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Original article

Assessment of knowledge, attitude, and practices of acute kidney injury incidence with co-administration of piperacillin/tazobactam and vancomycin among healthcare workers: A cross-sectional study

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ABSTRACT

Background: No studies have identified a link between acute kidney injury (AKI) incidence due to the co-administration of vancomycin and piperacillin/tazobactam (VPT) and healthcare providers' knowledge, attitudes, and practices. We aimed to (1) assess the knowledge, attitudes, and practices towards AKI due to VPT co-administration among healthcare providers in Saudi Arabia, and (2) examine the relationship between healthcare providers' knowledge and attitudes about AKI due to VPT co-administration and their practices.

Methods: This cross-sectional study was conducted between February 2022 and April 2022. Healthcare providers, including physicians, pharmacists, and nurses, were included in the study population. The correlation coefficient assessed the relationship between knowledge, attitude, and practice. Spearman's rho was used as a test statistic.

Results: Of the invited healthcare providers, 192 responded to the survey. A significant difference in knowledge was found among healthcare providers for two variables: the definition of AKI ($p < 0.001$) and appropriate management of AKI due to VPT ($p = 0.002$). Physicians were found to rely less on the most common causative organisms of infection to guide empirical antibiotic therapy ($p < 0.001$). In addition, physicians were less likely to switch piperacillin/tazobactam to cefepime or meropenem in combination with vancomycin with AKI incidence ($p = 0.001$). A positive attitude towards the perceived AKI risk with VPT was positively correlated with avoiding using VPT unless no alternatives were available (Rho = 0.336) and taking protective measures when using VPT (Rho = 0.461).

Conclusion: Deviation has been observed in the knowledge, attitudes, and practices of AKI incidence with the co-administration of piperacillin/tazobactam and vancomycin among healthcare workers. Interventions at the organizational level are recommended to guide best practices.

1. Introduction

Acute Kidney Injury (AKI) is defined by the American Kidney Injury Network (AKIN) and Kidney Disease Improving Global Outcomes (KDIGO) guidelines as an increase in the serum creatinine (SCr) level of $\geq$ 0.3 mg/dL or an increase of one and a half up to two from the baseline in stage one. In stage two, the rise in SCr doubles to triple from the baseline, and if it is more than triple or SCr of 4 mg/dL or the initiation of renal replacement therapy, it is classified as stage three (Mehta et al., 2007; Stevens and Levin, 2013). Bellomo et al. (2004) categorized the AKI into five sections, and the glomerular filtration rate (GFR) was essential in their categorization.

Abbreviations: AKI, Acute kidney injury; SCr, Serum creatinine; GFR, Glomerular filtration rate; VPT, Vancomycin and piperacillin/tazobactam.

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A pharmacovigilance study showed more than ten thousand patients had drug-induced AKI (Hosohata et al., 2019). Several mechanisms are involved in the pathogenesis of drug-induced AKI. One such mechanism is acute tubular nephritis (ATN), which is caused by ischemia, toxins, and tubular epithelial cell damage. Another important mechanism is acute interstitial nephritis (AIN), which can be caused, for example, by methicillin. The drug can form a covalent bond with the extracellular components of epithelial cells and cause an immunoglobulin E (IgE) cell-mediated late-phase hypersensitivity response. This reaction can damage or inflame the tubular epithelium and cause changes in the tubules and interstitium (Border et al., 1974; Brentjens et al., 1989; Nath and Norby, 2000; Silva, 2004).

Several systematic reviews and *meta*-analyses have identified a significantly higher incidence of AKI among patients who received a combination of vancomycin and piperacillin/tazobactam (VPT) than among those who received either vancomycin alone or with other beta-lactam antibiotics (Bellos et al., 2020; Chen et al., 2018; Luther et al., 2018). VPT resulted in significantly higher nephrotoxicity rates than vancomycin monotherapy (odds ratio (OR) 2.05, 95% confidence interval (CI) 1.17–3.46) and its concurrent use with meropenem (OR 1.84, 95% CI 1.02–3.10) or cefepime (OR 1.80, 95% CI 1.13–2.77) (Bellos et al. 2020). In addition, the incidence of AKI in patients receiving VPT was higher than in patients receiving vancomycin and other beta-lactam antibiotics (19.7–54.5% and 7.7–28.8 %, respectively) (Chen et al., 2018). Moreover, a higher rate of AKI was observed when using VPT compared with vancomycin alone (22.2% vs. 12.9%, respectively) (Luther et al., 2018).

