

Original Article

Assessment of acute kidney injury associated with the concomitant use of piperacillin/tazobactam and vancomycin in pediatric cancer patients

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Citation: Malik F, Shirazi OU, Akhtar A, Malik N, Aslam I, Akram W, et al. Assessment of acute kidney injury associated with the concomitant use of piperacillin/tazobactam and vancomycin in pediatric cancer patients. *J Basic Clin Med Sci*. 2024;3:34-41.

Received: 04 November 2024

Revised: 16 December 2024

Accepted: 23 December 2024

Published: 27 December 2024

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Abstract

This study aimed to evaluate the renal safety of concomitant piperacillin/tazobactam (Pip-Taz) and vancomycin in pediatric cancer patients by assessing changes in the serum creatinine (SCr) and blood urea nitrogen (BUN) levels. The hospital information system at Shaukat Khanum Memorial Cancer Hospital and Research Centre was used to extract the required information, and laboratory test results were collected for 100 randomly selected patients in whom both Pip-Taz and vancomycin were used. Patients were randomly selected using a computer-generated list to minimize selection bias. The data obtained were statistically analyzed using the Friedman test. Most patients who received Pip-Taz and vancomycin suffered from pre-B lymphocytic leukemia. The Friedman test revealed significant within-group differences in SCr and BUN over time ($\chi^2 = 299.945$, $p < 0.001$ for males; $\chi^2 = 170.162$, $p < 0.001$ for females), but all posttherapy values remained within normal physiological ranges. Posttherapy, vancomycin-treated patients had slightly lower SCr and BUN levels than did those receiving Pip-Taz, although all values remained within normal ranges. A similar trend was observed in females. These findings suggest that concomitant Pip-Taz and vancomycin did not result in significant nephrotoxicity, as all renal biomarker changes remained within normal ranges. No patients met the acute kidney injury (AKI) criteria during therapy. However, vancomycin-treated patients presented slightly greater reductions in creatinine and BUN levels than did Pip-Taz-treated patients, although this does not indicate improved renal function. Despite these findings, vancomycin's potential for nephrotoxicity remains an important consideration in pediatric treatment decisions.

Keywords

Acute kidney injury; Piperacillin-tazobactam; Vancomycin; Blood urea nitrogen; Nephrotoxicity; Creatinine; Pediatrics

1. Introduction

Piperacillin/tazobactam (Pip-Taz) is a combination antibiotic in which piperacillin inhibits bacterial cell wall synthesis, whereas tazobactam enhances its efficacy by inhibiting beta-lactamase enzymes [1,2]. It has been proven safe and effective in treating serious infections such as pelvic inflammatory disease, pneumonia, intra-abdominal infection, cellulitis, and sepsis [3,4]. This combination exhibits broad-spectrum activity against gram-positive bacteria (*Enterococcus faecalis*, *Staphylococcus epidermidis*, *Streptococcus agalactiae*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and *viridans group streptococci*), aerobic/facultative gram-negative microorganisms (*Acinetobacter bau-*

mannii, *Escherichia coli*, *Haemophilus influenzae*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and gram-negative anaerobes (*Bacteroides* species) [5].

Vancomycin is a glycopeptide antibiotic primarily used to treat serious gram-positive bacterial infections, including methicillin-resistant *Staphylococcus aureus* (MRSA) and coagulase-negative staphylococci [6]. Vancomycin also has activity against streptococci, enterococci, and certain anaerobic bacteria [7]. However, it is ineffective against gram-negative bacteria [8]. Owing to its limited spectrum, vancomycin is typically reserved for infections caused by gram-positive bacteria that are resistant to other antibiotics [9].

