European Review for Medical and Pharmacological Sciences 2022; 26: 3718-3725

The incidence of acute kidney injury in hospitalized patients receiving aminoglycoside antibiotics: a retrospective study

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Abstract. – OBJECTIVE: Our aim is to investigate the incidence and risk factors of acute kidney injury (AKI) in hospitalized patients who received aminoglycoside antibiotics.

MATERIALS AND METHODS: A retrospective analysis was performed on the electronic medical record information of inpatients who received aminoglycoside (AG) antibiotics in our center from January 2018 to December 2020. The diagnosis of AKI was based on serum creatinine changes. Several statistical methods, including chi square test and two sample Wilcoxon rank sum test, were used to evaluate the epidemiological characteristics of aminoglycosides associated AKI. The multivariate logistic regression analysis was used to screen the risk factors.

RESULTS: Finally, 8,040 patients who received AGs were included in the study. Among them, 494 patients (6.14%) were judged as incidence with AKI, while only 29 patients were diagnosed with AKI in the medical record. The multiple logistic regression analysis suggested that admission to ICU, complicated with diabetes mellitus, heart failure, anemia, shock, combined use of diuretics, β-lactam antibiotics, proton pump inhibitors were independent risk factors for AKI related to aminoglycosides.

CONCLUSIONS: It is urgent to improve the understanding and attention of AKI for medical workers, and the assessment of risk factors before the use of aminoglycosides should be contributed to the early prevention, diagnosis, and treatment of AKI.

Key Words:
Aminoglycosides, Acute kidney injury, Multiple logistic regression analysis, Risk factors, Missed diagnosis.

Introduction

Acute kidney injury (AKI) is a sudden episode of kidney failure or kidney damage that happens within a few hours or a few days, which is common in hospitalized patients[1,2]. Large amounts of medical and health resources have been devoted to patients with AKI, since it can always lead to poor prognosis and high mortality, and result in a sharp increase in social medical costs[3,4].

Acute kidney injury can be induced by many different causes. Kidney plays a central role in excreting and clearing xenobiotics (particularly medications) and is susceptible to the toxicity from these agents[5]. It was reported that 5%-20% of AKIs in hospitalized patients were caused by nephrotoxic drug exposure[6-9]. Recent reports[10-13] suggest that AKI is also a common symptom after COVID-19 and that its occurrence may be associated with medication.

Aminoglycoside antibiotics (AGs) are widely used in the treatment of severe infection of gram-negative bacteria[14]. AGs are one of the well-known medications with nephrotoxicity, since they can result in ubular swelling and even acute necrosis by blocking the regulation and transport of calcium[15]. However, few studies[2] focused on the incidence and severity distribution of AKI in hospitalized patients who received aminoglycoside antibiotics till now, which brought challenges to provide more specific and personalized reference for clinical decision-making.

In this study, we focused on the investigation of the incidence of AKI in hospitalized patients who received aminoglycoside antibiotics (AGs-A-

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KI) and the analysis of risk factors. The medical records of adult inpatients who received aminoglycosides (amikacin, etimicin and gentamicin) were collected to investigate the incidence, demographic characteristics and risk factors of AKI occurred during hospitalization.

Materials and Methods

Data Sources

The retrospective study was conducted in the First Affiliated Hospital of Shandong First Medical University, China. The data collection and analysis were performed on the hospital healthcare big data platform, which integrated multi-source data from hospital information system (HIS), electronic medical records (EMR), laboratory information management system (LIS), picture archiving and communication system (PACS) and nursing information system (NIS). The encrypted personal identification number was used as a unique identifier to interlink each person's data information. Data of demographic information, medication, diagnostics, laboratory testing, operation, and costs for study subjects were collected. A multidisciplinary research team, including clinical pharmacist, statistician, clinician, epidemiologist, and information engineer, was developed to ensure effective implementation of the study.

This study was approved, and patient written informed consent was waived by the Ethics Committee of First Affiliated Hospital of Shandong First Medical University (No. YXLL-KY-2022-024). There is no personally identifiable information in this manuscript.

Patient Eligibility

The clinical data of hospitalized patients who received AGs were collected. The patients were excluded if met any of the following criteria: (1) Hospital stay < 48h; (2) Age < 18 years; (3) GFR < 30 ml/min/1.73m^2 within 48 hours after admission; (4) AKI was diagnosed on admission; (5) less than 2 serum creatinine (Scr) test results during hospitalization; (6) the Scr values were always lower than 40 μmol/L during hospitalization; (7) the cases of AKI apparently unrelated to AGs were excluded; (8) cases with incomplete medical history information.