No studies have identified a link between the incidence of AKI and healthcare providers' knowledge, attitudes, and practices regarding VPT co-administration. Therefore, we aimed to (1) assess knowledge, attitude, and practices towards AKI due to VPT co-administration among healthcare providers in Saudi Arabia and (2) examine the relationship between healthcare providers' knowledge and attitudes about AKI due to VPT co-administration and their practices. This study aimed to identify areas for future research and quality improvement (QI) initiatives to promote antimicrobial therapy's safe and efficacious use.

2. Material and methods

2.1. Study design

This cross-sectional study of healthcare providers in Saudi Arabia was conducted between February 2022 and April 2022.

2.2. Study population

Healthcare providers, including physicians, pharmacists, and nurses, were included in the study population. The participants were recruited from different geographical areas, including the Northern, Eastern, Central, Western, and Southern Regions of Saudi Arabia. The questionnaire was distributed to the healthcare providers of all clinical departments using antibiotics. The interns working in the hospital were excluded. We used multiple social media platforms (Facebook, Twitter, LinkedIn, and WhatsApp) to distribute questionnaires. Additionally, healthcare providers were approached in person during their working hours, invited to participate in the study, and given an online questionnaire link.

2.3. Questionnaire development

After the literature review revealed the absence of a validated questionnaire, one was developed by the authors to include items to assess knowledge, attitude, and practice (KAP) on AKI incidence with VPT among healthcare workers. It was divided into four sections. The first comprised participants' social demographics, while the remaining three included questions to assess knowledge, attitude, and practice. A five-point Likert scale was used, ranging from 1 (strongly disagree) to 5 (strongly agree). The knowledge domain was designed to test healthcare providers' understanding of VPT use and AKI definition and management (16 questions). Knowledge about the appropriate use of VPT was measured by averaging the respondents' level of agreement with four statements as follows: the combination of VPT can be used as empiric antibiotic therapy for 1) sepsis due to an unknown source, 2) hospital-acquired pneumonia, 3) community-acquired pneumonia (reverse-coded), and 4) community-acquired intra-abdominal infections (reverse-coded). The higher the score, the higher the knowledge level. Knowledge about the appropriate management of AKI due to VPT was assessed by averaging the respondents' level of agreement with the following three statements: the AKI due to VPT can be treated by: 1) changing piperacillin/tazobactam to cefepime or meropenem, 2) stopping both medications and 3) renal replacement therapy without stopping the medications (reverse-coded). The attitude domain consisted of seven questions to measure healthcare providers' attitudes toward VPT and AKI. The final domain was the practice domain, which comprised ten questions to evaluate healthcare providers' VPT prescription, VPT monitoring, and AKI management. For example, we assessed whether healthcare providers took protective measures when using VPT by asking them about their level of agreement with the following statements: "I monitor the serum creatinine level to check for the incidence of acute kidney injury when co-administering piperacillin/tazobactam and vancomycin," and "I take preventive measures when I order piperacillin/tazobactam and vancomycin combination in a patient." The responses to these two statements were averaged and analyzed. The questionnaire was sent to five experts in the field for content and face validity. The questionnaire was adjusted based on the experts' recommendations and comments.

The reliability of the questionnaire was assessed using Cronbach's α. Some questions were removed to maintain acceptable internal consistency of the Likert-scale questions: one was removed from the knowledge section, two from the attitude section, and one from the practice section.

2.4. Ethical approval

Approval from the King Faisal University (KFU) Institutional Review Board (IRB) was obtained before conducting the study (Protocol No. KFU-REC-2021- DEC -EA000294). Agreeing to participate in the survey was used in place of informed consent. The questionnaire did not ask for or require any identifiable information from the participants, except for sociodemographic details, to report their baseline characteristics.

