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The frequency, risk factors, onset time, and outcome of acute kidney injury induced by vancomycin, colistin, and liposomal amphotericin B in hospitalized patients

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ABSTRACT

Introduction: Medications are among the major causes of acute kidney injury (AKI) in hospitalized patients.

Objectives: This study aimed to explore the frequency, characteristics, risk factors, and clinical outcomes of AKI induced by vancomycin, colistin, and liposomal amphotericin B (L-AmB) in hospitalized patients across various wards of two educational hospitals in Shiraz, Iran.

Patients and Methods: From October 2022 to May 2023, an observational cross-sectional study was conducted in both intensive care unit (ICU) and non-ICU wards of Namazi and Shahid Faghihi hospitals, Shiraz, Iran. Patients aged 18 and older, without a documented history of AKI or chronic kidney disease, scheduled to receive treatment with vancomycin, colistin, or L-AmB for at least one week, were considered eligible. Relevant data, including demographic, clinical, and laboratory findings, were collected.

Results: AKI was observed in 36 (34.3%) out of 105 patients during treatment. The incidence rates of AKI were 29%, 55%, and 31.1% in vancomycin, colistin, and L-AmB recipients, respectively. The mean ± SD time to AKI onset was 5.44 ± 2.04 days (range; 3 to 13 days). Dehydration at admission significantly increased the risk of antibiotic-induced AKI (odds ratio [OR] = 3.686, 95% confidence interval [CI] = 1.226–11.081, $P = 0.020$). Co-administration of aminoglycosides (OR = 8.422, 95% CI = 1.846 – 38.426, $P = 0.006$), diuretics (OR = 3.763, 95% CI = 1.092–12.965, $P = 0.036$), and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (OR = 7.149, 95% CI = 1.534–33.308, $P = 0.012$) were also identified as independent risk factors. The in-hospital mortality rate was significantly higher in patients with AKI than in those without AKI (8.6% vs. 6.7%; $P < 0.044$).

Conclusion: AKI induced by vancomycin, colistin, and L-AmB occurred in about one-third of our study population, primarily within five days of initiating treatment. Dehydration and co-administration of nephrotoxic medications were significantly associated with AKI. Clinicians should explicitly address these factors in preventive strategies to reduce antibiotic-induced AKI in hospitalized patients.

Implication for health policy/practice/research/medical education:
Acute kidney injury (AKI) induced by vancomycin, colistin, and liposomal amphotericin B (L-AmB) is common in hospitalized patients and develops during the early phase of treatment. Antibiotic nephrotoxicity is non-oliguric and mostly mild. Dehydration upon admission and the co-administration of diuretics, aminoglycosides, and angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARBs) were shown to be significantly associated with antibiotic-induced AKI. Therefore, volume status upon admission, correcting possible dehydration/volume depletion, and avoiding the concurrent administration of agents with known nephrotoxic effects, whenever possible, are prudent approaches to prevent or minimize antibiotic-induced AKI. Antibiotic-induced AKI can be managed by only dose adjustment or temporary discontinuation of the offending agent.

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Original

Introduction

Acute kidney injury (AKI) affects over 13 million people and results in 1.7 million annual deaths worldwide (1). It is a common problem among hospitalized patients, particularly those in intensive care units (ICUs). AKI occurs in about 3%-7% of hospitalized and 25%-60% of ICU patients (2). Patients with AKI may exhibit a 4- to 10-fold increase in mortality and prolonged hospital stays than those without AKI. On the other hand, about one-fourth of all hospital medications are potentially nephrotoxic (3). Therefore, drug-induced kidney disease accounts for about 19-26% of cases of AKI among hospitalized patients, particularly critically ill subjects (4).

Antibiotics are among the most frequently prescribed medications; over half of hospitalized patients may receive at least one antibiotic (5). On the other hand, both physicians and pharmacists have selected and scored antibiotics as agents with remarkable nephrotoxicity potential in critically ill patients in adults. Amphotericin B (AmB), aminoglycosides, polymyxins, and vancomycin are prominent examples in this regard (6). According to the AKI-Epidemiologic Prospective Investigation (AKI-EPI) international cross-sectional study which conducted in 97 centers on patients during the first week of ICU admission, diuretics (32.4%), non-steroidal anti-inflammatory drugs (NSAIDs) (11.9%), aminoglycosides (6.8%), glycopeptides (1.4%), and contrast media (2.1%) accounted for the most cases of drug-induced kidney disease (7). Regarding amphotericin B nephrotoxicity, its incidence has been ranged from 30% to 80% (8). Similarly, polymyxin nephrotoxicity has been identified in 0% to 60% of its recipients (9).

Considering the high frequency and significant impact of AKI on the healthcare setting, having adequate knowledge about the status of this significant health problem in different clinical settings in our country is deemed necessary.

Objectives

The present study aimed to investigate the incidence, characteristics, potential risk factors, and clinical outcomes of AKI induced by vancomycin, colistin, and liposomal amphotericin B (L-AmB) among hospitalized patients in various wards of the two largest educational hospitals in Shiraz, southwest of Iran.

Patients and Methods

Study Type, Setting, and Duration

During seven months from October 2022 to May 2023, an observational, cross-sectional study was conducted across various ICU and non-ICU wards of Namazi and Shahid Faghihi hospitals, which are two educational and healthcare settings affiliated with Shiraz University of Medical Sciences, Shiraz, Iran.

Study Population

Individuals eligible for recruiting into the study met the following inclusion/exclusion criteria: 1) Aged 18 years or older, 2) a minimum of one-week treatment duration with vancomycin, colistin, or L-AmB, 3) no documented history of AKI (characterized by an increase in serum creatinine [SCr] of ≥ 0.3 mg/dL within 48 hours, an increase of ≥ 1.5 times from the baseline in the preceding 7 days, or a urine volume < 0.5 mL/kg/h for 6 hours) (10), 4) a history of chronic kidney disease (defined as estimated glomerular filtration rate [eGFR] less than 60 mL/min/1.73 m^2), 5) a history of temporary/maintenance hemodialysis or peritoneal dialysis, and 6) no participation in any simultaneous clinical trial that may impact the incidence or pattern of AKI.

