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Factors related to antibiotic-associated diarrhea in patients in the intensive care unit receiving antifungals: a single-center retrospective study

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Abstract

Objective: To analyze factors related to antibiotic-associated diarrhea (AAD) in patients in the intensive care unit (ICU) receiving antifungals with the aim of informing rational antibiotic use.

Methods: Sex, age, medical history, use of proton pump inhibitors, administration of parenteral nutrition, albumin level, occurrence of AAD, type of antibiotics, duration of ICU admission, and prognosis were retrospectively analyzed. The associations of age, sex, medical history, and other factors with AAD were associated by logistic regression.

Results: In total, 284 patients were enrolled (antifungals, n = 110; no antifungals, n = 174). The total incidence of AAD was 32.39%. The incidence of AAD was significantly different between the groups (52.73% vs. 19.54%). The duration of proton pump inhibitor therapy, duration of antifungal therapy, enzyme inhibitor antibiotic use, and azithromycin use were associated with AAD in ICU patients receiving antifungal therapy. The mean duration of ICU admission was higher in patients receiving antifungal therapy (20.14 ± 11.50 vs. 14.48 ± 8.54 days). There was no significant difference in ICU mortality rates.

Conclusion: The duration of proton pump inhibitor therapy, duration of antifungal therapy, use of enzyme inhibitor antibiotics, and use of azithromycins were associated with AAD in ICU patients receiving antifungal therapy.

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Introduction

Antibiotic-associated diarrhea (AAD) is a syndrome of disrupted intestinal flora that is caused by antibiotic administration and cannot be explained by other causes of diarrhea.[1,2] It is a general term for a disorder of the intestinal flora with diarrhea as the main symptom. The incidence rate of AAD varies from 5% to 35%[3,4] depending on the type of antibiotic and patient demographics. Generally, patients show symptoms as soon as a few hours after antibiotic administration to as late as 6 to 8 weeks after antibiotic discontinuation.

When using a certain antibiotic, the balance of the gut microflora may be disrupted. As a result, antibiotic-sensitive bacteria are killed or suppressed while drug-resistant bacteria multiply, disrupting the intestinal flora and causing enteritis and diarrhea. *Clostridium difficile* is the most common pathogen.[3,5–9] In recent years, AAD has exhibited an increasing incidence rate and has become an important disease related to nosocomial infection. Accordingly, the cost and length of hospital stay are rising along with the mortality rate.[10–13] Among patients admitted to the intensive care unit (ICU), the incidence rate is much higher and the condition is more severe.[2,14] Among all patients with AAD, more than 20% experience initial treatment failure and 40% to 60% experience a relapse.[10,15] Therefore, prevention of AAD is essential for patients in the ICU.

Previous research has suggested that almost all antibiotics can cause AAD.[3] Risk factors for AAD include the type of antibiotic, use of a combination of antibiotics, and the length of hospital stay.[13,16] However, past research focused mainly on the general population; few studies have examined the risk factors for AAD in patients with critical conditions. Our previous studies[2] established that the use of antifungal drugs is related to the occurrence of AAD among patients in the ICU. However, there have been no further studies on how antifungal drugs affect AAD. Antifungal antibiotics are more commonly used in ICU patients because of the critical condition of these patients.[17,18] Therefore, this study was performed to explore the factors related to AAD in ICU patients receiving antifungals.

Methods

Patient population

The population of interest comprised critically ill patients admitted to the ICU of the First Affiliated Hospital of Xi'an Jiaotong University from 1 January 2014 to 31 December 2015, in addition to patients receiving first-line antibiotic therapy. Patients treated with an antifungal drug were enrolled in the antifungal group (case group), and those not treated with an antifungal drug were enrolled in the no antifungal group (control group). Patients in the antifungal group were divided into either the AAD group or the no AAD group according to whether AAD occurred.

The inclusion criteria were receipt of first-line antibiotic therapy during the study period and treatment with antibiotic

therapy for more than 3 days.[16] The exclusion criteria were no antibiotic use, multiple admissions to the ICU within 1 month, a previous diagnosis of AAD within the previous 3 months, diarrhea of other causes, and incomplete or missing case file data. All study participants provided informed consent. This study was reviewed and approved by the First Affiliated Hospital of Xi'an Jiaotong University Ethics Committee (No. XJTU1AF2018LSK-097).