2.5. Sample size

Using the Raosoft® sample size calculator, based on the estimated population of healthcare providers in Saudi Arabia according to the 2021 Ministry of Health (MOH) data, with a confidence interval (CI) of 95%, margin of error of 5%, and response distribution of 50%, a minimum sample size of 378 participants was needed for this study. Therefore, the required sample size was rounded off to 400 participants.

2.6. Statistical analysis

Continuous data were summarized as mean with standard deviation (SD) or median with interquartile range (IQR), depending on

the normality of the distribution. Categorical data were presented as numbers and percentages. Skewness and kurtosis were used to assess the data normality. We also graphically examined the distribution using a histogram. The p-values for the mean differences were determined using a one-way analysis of variance (ANOVA). Statistical significance was set at $p < 0.05$. The correlation coefficient assessed the relationship between knowledge, attitude, and practice. Spearman's rho was used as a test statistic. The significance of the correlation was measured at p-values of 0.01 or 0.05 (2-tailed). Statistical analyses were performed using the SPSS Statistics software (IBM, Armonk, New York, United States).

3. Results

Of the invited healthcare providers, 192 responded to the survey. One hundred seventy-seven individuals were included in the final analyses after excluding participants who did not meet the inclusion criteria.

3.1. Participants and baseline characteristics

The mean age of the participants was 33.1 years (±6.1). There were 102 (57.6 %) male participants. Most responses were from pharmacists not specialized in nephrology or infectious diseases; 84 (89.4%). Only six (6.4%) specialized in nephrology, and four (4.3%) specialized in infectious diseases. Physicians who were not nephrologists or infectious disease specialists accounted for 49 participants (81.7%). Only nine (15.0%) were nephrologists, and two (3.3%) were infectious disease specialists. Twenty (87.0%) nurses did not specialize in nephrology or infectious diseases. Only two nurses (8.7%) specialized in nephrology, and one (4.3%) in infectious diseases. Most responders worked at Ministry of Health (MOH) hospitals. An equal number of responders had years of experience ranging from one to four years and five to nine years; 59 (33.3%). Five participants (2.8 %) had > 20 years of experience. The participants were from different geographic regions of Saudi Arabia. However, the majority were from the western region, 54 (30.5%) (Table 1).

3.2. Healthcare providers' knowledge of AKI with VPT

Findings regarding healthcare providers' knowledge are presented in Table 2. We found a significant difference in knowledge between physicians, pharmacists, and nurses regarding two variables: the definition of AKI ($p < 0.001$) and the appropriate management of AKI due to VPT ($p = 0.002$). For the first variable, physicians demonstrated a high knowledge level, whereas pharmacists and nurses demonstrated a moderate level of knowledge. All healthcare providers demonstrated moderate knowledge levels for the second variable. In the post-hoc analysis (Table 3), a significant difference between the two variables was observed between physicians and pharmacists.

3.3. Healthcare providers' attitude towards AKI with VPT

In the attitude scale towards the perceived AKI risk due to VPT, the physicians' mean score was 4.29, indicating a good attitude. The pharmacists' mean score was 3.77, indicating a neutral attitude. Nurses' neutral attitudes were indicated by a mean score of 3.90. The difference between the healthcare workers was statistically significant ($p < 0.001$) (Table 2). In the post hoc analysis (Table 3), a significant difference was observed only between physicians and pharmacists ($p < 0.001$).

Physicians' attitude toward the clinical implications of AKI risk due to VPT averaged a score of 4.16, indicating a good attitude. However, the pharmacists averaged 3.14, indicating a neutral attitude. Moreover, the nurses' mean score was 3.44, indicating a neutral attitude. The difference between the healthcare workers was statistically significant ($p < 0.001$). In the post hoc analysis, a significant difference was observed explicitly between physicians and pharmacists ($p < 0.001$) and between physicians and nurses ($p = 0.004$).

3.4. Healthcare providers' practices in AKI with VPT

Physicians were found to rely less on the most common causative organisms for infection than pharmacists and nurses to guide empirical antibiotic therapy ($p < 0.001$) (Table 2). Specifically, the difference in practice level was more significant between physicians and pharmacists in the post-hoc analysis ($p < 0.001$) (Table 3).