In clinical practice, vancomycin and Pip-Taz dosages in pediatric patients are weight-based [10]. Vancomycin is typically administered at 40–60 mg/kg/day every 6–8 hours, with dosing adjusted on the basis of therapeutic drug monitoring (TDM) to maintain target serum trough levels [11,12]. Pip-Taz is given at 90 mg/kg QID on the basis of the piperacillin component [13]. Renal function tests, especially creatinine clearance, are important for assessing vancomycin and Pip-Taz dosing since both drugs are renally excreted. Pip-Taz, vancomycin, and their combination are frequently used in the management of febrile neutropenia [14,15]. Their coadministration provides broad-spectrum coverage against bacterial infections in immunocompromised patients [16,17,18,19].

Several studies have reported an increased risk of acute renal toxicity associated with Pip-Taz, often evidenced by elevations in baseline serum creatinine (SCr) levels determined at hospital admission [20,21]. Studies in adult patients have reported an increased risk of acute kidney injury (AKI) with concomitant Pip-Taz and vancomycin use, with the incidence of AKI reaching 34.8% in some cohorts. However, limited data exist regarding this risk in pediatric oncology patients, necessitating further investigation [22]. Given the limited pediatric data on this topic, this study aimed to evaluate the renal safety of concomitant Pip-Taz and vancomycin in pediatric cancer patients by assessing changes in SCr and blood urea nitrogen (BUN) levels.

2. Materials and methods

The study included pediatric oncology patients diagnosed with febrile neutropenia at Shaukat Khanum Memorial Cancer Hospital and Research Center, Lahore, Pakistan. A total of 100 pediatric oncology patients meeting the inclusion criteria were randomly selected using a computer-generated list to minimize selection bias. The laboratory test results were retrieved for analysis. Patients who had a fever ($> 38.5^{\circ}\text{C}$ on one event or $> 38^{\circ}\text{C}$ on at least two events within 12 hours) were eligible for inclusion in the retrospective analysis. For each included patient, the SCr and BUN values were obtained from the hospital's laboratory information system. These laboratory tests are routinely conducted as part of standard patient care for febrile neutropenia and were not performed specifically for this study.

AKI was defined using the Kidney Disease: Improving Global Outcomes (KDIGO) criteria as an increase in SCr of ≥ 0.3 mg/dL within 48 hours or ≥ 1.5 times the baseline level within 7 days. None of the patients in this study met these criteria. Nephrotoxicity was assessed on the basis of these creatinine changes, whereas changes in BUN were analyzed but not used as a primary criterion for nephrotoxicity.

The study was conducted between June 2021 and December 2022. The study population comprised male and female pediatric oncology patients with various infections. Among the 100 patients included in the study, 64 were male and 36 were female, with ages ranging from 3 months to 15 years. All these patients received several courses of piperacillin–tazobactam and vancomycin during the study period, but only the primary course with a minimum of seven days of therapy was used in the analysis. Patients with

missing or inadequate laboratory samples, those treated exclusively in the outpatient department (OPD), and those who received preoperative antibiotics were excluded. Patients with chronic kidney disease or other preexisting renal conditions and those who received less than 48 hours of empiric Pip-Taz and vancomycin therapy were also excluded. This was a retrospective cohort study, as the data were collected from the Hospital Information System, and this study was exempt from ethical review by the Shaukat Khanum Memorial Hospital Institutional Review Board (IRB) (No. EX-04-05-23-01), as it involved a retrospective analysis of existing data without direct patient intervention.

Statistical analysis was conducted using SPSS (v26.0). Categorical variables (sex, diagnosis) are reported as percentages and frequencies. The Friedman test, a nonparametric test for repeated measures, was used to assess within-group changes in renal biomarkers over time. Statistical significance was set at $p < 0.05$.

3. Results

Table 1 summarizes the primary diagnoses of the study population. The most common diagnosis in males was pre-B-cell acute lymphoblastic leukemia ($n = 23$), followed by Burkitt's lymphoma ($n = 9$) and osteosarcoma ($n = 8$). In females, pre-B-cell acute lymphoblastic leukemia ($n = 14$) was the most prevalent, with Hodgkin lymphoma ($n = 5$) and Burkitt's lymphoma ($n = 4$) also occurring frequently. Other diagnoses included anaplastic large-cell lymphoma ($n = 4$), diffuse large B-cell lymphoma ($n = 8$), and Wilms tumor ($n = 8$). Males were more commonly affected (64%) than females (36%) across most diagnoses, except for rhabdomyosarcoma (RMS), where the male-to-female ratio was equal (2:2).