Research methods

Diagnosis of AAD. The World Health Organization defines diarrhea in adults and children as "the passage of three or more loose or liquid stools per day, or more frequently than is normal for the individual."[19] In clinical studies, diarrhea in adults is usually defined as three or more liquid stools per day for at least 2 days.[5]

AAD is defined as diarrhea associated with antibiotic exposure, either while on antibiotics or for up to 8 weeks after antibiotics have been discontinued.[20] Symptoms can vary from mild self-limited disease to the more serious and severe *C. difficile*-associated diarrhea.[5,21]

Data collection. Detailed records of all patient-related data were collected. These data included sex, age, medical history, administration of parenteral nutrition, use of proton pump inhibitors, Acute Physiology and Chronic Health Evaluation (APACHE) II score upon admission to the ICU, albumin level, type of antibiotics, occurrence of AAD, duration of ICU admission, and prognosis.

Statistical analysis. PASW Statistics for Windows, Version 18.0 (SPSS Inc., Chicago, IL, USA) was used to analyze all relevant data. The data are expressed as mean ± standard deviation and relative percentage, and correlations between groups were tested by the X^2 method. After the data of all groups had been tested for homogeneity of variance and a normal distribution, independent-sample t-tests were used to calculate significant differences between the groups, and statistical significance was set at $P < 0.05$. We used a logistic regression model to investigate the associations of age, sex, medical history, and other factors with AAD. A univariate logistic regression analysis was performed for each variable. Then, each variable with a P value of <0.05 in the univariate analysis was simultaneously entered into the multivariable regression model to identify AAD-related factors.

Results

General information

In total, 284 patients were enrolled (174 men and 110 women; mean age, 53.05 ± 21.74 years). The overall incidence of AAD was 32.39%, and AAD occurred mainly in patients who had used antibiotics for 7.53 ± 4.79 days. The antifungal group comprised 110 patients (71 men and 39 women; mean age, 55.88 ± 21.78 years), and the no antifungal group comprised 174 patients (103 men and 71 women; mean age, 51.26 ± 21.58 years). There were no significant differences between the two groups of patients in terms of age, sex, hypertensive state, prevalence of diabetes, use of parenteral nutrition, use of proton pump inhibitors, or APACHE II score at admission to the ICU, indicating good matching between the two groups. However, the incidence of AAD between the two groups was statistically significant; the incidence was higher in the antifungal group than in the no antifungal group (52.73% vs. 19.54%, respectively; $P < 0.001$) (Table 1).

The patients in the antifungal group were divided into either the AAD group

Table 1. Clinical characteristics of all patients.

Variables	Antifungals	No antifungals	P
No. of patients	110	174	
Age, years	55.88 ± 21.78	51.26 ± 21.58	0.081
Male/female	71/39	103/71	0.384
Hypertension	33 (30.00)	43 (24.71)	0.338
Diabetes	13 (11.82)	18 (10.34)	0.700
Parenteral nutrition	62 (56.36)	118 (67.82)	0.057
Use proton pump inhibitors	97 (88.18)	158 (90.80)	0.547
APACHE II score at admission to the ICU, points	17.93 ± 6.80	16.11 ± 7.76	0.054
AAD	58 (52.73)	34 (19.54)	<0.001

Data are presented as n, mean ± standard deviation, or n (%).
APACHE, Acute Physiology And Chronic Health Evaluation; ICU, intensive care unit; AAD, antibiotic-associated diarrhea.

Table 2. Clinical characteristics of patients using antifungal drugs.

Variables	AAD	No AAD	P
No. of patients	58	52	
Age, years	58.72 ± 23.66	52.71 ± 19.20	0.149
Male/female	40/18	31/21	0.325
Hypertension	20 (34.48)	13 (25.00)	0.304
Diabetes	6 (10.34)	7 (13.46)	0.769
Parenteral nutrition	31 (53.45)	31 (59.62)	0.561
Use proton pump inhibitors	48 (82.76)	49 (94.23)	0.079
Prophylactic use of probiotics	45 (77.59)	39 (75.00)	0.824
Albumin level, g/L	29.45 ± 7.41	31.04 ± 6.54	0.237
APACHE II score at admission to the ICU, points	17.71 ± 6.69	18.00 ± 6.30	0.814

Data are presented as n, mean ± standard deviation, or n (%).
APACHE, Acute Physiology And Chronic Health Evaluation; ICU, intensive care unit; AAD, antibiotic-associated diarrhea.

