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Retrospective Study

Risk factors, incidence, and morbidity associated with antibiotic-associated diarrhea in intensive care unit patients receiving antibiotic monotherapy

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Abstract**BACKGROUND**

This study aimed to identify factors associated with antibiotic-associated diarrhea (AAD) in patients in the department of intensive care medicine who received antibiotic monotherapy in order to reduce the incidence of AAD and improve rational use of antibiotics in these patients.

AIM

To report the incidence of AAD and the factors associated with AAD in patients receiving antibiotic monotherapy.

METHODS

The study used a single-center retrospective design. A total of 209 patients were enrolled. Patients were divided into two groups: No-AAD group (without AAD) and AAD group (with AAD). There were 45 cases in the AAD group and 164 cases in the no-AAD group. Clinical data of all patients were collected. Data were analyzed using SPSS (version 18.0), and statistical significance was set at $P < 0.05$.

RESULTS

The overall incidence of AAD was 21.53%. Age [odds ratio (OR) 1.022, 95% confidence interval (CI): 1.001-1.044, $P = 0.040$], proton pump inhibitor usage time (OR 1.129, 95%CI: 1.020-1.249, $P = 0.019$), antibiotic usage time (OR 1.163, 95%CI: 1.024-1.320, $P = 0.020$), and intensive care unit (ICU) stay time (OR 1.133, 95%CI: 1.041-1.234, $P = 0.004$) were associated with AAD in ICU patients receiving antibiotic monotherapy. mean \pm SD ICU stay time was lower in the no-AAD group (8.49 ± 6.31 vs 15.89 ± 10.69 , $P < 0.001$). However, there was no significant difference in ICU-related mortality rates between the two groups ($P = 0.729$).

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CONCLUSION

Older age, longer ICU stay time, duration of use of proton pump inhibitors, and duration of antibiotic increase the incidence of AAD in ICU patients receiving antibiotic monotherapy.

Key words: Diarrhea; Intensive care unit; Critically ill; Mortality; Antibiotics; Monotherapy

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Core tip: In this retrospective study, clinical data were retrospectively analyzed in patients hospitalized at the First Affiliated Hospital of Xi'an Jiaotong University. Factors related to antibiotic-associated diarrhea (AAD) were analyzed in critically ill patients receiving antibiotic monotherapy. The total incidence of AAD was 21.53%. Patients with AAD had a longer intensive care unit (ICU) stay time than patients without AAD (15.89 ± 10.69 vs 8.49 ± 6.31 , $P < 0.001$). Older age, longer ICU stay time, duration of use of proton pump inhibitors and duration of antibiotic increase the incidence of AAD in ICU patients receiving antibiotic monotherapy.

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INTRODUCTION

Antibiotic-associated diarrhea (AAD) is diarrhea associated with antibiotic administration^[1]. Symptoms can range from mildly self-limiting disease to more severe *Clostridium difficile*-associated diarrhea (CDAD). Due to the widespread use of antibiotics, the incidence of AAD has gradually increased and has been reported to be as high as 35% in some studies^[2,3]. This increase is directly related to the use of antibiotics^[4]. CDAD accounts for approximately 10%-20% of AAD^[5] and is thus considered a common pathogen causing AAD^[2,6]. AAD has become an important nosocomial disease, especially in critically ill patients. The incidence of AAD in the intensive care unit (ICU) is growing, and it is becoming a serious condition^[7]. Therefore, prevention of AAD is essential for critically ill patients.

Different types of antibiotics present different risks for AAD^[2]. Currently, studies on AAD^[8-10] found in the literature are primarily focused on ordinary patients, but a study on AAD in critically ill individuals showed that the incidence of AAD can be as high as 21.6% in cases where antibiotic monotherapy is applied^[7]. However, the factors that are associated with AAD in ICU patients with antibiotic monotherapy have not been further explored. Therefore, we aimed to investigate the factors related to AAD in ICU patients receiving antibiotic monotherapy and to provide evidence for clinical anti-infective treatment in critically ill patients.

MATERIALS AND METHODS

Design, participants, and inclusion/exclusion criteria

The study used a single-center retrospective case-control study design. From January 2014 to February 2017, patients admitted to the ICU of the First Affiliated Hospital of Xi'an Jiaotong University and who received antibiotic monotherapy were enrolled in the study. Patients were divided into two groups: AAD and no-AAD groups (without AAD). ICU patients with the following three inclusion criteria were included in the study: (1) Antibiotic therapy was received for the first time during the study period; (2) Antibiotic monotherapy was taken by the patient for ≥ 3 d^[11]; and (3) The age of the patient was ≥ 18 -years-old. Exclusion criteria included the following: (1) Admissions to the ICU ≥ 2 times within 1 mo; (2) AAD diagnosed within the last 3 mo; (3) No antibiotic use or combined administration of antibiotics; and (4) Case file data were incomplete or missing^[7]. Informed consent was provided by all study participants.