Table 1. Primary diagnosis across the selected population for studies ($N = 100$).

Diagnosis	Male ($n = 64$)	Female ($n = 36$)
	Frequency (%)	Frequency (%)
Anaplastic large-cell lymphoma	2 (2.00)	2 (2.00)
Burkitt's	9 (9.00)	4 (4.00)
Diffuse large B-cell lymphoma	6 (6.00)	2 (2.00)
Ewing Sarcoma	5 (5.00)	2 (2.00)
Hodgkin lymphoma	1 (1.00)	5 (5.00)
Non-Hodgkin lymphoma	2 (2.00)	1 (1.00)
Osteosarcoma	8 (8.00)	2 (2.00)
Pre-B-Cell Acute lymphoblastic leukemia	23 (23.00)	14 (14.00)
Rhabdomyosarcoma	2 (2.00)	2 (2.00)
Wilms Tumor	6 (6.00)	2 (2.00)

Figure 1 shows the distribution of gram-positive infections, with the most frequent being *Streptococcus aureus* in wounds (24%), followed by MRSA in blood (18%) and *Streptococcus viridians* in blood (13%). Other infections include *Streptococcus aureus* in the blood (12%), MSSA in the blood (11%), and MSSA in the wound (7%), along with *Enterococcus* in the blood (4%), MRSA in the wound (3%), cellulitis (2%), and abnormal X-ray (6%). These infections were observed in all 100 patients.

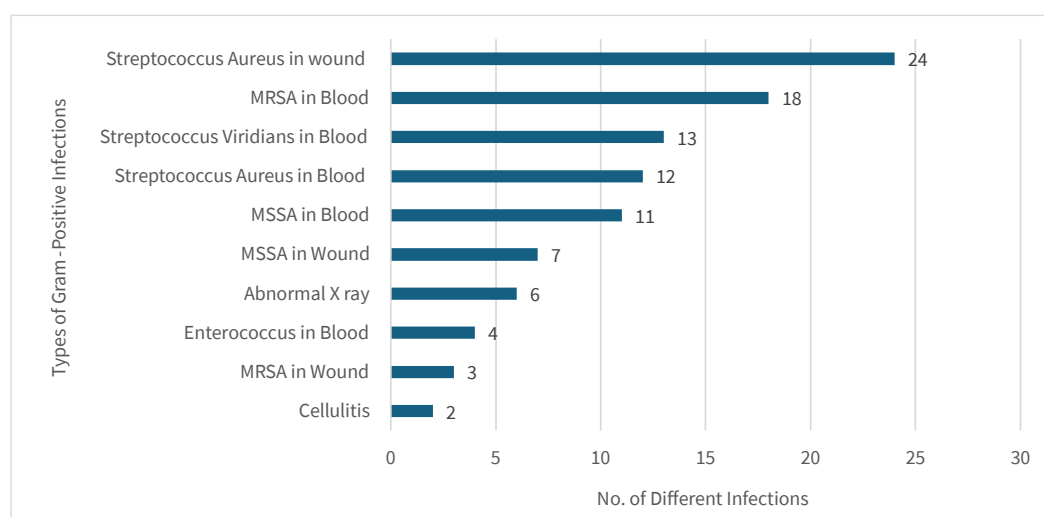


Figure 1. Types of gram-positive infections.

Figure 2 illustrates the distribution of gram-negative infections, with *Pseudomonas* in the blood being the most common at 41% (41 cases). This is followed by febrile neutropenia, which accounts for 25% (25 patients), and *E. coli* in the urine, which is found in 13% (13 patients). Respiratory distress was observed in 8% (8 patients), *E. coli* in the blood in 6% (6 patients), *Pseudomonas* in the urine in 4% (4 patients), and intraabdominal infection in 3% (3 patients). These results represent a total of 100 cases, accounting for 100% of the gram-negative infections.