or no AAD group according to whether AAD occurred. The AAD group comprised 58 patients (40 men and 18 women; mean age, 58.72 ± 23.66 years) and the no AAD group comprised 52 patients (31 men and 21 women; mean age, 52.71 ± 19.20 years). AAD occurred mainly in patients who had used antifungal antibiotics for 6.30 ± 3.47 days. There were no significant differences between the two groups of patients in terms of age, sex, prevalence of diabetes, hypertensive state, prophylactic use of probiotics, use of parenteral nutrition, APACHE II score at admission to the ICU, albumin level, or use of proton pump inhibitors, indicating good matching between the two groups (Table 2).

Antifungals and AAD

Of the 284 patients enrolled, 110 (38.73%) were treated with an antifungal antibiotic. For critically ill patients in the ICU, echinocandins and azoles are often selected as antifungal antibiotics. Fluconazole (73.20%), voriconazole (14.43%), and itraconazole (12.37%) were frequently selected azoles. There was no significant difference

Table 3. Azoles, echinocandins, and AAD.

Variables	AAD	No AAD	P
No. of patients	58	52	
Echinocandins	9 (15.52)	4 (7.69)	0.247
Azoles	49 (84.48)	48 (92.31)	
Fluconazole[1]	34	37	>0.05*
Voriconazole[2]	6	6	
Itraconazole[3]	9	5	

Data are presented as n or n (%).
*P > 0.05 for comparison between 1 and 2, between 1 and 3, and between 2 and 3.
AAD, antibiotic-associated diarrhea.

in the incidence of AAD among the different antifungal drugs (Table 3).

Identification of factors related to AAD in critically ill patients receiving antifungals by univariate and multivariate regression analyses

The univariate regression analysis of the risk factors associated with AAD showed that the proton pump inhibitor treatment time, antifungal treatment time, use of enzyme inhibitors, use of azithromycins, and the ICU stay time were associated with AAD in ICU patients receiving antifungals. However, the albumin level and APACHE II score at admission to the ICU as well as the use of parenteral nutrition, cephalosporins, carbapenems, quinolones, glycopeptides, and oxazolidinones were not associated with AAD in ICU patients (Table 4).

The risk factors associated with AAD in ICU patients receiving antifungals even after the multivariate regression analysis were the proton pump inhibitor treatment time (odds ratio [OR], 1.233; 95% confidence interval [CI], 1.111–1.369; $P < 0.001$), antifungal treatment time (OR, 1.190; 95% CI, 1.047–1.351; $P = 0.008$), use of enzyme inhibitor antibiotics (OR, 3.297; 95% CI, 1.145–9.489; $P = 0.027$), and use of azithromycins (OR, 27.130; 95% CI, 2.488–295.877; $P = 0.007$) (Table 4).

Prognostic evaluation

Among the 110 patients receiving antifungals, 66 were discharged or transferred to other departments, 31 were discharged automatically, and 13 died. The duration of ICU admission (20.14 ± 11.50 vs. 14.48 ± 8.54 days, $P = 0.005$) and antifungal treatment time (12.72 ± 6.27 vs. 8.52 ± 5.53 days, $P < 0.001$) were significantly higher among patients with than without AAD. There was no significant difference in mortality in the ICU between the two groups (Table 5).

Discussion

With the extensive use of antibiotics, the incidence of AAD has increased on an annual basis and has become the most common intestinal infectious disease.[22,23] After the application of antimicrobial drugs, most of the sensitive bacterial species in the intestinal tract are inhibited, and the resistant bacteria reproduce, thus causing diarrhea and inducing AAD.[3,24] The main clinical manifestations of AAD are diarrhea, toxic megacolon, and multiple organ dysfunction, among other symptoms.

The main cause of AAD is believed to be the abuse of antibiotics, especially broad-spectrum antibiotics.[25] Of course, antifungal drugs are also included among broad-spectrum antibiotics. However, the present study showed a higher incidence of AAD in the antifungal group among the ICU patients, and the difference was statistically significant; this is the first report of this finding.[16] The higher incidence of AAD in the antifungal group may be related to the following factors. Published studies to date have mainly focused on the general population rather than critically ill patients.

Table 4. Factors related to AAD in ICU patients receiving antifungals by univariate and multivariate regression analyses.