Our study also found that physicians tended to take protective measures when using VPT more often than pharmacists and nurses ($p = 0.042$), with a significant difference between physicians and pharmacists ($p = 0.038$). Taking protective measures when using VPT was measured by the level of agreement to the following statements: "I monitor the serum creatinine to check for the incidence of acute kidney injury when co-administering piperacillin/-tazobactam and vancomycin" and "I take protective measures when I order or administer the piperacillin/tazobactam and vancomycin combination to a patient." However, physicians were less likely to discontinue vancomycin with AKI incidence than pharmacists and nurses ($p = 0.037$), but the difference in practice did not continue to be significant in the post-hoc analysis. In addition, physicians were less likely to change piperacillin/tazobactam to either cefepime or meropenem in combination with vancomycin for AKI incidence than pharmacists and nurses ($p = 0.001$). This difference was prominent between physicians and pharmacists in post-hoc analysis ($p = 0.001$).

When AKI occurred, physicians were found to be less likely than pharmacists and nurses to obtain serum vancomycin levels to check if the elevated level had contributed to the incidence ($p < 0.001$), and a significant difference was observed in the post-hoc analysis. However, all healthcare providers were willing to consult infectious diseases or nephrology specialists when AKI occurred, with no significant difference observed between them ($p = 0.884$).

3.5. Correlation between healthcare providers' knowledge, attitudes, and practice

When correlating the healthcare providers' practices regarding AKI with VPT with their knowledge (Table 4), a low positive correlation (Rho = 0.485) was found between the healthcare providers' knowledge of the appropriate management of AKI due to VPT and the practice of relying on the most common causative organisms for an infection to guide empiric antibiotic therapy. This correlation was moderate when it was measured in the physicians only (Rho = 0.562). Knowledge of the appropriate management of AKI due to VPT was also correlated positively, but weakly, with the practice of changing piperacillin/tazobactam to either cefepime or meropenem in combination with vancomycin with AKI incidence (Rho = 0.448). However, the correlation became weaker (Rho = 0.305) when it was tested on physicians only. Finally, physicians' knowledge of the appropriate management of AKI due to VPT was positively correlated with obtaining serum vancomycin levels to check if the elevated level has contributed to AKI incidence (Rho = 0.431) or consulting infectious disease or nephrology specialists when AKI occurs (Rho = 0.339) (Table 5).

When correlating the healthcare providers' practice regarding AKI with VPT with their attitude (Table 4), the positive attitude

Table 1
Characteristics of Healthcare Workers by Profession.

Variables	Total sample (n = 177)	Physicians (n = 60)	Pharmacists (n = 94)	Nurses (n = 23)
Age in years, mean (SD)	33.1 (6.1)	36.9 (5.9)	31.3 (5.6)	32.2 (5.3)
Male, n (%)	**102 (57.6%)**	**43 (71.7%)**	**50 (53.2%)**	**9 (39.1%)**
Specialty, n (%)				
Infectious diseases	7 (4.0%)	2 (3.3%)	4 (4.3%)	1 (4.3%)
Nephrology	17 (9.6%)	9 (15.0%)	6 (6.4%)	2 (8.7%)
Other	153 (86.4%)	49 (81.7%)	84 (89.4%)	20 (87.0%)
Years of experience, n (%)				
<1 year	32 (18.1%)	6 (10.0%)	21 (22.3%)	5 (21.7%)
1 – < 5 years	59 (33.3%)	22 (36.7%)	28 (29.8%)	9 (39.1%)
5 – < 10 years	59 (33.3%)	29 (48.3%)	25 (26.6%)	5 (21.7%)
10 – 20 years	22 (12.4%)	2 (3.3%)	16 (17.0%)	4 (17.4%)
>20 years	5 (2.8%)	1 (1.7%)	4 (4.3%)	0 (0.0%)
Institution type, n (%)				
Ministry of Health hospital	90 (50.8%)	36 (60.0%)	42 (44.7%)	12 (52.2%)
Academic/teaching hospital	21 (11.9%)	6 (10.0%)	12 (12.8%)	3 (13.0%)
Military hospital	21 (11.9%)	5 (8.3%)	13 (13.8%)	3 (13.0%)
Private hospital	41 (23.2%)	12 (20.0%)	24 (25.5%)	5 (21.7%)
Other	4 (2.3%)	1 (1.7%)	3 (3.2%)	0 (0.0%)
Region, n (%)				
Eastern	42 (23.7%)	11 (18.3%)	22 (23.4%)	9 (39.1%)
Central	35 (19.8%)	9 (15.0%)	20 (21.3%)	6 (26.1%)
Western	54 (30.5%)	31 (51.7%)	18 (19.1%)	5 (21.7%)
Northern	28 (15.8%)	5 (8.3%)	21 (22.3%)	2 (8.7%)
Southern	18 (10.2%)	4 (6.7%)	13 (13.8%)	1 (4.3%)