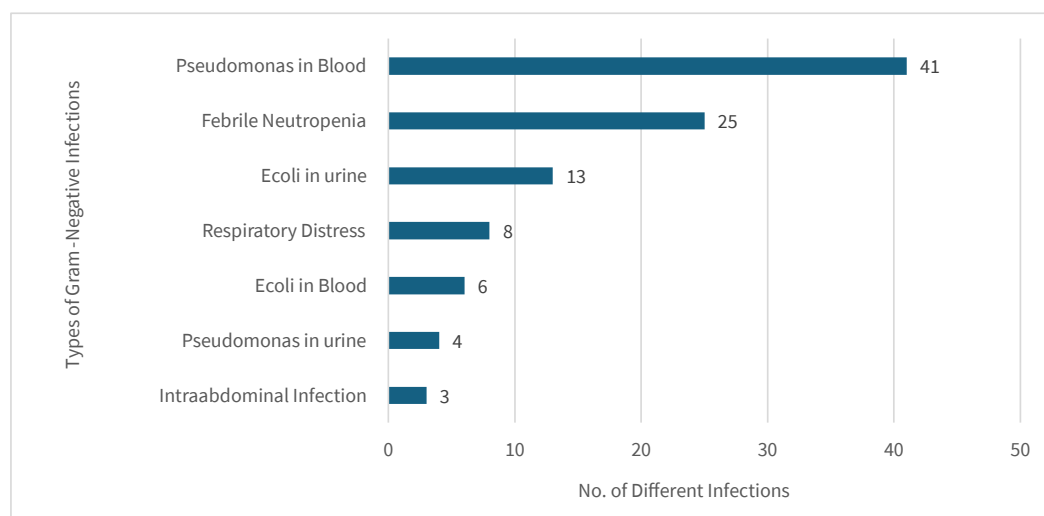


Figure 2. Types of gram-negative infections.

Table 2 compares pre- and posttherapy creatinine and BUN levels to assess changes in renal function. The study included 36 female patients (mean age: 5.1 ± 1.03 years) and 64 male patients (mean age: 5.2 ± 2.05 years). Among females, creatinine levels ranged from 0.29 to 0.76 mg/dL before therapy and from 0.29 to 0.77 mg/dL after therapy. For males, creatinine levels ranged from 0.31 to 0.70 mg/dL before therapy and from 0.31 to 0.72 mg/dL after therapy. Similarly, BUN levels in females ranged from 7 to 15 mg/dL before therapy and from 9 to 16 mg/dL after therapy, whereas in males, BUN levels ranged from 5 to 14 mg/dL before therapy and from 6 to 15 mg/dL after therapy. These findings indicate minor fluctuations in renal biomarkers posttherapy, but all values remained within normal physiological limits, suggesting no significant renal impairment.

Table 2. Descriptive statistics of renal function parameters by sex before and after treatment with vancomycin and Pip-Taz.

Gender	Age (in years)	Creatinine (mg/dl)	Creatinine After Pip-Taz (mg/dl)	Creatinine After Vancomycin (mg/dl)	Baseline BUN (mg/dl)	BUN After Pip-Taz (mg/dl)	BUN After Vancomycin (mg/dl)
			Min – Max	Min – Max		Min – Max	Min – Max
Female	5.1 ± 1.03	0.29 – 0.76	0.29 – 0.86	0.29 – 0.77	7.00 – 15.00	8.00 – 15.00	9.00 – 16.00
Male	5.2 ± 2.05	0.31 – 0.70	0.29 – 0.71	0.31 – 0.72	5.00 – 14.00	5.00 – 14.00	6.00 – 15.00

Range: [Min – Max].

Table 3 presents the Friedman test results, which revealed statistically significant within-group differences in renal function parameters (creatinine and BUN) over time. The changes in renal function parameters were significant in both males ($\chi^2 = 299.945$, $p < 0.001$) and females ($\chi^2 = 170.162$, $p < 0.001$) after treatment with Pip-Taz and vancomycin.