	Univariate regression analysis		Multivariate regression analysis	
Related factors	OR (95% CI)	P	OR (95% CI)	P
Age	1.013 (0.995–1.031)	0.149		
Male sex	1.505 (0.687–3.301)	0.307		
Use of proton pump inhibitors	3.403 (0.882–13.129)	0.075		
Proton pump inhibitor treatment time	1.155 (1.058–1.261)	0.001	1.233 (1.111–1.369)	<0.001
Parenteral nutrition	1.350 (0.629–2.895)	0.441		
Preventive use of probiotics	0.867 (0.359–2.090)	0.75		
Albumin level	1.034 (0.979–1.092)	0.236		
Hypertension	1.579 (0.689–3.617)	0.28		
Diabetes	1.348 (0.422–4.305)	0.614		
APACHE II score at admission to ICU	1.007 (0.950–1.067)	0.812		
ICU stay time	1.062 (1.017–1.109)	0.007	1.017 (0.950–1.088)	0.630
Antifungal treatment time	1.132 (1.053–1.217)	0.001	1.190 (1.047–1.351)	0.008
Cephalosporins	2.200 (0.709–6.823)	0.172		
Carbapenem	1.055 (0.497–2.237)	0.889		
Enzyme inhibitors[1]	3.252 (1.351–7.824)	0.008	3.297 (1.145–9.489)	0.027
Quinolones	1.096 (0.429–2.798)	0.849		
Glycopeptides[2]	1.143 (0.433–3.013)	0.787		
Oxazolidinones	1.645 (0.762–3.552)	0.205		
Anti-anaerobic bacteria antibiotics[3]	0.880 (0.305–2.541)	0.813		
Azithromycins	5.091 (1.029–25.190)	0.046	27.130 (2.488–295.877)	0.007

OR, odds ratio; CI, confidence interval; APACHE, Acute Physiology And Chronic Health Evaluation; ICU, intensive care unit; AAD, antibiotic-associated diarrhea.
[1]Enzyme inhibitors were piperacillin-tazobactam and sulbactam-cefoperazone.
[2]Glycopeptides were vancomycin and teicoplanin.
[3]Anti-anaerobic bacteria antibiotic was metronidazole.

Table 5. Prognosis of patients receiving antifungals with and without AAD.

Variables	AAD	No AAD	P
No. of patients	58	52	
ICU stay time, days	20.14 ± 11.50	14.48 ± 8.54	0.005
Antifungal use time, days	12.72 ± 6.27	8.52 ± 5.53	<0.001
Prognosis in ICU			
Improved	40 (68.97)	26 (50.00)[1]	0.339*
Discontinuation of treatment	12 (20.69)	19 (36.54)	
Death	6 (10.34)	7 (13.46)[2]	

Data are presented as n, mean ± standard deviation, or n (%).
*Comparison between 1 and 2.
ICU, intensive care unit; AAD, antibiotic-associated diarrhea.

Conversely, the antifungal treatments in our study were a combination of antifungal drugs and other antibiotics, not antifungal drugs alone. The main reason for the difference in the use of antibiotics is related to the patient's condition. Patients in the ICU are in critical condition, especially patients receiving antifungal therapy, and

other infectious pathogens are present at the same time. Therefore, antifungal drugs are often used in combination with other antibiotics, making AAD more likely to be induced. However, further analysis showed no statistically significant difference in the incidence of AAD, regardless of whether azole or echinocandin antifungal drugs were used and regardless of the different azole antifungal drugs that were used. A larger sample will be needed to confirm this in the future. However, knowing that the use of antifungal drugs may increase the risk of AAD in ICU patients is clinically useful.

Studies among the general population have shown that exposure to antibiotics is a risk factor for the development of AAD, especially when two or more antibiotics are used together[2,25] and when the course lasts more than 3 days. Additionally, the length of hospital stay and the duration of exposure to antibiotics are risk factors for AAD.[13,16] One study showed that administration of parenteral nutrition, use of enzyme inhibitor antibiotics, and the combination of antibiotics were associated with AAD in ICU patients.[2] Our study showed that the proton pump inhibitor treatment time, antifungal treatment time, use of enzyme inhibitor antibiotics, and use of azithromycins were associated with AAD in ICU patients receiving antifungals.

