

The Effect of Clinical Pharmacist Intervention on Renal Function Impairment in Patients with Antimicrobial-Induced Acute Kidney Injury in ICU

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Objective: The purpose of this study was to analyze the improvement effect of clinical pharmacist intervention on renal function impairment in patients with antimicrobial-induced acute kidney injury (AKI).

Methods: A total of 145 patients with AKI caused by antibiotics admitted to the ICU department were selected as the research subjects. The patients were divided into the control group (n=57) and the intervention group (n=88) according to whether there were ICU specialist clinical pharmacists involved in clinical treatment. The renal function outcome and infection control were evaluated in the two groups.

Results: The proportion of renal function outcome in the intervention group was 88.6%, which was significantly higher than that in the control group. However, there was no statistically significant difference in infection control between the two groups. For the intervention group, the clinical pharmacists adopted three intervention methods: dose adjustment, drug replacement and CRRT treatment, respectively, according to the disease conditions of AKI patients. Among them, dose adjustment and drug replacement were the most frequently used intervention methods. In addition, the proportion of renal function outcome was higher in the group of patients who changed antibiotics and underwent CRRT, which were 93.1% and 100%, respectively. The adjusted-dose group had the highest infection control rate at 82.1%. However, there were no statistically significant differences in renal function outcomes and infection control among the three interventions.

Conclusion: Clinical pharmacists participating in the clinical treatment of patients with antimicrobial-induced AKI in ICU can effectively improve the renal function of patients.

Keywords: clinical pharmacists, acute kidney injury, antimicrobial, renal function

Introduction

Acute kidney injury (AKI) is a common multidisciplinary clinical critical illness, and its incidence is increasing year by year.^{1,2} Globally, there are approximately 13.3 million new cases of AKI each year, and nearly 1.7 million deaths due to AKI and its complications.³ In the intensive care unit (ICU), patients often have multiple risk factors, including sepsis, surgery, shock, advanced age, heart failure, use of contrast agents and nephrotoxic drugs, and have a higher incidence and mortality of AKI.⁴ Drugs have been reported to be the third leading cause of AKI with poor prognosis, especially in critically ill patients.⁵ With the increasing number of new antibacterial drugs and their wide clinical application, antibacterial drug-related AKI is increasing. Antibiotic-related AKI refers to new kidney injury or exacerbation of existing kidney disease after the use of antibiotics.⁶ It has been reported that about 40% of AKI in China is caused by drugs, of which antibiotics are the most common type of drugs.⁶ A systematic review of drug-induced AKI in the Chinese population showed that among drug-related AKI, 47.5% of the drugs were antimicrobials.⁷ Misuse or irrational use of antimicrobials increases the risk of bacterial resistance and/or adverse drug reactions.⁸ It is particularly important to implement therapeutic drug monitoring and individualized medication according to the patient's clinical situation.

Pharmaceutical services led by clinical pharmacists play an important role in the prevention and treatment of nosocomial infections. As a member of the medical team, clinical pharmacists play an important role in drug use, especially in drug concentration monitoring and drug monitoring.⁹ During the treatment of AKI patients, clinical pharmacists assist physicians in formulating treatment plans, strengthen pharmaceutical care for anti-infective treatment, and provide targeted suggestions and improvement measures, including adjustment of concomitant drugs and drug doses.¹⁰ The purpose of this study was to analyze the improvement effect of clinical pharmacist intervention on renal function impairment in patients with antimicrobial-induced AKI. We hope to provide reference and thinking for clinical pharmacists to carry out antimicrobial pharmaceutical services in ICU.

Materials and Methods

Objects

Patients with AKI caused by antibiotics admitted to the ICU department from 2016 to 2018 (control group) and 2019 to 2021 (intervention group) were selected as the research subjects. Among them, there were 57 cases in the control group and 88 cases in the intervention group. The control group was given routine treatment by clinicians. In the intervention group, in addition to routine treatment given by clinicians, ICU specialist clinical pharmacists participated in clinical treatment. The basic conditions of the two groups of patients are shown in Table 1. This study obtained written informed consent from all participants before participating in the study, which also was approved by Medical Ethics Committee of Weihai Municipal Hospital [2020048].