In males, the baseline creatinine level was 0.491 ± 0.119 , with a mean rank of 2.85, which decreased after treatment with both drugs. Posttreatment, the creatinine level decreased to 0.475 ± 0.119 (mean rank 1.87) with Pip-Taz and to 0.465 ± 0.121 (mean rank 1.28) with vancomycin, although these changes remained within normal ranges and did not indicate a direct renal benefit. Similarly, the baseline BUN level was 11.31 ± 2.130 (mean rank 5.77), which decreased to 10.19 ± 1.934 (mean rank 4.99) with Pip-Taz and to 8.98 ± 2.250 (mean rank 4.24) with vancomycin. The chi-square value of 299.945 and p value < 0.001 confirmed significant within-group changes; however, all values remained within normal physiological limits, indicating no renal dysfunction or improvement.

Among females, the creatinine level decreased from 0.501 ± 0.148 (mean rank 2.90) to 0.484 ± 0.158 (mean rank 1.97) with Pip-Taz and further decreased to 0.454 ± 0.146 (mean rank 1.13) with vancomycin. However, these reductions do not suggest improved renal function but rather normal physiological variations. Similarly, the baseline BUN level was 12.83 ± 1.96 (mean rank 5.71), decreasing to 11.89 ± 1.72 (mean rank 5.10) with Pip-Taz and further to 10.19 ± 1.47 (mean rank 4.19) with vancomycin. The chi-square value of 170.162 and p value < 0.001 indicated statistically significant within-group differences across time points.

Both Pip-Taz and vancomycin were associated with reductions in creatinine and BUN levels. Vancomycin resulted in greater decreases in both parameters; however, these changes remained within normal ranges and did not imply improved renal function.

Table 3. Changes in renal function parameters over time with Pip-Taz and vancomycin treatment.

Gender		Measure	N	Mean ± SD	Mean Rank	Chi-Square (χ^2)	df	p value
Male	Creatinine	Baseline	64	0.491 ± 0.119	2.85	299.94	5	< 0.001 *
		Post Treatment Piptaz		0.475 ± 0.119	1.87			
		Post Treatment Vancomycin		0.465 ± 0.121	1.28			
Female	BUN	Baseline	36	11.310 ± 2.130	5.77	170.16	5	< 0.001 *
		Post Treatment Piptaz		10.190 ± 1.934	4.99			
		Post Treatment Vancomycin		8.980 ± 2.250	4.24			
Male	Creatinine	Baseline	64	0.501 ± 0.148	2.90	170.16	5	< 0.001 *
		Post Treatment Piptaz		0.484 ± 0.158	1.97			
		Post Treatment Vancomycin		0.454 ± 0.146	1.13			
Female	BUN	Baseline	36	12.830 ± 1.960	5.71			

Gender	Measure	N	Mean $\pm$ SD	Mean Rank	Chi-Square (χ^2)	df	p value
	Post Treatment Piptaz		11.890 $\pm$ 1.720	5.10			
	Post Treatment Vancomycin		10.190 $\pm$ 1.470	4.19			

* Changes were assessed using the Friedman test. ** Significant value ($p \leq 0.05$). *** BUN = Blood urea nitrogen

4. Discussion

This study assessed renal function changes associated with concomitant Pip-Taz and vancomycin in pediatric cancer patients by evaluating creatinine and BUN levels. The primary finding was that although mild fluctuations in creatinine and BUN levels were observed, all posttherapy values remained within normal physiological limits. Importantly, no cases of AKI were identified, and all biomarker variations were within the expected ranges. These findings suggest that the combination of Pip-Taz and vancomycin did not result in clinically significant nephrotoxicity in this study population.