Another study showed that the use of proton pump inhibitors and hypoproteinemia are associated with AAD and that in particular, there is a significant correlation with the recurrence of *C. difficile* colitis.[26] In the present study, neither the use of proton pump inhibitors nor the albumin level was statistically significant, suggesting that the sample size was small. In addition, hospitalized patients in the ICU have serious illnesses, and human albumin may have been infused prior to ICU entry in some of these patients. In the future, data on human serum albumin intervention should be recorded because it may interfere with the statistical results. The proportion of patients who used proton pump inhibitors in this study was higher (89.81%), resulting in a smaller number of patients without proton pump inhibitors (10.19%); this may have been the cause of the difference in the analysis results. However, the regression analysis showed that the proton pump inhibitor treatment time was associated with AAD in ICU patients receiving antifungals, which is consistent with the literature.[27] It is useful to realize that prolonged use of proton pump inhibitors may increase the risk of AAD occurrence in ICU patients, especially in patients receiving antifungals. Future prospective studies may further clarify the relationship among the albumin level, proton pump inhibitor treatment time, and occurrence of AAD.

Several studies have suggested that lincomycin, azithromycin, cephalosporins, and penicillin antibiotics are more likely to cause AAD than other types of antibiotics.[3,5,28,29] AAD is especially more likely to occur when these are combined with other antibiotics.[2] Our study showed that the use of azithromycin and enzyme inhibitors was associated with AAD in ICU patients receiving antifungals, which is consistent with the literature.[2] Our study also showed that the antifungal treatment time was associated with AAD in ICU patients. The incidence of AAD in ICU patients receiving antifungals was as high as 52.73%. The condition of these patients receiving antifungals may be more severe than previously thought. Furthermore, for those with confirmed or suspected fungal infections, immunity may be weakened, making them prone to developing AAD. Of course, antifungal agents may also be associated with an earlier disturbance of the intestinal flora, resulting in an increased incidence of AAD. The occurrence of AAD in ICU patients receiving antifungals was noted at a mean of 6.30 ± 3.47 days after

treatment initiation, especially in those who were treated with combined antibiotics; the shortest time until the appearance of AAD was approximately 24 hours. Patients in the ICU are in critical condition, and it is difficult to discontinue administration of these relevant antibiotics, even if AAD appears. The antifungal treatment time (12.72 ± 6.27 vs. 8.52 ± 5.53 days, $P < 0.001$) was significantly higher among patients with than without AAD. For critically ill patients who require long-term antifungal therapy, clinicians should be alert to the potential occurrence of AAD.

Some studies have also indicated that admission to the hospital for more than 2 weeks is correlated with the occurrence of AAD.[13,16] The duration of ICU admission (17.88 ± 11.11 vs. 9.44 ± 6.68 days) was significantly lower in the no AAD group ($P < 0.001$), indicating that the occurrence of AAD could prolong the duration of ICU admission of critically ill patients. However, there was no significant difference in mortality between these two groups, and although this is consistent with our previous study,[2] it is not consistent with previous reports in the literature. This may be influenced by specific customs in different parts of China; for example, in rural areas around Shaanxi, many families request discharge of critically ill patients while they are still alive. These patients are classified as "automatic discharge" in the health statistics; as such, they cannot be classified into either the "survival" or "death" statistics. This might be the main cause of the difference in mortality reported in the literature.[2]

Conclusion

Use of antifungal drugs is directly related to the occurrence of AAD in ICU patients, especially when using antifungal drugs for a long time. Further studies have shown that use of enzyme inhibitor antibiotics, use of azithromycins, and the proton pump inhibitor treatment time are associated with AAD in ICU patients receiving antifungals. Moreover, the duration of ICU admission was significantly longer after the development of AAD. Therefore, to prevent the occurrence of AAD in ICU patients, strict control of the indications for clinical antibiotic use is recommended, combinations of antibiotics should be avoided, and the duration of time for which antibiotics such as antifungal drugs are used should be shortened as much as possible. Additional studies of the association between antifungal drug use and the incidence of AAD in ICU patients are needed to better guide clinical treatment.

Two main limitations should be taken into consideration when interpreting the results of the present study. First, this was a retrospective study. Other studies have identified factors that may be associated with AAD, and these factors were not included in our investigation because they were not present among the patients' clinical data. One such factor is antibiotic use in patients within 3 months prior to admission. Second, our data source was a single center. Thus, our results are subject to several potential biases, including some factors related to AAD. Prospective studies are needed to confirm this in the future.

Declaration of conflicting interests

The authors declare that there is no conflict of interest.

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