According to the AKI diagnostic criteria,¹¹ AKI was determined by the presence of one of the following: (1) an increase in serum creatinine of $26.5 \mu\text{mol}\cdot\text{L}^{-1}$ at 48 hours or more than 50% from baseline at 7 days according to Kidney Disease Improvement Global Organization; (2) serum cystatin C ($>1.1 \text{ mg}\cdot\text{L}^{-1}$); (3) urine output ($<0.5 \text{ mL}\cdot(\text{kg}\cdot\text{h})^{-1}$ for

Table 1 Comparison of the General Situation of AKI Patients in the Intervention Group and the Control Group

Parameter		Intervention Group (n=88)	Control Group (n=57)	t/χ^2	p
Age (year) Mean $\pm$ SD		65.3 $\pm$ 12.2	67.9 $\pm$ 10.6	1.536	0.127
Gender (n, %)	Male	69(78.41)	43(75.44)	0.43	0.512
	Female	19(21.59)	14(24.56)		
Reason for admission	Miocardial infarction	23 (26.14)	15 (17.05)	0.091	0.763
	Cerebral hemorrhage	28 (31.82)	14 (24.56)	1.572	0.210
	Severe pneumonia	15 (17.05)	9 (15.79)	0.374	0.541
	Multi-injury	17 (19.32)	12(21.05)	0.014	0.906
	Others	5(5.68)	7(12.28)	0.680	0.410
Disease History (n, %)	Diabetes	15(17.05)	10(17.54)	0.04	0.842
	Cardiovascular disease	37(42.05)	18(31.58)	1.108	0.293
	Chronic renal insufficiency	26(29.55)	21(36.84)	0.491	0.484
Clinical manifestations (n, %)	Decreased urine output	52(59.09)	30(52.63)	1.231	0.267
	Proteinuria, urine leukocytes	21(23.86)	15(26.32)	0.111	0.738
	Other				
	Decreased urine output	11(12.50)	12(21.05)	0.207	0.649
Creatinine ($\mu\text{mol}\cdot\text{L}^{-1}$)		283.8 $\pm$ 126.9	254.7 $\pm$ 89.9	1.611	0.109
Cystatin C ($\text{mg}\cdot\text{L}^{-1}$)		4.5 $\pm$ 3.1	5.1 $\pm$ 3.6	1.009	0.315
Average number of days in hospital (days)		11.4 $\pm$ 5.1	14.1 $\pm$ 6.8	1.898	0.06
AKI occurs after drug administration (hours)		58.8 $\pm$ 28.3	39.9 $\pm$ 24.2	1.893	0.06

Abbreviation: AKI, acute kidney injury.

>6 hours or more). Inclusion criteria: patients using antimicrobial drugs before the onset of AKI, using Excel software and applying computerized C# language to prepare a graph of the relationship between serum creatinine, cystatin C changes and medication use, based on the Naranjo assessment scale,¹² and the criteria for association evaluation were: certain: ≥ 9 points, very likely: 5–8 points, probable: 1–4 points, and unlikely: ≤ 0 points. The patients were included in the study if the association between antibiotics and AKI was ≥ 1 . Exclusion criteria: (1) AKI was diagnosed at admission; (2) glomerular filtration rate ≤ 15 mL·min⁻¹ at admission; (3) those with a history of systemic diseases leading to renal injury; (4) history of kidney or urinary calculi; (5) higher body fat ratio, septic shock and surgery; (6) combined use of other drugs that can significantly cause renal injury (such as imidazole sedatives, glucocorticoids, opioids, angiotensin II receptor blockers, angiotensin converting enzyme inhibitors and non-steroidal anti-inflammatory drugs); (7) Severe heart failure (LVEF<35% or NYHA grade IV); (8) diabetes; (9) abnormal liver function (alanine aminotransferase (ALT) or aspartate aminotransferase (AST) ≥ 3 times the upper limit of normal value; (10) incomplete and untraceable medical records.