Case Definition

The AKI diagnostic criteria issued by KDIGO (Kidney Disease Improving Global Outcomes) 2012 guidelines[16] was employed in this study. In addition, the AKI group were further divided into AKI I-III stages according to the AKI staging criteria to observe the severity of AKI. The diagnostic and staging criteria were shown in Table I.

The association between AGs reception and AKI occurrence was also analyzed with the judgment of nephrology clinician and clinical pharmacist, mainly based on the temporal logic relation. The AKIs occurred prior to the use of AGs and the pathological creatinine elevation were excluded.

Statistical Analysis

For the measurement data, Kolmogorov Smirnov (K-S) test was employed to test the normality first. A p-value ≥ 0.05 suggested obeying the normal distribution, while p < 0.05 suggested disobeying the normal distribution. The data obeying the normal distribution were expressed by mean ± SD, and the difference between groups was tested by t-test or analysis of variance. The data disobeying the normal distribution were expressed by the median and interquartile spacing, and comparison between groups adopted Wilcoxon rank sum test. For counting data, the number of cases (n) or constituent ratio (%) were used to express. Chi-square test was employed for comparison between groups.

Table I. Diagnostic criteria of AKI according to KDIGO 2012 guidelines.

AKI can be diagnosed if one of the following criterias is met:
1 Within 48 hours, the absolute value of serum creatinine (Scr) increased ≥ 0.3 mg/dl (26.5 μmol/L);
2 Known or speculated increase of Scr within 7 days ≥ 1.5 times of baseline value;
3 Urine volume ≤ 0.5 ml/kg/h for more than 6 h.

AKI stage I: Scr with 1.5-1.9 times of the basic value, or increase ≥ 0.3 mg/dl (≥ 26.5 μmol/L); or urine volume < 0.5 mg/kg/h, lasting 6-12 h; AKI stage II: Scr with 2.0-2.9 times of the basic value; or urine volume < 0.5 mg/kg/h, lasting ≥ 12 h; AKI stage III: Scr with 3.0 times of the basic value or increase to ≥ 4.0mg/dl (353.6 μmol/L), or start renal replacement therapy, or age < 18 years, and estimated GFR < 35 ml/(min·1.73 m^2); or urine volume < 0.5 mg/kg/h, lasting ≥ 24 h or no urine ≥ 12 h.

Table II. AKI prevalence of three aminoglycosides.

Drugs	AKI group (n)	Non-AKI group (n)	Incidence rate (%)	χ^2 value	*p*-value
Gentamicin	138	868	13.72		
Amikacin	50	289	14.75	176.88	< 0.001
Etimicin	348	7190	4.62		

Note: Chi-square test.

The investigated variables were taken as independent variables and AKI groups as dependent variables, and the chi-square test was used for univariate analysis. Then, the variables with $p < 0.05$ in univariate analysis were included in multivariate logistic regression analysis to identify the significant independent risk factors of acute renal injury caused by aminoglycosides in hospitalized patients. The analysis results were expressed in odds ratio (OR) and 95% confidence interval (95% CI).

All analyses were conducted using R software (version 3.6.3). The level of statistical significance was 0.05 (two-sided).

Results

Incidence of AKI

From January 2018 to December 2020, there were 327440 patients discharged from our center. A total of 8040 inpatients were included in this study. Among them, the overall incidence rate of AKI was 6.14% (494/8040). The proportion of stage I, II and III in the AKI group was 69.43% (343/494), 18.83% (93/494) and 11.74% (58/494), respectively. The specific AKI incidence rates of patients receiving gentamycin, amikacin and etimicin were 13.72%, 14.75% and 4.62% respectively, and there was a significant difference between the three groups (c^2: 176.88, $p < 0.001$), as shown in Table II.

Medical Characteristics and Insurance Information

In the AKI group, there were 311 males (62.96%) and 183 females (37.04%), and there were 5,030 males (66.66%) and 2,516 females (33.34%) in the non-AKI group. There was no significant gender difference in the incidence of AKI (c^2: 2.85, $p = 0.091$).