Data collection

Daily surveys were conducted within the hospital information system (HIS) in the initial investigation stage. This systematic approach enabled us to identify and monitor all eligible patients scheduled to receive vancomycin, colistin, or L-AmB. A dedicated data sheet was designed for each enrolled subject, facilitating the systematic collection of required information. These variables comprised demographic (age, gender, and weight) and clinical characteristics (dosage, treatment duration, and indication of vancomycin, colistin, and L-AmB), along with co-administered medications, co-morbidities, duration of hospital stay, mortality rate, and the need for dialysis.

Daily monitoring of laboratory parameters, including conventional kidney function index (SCr and blood urea nitrogen [BUN]), was undertaken throughout the antibiotic therapy course. This practice was under the established protocols observed in the respective wards. The assessment and documentation of the hydration status of patients were carried out. Dehydration was identified if the ratio of the patient's BUN to SCr surpassed 20, or there was a documented history of fluid or blood loss and the positive signs/symptoms of dehydration on physical examination, such as sunken eyes, poor skin turgor, weak radial pulse, dizziness, and dry mucous membrane (11). The biochemical analysis of BUN and SCr along with electrolytes was carried out using an auto-analyzer manufactured by Shanghai Xunda Medical Instrument. The quantification of SCr levels was achieved by the modified Jaffe colorimetric method.

Study endpoints

The primary endpoint was the development of AKI. This condition was defined by an increase in SCr of ≥0.3 mg/dL within 48 hours, a rise of ≥1.5 times the baseline over the preceding seven days, or a urine volume <0.5 mL/kg/h for a continuous 6-hour period (10). The AKI diagnosis criteria were under the Kidney Diseases Improving Global

Outcomes (KDIGO) clinical practice guideline for AKI 2012, usually used to define drug-induced kidney disease (12). The patient's baseline GFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration 2021 (CKD-EPI 2021) formula.

AKI severity was assessed as a secondary endpoint using the KDIGO AKI staging criteria (10). According to the KDIGO criteria, AKI is categorized into three stages. Stage 1 is characterized by a SCr elevation of 0.3 mg/dL or more, 1.5-1.9 times the baseline level, or reduced urine output below 0.5 mL/kg/h for 6-12 hours. Stage 2 is identified by a SCr rise to 2-2.9 times the baseline level or urine output less than 0.5 mL/kg per hour for 12 or more hours. In stage 3, SCr increases to 3 times the baseline level, surpasses 4.0 mg/dL, or necessitates initiation of kidney replacement therapy (KRT). Stage 3 also includes patients with urine output less than 0.3 mL/kg per hour for 24 hours or more or anuria persisting for 12 hours or more. Concerning electrolyte disorders, hypokalemia and hypomagnesemia were defined as serum potassium and magnesium levels less than 3 mEq/L and 1.2 mEq/L, respectively (13).

Hospitalization duration, in-hospital mortality rate, and the need for hemodialysis in the cohort were considered as tertiary endpoints.

Statistical analysis

The statistical analyses were conducted using the Statistical Package for the Social Sciences (SPSS) version 25 software (IBM, Chicago, United States). Categorical variables were presented as percentages. The Kolmogorov-Smirnov test was employed to assess the normal distribution of continuous variables. Normally and non-normally distributed continuous variables were expressed as mean ± standard deviation (SD) and median (interquartile range), respectively. In addition, the chi-square or Fisher's exact test was conducted to assess potential associations among categorical variables. Parametric continuous variables were assessed using the independent *t* test, while non-parametric continuous variables were analyzed using the Mann-Whitney U test. Comparison of the mean values of SCr and serum potassium during vancomycin, colistin, and L-AmB treatment within and between patients with and without AKI was performed by the one-way analysis of variance (ANOVA) with repeated measures. Moreover, logistic regression analysis was employed to identify risk factors associated with AKI. Independent variables included age, gender, cumulative dose of studied medications, baseline GFR value, patients' dehydration status upon admission, primary diagnosis of sepsis at hospitalization, co-administration of prominent nephrotoxic agents (aminoglycosides, acyclovir, diuretics, corticosteroids [in the case of L-AmB], ACEIs/ARBs, NSAIDs, vasopressors, and cyclosporine/tacrolimus), and comorbidities (hypertension and diabetes mellitus). On the other hand, vancomycin, colistin, or L-AmB nephrotoxicity was considered the dependent variable. In the initial phase (univariate analysis), each independent variable was entered into the model individually to identify potential associations. Subsequently, variables with *P* values below 0.2 were selected and subjected to multivariate logistic regression analysis. This analysis was performed by logistic regression, providing odds ratios (OR) and a 95% confidence interval (CI). Except for the initial step of logistic regression analysis in which *P* values were set at <0.2, the threshold for statistical significance in all the above analyses was *P* values below 0.05.

Results

During the 7-month study period, 135 patients were primarily screened. Among them, 105 individuals fulfilled the inclusion criteria for being recruited into the study. Figure 1 illustrates the study flowchart.

The demographic, clinical, and laboratory characteristics of patients are listed in Table 1. Over half of the cohort (62.9%) was admitted to non-ICU wards, while the remaining one-third (37.1%) were hospitalized in the ICU wards. The most common diagnoses at hospital admission were sepsis (20%) and meningitis (20%), followed by pneumonia (10.5%). Among the total of 105 patients, 69 (65.7%) were given vancomycin, followed by colistin (n=20, 19%) and L-AmB (n=16, 15.2%). The cumulative doses of vancomycin, colistin, and L-AmB given to the cohort were 17.91±4.17 g, 62.55±12.96 million units, and 2375.00±503.65 mg, respectively. The mean ± SD infusion duration of vancomycin, colistin, and L-AmB was 0.84±0.20 hours (range; 0.5 to one hour), 0.93±0.11 hours (range: 0.75 to one hour), and 1.84±0.23 hours (range; 1.5 to two hours), respectively. The most frequent co-morbidity among the participants was hypertension (41.9%), followed by diabetes mellitus (25.7%). Forty-six (43.8%) patients had signs of dehydration at baseline and before starting the studied medications. In terms of administration of potentially nephrotoxic medications, corticosteroids were the most commonly prescribed agent (26.7%), followed by diuretics (22.9%), ACEIs/ARBs (17.1%), and NSAIDs (17.1%). No patient received iodinated contrast media.