SD: Standard deviation.

Table 2
Knowledge, attitude, and practices of acute kidney injury incidence with the co-administration of piperacillin/tazobactam and vancomycin among healthcare workers.

Variables	Physicians (n = 60)	Pharmacists (n = 94)	Nurses (n = 23)	P value†
Knowledge, mean (SD)				
Knowledge about the appropriate use for VPT	3.30 (0.38)	3.20 (0.53)	3.02 (0.42)	0.061
Knowledge about the definition of AKI	4.13 (0.69)	3.61 (0.77)	3.86 (0.61)	< 0.001
Knowledge about the AKI due to VPT	3.08 (0.79)	3.10 (0.54)	3.20 (0.49)	0.612
Knowledge about the plausible mechanism of the AKI due to VPT	3.69 (0.61)	3.55 (0.62)	3.07 (0.48)	0.313
Knowledge about the appropriate management of AKI due to VPT	2.91 (0.55)	3.24 (0.61)	2.90 (0.62)	0.002
Attitude, mean (SD)				
Perceived AKI risk	4.29 (0.28)	3.77 (0.76)	3.90 (0.55)	< 0.001
Clinical implications of AKI risk	4.16 (0.82)	3.14 (0.92)	3.44 (1.04)	< 0.001
Practice, mean (SD)				
Use VPT as the first-line empiric therapy for patients with suspected infections requiring broad-spectrum coverage	2.92 (1.26)	3.07 (1.28)	2.70 (1.22)	0.405
Rely on the most common causative organisms for an infection to guide the empiric antibiotic therapy	2.60 (1.44)	3.40 (1.12)	3.35 (0.94)	< 0.001
Avoid using VPT unless no alternatives are available	3.77 (1.17)	3.44 (1.17)	3.39 (1.31)	0.198
Take protective measures when using VPT	4.08 (0.51)	3.79 (0.79)	3.85 (0.65)	0.042
Discontinue VPT with AKI	3.16 (0.44)	3.11 (0.57)	3.11 (0.45)	0.820
Discontinue vancomycin with AKI	2.68 (0.98)	3.10 (1.06)	3.17 (1.15)	0.037
Change to either cefepime or meropenem in combination with vancomycin with AKI	2.82 (1.11)	3.40 (0.88)	3.30 (0.88)	0.001
Obtain vancomycin level with AKI	2.25 (1.08)	3.38 (1.19)	3.26 (0.86)	< 0.001
Consult infectious disease or nephrology specialists when AKI occurs	3.93 (0.90)	3.87 (0.95)	3.96 (0.83)	0.884

†The p-values for the mean differences were obtained from one-way ANOVA.
SD: Standard deviation; VPT: vancomycin + piperacillin/tazobactam; AKI: acute kidney injury.

towards the perceived AKI risk with VPT correlated positively with the practice of avoiding using VPT unless no alternatives were available (Rho = 0.336) or with taking protective measures when using VPT (Rho = 0.461). On the other hand, despite having a positive attitude towards the clinical implications of AKI risk with VPT co-administration, it correlated negatively with the practice of discontinuing vancomycin when AKI occurs (Rho = -0.381) or with obtaining serum vancomycin levels to check if the elevated level has contributed to AKI incidence (Rho = -0.373). This negative correlation became lower when the physicians' responses were tested (Table 5), which could be explained by the fact that pharmacists, not physicians, usually manage vancomycin dosing and monitoring.