The median age of AKI group was 65.0 (54, 75) years and that of non-AKI group was 60.0 (50, 69) years. The overall incidence rate of three age groups was significantly different. The incidence rates of the youth group (18-40 years old), the middle-aged group (41-65 years old) and the elderly group (> 65 years old) were 4.85%, 5.06% and 8.24% respectively, among which the elderly group had the highest incidence of AKI (c^2: 32.72, $p < 0.001$). For smoking history, there was no significant difference between the two groups (32.19% *vs.* 30.94%, $p = 0.563$).

As shown in Table III, the median length of stay was 20.10 (13.97, 29.08) days in the AKI group, and the median total cost of hospitalization was 87605.68 (45351.86, 143612.1) Chinese Yuan (CNY). The median length of stay of patients in non-AKI group was 13.18 (9.07, 19.98) days, and the median total cost of hospitalization was 35863.06 (21531.69, 67247.34) CNY. The length of stay and total cost of patients in non-AKI group were significantly lower than those in AKI group ($p < 0.001$)

The AKI patients were distributed in 24 clinical departments of the hospital. As shown in the **Supplementary Table I**, the departments with high composition were urology (18.8%), ICU (15.6%), neurosurgery (13.0%), hematology (8.9%), internal medicine-cardiovascular department (5.9%) and gastroenterology (5.9%). In AKI group, 130 patients were transferred to another department

Table III. Medical insurance information of two groups.

Project	AKI group	Non-AKI group	*Z* value	*p*-value
Length of stay (days)	20.1 (13.97, 29.08)	13.18 (9.07, 19.98)	1162779	< 0.001
Total hospitalization expenses (yuan)	87605.68 (45351.86,143612.1)	35863.06 (21531.69,67247.34)	906923	< 0.001

Note: Double sample Wilcoxon test.

during hospitalization, of which 49.23% (64/130) were transferred to ICU. Compared with 6.48% (63/972) in the non-AKI group, the proportion of transferred to ICU increased significantly (c^2: 438.13, $p < 0.001$).

Diagnosis and Prognosis of AGs-AKIs

Only 29 patients in the AKI group were clearly diagnosed as acute kidney injury on the first page of medical records. The diagnosis rate was 5.87% (29/494), while the missed diagnosis rate was 94.13%. As shown in the **Supplementary Table I**, the departments with high missed diagnosis rates were urology (98.92%), neurosurgery (98.44%), hematology (97.73%), thoracic surgery (95.83%), and oncology (92.86%).

In terms of treatment, 12 patients diagnosed as AKI received continuous renal replacement therapy (CRRT) during hospitalization, even symptomatic support treatment, such as fluid management and nutritional support. Due to the low diagnosis rates, most patients with AKI did not receive timely treatment. It resulted that in 45.5% of AKI patients had not yet recovered renal function when discharged. Nearly half of AKI patients still had abnormal serum creatinine level at discharge, which may also be one of the reasons for their readmission.

Analysis of Risk Factors for Aminoglycosides Associated AKI

The possible risk factors were studied with univariate analysis. As shown in **Supplementary Table II**, the single factor analysis suggested that several factors may be related to AGs-AKI ($p < 0.05$), including age, admission to ICU, complicated with hypertension, diabetes, chronic kidney disease (CKD), pneumonia, coronary heart disease (CHD), heart failure, stroke, anemia, shock, combined use of diuretics, β-Lactam antibiotics, proton pump inhibitors, non-steroidal anti-inflammatory drugs, ACEI, ARB, cardiac surgery, and angiographic operation.

The single factors related to AGs-AKI were further analyzed with multivariate logistic regression analysis. As shown in Table IV, the results suggested that several factors would increase the risk of AKI, including admission to ICU (OR: 3.11, 95% CI: 2.32-4.17), complicated with diabetes (OR: 1.42, 95% CI: 1.10-1.81), heart failure (OR: 2.53, 95% CI: 1.65-3.85), anemia (OR: 1.48, 95% CI: 1.06-2.06), shock (OR: 1.93, 95% CI: 1.27-2.90), combined use of diuretics (OR: 6.74, 95% CI: 5.23-8.74), β-Lactam antibiotics (OR: 1.38, 95% CI: 1.09-1.75) and proton pump inhibitors (OR: 1.47, 95% CI: 1.17-1.85).