Intervention Methods

The study flow chart was detailed in Figure 1.

The ICU specialist clinical pharmacist provides pharmaceutical care of the patient and offers three interventions to the clinician: adjustment of antimicrobial drug dose (Dose adjustment group), change of antimicrobial drug species (Drug change group), and use of continuous renal replacement therapy (CRRT) (CRRT group), taking into account the actual condition of the patient. The specific operations include (1) clinical pharmacists calculate Ccr based on serum creatinine values using the Cockcroft-Gault (C-G) formula,¹³ and make dose adjustment for antimicrobial drugs used in patients with Ccr <50 mL·min⁻¹; (2) carry out vancomycin blood concentration monitoring according to existing conditions, and adjust vancomycin dose according to the trough concentration value; (3) change the dose of vancomycin according to the (3) replace the antimicrobial drug species with low nephrotoxicity according to the results of drug sensitivity

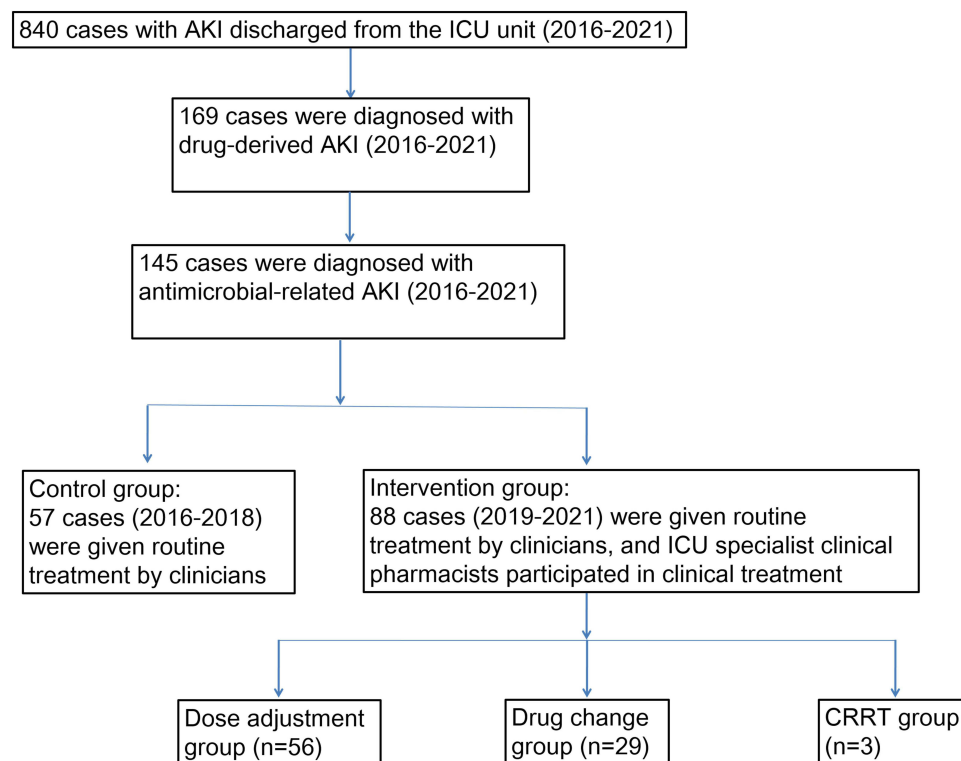


Figure 1 Flow chart of the trial. ICU, intensive care unit; AKI, acute kidney injury; CRRT, continuous renal replacement therapy.

experiments; (4) treat with CRRT if necessary, and clinical pharmacists provide the dose adjustment plan of antimicrobial drugs during CRRT.

C-G formula: $Ccr = [(140 - \text{age}) \times \text{body weight (kg)}] / [0.818 \times \text{serum creatinine } (\mu\text{mol-L}^{-1})]$; for women, the calculation was based on the result $\times 0.85$.