Among the cohort, 36 patients (34.3%) developed AKI during hospital stay. The incidence rates of AKI in patients hospitalized in ICU and non-ICU wards were 43.6% and 28.8%, respectively. The incidence rates of AKI in vancomycin, colistin, and L-AmB recipients were 29%, 55%, and 31.1%, respectively.

The mean ± SD time duration between the initiation of antibiotic therapy and the onset of AKI was 5.44±2.04 days, ranging from 3 to 13 days. This value for vancomycin nephrotoxicity was 5.80±1.73 days, ranging from 3 to 9 days. Similarly, colistin nephrotoxicity exhibited a mean ± SD onset of 5.73±2.53 days, with minimum and maximum

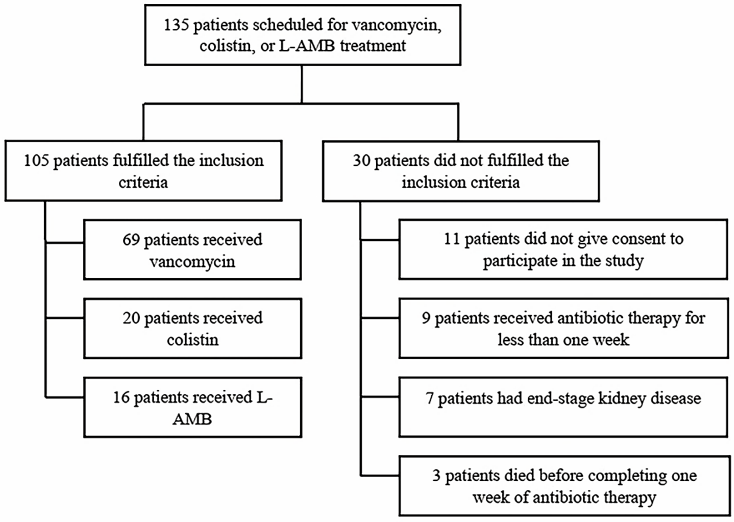

Figure 1. Patient selection and flowchart of the study.

values of 4 and 13 days, respectively. Finally, L-AmB nephrotoxicity had a mean ± SD onset of 3.40 ± 0.54 days, ranging from 3 to 4 days. Twenty-three (63.9%) out of 36 patients diagnosed with AKI were categorized as stage 1, 8 (22.2%) were categorized as stage 2, and the remaining 5 subjects (13.9%) exhibited stage 3 AKI.

The pattern of changes in SCr levels during days 1 to 7 of treatment with vancomycin, colistin, and L-AmB is depicted in Figure 2. Tables 2 to 4 also display the mean (95% CI) difference in SCr values on days 1 to 7 of treatment with vancomycin, colistin, and L-AmB between patients with and without AKI. The overall changes in mean (95% CI) SCr values for vancomycin, colistin, and L-AmB were statistically significant within patients with and without AKI ($P<0.001$ for vancomycin, $P=0.002$ for colistin, and $P<0.001$ for L-AmB). Similarly, the overall changes in the mean (95% CI) SCr values for vancomycin (0.515 [0.333 to 0.697], $P<0.001$) and L-AmB (0.873 [0.568 to 1.177], $P<0.001$) were statistically significant between patients with and without AKI. In contrast, the mean (95% CI) difference in SCr levels between patients with and without colistin nephrotoxicity was not statistically significant (0.186 [- 0.124 to 0.496], $P=0.224$).

Table 1. Demographic and clinical characteristics of the study population (n= 105)

Characteristics	Value
Gender: Male/Female, n (%)	60 (57.1)/45 (42.9)
Age (in years), mean (SD)	54.96 (19.91)
Care setting: Non-ICU/ICU, n (%)	66 (62.9)/39 (37.1)
Co-morbidities	
Hypertension, n (%)	44 (41.9)
Diabetes, n (%)	27 (25.7)
Primary diagnosis at hospitalization	
Sepsis, n (%)	21 (20)
Meningitis, n (%)	21 (20)
Pneumonia, n (%)	11 (10.5)
Neutropenic fever, n (%)	10 (9.5)
Diabetic foot, n (%)	9 (8.6)
Mucormycosis, n (%)	4 (3.8)
Other infectious diseases, n (%)	29 (27.6)

During the antibiotic therapy course, hypokalemia was observed in 17 (16.2%) out of 105 patients, while only three subjects (2.9%) developed hypomagnesemia. In our cohort, a higher incidence of hypokalemia was observed in L-AmB recipients (37.5%) compared to those who received vancomycin (13.0%) and colistin (10.0%). In any of the participants, hypomagnesemia was not observed following either vancomycin or colistin therapy. In contrast, among those administered L-AmB, 3 patients experienced at least one episode of hypomagnesemia. Figure 3 demonstrates the changing pattern of serum potassium levels during days one to 7 of treatment with vancomycin, colistin, and L-AmB. The overall changes in mean (95% CI) serum potassium values during the vancomycin, colistin, and L-AmB treatment course were not statistically significant within patients with or without nephrotoxicity ($P=0.221$ for vancomycin, $P=0.221$ for colistin, and $P=0.481$ for L-AmB). Likewise, the overall changes in mean (95% CI) serum potassium levels for colistin (0.137 [-0.197 to 0.470], $P=0.4$) and L-AmB (0.098 [-0.220 to 0.415], $P=0.521$) did not show any statistical significance between patients with and without AKI. Conversely, the mean difference in serum potassium levels between patients with and without vancomycin nephrotoxicity was statistically significant (0.263 [0.104 to