The First Affiliated Hospital of Xi'an Jiaotong University Ethics committee reviewed and approved the study, No. XJTU1AF2018LSL-011.

Baseline characteristics and data on diabetes, gastrointestinal surgery, using of proton pump inhibitors, albumin levels, antibiotics, duration of ICU length of stay, APACHE II score were retrospectively collected and analyzed.

Research methods

Diagnosis of AAD: In clinical studies, diarrhea in adults is usually defined as ≥ 3 liquid stools/d for ≥ 2 d^[12,13]. AAD is defined as diarrhea related to antibiotic treatment, either while the individual is receiving antibiotics or for up to 8 wk after antibiotics have been discontinued^[13], and a smear of the stool has a dysbacteriosis. Dysbacteriosis is defined as an imbalance of the ratio of cocci and bacillus in fecal smears (adult reference value 3:7), fecal examination with mold and/or hyphae, and bifidobacteria/enterobacteria < 1 , or stool culture to detect pathogenic bacteria such as *Staphylococcus*, *Escherichia coli*, or mold. Symptoms can vary from mild, self-limited disease to more serious and severe CDAD^[12].

Statistical analysis: SPSS18.0 statistical software (Chicago, IL, United States) was used to analyze all the relevant data. The data of all groups were tested for normal distribution and variance uniformity. The difference between the two groups of measurement data was compared using an independent sample t test, and the results were expressed as mean \pm SD. The count data were expressed as the number of cases and relative percentages, and the two groups were compared with the χ^2 method. $P < 0.05$ was used as the criterion of significance difference in the results. Independent risk factors were evaluated using univariate and multivariate logistic regression analyses to determine AAD-related factors.

RESULTS

Patient characteristics

Overall, 209 patients were enrolled, including 117 men and 92 women (average age: 54.12 ± 21.74 years). The total incidence of AAD was 21.5%. The AAD group was comprised of 45 patients, including 26 men and 19 women (average age: 62.93 ± 22.43 years). The no-AAD group was comprised of 164 patients, including 91 men and 73 women (average age: 51.70 ± 20.97 years) (Table 1).

Statistically significant differences (all $P < 0.05$) were found between the two groups on the following variables: mean age, incidence of diabetes, duration of use of proton pump inhibitors, and duration of taking antibiotics (10.24 ± 5.94 vs 6.19 ± 3.11 , $P < 0.001$). Compared to no AAD patients, AAD patients had longer ICU stay times (15.89 ± 10.69 d vs 8.49 ± 6.31 d, $P < 0.001$). However, statistically significant differences were not found between the two groups on the following variables: sex, hypertension, parenteral nutrition, gastrointestinal surgery, fasting time exceeding 72 h, albumin levels, white blood cell count, use of glucocorticoid supplements, APACHE II score, or ICU mortality (Table 1).

Infection sites and use of antibiotics

Out of the 209 patients, there were 138 (66.03%) cases of lung infection, 18 (8.61%) cases of urinary tract infection, 14 (6.70%) cases of abdominal infection, 9 (4.31%) cases of hematogenously disseminated infection, 7 (3.35%) cases of central nervous system infection, and 23 (11.00%) cases of other types of infections, including skin and soft tissue infection, pericarditis, appendicitis, pancreatitis, and peritonitis (Table 2).

Antibiotic monotherapy and AAD

Of the 209 patients enrolled, 125 (59.81%) were treated with beta-lactam plus enzyme inhibitors; 39 (18.66%) patients were treated with carbapenem antibiotics; 23 (11.00%) patients were treated with cephalosporin antibiotics; 12 (5.74%) patients were treated with quinolone antibiotics; 4 (1.91%) patients were treated with antifungals; 2 (0.96%) patients were treated with glycopeptides; and 4 (1.91%) patients were treated with oxazolidinone antibiotics; and 2 (0.96%) patients were treated with glycopeptides. There was a higher incidence of ADD in patients who received beta-lactam plus enzyme inhibitors than patients who were not administered this type of therapy (26.40% vs 14.29% , $P = 0.037$). There were no significant differences in incidence of AAD with other forms of antibiotic monotherapy (Table 3).