4. Discussion

To the best of our knowledge, this study is the first in Saudi Arabia and in the Gulf Cooperation Council (GCC) countries to evaluate healthcare workers' knowledge, attitudes, and practices regarding the incidence of AKI when co-administering VPT.

Appropriate knowledge of the incidence of AKI after co-administration of VPT is crucial to ensure the safe use of medications (Hosohata et al., 2019). Therefore, our study assessed health workers' knowledge in three main sections: knowledge about AKI, appropriate use of VPT, and risk of AKI when administering VPT simultaneously.

Table 3
Results of Post-hoc analysis showing the differences between physicians, pharmacists, and nurses in terms of their knowledge, attitude, practice.

Outcomes		P value
Knowledge about the definition of AKI		
	Physicians vs. Pharmacists	< 0.001
	Physicians vs. Nurses	0.357
	Pharmacists vs. Nurses	0.442
Knowledge about the appropriate management of AKI due to VPT		
	Physicians vs. Pharmacists	0.002
	Physicians vs. Nurses	0.173
	Pharmacists vs. Nurses	0.626
Perceived AKI risk		
	Physicians vs. Pharmacists	< 0.001
	Physicians vs. Nurses	0.089
	Pharmacists vs. Nurses	1.000
Clinical implications of AKI risk		
	Physicians vs. Pharmacists	< 0.001
	Physicians vs. Nurses	0.004
	Pharmacists vs. Nurses	0.479
Rely on the most common causative organisms for an infection to guide the empiric antibiotic therapy		
	Physicians vs. Pharmacists	< 0.001
	Physicians vs. Nurses	0.040
	Pharmacists vs. Nurses	1.000
Take protective measures when using VPT		
	Physicians vs. Pharmacists	0.038
	Physicians vs. Nurses	0.548
	Pharmacists vs. Nurses	1.000
Discontinue vancomycin		
	Physicians vs. Pharmacists	0.054
	Physicians vs. Nurses	0.173
	Pharmacists vs. Nurses	1.000
Change to either cefepime or meropenem in combination with vancomycin		
	Physicians vs. Pharmacists	0.001
	Physicians vs. Nurses	0.123
	Pharmacists vs. Nurses	1.000
Obtain vancomycin level		
	Physicians vs. Pharmacists	< 0.001
	Physicians vs. Nurses	0.001
	Pharmacists vs. Nurses	1.000

VPT: vancomycin + piperacillin/tazobactam; AKI: acute kidney injury.

Previous studies showed that non-nephrology doctors and nurses have moderate to good knowledge of AKI (Adejumo et al., 2017; Rajora et al., 2022, Salman et al., 2021). Our study supported those results by indicating that most respondents showed sufficient knowledge about AKI. However, pharmacists' knowledge was the lowest in this parameter, with a significant difference when comparing physicians and pharmacists ($p < 0.001$). In addition, our study showed that healthcare workers have moderate knowledge about the risk of AKI when administering VPT together, but no difference was observed in the knowledge level between physicians, pharmacists, and nurses ($p = 0.612$). One study conducted among healthcare professionals (comparing physicians and pharmacists at different career levels) showed that 77.8% of respondents agreed that vancomycin could cause AKI (Alabdan et al., 2018).

Antibiotic misuse is a significant factor in antibiotic resistance (Abdelaziz et al., 2019). A study conducted in Indonesia showed that 32% of the participants chose either incorrect answers or "do not know" choices when asked about the possibility of causing antibiotic resistance by misusing antibiotics (Karuniawati et al., 2021). In our study, healthcare workers demonstrated a fair level of practice in terms of relying on the most common causative organisms for an infection to guide empiric antibiotic therapy, which is considered one of the principles for ensuring the appropriate use of antibiotics rather than using VPT as the first-line option. Physicians, in particular, exhibited the lowest level of practice, with a significant difference observed between physician and pharmacist practices ($p < 0.001$). This could be considered a sign of an increased risk of antibiotic resistance since VPT is widely used in hospital settings.