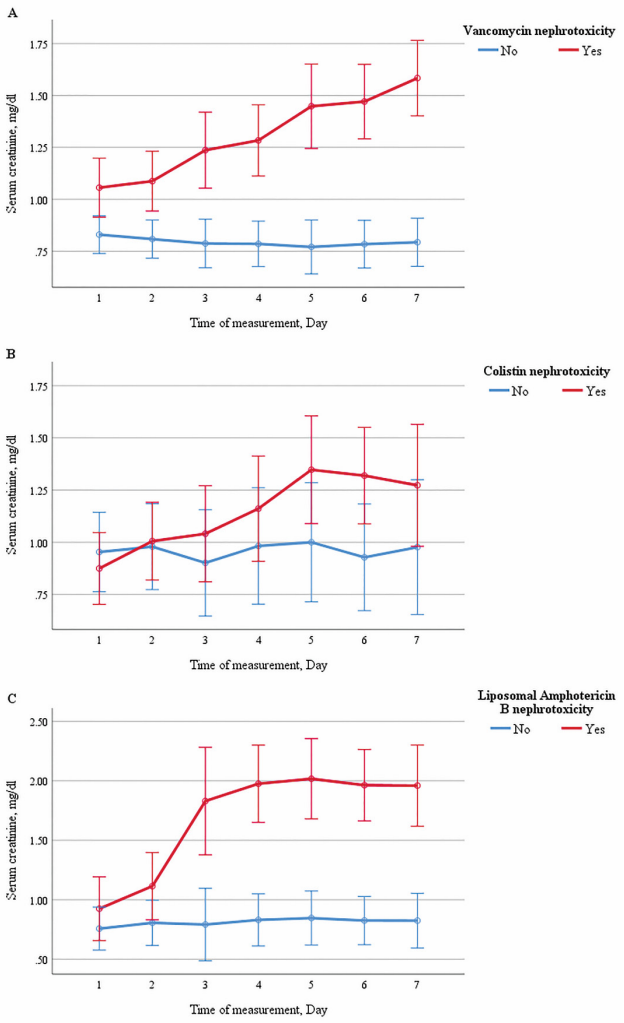

Figure 2. The comparison of serum creatinine levels during the course of vancomycin (A), colistin (B), and Liposomal amphotericin B (C) treatment between patients with and without AKI. The graph includes mean values along with a 95% confidence interval.

0.422], $P=0.002$).

Throughout the antibiotic therapy course in the hospital, none of the patients with AKI experienced oliguria. In addition, no case of life-threatening arrhythmia or rhabdomyolysis related to electrolyte disorders was observed in the cohort.

Table 2. Mean (95% CI) difference in serum creatinine values during days 1 to 7 of vancomycin treatment between patients with and without nephrotoxicity

Time	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Day 1	.	0.052 (-0.017 to 0.123) [0.137]	0.222 (0.099 to 0.346) [0.002]	0.271 (0.171 to 0.372) [< 0.001]	0.451 (0.293 to 0.609) [< 0.001]	0.460 (0.306 to 0.614) [< 0.001]	0.564 (0.402 to 0.725) [< 0.001]
Day 2	.	.	0.170 (0.044 to 0.295) [0.039]	0.219 (0.120 to 0.317) [< 0.001]	0.398 (0.241 to 0.554) [< 0.001]	0.407 (0.259 to 0.555) [< 0.001]	0.511 (0.359 to 0.662) [< 0.001]
Day 3	.	.	.	0.049 (-0.078 to 0.176) [0.046]	0.228 (0.004 to 0.416) [0.001]	0.237 (0.038 to 0.435) [0.001]	0.341 (0.125 to 0.556) [< 0.001]
Day 4	.	.	.	.	0.179 (0.046 to 0.311) [0.066]	0.188 (0.047 to 0.328) [0.098]	0.292 (0.133 to 0.450) [0.016]
Day 5	.	.	.	.	.	0.009 (-0.088 to 0.106) [0.592]	0.112 (-0.044 to 0.270) [0.726]
Day 6	.	.	.	.	.	.	0.103 (-0.024 to 0.232) [0.512]
Day 7	.	.	.	.	.	.	.

Note: *P* values for each comparison are provided in brackets.

Table 3. Mean (95% CI) difference in serum creatinine values during days 1 to 7 of colistin treatment between patients with and without nephrotoxicity

Time	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Day 1	.	0.105 (-0.067 to 0.278) [0.218]	0.218 (-0.049 to 0.486) [0.080]	0.257 (-0.016 to 0.531) [0.044]	0.426 (0.160 to 0.692) [0.004]	0.470 (0.220 to 0.719) [0.001]	0.374 (0.046 to 0.703) [0.027]
Day 2	.	.	0.113 (-0.048 to 0.275) [0.094]	0.152 (-0.042 to 0.346) [0.138]	0.320 (0.073 to 0.567) [0.018]	0.364 (0.129 to 0.600) [0.009]	0.269 (-0.034 to 0.573) [0.094]
Day 3	.	.	.	0.038 (-0.148 to 0.226) [0.970]	0.207 (-0.065 to 0.480) [0.102]	0.251 (0.004 to 0.498) [0.037]	0.156 (-0.139 to 0.452) [0.361]
Day 4	.	.	.	.	0.168 (-0.0007 to 0.337) [0.020]	0.212 (-0.042 to 0.467) [0.138]	0.117 (-0.189 to 0.423) [0.494]
Day 5	.	.	.	.	.	0.044 (-0.176 to 0.265) [0.323]	-0.051 (-0.312 to 0.210) [0.879]
Day 6	.	.	.	.	.	.	-0.095 (-0.269 to 0.079) [0.052]
Day 7	.	.	.	.	.	.	.

Note: *P* values for each comparison are provided in brackets.