Factors associated with AAD in ICU patients receiving antibiotic monotherapy

Univariate logistic regression analysis of the factors related to AAD showed that duration of proton pump inhibitor use, age, diabetes, beta-lactam plus enzyme

Table 1 Patient characteristics

Variables	AAD	No AAD	P value
No. of patients	45	164	
Age, yr	62.93 ± 22.43	51.70 ± 20.97	0.002
Male/female	26/19	91/73	0.784
Hypertension, n (%)	18 (40.00)	47 (28.66)	0.145
Diabetes, n (%)	12 (26.67)	23 (14.02)	0.044
Parenteral nutrition, n (%)	27 (60.00)	82 (50.00)	0.249
proton pump inhibitors, n (%)	38 (84.44)	145 (88.41)	0.475
Duration of proton pump inhibitors, h	10.05 ± 9.67	6.88 ± 5.28	0.007
Gastrointestinal surgery, n (%)	3 (6.67)	8 (4.88)	0.921
Fasting time exceeding 72 h, n (%)	18 (40.00)	81 (49.39)	0.264
Use of glucocorticoid, n (%)	14 (31.11)	65 (39.63)	0.296
Albumin levels, g/L	31.87 ± 5.52	32.28 ± 8.14	0.746
White blood cell count into the ICU, × 10 ⁹ /L	13.66 ± 8.59	13.11 ± 6.98	0.658
APACHE II score at admission into the ICU, points	18.45 ± 7.33	16.63 ± 8.05	0.177
Duration of antibiotic, d	10.24 ± 5.94	6.19 ± 3.11	< 0.001
ICU stay time, d	15.89 ± 10.69	8.49 ± 6.31	< 0.001
ICU mortality, n (%)	3 (6.67)	16 (9.76)	0.729

AAD: Antibiotic-associated diarrhea; ICU: Intensive care unit.

inhibitors, ICU stay time, and duration of antibiotic administration were all related to AAD incidence in ICU patients receiving antibiotic monotherapy (Table 4).

Multivariate logistic regression analysis showed that age [odds ratio (OR) 1.022, 95% confidence interval (CI): 1.001-1.044, $P = 0.040$], ICU stay time (OR 1.133, 95%CI: 1.041-1.234, $P = 0.004$), proton pump inhibitor usage time (OR 1.129, 95%CI: 1.020-1.249, $P = 0.019$), and duration of antibiotic (OR 1.163, 95%CI 1.024-1.320, $P = 0.020$) were risk factors related to AAD in ICU patients receiving antibiotic monotherapy (Table 4).

DISCUSSION

Use of antibiotics has increased over the past few decades. However, widespread use of antibiotics destroys normal intestinal flora, causing intestinal flora disorder, which in turn results in patients presenting with a variety of clinical symptoms. These symptoms may include mild diarrhea, fever, abdominal pain, abdominal distension, elevated white blood cell count, or toxic megacolon, toxic shock, multiple organ dysfunction, and even death^[8]. Based on severe intestinal flora disorder, critically ill patients are often infected with pathogenic bacteria such as *Clostridium difficile*, *Staphylococcus aureus*, and *Candida albicans*. Studies have shown that many factors, such as length of time of antibiotic use, combined use of antibiotics, older age, and serum albumin levels, are associated with the occurrence of AAD^[7]. Studies have shown that AAD can prolong hospital stays, increase medical costs, and increase risk of death^[14]. AAD has recently become the most common intestinal infectious disease in hospital patients^[15,16].

Antifungals, beta-lactam plus enzyme inhibitor, and many antibiotics can cause AAD^[2,3,7,12]. Our study shows that an increased risk of AAD occurs when a beta-lactam plus enzyme inhibitors is used alone, which is consistent with the results of a previous study^[3]. Studies have found that cephalosporins are important predisposing factors for AAD^[17]. However, our study showed no significant difference in the incidence of AAD between use and non-use of cephalosporin antibiotics. This is inconsistent with current research. The main reason for the inconsistency may be associated with the empirical use of antibiotics and the specific medical condition of the ICU patient. In addition, patients in the ICU are in critical condition, and therefore, antibiotics of a high grade with a broad spectrum are often selected for their treatment. The use of cephalosporins was lower in the ICU; hence, our study was limited by a small sample size, where only 11.00% of patients used cephalosporin antibiotics alone. Reports in the literature have indicated that the duration of exposure to antibiotics and the length of hospital stay are risk factors for AAD, especially when the course lasts more

Table 2 Infection sites of patients

Infection sites	AAD (%)	No AAD (%)	P value
No. of patients	45	164	
Lung infection	34 (75.56)	104 (63.41)	0.128
Abdominal infection	3 (6.67)	11 (6.71)	0.992
Hematogenously disseminated infection	1 (2.22)	8 (4.88)	0.717
Central nervous system infection	1 (2.22)	6 (3.66)	0.995
Urinary tract infection	2 (4.44)	16 (9.76)	0.409
Other	4 (8.89)	19 (11.58)	0.808

AAD: Antibiotic-associated diarrhea.

than 3 d and when two or more antibiotics are used together^[9,11]. In our study, we found that the consistent results, duration of antibiotic use and the ICU stay time were risk factors for acquiring AAD in ICU patients receiving antibiotic monotherapy.

