed infections (N=2 for each). Notably, these patients required shorter vancomycin courses with a mean duration of less than 11 days.

Vancomycin Exposure and Target Attainment

Among the 60 patients treated with an initial empiric starting dose (40-60 mg/kg daily) of vancomycin, 23 (38.3%) reached target trough concentrations with the initial prescribed dose. Target attainment occurred in 4 of 19 neonates (21.1%), 3 of 11 infants (27.3%), 7 of 14 children (50%), and 9 of 15 adolescents (60%) (Figure 2). The mean daily dose required to reach therapeutic levels was 39.5 ±9.3 mg/kg for neonates, 46.3 ± 6.8 mg/kg for infants, 50.6 ±10.2 mg/kg for children, and 50.9 ± 15.6 mg/kg for adolescents.

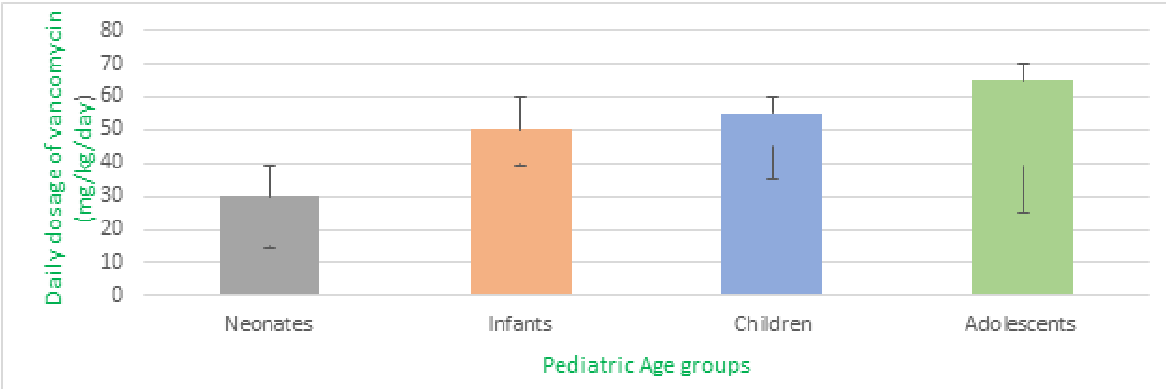

Figure 2: Box-Whisker plot comparing the mean daily dose of Vancomycin needed to reach the required therapeutic trough levels (10-20 mg/mL) across the pediatric ages (N=60). Error bars represent the standard deviation.

Table 3: Vancomycin serum level variations depending on the daily dose (N=60).

Vancomycin serum levels (mg/L)-n (%)	Vancomycin daily dose (mg/kg/day)				
	≤40 (n=19)	41-50 (n=12)	51-60 (n=14)	61-70 (n=9)	≥71 (n=6)
≤5	7 (36.8%)	3 (25.0%)	4 (28.6%)	5 (55.6%)	2 (33.3%)
6-9	5 (26.3%)	2 (16.7%)	2 (14.3%)	2 (22.2%)	1 (16.7%)
10-14	3 (15.8%)	3 (25.5%)	3 (21.4%)	1 (11.1%)	1 (16.7%)
15-20	3 (15.8%)	2 (16.7%)	4 (28.6%)	1 (11.1%)	0 (0.0%)
≥ 21	1 (5.3%)	2 (16.7%)	1 (2.43%)	0 (0.0%)	2 (33.3%)

In patients who received ≤40 mg/kg/day (N= 19), the majority had serum levels of ≤5 mg/L (36.8%), or between 6-9 mg/L (26.3%), suggesting potential under dosing. As the daily dose of vancomycin increases, there is a notable shift in the serum level distribution. In the 41-50 mg/kg/day group (12 patients), a higher percentage of 25.5% and 16.7% achieved serum levels in the 10-14 mg/L, and 14-20 mg/L, respectively. However, a significant proportion (41.7%) remained below this therapeutic window. Interestingly, in the 51-60 mg/kg/day group (14 patients), there was a more pronounced shift towards therapeutic levels, with 28.6% achieving serum levels of 15-20 mg/L. Increasing doses beyond 60 mg/kg resulted in a majority of patients presenting with subtherapeutic levels (88.9%) with the dose range 61-70 mg/kg/day or a substantial increase in the rates of supratherapeutic levels (33%) in patients who received doses > 70 mg/kg/day (Table 3). The odds of inadequate target attainment estimated from logistic regression were not significantly associated with any of the studied age categories **(Figure 3)**. Overall, 67 (67.7%) of the 99 vancomycin courses resulted in eventual subtherapeutic levels (<10 mg/L). Nephrotoxicity, as defined by a ≥30% increase in serum creatinine from baseline, occurred with 10 (10%) of treatment courses. Risk factors for nephrotoxicity included concomitant nephrotoxins in 4 cases and prolonged duration of treatment for 6 cases.