Table 4. Mean (95% CI) difference in serum creatinine values during days 1 to 7 of L-AmB treatment between patients with and without nephrotoxicity

Time	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Day 1	.	0.140 (-0.026 to 0.308) [0.093]	0.871 (0.290 to 1.452) [0.004]	0.978 (0.553 to 1.403) [0.002]	1.004 (0.533 to 1.475) [0.004]	0.971 (0.500 to 1.443) [0.003]	0.968 (0.462 to 1.474) [0.005]
Day 2	.	.	0.730 (0.199 to 1.261) [0.008]	0.837 (0.431 to 1.243) [0.002]	0.864 (0.419 to 1.308) [0.003]	0.830 (0.374 to 1.287) [0.004]	0.827 (0.341 to 1.313) [0.008]
Day 3	.	.	.	0.106 (-0.334 to 0.548) [0.691]	0.133 (-0.392 to 0.659) [1.000]	0.100 (-0.394 to 0.594) [0.691]	0.097 (-0.419 to 0.613) [0.692]
Day 4	.	.	.	.	0.026 (-0.144 to 0.197) [0.691]	-0.006 (-0.153 to 0.140) [0.650]	-0.009 (-0.172 to 0.152) [0.865]
Day 5	.	.	.	.	.	-0.033 (-0.181 to 0.115) [0.496]	-0.036 (-0.181 to 0.108) [0.496]
Day 6	.	.	.	.	.	.	-0.003 (-0.063 to 0.057) [1.000]
Day 7	.	.	.	.	.	.	.

Note: *P* values for each comparison are provided in brackets.

The mean ± SD duration of hospitalization did not differ significantly between patients with AKI and those without AKI, with respective values of 34.64±22.71 days and 28.88±19.95 days ($P=0.214$). The in-hospital mortality rate was significantly higher in patients with AKI than in those without AKI (8.6% versus 6.7%, respectively; $P<0.044$). During hospitalization, four patients (3.8%) with AKI and three patients (2.9%) without AKI received hemodialysis, which was comparable between the two groups ($P=0.214$).

Concerning univariate analysis results, hypertension as comorbidity ($P<0.001$), baseline eGFR ($P=0.167$), patients' dehydration upon admission ($P=0.003$), ICU admission ($P=0.125$), and the concurrent administration of aminoglycosides ($P=0.007$), diuretics ($P=0.002$), ACEIs/ARBs ($P=0.003$), and NSAIDs ($P=0.128$) were identified and chosen for further consideration. After adjusting for selected variables in the multivariate logistic regression model, patients' dehydration upon admission (OR = 3.686, 95% CI = 1.226–11.081, $P=0.020$), the co-administration of aminoglycosides (OR = 8.422, 95% CI = 1.846–38.426, $P=0.006$), diuretics (OR = 3.763, 95% CI = 1.092–12.965, $P=0.036$), and ACEIs/ARBs (OR = 7.149, 95% CI = 1.534 – 33.308, $P=0.012$) remained significantly associated with AKI induced by vancomycin, colistin, or L-AmB (Table 5).

In 52.8% of patients diagnosed with AKI, the responsible antibiotic was discontinued, while in 47.2% of cases, treatment was continued with the adjusted antibiotic dose. Vancomycin and colistin were discontinued in 45% and 45.5% of patients with AKI, respectively. Antibiotic dosages were adjusted for 55% and 54.5% of patients receiving vancomycin and colistin, respectively. On the other hand, L-AmB was discontinued in all patients within 3 to 4 days following the development of AKI.

In patients with AKI, discontinuing the responsible

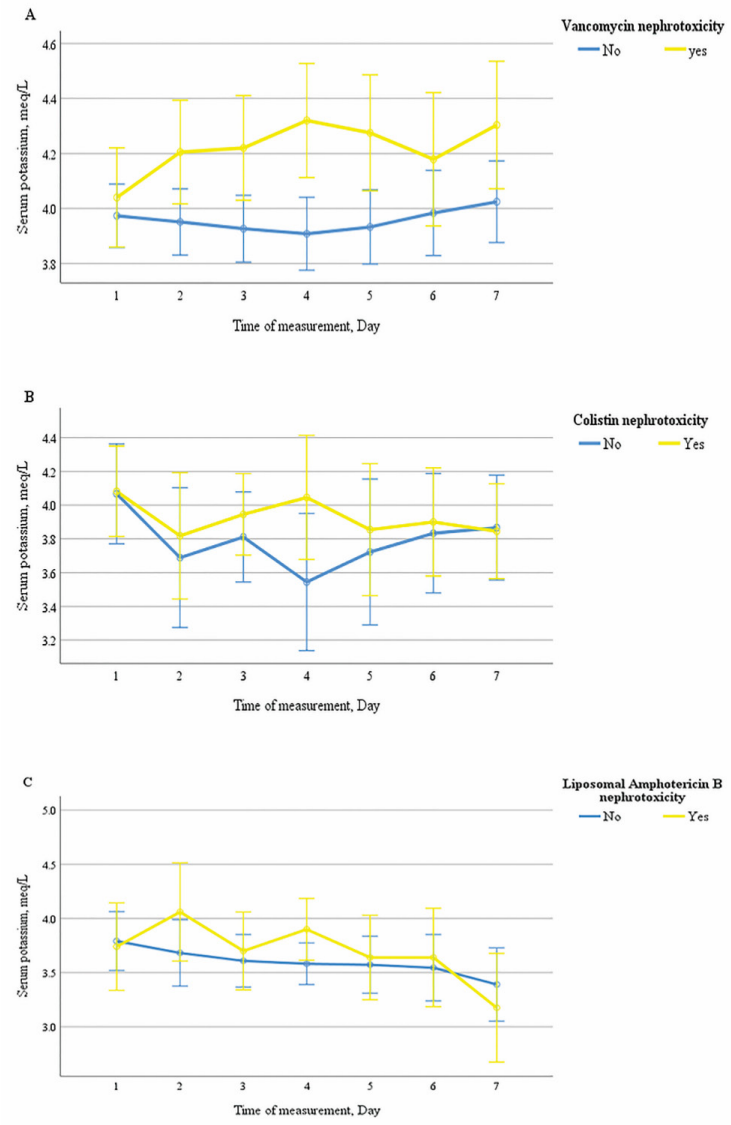

Figure 3. The comparison of serum potassium levels during various days of vancomycin (A), colistin (B), and liposomal amphotericin B (C) treatment between patients with and without AKI. The graph includes mean values along with a 95% confidence interval.

antibiotic decreased SCr levels to 1.16±0.10 mg/dL. In contrast, in those who continued treatment after dose adjustment, SCr levels decreased to 1.26±0.09 mg/dL. These reductions were comparable between both groups ($P=0.505$). The decrease in SCr levels after discontinuing the studied antibiotic was observed within a median period of 2.5 days (ranging from one to 34 days) and exhibited statistical significance compared to baseline values ($P=0.001$).