Univariate and Multivariate Analysis of Influencing AKI Stages

The stages may reflect the severity of AKI. The AKI patients were further divided into mild (stage I) AKI and severe (stage II and III) AKI groups. As shown in **Supplementary Table III**, compared with patients without diuretics, the combined use of diuretics would significantly increase the severity of AKI (OR: 2.80, 95% CI: 1.40-5.63). Compared with patients without shock, suffering from shock would significantly increase the severity of AKI (OR: 2.00, 95% CI: 1.06-3.77).

Discussion

Incidence and Analysis of AKI

In this study, the overall incidence rate of aminoglycosides associated AKI with KDIGO 2012 diagnostic criteria was 6.14% (494/8040). Compared with early aminoglycoside antibiotics (gentamicin, tobramycin, etc), etimicin has significantly reduced the incidence of AKI. In clinic practice, gentamicin is mainly used for external flushing, instead of intravenous drip or oral administration, which may effectively reduce the occurrence of AKI.

Compared with youth group and middle-aged group, the incidence of AG-AKI increased significantly in elderly patients. Besides, the median age of AKI group was larger than that of non-AKI group. It may be due to the physical conditions of elderly patients have decreased, including renal structure and function, physiological and metabolic function. In addition, elderly patients are often complicated with a variety of diseases, such as hypertension, coronary heart disease, anemia, etc. At the same time, they are treated with multiple medications, which may increase the susceptibility of elderly patients to renal injury factors[17,18]. Compared with the non-AKI group, the proportion of patients transferred to ICU, length of stay in hospital and total cost of hospitalization in the AKI group increased significantly ($p < 0.001$), which suggested economic and medical burden to patients and society.

Missed Diagnosis of AGs-AKI

In the study, only 5.87% (29/494) cases were clearly diagnosed as AKI. The high missed dia-

Table IV. Multivariate logistic analysis of risk factors for AKI.

Influence factors		β value	Wald value	OR (95%CI)	*p*-value
Age	Middle aged	-0.10	0.34	0.90 (0.64-1.29)	0.562
	Elderly	-0.21	1.24	0.81 (0.56-1.18)	0.266
Hypertension					0.816
	Yes	0.03	0.05	1.03 (0.81-1.31)	
	No				
Diabetes					0.006
	Yes	0.35	7.63	1.42 (1.10-1.81)	
	No				
Chronic kidney disease (CKD)					0.328
	Yes	0.35	0.96	1.42 (0.68-2.84)	
	No				
Pneumonia					0.914
	Yes	0.01	0.01	1.01 (0.78-1.30)	
	No				
Coronary heart disease (CHD)					0.543
	Yes	0.08	0.37	1.09 (0.83-1.42)	
	No				
Heart failure					< 0.001
	Yes	0.93	18.41	2.53 (1.65-3.85)	
	No				
Stroke					0.962
	Yes	-0.01	0.002	0.99 (0.77-1.27)	
	No				
Anemia					0.02
	Yes	0.39	5.39	1.48 (1.06-2.06)	
	No				
Shock					0.002
	Yes	0.66	9.79	1.93 (1.27-2.90)	
	No				
Diuretics					< 0.001
	Yes	1.91	211.77	6.74 (5.23-8.74)	
	No				
β-Lactam antibiotics					
	Yes	0.32	7.26	1.38 (1.09-1.75)	0.007
	No				
Proton pump inhibitors					0.001
	Yes	0.38	10.99	1.47 (1.17-1.85)	
	No				
Non-steroidal anti-inflammatory drugs					0.467
	Yes	-0.10	0.53	0.91 (0.70-1.17)	
	No				
ARB					0.675
	Yes	0.07	0.18	1.07 (0.78-1.46)	
	No				
ACEI					0.147
	Yes	0.35	2.10	1.42 (0.87-2.24)	
	No				
Cardiac surgery					
	Yes	0.64	1.45	1.89 (0.60-4.96)	0.228
	No				
Angiographic operation					0.765
	Yes	-0.07	0.09	0.93 (0.56-1.48)	
	No				
ICU					< 0.001
	Yes	1.14	57.45	3.11 (2.32-4.17)	
	No				

Note: Binary logistic regression analysis.