In terms of taking the required protective measures, a study by Blair and colleagues agreed that taking protective measures is necessary, especially in patients at high risk of VPT toxicity (Blair et al., 2021). Our study showed that physicians tend to take required protective measures when using VPT more than pharmacists and nurses ($p = 0.042$). The protective measures included implementing an antimicrobial stewardship program, receiving the shortest recommended duration of VPT, as AKI risk was reduced by a shorter duration, and identifying all nephrotoxic medications and monitoring kidney functions closely (Blair et al., 2021; Traversa et al., 2021). In order to ensure the protective measures are followed, our study recommended developing institutional guidelines for VPT monitoring and utilization and implementing regulations and policies that restrict the prescribing of VPT to specialized physicians to ensure safe medication use.

Additionally, our study showed a significant difference between physicians and pharmacists in their tendency to change piperacillin/tazobactam to meropenem or cefepime in combination with vancomycin when AKI occurred ($p = 0.001$). Many studies that

Table 4
Correlation analysis between health workers' knowledge, attitudes, and practice (n = 177).

Practice Variables	Knowledge Variables					Attitude Variables	
	Appropriate use	Definition of AKI	AKI due to VPT	Plausible mechanisms of the AKI due to VPT	Appropriate management of AKI due to VPT	Perceived AKI risk	Clinical implications of AKI risk
Use VPT as the first-line empiric therapy for patients with suspected infections requiring broad-spectrum coverage	0.219**	−0.077	−0.122	0.013	−0.261**	0.021	−0.322**
Rely on the most common causative organisms for an infection to guide the empiric antibiotic therapy	−0.059	0.002	−0.018	−0.076	0.485**	−0.095	−0.124
Avoid using VPT unless no alternatives are available	0.105	0.255**	−0.019	0.293**	0.013	0.336**	0.193*
Take protective measures when using VPT	0.192*	0.270**	−0.019	0.304**	0.085	0.461**	0.333**
Discontinue VPT	−0.009	0.119	0.124	0.003	0.197**	0.167*	0.166*
Discontinue vancomycin	−0.116	−0.221**	0.053	−0.031	0.161*	−0.225**	−0.381**
Change to either cefepime or meropenem in combination with vancomycin	−0.254**	−0.041	0.022	0.100	0.448**	−0.033	−0.096
Obtain vancomycin level	−0.056	−0.288**	0.029	−0.174*	0.307**	−0.323**	−0.373**
Consult infectious disease or nephrology specialists when AKI occurs	0.003	0.154*	0.012	0.270**	0.238**	0.183*	0.165*

Spearman's Rho was used as test statistic. ** Correlation is significant at the 0.01 level (2-tailed); * Correlation is significant at the 0.05 level (2-tailed).
VPT: vancomycin + piperacillin/tazobactam; AKI: acute kidney injury.

Table 5
Correlation analysis between physicians' knowledge, attitudes, and practice (n = 60).

Practice Variables	Knowledge Variables					Attitude Variables	
	Appropriate use	Definition of AKI	AKI due to VPT	Plausible mechanisms of the AKI due to VPT	Appropriate management of AKI due to VPT	Perceived AKI risk	Clinical implications of AKI risk
Use VPT as the first-line empiric therapy for patients with suspected infections requiring broad-spectrum coverage	0.288*	−0.126	−0.234	0.053	−0.461**	0.195	−0.108
Rely on the most common causative organisms for an infection to guide the empiric antibiotic therapy	−0.118	−0.002	−0.006	−0.003	0.562**	−0.171	0.007
Avoid using VPT unless no alternatives are available	0.347**	0.173	0.089	0.345**	−0.094	0.390**	0.028
Take protective measures when using VPT	−0.043	0.110	−0.188	0.151	0.212	0.198	0.268*
Discontinue VPT	−0.063	0.226	0.040	0.124	0.223	0.039	0.270*
Discontinue vancomycin	−0.114	−0.349**	0.002	−0.285*	0.337**	−0.238	−0.147
Change to either cefepime or meropenem in combination with vancomycin	−0.415**	−0.102	−0.119	0.001	0.305*	−0.260*	0.036
Obtain vancomycin level	−0.191	−0.320*	0.043	−0.278*	0.431**	−0.267*	−0.021
Consult infectious disease or nephrology specialists when AKI occurs	−0.236	0.130	−0.082	0.161	0.339**	−0.112	0.229