Discussion

Medications, particularly in hospitalized patients, significantly contribute to the occurrence of AKI, a severe and prevalent condition associated with high morbidity and mortality on a global scale (14). Globally, 17% to 26% of AKIs are attributed to drugs (15). In Asian countries, particularly in China, drug-induced AKIs are more prevalent, accounting for approximately 40%, with antimicrobial agents identified as the primary nephrotoxic drugs (16,17). In a study conducted by Che et al (18) across 17 hospitals in Shanghai, China, with a focus on the middle-class population, 47.8% of drug-induced AKI events (166 out of 347) were found to be associated with antibiotics. In our investigation, about one-third of the cohort (34.3%) developed AKI during antibiotic treatment. This rate was similar to that reported from Asian countries (16). The difference in the rate of antibiotic-induced AKI can be justified partially by the type of study, definition criteria for AKI, type of investigated antibiotics, and the duration of follow-up. In the term of definition criteria for example, we used the KDIGO 2012 definition, which is currently a popular one for drug-induced AKI (12).

In our study, the incidence of vancomycin-induced AKI was 29%, with a mean ± SD onset of 5.80±1.73 days. In

Table 5. Factors potentially associated with antibiotic-induced AKI in the study population

Characteristics	Patients with AKI (n=36)	Patients without AKI (n=69)	Univariate model		Multivariate model	
			P value	OR (95% CI)	*P* value	OR (95% CI)
Age years, Mean (SD)	56.36 ±18.84	54.23 ±20.54	0.602	1.005 (0.985–1.026)		
Gender: Male/Female, n	22/14	38/31	0.553	1.282 (0.564–2.914)		
Baseline GFR, mL/min/1.73 m^2, Mean (SD)	86.77 ±27.66	93.88 ±23.15	0.167	0.988 (0.970–1.005)	0.733	0.996 (0.975–1.018)
Co-morbidities						
Diabetes, n (%)	12 (11.4%)	15 (14.3%)	0.200	1.800 (0.733–4.421)		
Hypertension, n (%)	24 (22.9%)	20 (19%)	<0.001	4.900 (2.060–11.654)	0.697	1.306 (0.339–5.028)
Patients' dehydration upon admission, n (%)	23 (21.9%)	23 (21.9%)	0.003	3.538 (1.521–8.233)	0.020	3.686 (1.226–11.081)
Primary diagnosis of sepsis at hospitalization, n (%)	8 (7.6%)	13 (12.4%)	0.681	1.231 (0.457–3.315)		
Co-administered medications						
Aminoglycosides, n (%)	10 (9.5%)	5 (4.8%)	0.007	4.923 (1.534–15.803)	0.006	8.422 (1.846–38.426)
Diuretics, n (%)	15 (14.3%)	9 (8.6%)	0.002	4.683 (1.784–12.289)	0.036	3.763 (1.092–12.965)
NSAIDs, n (%)	9 (8.6%)	9 (8.6%)	0.128	2.222 (0.794–6.222)	0.400	1.751 (0.475–6.452)
ACEI/ARB, n (%)	12 (11.4%)	6 (5.7%)	0.003	5.250 (1.771–15.567)	0.012	7.149 (1.534–33.308)
Corticosteroids, n (%)	10 (9.5%)	18 (17.1%)	0.852	1.090 (0.440–2.696)		
Acyclovir, n (%)	3 (2.9%)	5 (4.8%)	0.842	1.164 (0.262–5.172)		
Vasopressor, n (%)	3 (2.9%)	2 (1.9%)	0.235	3.045 (0.485– 19.120)		
Cyclosporine/Tacrolimus, n (%)	1 (1%)	1 (1%)	0.642	1.943 (0.118–32.002)		
Cumulative dose						
Vancomycin in g, Mean (SD)	16.90 ±2.36	18.33 ±4.67	0.203	0.908 (0.782–1.054)		
Liposomal amphotericin B in mg, Mean (SD)	2150.00 ±269.25	2477.27±560.96	0.248	0.998 (0.995–1.001)		
Colistin in million units, Mean (SD)	60.55 ±17.23	65.00 ±3.96	0.454	0.971 (0.899–1.049)		
ICU Admission, n (%)	17 (16.2%)	22 (21%)	0.125	1.911 (0.836–4.372)	0.916	1.061 (0.350 –3.223)

Abbreviations: GFR, Glomerular filtration rate; NSAIDs, Non-steroidal anti-inflammatory drugs; ACEI/ARB, Angiotensin-converting enzyme inhibitors/angiotensin receptor blockers; ICU, Intensive care unit.

the literature, the incidence of vancomycin nephrotoxicity ranges from as low as 0% in the absence of concurrent nephrotoxic agent to more than 40% (19). It develops 4.3-17 days after initiating vancomycin therapy (20). This wide variation in the frequency of vancomycin nephrotoxicity is mainly related to the retrospective methodology and lack of a control group in the majority of studies, different study settings (critically ill patients versus non-critically ill patients), the presence of risk factors (particularly vancomycin trough levels, treatment duration/study follow-up, and co-administered nephrotoxic medications), and disparity in the definition of AKI.