Previous studies have reported a higher incidence of nephrotoxicity with vancomycin monotherapy and combination therapy with Pip-Taz, particularly in adult and critically ill patients. A reported nephrotoxicity rate of 3.8% for vancomycin monotherapy and 23.6% for combination therapy has been reported in hospitalized children [23]. However, our study did not observe nephrotoxic effects meeting the AKI criteria. This discrepancy may be due to differences in patient demographics, treatment duration, baseline renal function, or antibiotic dosing and monitoring strategies used in pediatric oncology patients.

Our findings align with prior research indicating that vancomycin-associated nephrotoxicity is dose dependent and primarily occurs at sustained trough concentrations > 20 mg/L [24]. Since our study population maintained vancomycin trough levels between 8–15 mg/L, the absence of AKI may reflect appropriate dosing strategies in pediatric oncology patients.

Therapeutic monitoring of vancomycin through the area under the curve/minimum inhibitory concentration (AUC/MIC) is used to ensure adequate bacterial killing while preventing excessive drug accumulation, which can lead to nephrotoxicity [25,26]. However, this study did not assess AUC/MIC values. Future studies should investigate how individualized vancomycin dosing strategies, including AUC-guided dosing and TDM, influence renal outcomes in pediatric patients.

Some studies have reported an association between Pip-Taz use and nephrotoxicity in pediatric patients with neutropenic fever [27]. However, our study did not observe significant renal function impairment with Pip-Taz use. It remains possible that renal function could be impacted in higher-risk subgroups or with prolonged exposure. Further investigations are needed to determine long-term renal safety in pediatric patients receiving combination therapy.

Although previous research has suggested that vancomycin exposure beyond 72 hours increases nephrotoxicity risk [28], our study did not specifically evaluate the effect of treatment duration on renal outcomes. Future studies should assess whether limiting vancomycin duration reduces nephrotoxicity in pediatric oncology patients.

Overall, this study provides valuable insight into the renal safety of Pip-Taz and vancomycin in pediatric cancer patients. No significant nephrotoxicity was observed, and all renal biomarker fluctuations remained within normal physiological ranges. However, further studies with larger sample sizes and longer follow-up periods are needed to confirm these findings and evaluate the impact of treatment duration and cumulative drug exposure.

5. Conclusions

While previous studies have reported nephrotoxicity with Pip-Taz and vancomycin, our study revealed that these antibiotics were well tolerated in pediatric cancer patients, with no significant renal impairment observed. Importantly, all posttherapy creatinine and BUN levels remained within normal physiological limits, and no cases of AKI were identified.

Patients in this study received varying durations of therapy, with some receiving extended courses of Pip-Taz and vancomycin. No significant changes in SCr or BUN were observed, although the impact of therapy duration on renal function requires further investigation. Similarly, even patients who received vancomycin within the upper limit of therapeutic trough levels (8–15 mg/L) did not show significant changes in kidney function. However, further research is needed to determine the renal safety of higher trough levels in pediatric oncology patients.

Overall, this study provides evidence that concomitant Pip-Taz and vancomycin did not result in clinically significant nephrotoxicity in this population. Further research with larger cohorts and longer follow-up periods is needed to confirm these findings and assess the impact of treatment duration on renal function.

Author contributions: Conceptualization, FM, OS, AA and NM; methodology, FM, OS, AA, IA, WA, and KA; software, FM, NM, IA, and WA; validation, OS, and AA; formal analysis, FM, NM, WA, and KA; investigation, FM, and NM; resources, OA, and AA; data curation, FM, IA, WA, and KA; writing—original draft preparation, FM, NM, IA, WA, and KA; writing—review and editing, OS, and AA; visualization, FM, WA, and KA; supervision, OS, and AA; project administration, FM, and NM. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no specific grant from the public, commercial, or not-for-profit funding agencies.

Ethics statement: This study was exempt from ethical review by the Shaukat Khanum Memorial Hospital IRB (No. EX-04-05-23-01), as it involved a retrospective analysis of existing data without direct patient intervention.

Consent to participate: Not Applicable.

Data availability: The data supporting this study's findings are available from Ali Akhtar upon reasonable request.

Acknowledgments: None.

Conflicts of interest: The authors declare no conflicts of interest.

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