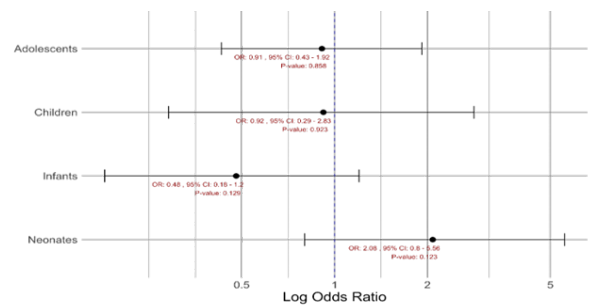

Figure 3: Adjusted odds ratios (OR) for the association between age groups and the achievement of therapeutic vancomycin serum levels. the vertical line at or 1 represents no difference in odds. points to the right of this line indicate higher odds of achieving therapeutic levels relative to the reference, and points to the left suggest lower odds. vertical bars represent the 95% confidence intervals for the estimated odds ratios.

Timing of sample collection

The median [IQR] interval between vancomycin doses was 2.1 days [1.4 - 3.2 days], with appropriately timed trough levels obtained a median of 30 minutes [15 - 48 minutes] before the next dose. Trough levels were appropriately collected at 1 hour in 80% of the first samples collected and in the subsequent collections made (Table 4).

Table 4: Interval between dose and vancomycin serum level collection

Therapeutic drug monitoring parameter	First collection (n=60)	All the collections (n=104)
The interval between the dose and the next collection (days)- n[%]		
Median [IQR]	2.1 (1.4-3.2)	2.2 (1.4-3.4)
The duration between collection and the next course (minutes)- n[%]		
Median [IQR]	30 (15.0-50.5)	32 (15.0-48.0)
Trough Collection time at 1 hour before the next dose) - n[%]	48 (80%)	80 (83.9%)

Assessment of Empiric Dosing Regimens

Of the 60 patients who received an initial empiric vancomycin dosing regimen for ≤ 5 days, 55 (91.7%) were dosed appropriately per IDSA guidelines while 5 (8.3%) received an incorrect regimen (Table 3). Among the 55 patients receiving a correct empiric regimen, 29 (52.7%) achieved initial vancomycin trough levels that were subtherapeutic, 25 (45.5%) had supratherapeutic levels, and 1 (1.8%) had indeterminate levels. The mean deviation below the therapeutic range was 9.3 mg/L for patients with subtherapeutic levels and 15.6 mg/L for those with supratherapeutic levels. Of the 5 patients who received an incorrect empirical regimen, 1 (20%) reached therapeutic levels, while 3 (60%) and 1 (20%) had subtherapeutic and supratherapeutic levels, respectively (Table 5).

Table 5: Implementation of the initial dosing regimen and the plasma concentrations

Dosing regimen (Correct initial dosing)	Total (n=60)
Within the therapeutic range [a]	55 (91.7%)
Sub-therapeutic [N, %]	29(52.7%)
Deviation [mg/L]; Median [IQR]	9.3; 20 (17.5)
Supra-therapeutic [N, %]	25 (45.5%)
Deviation [mg/L]; Median [IQR]	15.6; 55 (25.5)
Cannot be evaluated [b]	1(1.8%)
Dosing regimen* (Incorrect initial dosing)	Total (n=5)
Within the therapeutic range [b]	1 (20%)
Sub-therapeutic [N, %]	3 (60%)
Deviation [mg/L]; Median [IQR]	2.0; (1.5-5.2)
Supra-therapeutic [N, %]	1 (20%)
Deviation [mg/L]; Median [IQR]	6.3; (-)

IQR: Interquartile range
n= represents the number of target episodes
[b] Cannot be evaluated, or measurement of trough level done prematurely
[a] Targeted plasma concentration of Vancomycin [10-20 mg/L)
*Different interval than recommended in the guideline or a 10% dose deviation from hospital guideline

A total of 40 patients (67.7%) ultimately achieved target trough levels during the vancomycin course irrespective of initial dosing, a median of 3 days [IQR 2-5 days] and 2 regimens [IQR 1-3] were required to reach therapeutic concentrations with correct empirical dosing with a median of 2 doses (IQR 2-8) (Table 4). Of 4 patients not reaching target trough concentrations (80%) with incorrect empiric dosing over the observation period, the target with reached after a median of 2 days from dose modification after administering a median of 2 vancomycin doses (Table 6).