The incidence of AKI during colistin therapy in our study was high (55%), including 83.3% in the ICUs and 42.9% in non-ICU wards. The onset time of colistin nephrotoxicity in the cohort was 5.73±2.53 days. The rate of colistin nephrotoxicity varies significantly in the literature. The 2019 polymyxin use guidelines have estimated 20% to 50% nephrotoxicity rates for both polymyxins, including polymyxin E (colistin) and polymyxin B (21). A meta-analysis of five randomized clinical trials with 377 patients, mainly critically ill subjects, reported that the incidence of colistin nephrotoxicity was 36.2% (95% CI, 23.3%-51.3%) (9). It has been reported that the rise in SCr usually occurs within the first 5-7 days of colistin treatment (22). The wide variation in the rate of polymyxin nephrotoxicity is primarily due to disparity and heterogeneity in the definition of nephrotoxicity, study population, study methodology, medication dose, severity of illness, and also the presence of other potential confounders, such as co-administered nephrotoxic agents (9).

In the present survey, about one-third (31.1%) of L-AmB recipients developed AKI with a mean ± SD onset time of 3.40 ± 0.54 days. Since nephrotoxicity is generally the most clinically significant adverse reaction that limits the use of AmB deoxycholate (conventional), lipid-based formulations have been developed as a practical approach to minimize AmB nephrotoxicity while preserving its antifungal activity. Therefore, lipid formulations of AmB, particularly L-AmB, are substantially less nephrotoxic than conventional AmB (up to 80% of cases) (23). A systematic review and meta-analysis of randomized clinical trials (five trials comprising 1233 patients) also reported that the incidence rates of nephrotoxicity with conventional and L-AmB were 32.5% and 14.5%, respectively (8). At the time of our investigation, only the L-AmB formulation was available for use in our clinical settings. The wide variation in the rate of AmB nephrotoxicity mainly relies on the definition used and the presence of risk factors, particularly its cumulative dose.

Regarding clinical and laboratory manifestations in the present survey, the SCr changing pattern during treatment with studied antibiotics demonstrated a gradual increase in patients with AKI. Except for SCr changes between patients with and without AKI caused by colistin, other variations of SCr within and between groups reached the level of statistical significance in the cohort. In addition, no patient developed oliguria. Since the kidney condition in the cohort was unstable and dynamic, eGFR was not determined and compared between subjects with and without AKI. In the case of AmB nephrotoxicity, the SCr level usually does not increase by more than 2.5 mg/dL from baseline values (24). Regarding vancomycin nephrotoxicity, preliminary clinical studies have reported an increase in baseline SCr of 1-1.5 mg/dL (19). Finally, in line with our findings, most cases of drug-induced nephrotoxicity are acute and non-oliguric (12).

Electrolyte and acid/base imbalances may manifest as adverse effects of certain antimicrobials, including aminoglycosides, AmB, trimethoprim, and tetracycline, even without a decline in kidney function (25). In the course of treatment with conventional AmB, hypokalemia and hypomagnesemia frequently manifest in a dose-dependent manner, with hypokalemia reportedly occurring at rates as high as 75%-90% (26), and hypomagnesemia documented across a broad spectrum of frequencies from 15% to 100%. This variation is attributed to differences in the dosage and formulation of AmB. In terms of the latter issue, hypokalemia and hypomagnesemia are reported in 5%-26% and 6%-20% of recipients of AmB-lipid formulations, respectively (27). In line with this, hypokalemia was observed in 37.5% of patients who received L-AmB in our study, while hypomagnesemia occurred in 18.8%. Besides using the liposomal formulation of AmB, the absence of daily monitoring of serum magnesium levels among patients may also contribute to underdiagnoses and, consequently, a lower incidence of hypomagnesemia, as observed in our study. During the vancomycin therapy course, hypokalemia developed in 13% of our cohort. There is a paucity of data about electrolyte disorders secondary to vancomycin therapy. In a retrospective study conducted by Falcone et al on patients with bone and joint infections receiving multiple antibiotic therapy, vancomycin therapy was associated with any decrease in serum potassium level (OR = 2.7, 95% CI = 1.7–4.3, $P<0.001$) and also serum potassium level < 3.8 mEq/L (OR = 2.2, 95% CI = 1.3–3.8, $P=0.003$); however, there was no statistically significant correlation between vancomycin treatment and serum potassium levels below 3.5 mEq/L ($P=0.401$) (28). In our study, only one episode of hypokalemia was observed in two patients during the colistin treatment course. Similar to vancomycin, there is scarce data in the literature about electrolyte disorders associated with colistin. In this regard, available clinical evidence is only limited to a case report describing a barter-like syndrome and hypokalemia following colistin therapy (29).

Except for mortality rate, other studied clinical outcome indices, including the duration of hospital stay and the need for KRT, were comparable between patients with

and without AKI in our survey. Rhabdomyolysis and life-threatening arrhythmias due to electrolyte disorders were also absent in our cohort. In patients with AmB nephrotoxicity, up to 15% of cases may require dialysis, at least temporarily (30). A retrospective cohort study between January 2008 and March 2015 at Mayo Clinic in Rochester demonstrated that among 98 patients who experienced nephrotoxicity during L-AmB, 32 subjects exhibited complete recovery after a mean of 9.8 ± 7.8 days (31). Regarding vancomycin nephrotoxicity, up to three-quarters of the affected patients will either improve or recover entirely by discharge, often within a week or less (19). However, some subjects, particularly those with critical illness, may not experience full kidney function recovery. For example, a retrospective, multicenter, observational study on 188 adults with hospital-acquired, ventilator-associated, or healthcare-associated pneumonia in the ICU demonstrated that patients who developed vancomycin nephrotoxicity had significantly more extended median ICU and hospital stay (17 and 20 days, respectively) compared to those without nephrotoxicity (12 and 15 days, respectively) (32). Similar to AmB and vancomycin, most cases of polymyxin nephrotoxicity are also mild to moderate and expected to be reversible. However, up to 28% of patients affected by polymyxin nephrotoxicity may require KRT, at least temporarily (33). These possible disparities in the impact of drug-induced nephrotoxicity on clinical outcomes can be justified partially by the presence of different confounders, such as the severity of illness and clinical setting (critical care versus non-critical care) in investigated patients.