gnosis rate may be due to the fact that the medical staffs are not well informed about the disease and its consequences, especially in the surgery departments. Actually, health-care workers' awareness of CKD has improved considerably in the past years, however, the emphasis has been on controlling hypertension and diabetes as potential causes, without much attention on preventing AKI as a potential modifiable risk factor. Besides, the diagnosis of AKI relied on the changes of serum creatinine (Scr) and urine volume. The lack of continuous monitoring or low attention of dynamic renal function indicators may lead to more serious missed diagnoses. Therefore, it is urgent to improve the understanding and attention of AKI for medical workers. Lewington et al[3] also expressed concern about this issue. In addition, the clinical pharmacists are recommended to departments requiring special attention, since the clinical pharmacists are more aware of drug-induced diseases. The sufficient dynamic monitoring of renal indicators and adequate attention from the medical team will be very beneficial to improve the diagnosis rate of AG-AKI. It should be useful for improving the prognosis and outcome of AKI patients with early prevention and early treatment.

Analysis of Risk Factors of AGs-AKI

In this study, the risk factors for AGs-AKI were screened by univariate analysis (chi-square test) and multivariate logistic regression analysis.

The incidence rate of AG-AKI in ICU patients was significantly higher compared with those in other departments ($p < 0.001$), probably because ICU patients were complicated with more diseases and received more varieties of medications[19,20]. In addition, the poor basic body condition increased the sensitivity of these patients to renal injury factors, thus they were more likely to be affected by drugs and adverse reactions after medication on renal. Patients with diabetes, heart failure, anemia and shock should be cautious in using aminoglycoside antibiotics. The continuous progress of diabetes can cause serious burden on the kidney. In pathological mechanism and the sustained hyperglycemia will lead to the damage of proximal tubules and podocytes, the destruction of glomerular filtration barrier and the aggravation of nephrotoxicity[21]. The effects of heart failure, anemia and shock mainly involve the prerenal factors leading to acute kidney injury. The decline of body condition may lead to the decrease of effective blood volume and renal perfusion pressure, which can reduce the basic state of kidney and is more vulnerable to other nephrotoxic factors. In addition, when receiving the other nephrotoxic medications with different mechanisms (diuretics, β-lactam antibiotics, and proton pump inhibitors), it would result in a superposition effect of nephrotoxicity. Before the application of aminoglycosides, patients' physical condition should be comprehensively evaluated. If the above risk factors are combined, the drugs should be carefully selected, and the changes of renal function should be closely monitored.

The analysis results of influencing factors of AKI stages suggested that the use of aminoglycosides combined with diuretics would increase the severity of AKI. The combination of diuretics and aminoglycosides should be avoided in clinical practice, especially for patients with risk factors of AKI.

Limitations of This Study

Several limitations of this study should be mentioned here. First, only three typical aminoglycosides (gentamicin, amikacin and etimicin) usually used in our center were selected, which may limit the number of samples. In addition, aminoglycosides were well-known as nephrotoxic drug, the clinical application was limited, and the sample size was further reduced. Second, due to the complexity of treatment regiments and clinical data, the dose differences and plasmatic measurements of AGs were not considered in this study, which may result in the loss of some important issues. Third, as a retrospective study, it is difficult to accurately determine the causality between AKI and AGs. We can only make a judgment by reviewing electronic medical records. To some extent, this may result in bias. Fourth, in some cases, the lack of data on renal function indicators always lead to an inaccurate diagnosis of AKI.

Conclusions

In summary, a retrospective study was performed for the incidence and risk factors of acute kidney injury in hospitalized patients who received aminoglycoside antibiotics (AGs-AKI). The investigation of epidemiological characteristics of AGs-AKI indicated the high incidence rate of AGs-AKI (6.14%) in our center, while more than 90% AKIs were not detected and diagnosed in time. It is urgent to improve the understanding

and attention of AKI for medical workers. Several risk factors for AGs-AKI were screened out, including admission to ICU, complicated with diabetes, heart failure, anemia, shock, and combined use of diuretics, β-Lactam antibiotics, and proton pump inhibitors. Combined use of diuretics was also a risk factor affecting the severity of AKI, which can significantly increase the severity of AGs-AKI. We suggested that the incidence of AKI in hospitalized patients receiving aminoglycosides should be taken seriously by medical staff, and the risk factors for AKI need to be fully assessed before the patients receive aminoglycosides to avoid the incidence of AGs-AKI.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgements

The authors gratefully acknowledge the encouragement and support from Miss Chaoyue Yang and Miss Liying Zhao.

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