Evaluation Indicators

A gradual decrease in blood creatinine and cystatin C levels to baseline levels or normal levels, an increase in the patient's urine output, and a normal nature of urine were used as evaluation criteria for the regression of renal function.¹⁴

A significant decrease in inflammatory indicators, clearance or partial clearance of infection foci, and improvement in imaging were used as criteria for infection control.¹⁵

Statistical Analysis

Statistical analysis of the results was performed using SPSS 16. All continuous measurements are expressed as mean $\pm$ standard deviation. Student's *t*-test was used for comparisons between two groups, and analysis of variance was used for comparisons among three groups. The count data are expressed as percentages. The comparisons were performed with the chi square test or Fisher's exact test. The *p*-value <0.05 was considered statistically significant.

Results

General Situation And Antibiotic Categories of Patients

There were no significant differences between the intervention group and the control group in terms of age, gender, reason for admission, disease history, clinical manifestations, length of hospital stay, and duration of medication at the time of AKI (Table 1). In addition, there was no significant difference in serum creatinine and cystatin C levels between the two groups of AKI patients (Table 1). Analyzing the use of antibiotics in the two groups of patients, it was found that the top 4 types of antibiotics causing AKI cases were carbapenems, β -lactams, glycopeptides and aminoglycosides (Table 2). There was no significant difference between the two groups in terms of drug varieties and usage and dosage (Table 2).

Prognosis of AKI Patients in the Intervention and Control Groups

Subsequently, we assessed the prognosis of patients with AKI in the control and intervention groups by analyzing renal function outcomes and infection control. The results showed that the renal function outcome rate of AKI patients in the intervention group was 88.6%, which was significantly higher than that in the control group (Table 3). There was no difference in SOFA and APACHE scores between the two groups, indicating that there is no difference in the prognosis of the two groups (Table 3). However, there was no statistically significant difference in infection control between the two groups (Table 4).

Table 2 Comparison of Antibiotic Categories, Drugs, Usage and Dosage Between the Intervention Group and the Control Group (n, %)

Types		Usage and Dosage	Intervention Group (n=88)	Control Group (n=57)	χ^2	<i>p</i>
Carbapenems	Meropenem	1 g, ivdrip, q8h	26(29.5)	18(31.6)	0.068	0.795
	Biapenem	0.6g, ivdrip, q12h	13(14.8)	7(12.3)	0.181	0.671
β -lactams	Piperacillin/tazobactam	4.5g, ivdrip, q8h	11(12.5)	8(14)	0.072	0.789
	Cefoperazone/Tazobactam	3g, ivdrip, q8h	9(9.1)	6(10.5)	0.003	0.954
Glycopeptides	Vancomycin	1g, ivdrip, q12h	18(20.5)	11(19.3)	0.029	0.865
Aminoglycosides	Amikacin	0.2g, ivdrip, qd	6(6.8)	5(8.8)	0.188	0.664
Quinolones	Levofloxacin	0.5g, ivdrip, qd	4(4.6)	1(1.8)	0.188	0.664
Sulfonamides	SMZ/ TMP	960mg, po, tid	2(2.3)	1(1.8)	0.092	0.762

Abbreviations: SMZ, sulfamethoxazole; TMP, trimethoprim; ivdrip, intravenous drip; q8h, once every 8 hours; q12h, once every 12 hours; qd, once a day; po, take orally; tid, three times a day.