Among our cohort's investigated demographic, clinical, and laboratory parameters, volume depletion and co-administration of certain nephrotoxic medications (aminoglycosides, diuretics, and ACEIs/ARBs) were significantly associated with AKI. Volume depletion (dehydration), hypotension, or reduced adequate arterial volume are all recognized as significant risk factors contributing to the development of nephrotoxicity associated with different medication classes, including antimicrobial agents (34). Therefore, volume repletion and resolving dehydration are expected to be the mainstay and general approaches for both the prevention and management of antibiotic-associated AKI (14,35).

Several studies have identified the co-administration of nephrotoxic agents, such as aminoglycosides and furosemide, as an independent risk factor for antibiotic-associated AKI (36). In the case of vancomycin nephrotoxicity, particularly the concomitant administration of aminoglycosides can increase the risk of AKI (20). In addition to these nephrotoxic agents, a specific risk factor for drug-induced AKI encompasses a particular drug combination, notably known as the "triple whammy," which involves NSAIDs, ACEIs/ARBs, and diuretics (37). Finally, glucocorticoids may have a dual impact on antibiotic-induced AKI. In this regard, this class of medications may increase the risk of AmB nephrotoxicity (23). In contrast, preliminary data suggest the protective effects of glucocorticoids against colistin nephrotoxicity. The latter phenomenon is attributed to the fact that these agents induce P-glycoprotein, causing efflux of colistin from renal proximal tubular cell epithelium (38). Notably, the findings of at least a meta-analysis do not support the nephroprotective effect of combination therapy with glucocorticoids compared to monotherapy in polymyxin recipients (39).

The principal approach to AKI management in the present study was discontinuing the offending agent (52.8%). Decreasing the causative antibiotic dose (47.2%) was another therapeutic approach in our cohort. Generally, there are no definitive and specific treatment options for nephrotoxicity caused by AmB, vancomycin, and polymyxins. Supportive modalities rely on dose-de-escalation or discontinuing the causative agent, hydration, and performing KRT under certain conditions (34). In the case of AmB nephrotoxicity, the beneficial effects of liberal fluid infusion (like isotonic saline administration as daily fluid volume per weight more than or equal to a specified threshold started at the onset of AKI and continued for a determined period) against AmB-induced AKI have been demonstrated in a retrospective, multicenter, observational study (40).

Conclusion

About one-third (34.3%) of the cohort developed AKI due to vancomycin, colistin, or L-AmB, with the mean ± SD onset time of 5.44 ± 2.04 days after initiating the causative agent. Since most cases of AKI (63.9%) were categorized as stage 1 and all were non-oliguric, they were managed by only dose adjustment or temporary discontinuation of the offending antibiotic. Hypokalemia and hypomagnesemia were identified in 16.2% and 2.9% of the cohort, respectively. The in-hospital mortality rate was significantly higher in patients with AKI compared to those without AKI. Dehydration upon admission and the co-administration of diuretics, aminoglycosides, and ACEIs/ARBs were significantly associated with antibiotic-induced AKI. Therefore, taking into account the patient's volume status upon admission, correcting possible dehydration/volume depletion, and avoiding the concurrent administration of agents with known nephrotoxic effects, whenever possible, are prudent approaches to prevent or minimize antibiotic-induced AKI. Performing studies on larger sample sizes with longer duration of follow-up, determining and considering composite endpoints, such as significant adverse kidney events within 30 days (MAKE30), can give the healthcare team a more realistic view of the pattern, risk factors and clinical outcomes of antibiotic-induced AKI in our hospitalized patients.

Limitations of the study

The present study has several limitations, so our results should be interpreted cautiously. First, the cohort sample size was relatively small; therefore, type II error and the likelihood of statistical under-powering could not be ruled out. In particular, determining the risk factors of AKI for each antibiotic was not statistically feasible. In addition, the wide CI or OR for variables such as patients' dehydration upon admission, aminoglycosides, and ACEIs/ARBs in the multivariate logistic regression model can be justified in this way. Second, since the blood concentrations of vancomycin were not routinely measured and reported during the study period in these two clinical settings, assessing the possible association between vancomycin serum trough level and risk of AKI was not feasible. Third, given that most of the study participants were under polypharmacy and AKI is a multifactorial phenomenon, particularly in critically ill settings, attributing the identified nephrotoxicity merely to the investigated antibiotics seems to be irrational. Finally, although most cases of drug-induced AKI occur during the first two weeks of treatment, the development of full-blown nephrotoxicity can take several weeks. Accordingly, the duration of patient follow-up may be inadequate, and the possibility of underreporting may be present.

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Authors' contribution

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Conflicts of interest

Authors declare no conflict of interests.

Study Highlights

What is the current knowledge?

- Medications are among the major causes of AKI in hospitalized patients.
- Antibiotics are among the most frequently prescribed medications in hospitalized patients.

What is new here?

- About one-third (34.3%) of the cohort developed AKI due to vancomycin, colistin, or L-AmB.
- Most cases of antibiotic-induced AKI (63.9%) were categorized as stage 1 and all (100%) were non-oliguric.
- Most cases of antibiotic-induced AKI were managed by only dose adjustment or temporary discontinuation of the offending antibiotic.
- Dehydration upon admission and the co-administration of diuretics, aminoglycosides, and ACEIs/ARBs were significantly associated with antibiotic-induced AKI.
- In-hospital mortality rate was significantly higher in patients with AKI (8.6%) compared to those without AKI (6.7%).

Ethical issues

This study was conducted under the principles delineated in the Declaration of Helsinki and received ethical approval from the Ethics Committee of Shiraz University of Medical Sciences (Ethical code#IR.SUMS.MED.REC.1401.408). Accordingly, written informed consent was taken from all participants before any intervention. This study was extracted from Mojtaba Shabani-Borujeni's Ph.D. dissertation at Shiraz Pharmacy School (Thesis #24126). Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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