Spearman's Rho was used as test statistic. ** Correlation is significant at the 0.01 level (2-tailed); * Correlation is significant at the 0.05 level (2-tailed).
VPT: vancomycin + piperacillin/tazobactam; AKI: acute kidney injury.

compared VPT with meropenem or cefepime with vancomycin showed that the risk of AKI was higher in patients who received VPT than in those who received vancomycin with cefepime or meropenem (Bellos et al., 2020; Navalkele et al., 2017; Peyko et al., 2017). In contrast, several studies showed that the risk of AKI between VPT, cefepime in combination with vancomycin, or meropenem in combination with vancomycin was not statistically significant (Hammond et al., 2016; Al Yami, 2017; Schreier et al., 2019; Tookhi et al., 2021). As a result, some physicians could be reluctant to discontinue or switch VPT since the evidence is still controversial. That was demonstrated in our study as the physicians were found to be less likely to discontinue vancomycin or to change piperacillin/tazobactam to either cefepime or meropenem in patients with AKI.

Obtaining a vancomycin level, especially in a patient known or has a history of renal impairment, is essential in monitoring the efficacy and safety of vancomycin. A study by Robertson and colleagues observed that the risk of developing AKI was higher in patients receiving vancomycin doses > 4 g/d and vancomycin trough level > 20 mcg/mL (Robertson et al., 2018). A similar finding in critically ill patients also identified a higher risk of AKI with high initial vancomycin trough levels > 15 or > 20 mcg/mL (Blevins et al., 2019; Molina et al., 2020). In our study, we assessed the practice of healthcare providers in obtaining vancomycin levels when the AKI occurred. The physicians were found to be less likely than other healthcare providers to obtain serum vancomycin levels ($p < 0.001$).

Notably, nurses and pharmacists in Saudi Arabia do not have prescribing privileges. Therefore, it is challenging to evaluate their willingness to discontinue treatment. Pharmacists and nurses may suggest the discontinuation of therapy. However, there is a possibility that some respondents indicated that they would not discontinue therapy because of a lack of prescribing privileges. The same issue applies to ordering vancomycin levels since pharmacists and nurses in most medical facilities in Saudi Arabia cannot order vancomycin levels. Instead, they would have to ask physicians to do so. Therefore, they might be willing to order vancomycin levels when AKI occurs, but they might not be able to do so due to the ordering restrictions. Unfortunately, our study could not specifically distinguish between these findings.

4.1. Limitations

This study has some limitations. First, we could not keep track of the healthcare providers invited to complete the survey because of the different methods used to distribute it. Therefore, we were unable to determine response rates. Second, self-reported questionnaires that depend on participants' honesty and recall ability may be susceptible to recall bias. Third, our cross-sectional study limited our ability to identify causality between healthcare workers' knowledge, attitudes, practices, and study variables. Fourth, most respondents were male and pharmacists, which could have been a source of selection bias. Fifth, we should have included a screening question about the utilization of VPT in the participants' institutions. Sixth, we did not categorize the physicians based on their practice level (resident/fellows vs. consultants). However, we measured years of experience and included them in the analysis. Finally, the study had a small sample size and did not reach the calculated sample size, which may indicate that the findings of this study cannot be generalized to all healthcare providers in Saudi Arabia. However, the study is the first to assess the healthcare workers' knowledge, attitude, and practices in Saudi Arabia regarding the incidence of AKI due to co-administrating VPT.

4.2. Recommendations

Based on the findings of this study, we recommend the following: 1) developing and advocating educational programs and webinars to help raise healthcare workers' knowledge of the AKI risk with concomitant use of vancomycin and piperacillin/tazobactam, 2) developing institutional guidelines regarding the utilization of VPT and the best way of monitoring, and 3) implementation of regulations and policies (including prescribing restrictions) regarding VPT use and evaluation of compliance.

5. Conclusion

Our study findings indicate that the knowledge, attitude, and practices of acute kidney injury incidence with co-administration of piperacillin/tazobactam and vancomycin among some healthcare workers in Saudi Arabia deviate from the optimal level. Interventions at the organizational level are recommended to guide best practices to improve the appropriateness of empiric antibiotic therapy and the safety of piperacillin/tazobactam and vancomycin combination to decrease and adequately manage acute kidney injury cases.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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