Table 3 The Improvement of Renal Function in the Intervention Group and the Control Group (n, %)

Renal Function Improvement		Intervention Group (n=88)	Control Group (n=57)	χ^2	p
Total		78 (88.6)	25 (43.9)	33.709	<0.001
Meropenem		24 (27.3)	6 (10.5)	5.912	0.015
Biapenem		10 (11.4)	4 (7.0)	0.749	0.387
Piperacillin/tazobactam		10 (11.4)	4 (7.0)	0.749	0.387
Cefoperazone/Tazobactam		7 (8.0)	5 (8.8)	0.030	0.861
Vancomycin		16 (18.2)	5 (8.8)	2.473	0.116
Amikacin		5 (5.7)	0	1.865	0.172
Levofloxacin		4 (4.5)	1 (1.8)	1.044	0.307
SMZ/ TMP		2 (2.3)	0	0.174	0.677
SOFA	Day 1	5.93±2.08	6.02±1.93	0.249	0.804
	Day 3	5.25±2.05	5.34±2.01	0.257	0.798
	Day 5	3.94±2.43	4.04±2.31	0.227	0.821
APACHE	Admission	23.03±8.77	22.25±9.89	0.497	0.620
	Discharge or transfer	15.81±6.82	17.34±8.16	1.217	0.226

Abbreviations: SMZ, sulfamethoxazole; TMP, trimethoprim; SOFA, Sequential Organ Failure Assessment; APACHE, Acute Physiology and Chronic Health Evaluation.

Table 4 Infection Control of Patients in the Intervention Group and Control Group (n, %)

Infection Control	Intervention Group (n=88)	Control Group (n=57)	χ^2	p
Total	70 (79.5)	40 (70.2)	1.659	0.198
Meropenem	23 (26.1)	15 (26.3)	0.001	0.981
Biapenem	9 (10.2)	6 (10.5)	0.003	0.954
Piperacillin/tazobactam	9 (10.2)	3 (5.3)	0.564	0.453
Cefoperazone/Tazobactam	6 (6.8)	2 (3.5)	0.231	0.631
Vancomycin	15 (17.0)	9 (15.8)	0.040	0.842
Amikacin	3 (3.4)	4 (7.0)	0.352	0.553
Levofloxacin	4 (4.5)	1 (1.8)	0.188	0.664
SMZ/ TMP	1 (1.1)	0	0.048	0.826

Abbreviations: SMZ, sulfamethoxazole; TMP, trimethoprim.

The Effect of Different Intervention Methods on the Prognosis of AKI in the Intervention Group

For the intervention group, the clinical pharmacists adopted three intervention methods: adjusting the dose, changing the drug and CRRT treatment according to the disease conditions of the AKI patients. Among them, dose adjustment and drug replacement are the most frequently used intervention methods by clinical pharmacists. Moreover, we analyzed the improvement of the prognosis of patients with AKI in the intervention group by different intervention methods (Table 5). The proportion of renal function outcome in the patients who changed antibiotics and underwent CRRT was higher, which were 93.1% and 100%, respectively. Furthermore, the adjusted-dose group had the highest infection control rate at 82.1%. However, there were no statistically significant differences in renal function outcomes and infection control among the three interventions (Table 5).

Discussion

AKI has become one of the common clinical critical illnesses ICU patients are critically ill, have more underlying diseases, and some of them are accompanied by organ insufficiency, so AKI occurs more frequently. Studies have found that the incidence of AKI in critically ill patients ranges from 10% to 60%,¹⁶ and it is one of the diseases that affects the mortality and mortality of critically ill patients. Jiang et al¹⁷ reported a mortality rate of 27.7% for AKI in ICU patients

Table 5 The Effect of Different Intervention Methods on the Renal Function and Infection Control of AKI in the Intervention Group (n, %)

Drugs	Renal Function Improvement					Infection Control				
	Dose Adjustment Group (n=56)	Drug Change Group (n=29)	CRRT Group (n=3)	χ^2	p	Dose Adjustment Group (n=56)	Drug change Group (n=29)	CRRT Group (n=3)	χ^2	p
Total	48(85.7)	27(93.1)	3(100)	1.825	0.402	46(82.1)	22(75.9)	2(66.7)	0.742	0.69
Meropenem	18(90)	5(100)	1(100)			20(100)	3(80)	0		
Biapenem	2(50)	8(88.9)	0			2(50)	7(77.8)	0		
Piperacillin/tazobactam	7(87.5)	3(100)	0			6(75)	3(100)	0		
Cefoperazone/Tazobactam	4(80)	3(100)	0			4(80)	2(66.67)	0		
Vancomycin	13(86.7)	1(100)	2(100)			12(80)	1(100)	2(100)		
Amikacin	2(100)	3(75)	0			1(50)	2(66.7)	0		
Levofloxacin	0	4(100)	0			0	4(100)	0		
SMZ/ TMP	2(100)	0	0			1(50)	0	0		