Table 6: Duration required to reach Vancomycin therapeutic levels

Dosing regimen (Correct initial dosing)	Total (n=60)
Target reached [N, %]	40 (67.7%)
Number of days required to reach the target	3
Median [IQR]	(2-5)
Number of doses required to reach the target	2
Median [IQR]	(2-8)
Number of different dosing regimens required to reach the target	2
Median [IQR]	(1-3)
Dosing regimen* (Incorrect initial dosing)	Total (n=5)
Target not reached	4 (80%)
Number of days required to reach the target	2
Median [IQR]	(-)
Number of doses required to reach the target	2
Median [IQR]	(-)
Number of different dosing regimens required to reach the target	2
Median [IQR]	(-)

IQR: Interquartile range

n= represents the number of target episodes

*Different interval than recommended in the guideline or a 10% dose deviation from hospital guideline

DISCUSSION

Vancomycin is a critical antibiotic for treating life-threatening Gram-positive bacterial infections, but its optimal use in pediatric patients requires careful consideration of age-related pharmacokinetic variations. [15,16]

Conducting pharmacokinetic studies in the Iraqi pediatric population is vital. Understanding how vancomycin behaves in Iraqi children's bodies will allow for the development of precise dosing regimens, further optimizing therapy and minimizing the risk of toxicity. [9] Therefore, this single-centered, prospective observational study primarily aimed to evaluate the effectiveness of empirical vancomycin dosing regimens in achieving target trough concentrations in a diverse pediatric population, spanning from neonates to adolescents.

In the United States, guidelines from the American Society of Health-System Pharmacists (ASHP) provide a comprehensive framework for vancomycin TDM in pediatric patients.[18] A vancomycin dosing algorithm based on estimated glomerular filtration rate from creatinine and cystatin C levels (eGFRcr-cys) improves target trough concentration achievement.[19] European countries have established national guidelines and quality assurance programs for TDM.[20,21] In contrast, the Iraqi healthcare system might be facing significant hurdles in implementing TDM for its pediatric population.

There is a study, that highlights a concerningly low success rate of achieving target trough concentrations (38.3%) on the initial dose. This significantly underperforms compared to adult studies, where success rates often exceed 50%.[22-24] This discrepancy emphasizes the need for age-specific dosing strategies in pediatric patients, particularly neonates and infants who exhibit the lowest success rates (21.1% and 27.3%, respectively).

The observed increase in success with age (50% for children and 60% for adolescents) aligns with pharmacokinetic changes associated with maturation. vancomycin trough concentrations below 10 μg/mL are associated with inadequate therapy and an increased risk of developing bacterial resistance.

The high prevalence of subtherapeutic vancomycin levels (67.7%) further amplifies concerns about underdosing. This not only risks treatment failure but also potentially prolongs therapy duration, increasing exposure to potential adverse effects. The median time of 3 days to reach therapeutic levels reinforces the need for close monitoring and frequent dose adjustments in pediatric patients. the importance of therapeutic drug monitoring (TDM) to individualize vancomycin dosing and optimize outcomes.[25]

The 10% incidence of nephrotoxicity in the study aligns with known risks associated with vancomycin, particularly in neonates and patients with pre-existing renal compromise.[26-28] However, despite the short term of use, this figure is deemed alarming in comparison to theother study.[29,30] Long-term vancomycin therapy usually carries a higher risk of nephrotoxicity, necessitating careful monitoring and consideration of alternative antibiotics when feasible.[31] This may also raise a question about the co-administered antibiotics.[31-34]

Overall, the findings of the current work indicated a substantial insufficiency in achieving therapeutic trough levels with the current standard dosing regimens recommended by IDSA guidelines.[35] Notably, only 38.3% of patients reached the target trough concentrations with their initial guidelines-informed vancomycin dose. This deviation was particularly pronounced in neonates and infants, indicating a potential need for more individualized dosing strategies in these younger age groups. Importantly, we found a high frequency of subtherapeutic levels, particularly in lower dosing ranges, suggesting that current empirical dosing may often lead to underdosing. The occurrence of nephrotoxicity in 10% of the treatment courses signifies the critical need to balance effective dosing with safety considerations.[36,37]

CONCLUSION

Based on the results of low concentration of vancomycin in pediatric patients, it is the cornerstone of effective and safe treatment in this vulnerable population. Based on the study findings, standard vancomycin dosing regimens may need to be reevaluated, particularly in neonates and neonates, suggesting a need for more specific vancomycin dosing strategies. The high frequency of subtherapeutic levels suggests that current empiric dosing guidelines may often be inadequate, particularly for younger patients. Distinct pharmacokinetic and pharmacodynamic considerations in children are necessary to ensure effective, safe, and personalized administration of vancomycin in pediatric healthcare settings.

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CONFLICT OF INTEREST
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AUTHORS' CONTRIBUTION

The following authors have made substantial contributions to the manuscript as under:

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All the authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.