Age and underlying diseases are risk factors for AAD^[18,19]. One study found that older patients are more prone to AAD^[20]. Additional research studies have pointed out that the incidence of AAD in patients ≥ 65 -years-old is 10%-37%^[21]. Patients with chronic underlying diseases and multiple organ dysfunction, who are on antibiotic treatment, may also be more prone to AAD^[18,19]. Our study found that patients in the AAD group were older, which tells us that patients with older age have a higher incidence of AAD. More chronic underlying diseases and worse organ and intestinal function in the older patient may contribute to the higher incidence of AAD. Although our study showed that the incidence of diabetes was significantly different between the patients with AAD and those without AAD, the multivariate logistic regression analysis did not show any correlation with AAD. This may be related to the specific ICU patients admitted during our study period, who may have had differences in risk factors for AAD.

In our study, the duration of use of proton pump inhibitors was related to AAD in patients receiving antibiotic monotherapy, which is the same as reported in the literature^[22,23]. Therefore, prolonging the proton pump inhibitor usage time may increase the risk of AAD in ICU patients. In our study, albumin levels were not associated with AAD, which is not consistent with the literature^[23]. This may be because human serum albumin may have been infused in some patients prior to ICU admission^[3,7]. Gastrointestinal surgery and use of glucocorticoids were also not associated with AAD. This may be related to the small sample size of patients we included. Prospective studies are needed to clarify further the association between gastrointestinal surgery, use of glucocorticoids, albumin levels, and AAD.

Our study found that ICU stay time was a risk factor for AAD patients receiving antibiotic monotherapy. Previous studies have also shown that the longer the hospital stay, the higher the risk of AAD, and stays in a hospital for ≥ 2 wk are correlated with incidence of AAD^[9,11]. The longer hospital stay time of ICU patients indicates more severe patient condition, more risk factors for AAD, and increased potential for contracting AAD. The ICU stay time (8.49 ± 6.31 d vs 15.89 ± 10.69 d) was lower in the no-AAD group than in the AAD group ($P < 0.001$), indicating that AAD prolongs the ICU stay time of ICU patients. However, there was no significant difference in ICU-related mortality rates between the two groups. This may be influenced by the fact that some ICU patients stop treatment for various reasons and cannot be counted in either "survival" or "death" statistics. This might be a primary reason for the mortality difference reported in the literature. In future studies, a larger sample of patients and prospective designs will be needed to determine if there is a statistically significant difference in mortality between the two groups.

Some limitations need to be considered when interpreting the results of this study. First, a single-center experience limits generalizability, and despite multivariate associations, the low number of patients limited further analyses and by extension the conclusions that can be drawn. Second, because there were only 45 patients in the AAD group and many explanatory variables were included in the multivariate logistic regression analysis, the regression model was unstable. Third, given the retrospective design of the study, there may have been some confounding factors. For example, the protective effects of probiotics for AAD have been established, but our study did not include probiotics. Therefore, the results of analyses of some factors related to AAD could be subject to several potential biases. Future prospective studies are needed to confirm our findings.

Table 3 Antibiotic monotherapy and antibiotic-associated diarrhea, *n* (%)

Variables	AAD	No AAD	<i>P</i> value
No. of patients	45	164	
Beta-lactam plus enzyme inhibitors	33 (73.34)	92 (56.10)	0.037
Carbapenems	7 (15.56)	32 (19.51)	0.564
Cephalosporins	1 (2.22)	22 (13.41)	0.063
Quinolones	2 (4.44)	10 (6.10)	0.952
Antifungals	2 (4.44)	2 (1.22)	0.433
Glycopeptides	0 (0.00)	2 (1.22)	-
Oxazolidinones	0 (0.00)	4 (2.44)	-

The Beta-lactam plus enzyme inhibitor antibiotics were piperacillin-tazobactam and cefoperazone-sulbactam. AAD: Antibiotic-associated diarrhea.