Abbreviations: CRRT, continuous renal replacement therapy; SMZ, sulfamethoxazole; TMP, trimethoprim.

during hospitalization. Drugs are one of the important factors that cause AKI in hospitalized patients.¹⁸ The widespread use of antibiotics has led to an increase in clinical adverse reactions year by year, which has become the main cause of drug-related renal damage. A retrospective study found that the rate of AKI caused by antibiotics was 63%. The medication structure varies by region and department, and the results of studies vary.¹⁹ In the current study, the top 4 classes of antibacterial drugs that cause AKI are carbapenems, β -lactams, glycopeptides, and aminoglycosides. Amikacin and vancomycin caused the highest rates of AKI compared with the number of antimicrobials used in ICU wards during the same period.

Effective antimicrobial stewardship (AMS) produces positive clinical outcomes.²⁰ The goal of AMS in the ICU is to optimize antimicrobial use.²¹ Clinical pharmacists are an important part of AMS. Clinical pharmacists have professional knowledge in pharmacokinetics and pharmacodynamics, which is beneficial for adjusting the dose of antibiotics used in critically ill patients.²² An AMS team including clinical pharmacists can shorten the duration of antibacterial treatment and reduce the occurrence of infectious complications.^{23,24} Absence of clinical pharmacists results in increased use of restricted antibiotics and prolonged duration of antibiotic therapy.²⁵ In ICU management without clinical pharmacist participation, patients with community-acquired infections, hospital-acquired infections, and sepsis had increased mortality.^{24,26} In the current study, we found that clinical pharmacist intervention can significantly improve renal function in patients with antimicrobial-induced AKI. CRRT is the mainstay of treatment for AKI.²⁷ The choice of drug dose and dosing interval is a complex issue due to the large variability in the pharmacokinetic parameters of antimicrobials among patients undergoing CRRT. Underdose directly leads to treatment failure and bacterial resistance, while overdose leads to increased drug toxicity.²⁸ Zarbock et al²⁹ proposed that early initiation of CRRT could help reduce 90-day mortality in patients with severe AKI. Dose adjustment and changing the variety of antimicrobial drugs are the most commonly used intervention methods for clinical pharmacists in the current study, and the infection control rate is the highest in the dose adjustment group. What is more, changing the type of drugs and using CRRT is more conducive to the improvement of renal function in patients. In this study, the clinical pharmacists adopted three intervention methods: adjusting the dose, changing the drug and CRRT treatment according to the disease conditions of the AKI patients. The intervention of pharmacists plays an important role in improving renal injury.

There are still many deficiencies in this study. Firstly, there is a lack of long-term mechanism analysis for the rational application of antibiotics, such as the detection rate, drug resistance rate and economy of pathogenic bacteria. Secondly, the data of this study is a single center, and the time and space span is relatively limited. And the sample size of this study is not large enough. Nonetheless, this study explored the mode of antimicrobial management of clinical pharmacists in ICU, which provided reference and thinking for further optimizing clinical pharmacy services.

In conclusion, clinical pharmacists participating in the clinical treatment of patients with antimicrobial-induced AKI in ICU can effectively improve the renal function of patients. Among the commonly used intervention methods,

comparing with adjusting drug dose choosing to change the variety of drugs and use CRRT is more conducive to the improvement of the renal function of AKI patients.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Weihai Municipal Hospital, Cheeloo College of Medicine, Shandong University. All participants signed an informed consent form for inclusion in the study.

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Disclosure

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