In conclusion, the incidence of AAD was high in ICU patients receiving antibiotic monotherapy, especially the use of the beta-lactam plus enzyme inhibitor antibiotics. Longer ICU stay time, duration of antibiotic, and duration of use of proton pump inhibitors increase the risk of AAD. Therefore, in order to prevent AAD in ICU patients, antibiotics should be used rationally, and the use and use time of auxiliary drugs such as proton pump inhibitors should be strictly controlled. More relevant research is needed in the future to analyze antibiotic use and AAD.

Table 4 Factors related to antibiotic-associated diarrhea in critically ill patients receiving antibiotic monotherapy

Related factors	Univariate logistic regression analysis		Multivariate logistic regression analysis	
	OR (95%CI)	P value	OR (95%CI)	P value
Age	1.026 (1.009-1.044)	0.003	1.022 (1.001-1.044)	0.040
Gender	1.098 (0.563-2.139)	0.784		
Proton pump inhibitors	1.406 (0.551-3.589)	0.476		
Duration of proton pump inhibitors	1.064 (1.013-1.117)	0.013	1.129 (1.020-1.249)	0.019
Parenteral nutrition	1.482 (0.758-2.898)	0.251		
Albumin levels	1.007 (0.964-1.052)	0.745		
Hypertension	1.660 (0.836-3.295)	0.148		
Diabetes	2.229 (1.007-4.933)	0.048	1.072 (0.345-3.333)	0.904
ICU stay time	1.111 (1.062-1.162)	< 0.001	1.133 (1.041-1.234)	0.004
APACHE II score at admission into the ICU	1.029 (0.987-1.073)	0.179		
Duration of antibiotic	1.247 (1.139-1.367)	< 0.001	1.163 (1.024-1.320)	0.020
Gastrointestinal surgery	1.393 (0.354-5.481)	0.635		
Fasting time exceeding 72 h	1.022 (0.887-1.179)	0.265		
Glucocorticoid	1.454 (0.719-2.941)	0.298		
White blood cell count into the ICU	1.010 (0.967-1.055)	0.656		
Infection sites	1.097 (0.923-1.303)	0.294		
Cephalosporins	6.817 (0.893-52.026)	0.064		
Carbapenems	1.316 (0.538-3.217)	0.547		
Beta-lactam plus enzyme inhibitors	2.152 (1.038-4.462)	0.039	1.480 (0.594-3.688)	0.400
Quinolones	1.396 (0.295-6.613)	0.674		
Antifungals	3.767 (0.516-27.522)	0.191		

Beta-lactam plus enzyme inhibitor antibiotics were piperacillin-tazobactam and cefoperazone-sulbactam. ICU: Intensive care unit; OR: Odds ratio; CI: Confidence interval.

ARTICLE HIGHLIGHTS

Research background

Antibiotic-associated diarrhea (AAD) is diarrhea associated with antibiotic administration. Its incidence has gradually increased and has been reported to be as high as 35% in some studies. AAD has become an important nosocomial disease, especially in critically ill patients. Therefore, we aimed to investigate the factors related to AAD in intensive care unit (ICU) patients receiving antibiotic monotherapy and to provide evidence for clinical anti-infective treatment in critically ill patients.

Research motivation

Currently, research studies on AAD found in the literature are primarily focused on ordinary patients, but a study on AAD in critically ill individuals showed that the incidence of AAD can be as high as 21.6% in cases where antibiotic monotherapy is applied. However, the factors that are associated with AAD in ICU patients with antibiotic monotherapy have not been further explored.

Research objectives

This study aimed to identify factors related to AAD in patients in the ICU receiving antibiotic monotherapy to reduce the incidence of AAD and improve rational use of antibiotics in these patients.

Research methods

A total of 209 patients were enrolled from the ICU of the First Affiliated Hospital of Xi'an Jiaotong University and received antibiotic monotherapy from January 2014 to February 2017. There were 45 cases in the AAD group and 164 cases in the no-AAD group.

Research results

The overall incidence of AAD was 21.53%. Age, proton pump inhibitor usage time, duration of antibiotic, and ICU stay time were associated with AAD. Mean ICU stay time was lower in the no-AAD group (8.49 ± 6.31 vs 15.89 ± 10.69 , $P < 0.001$). However, there was no significant difference in ICU-related mortality rates between the two groups.

Research conclusions

Older age, longer ICU stay time, proton pump inhibitor usage time, and duration of antibiotic increase the incidence of AAD in ICU patients receiving antibiotic monotherapy.

Research perspectives

We aimed to investigate the factors related to AAD in ICU patients receiving antibiotic monotherapy and provide evidence for clinical anti-infective treatment in critically ill patients.

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