MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2018; 24: 5000-5007
DOI: 10.12659/MSM.911308

Received: 2018.05.23
Accepted: 2018.07.06
Published: 2018.07.18

Risk Factors for Antibiotic-Associated Diarrhea in Critically Ill Patients

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF Guo Litao*
ABDEF Sun Jingjing*
ACEF Liu Yu
ACDF Zhang Lei
ABDF He Xiaona
ADEF Zhu Zhijing

Department of Critical Care Medicine, The First Affiliated Hospital of Xi'an Jiaotong University, Xi'an, Shaanxi, P.R. China

* Guo Litao and Sun Jingjing contributed equally to this paper

Corresponding Author: Guo Litao: e-mail: glt02@163.com
Source of support: Departmental sources

Background: We analyzed the factors related to AAD to inform the rational use of antibiotics in critically ill patients and to reduce the incidence of AAD by providing a reference for antibiotic use in the clinical setting.

Material/Methods: This study was a retrospective analysis of the clinical data of patients who were hospitalized in the ICU of the First Teaching Hospital of Xi'an Jiaotong University from January 1, 2015 to December 31, 2016. Patients with AAD were assigned to the case group, and all others were assigned to the control group. Basic data were collected for all the selected patients. All the relevant data were analyzed with univariate or multivariate regression analyses, and P<0.05 was considered statistical significance.

Results: A total of 293 patients were enrolled. Statistical analyses showed that gender (OR 1.915; 95% [CI] 1.061–3.455; P=0.031), parenteral nutrition (OR 1.877; 95% [CI] 1.043–3.377; P=0.036), preventive use of probiotics (OR 0.497; 95% [CI] 0.285–0.866; P=0.014), APACHE II score upon admission to the ICU (OR 0.961; 95% [CI] 0.927–0.998; P=0.037) and use of enzyme-inhibitor antibiotics (OR 1.899; 95% [CI] 1.044–3.420; P=0.016) were associated with AAD. Further subgroup analysis by gender showed that parenteral nutrition (OR 2.144; 95% [CI] 1.064–4.322; P=0.033), preventive use of probiotics (OR 0.367; 95% [CI] 0.186–0.722; P=0.004), and APACHE II score upon admission to the ICU (OR 1.055; 95% [CI] 1.011–1.101; P=0.014) were associated with AAD in critically ill male patients. Age (OR 0.975; 95% [CI] 0.951–0.999; P=0.041) and use of carbapenem antibiotics (OR 4.826; 95% [CI] 1.011–23.030; P=0.048) were associated with AAD in critically ill female patients.

Conclusions: Parenteral nutrition, prophylactic use of probiotics, use of enzyme-inhibitor antibiotics, and use of combinations of antibiotics were associated with AAD in critically ill patients. The prophylactic use of probiotics may be a protective factor in AAD.

MeSH Keywords: Antifungal Agents • *Clostridium Difficile* • Diarrhea • Enterocolitis, Pseudomembranous

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/911308

2907 6 — 32

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Background

Antibiotic-associated diarrhea (AAD) is a syndrome of disrupted intestinal flora caused by antibiotics, which cannot be explained by other causes of diarrhea [1], and diarrhea is the main symptom. The incidence of AAD is about 5–35% of patients treated with antibiotics [2–5] and varies due to differences in populations and types of antibiotics used. Its occurrence varies from several hours after the commencement of antibiotic therapy to 6–8 weeks after antibiotic therapy is discontinued. In the intensive care unit (ICU), the incidence is much higher and clinical outcomes are worse [6]. The main clinical manifestations of AAD are diarrhea, mainly as watery stool, although there may be mucus, pus, or blood in the stool; increased white blood cell count; fever; abdominal pain; abdominal distension; toxic megacolon; multiple organ dysfunction; and other symptoms [4]. A characteristic of the disease is the appearance of a large amount of intestinal pseudomembranous mucosa floating on the watery stools. This situation undoubtedly aggravates the condition of a critically ill patient, leading to increased risk of death.

The microflora in the gut are interdependent and generally do not cause disease. When using a certain antibiotic, this balance 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 [2,7]. AAD is predominantly caused by *Clostridium difficile* (CD), *Klebsiella* sp., and *Staphylococcus aureus*, as well as some fungi and viruses. *Clostridium difficile* is the most common pathogen [8,9]. Initial treatment fails in over 20% of patients with AAD due to CD infection, and relapse occurs in 40–60% of patients [10,11]. Therefore, the prevention of AAD is essential in critically ill patients.

The incidence of AAD is rising, and it has become an important nosocomial infectious disease, resulting in increased hospitalization costs, longer hospital stays, and higher mortality [10,12–14]. It is even more problematic in already critically ill patients. The relevant factors that result in AAD are not yet clear. Currently it is believed that the main cause of AAD is the misuse of antibiotics, especially broad-spectrum antibiotics [3]. When 2 or more antibiotics are combined, the chance of AAD increases significantly [15,16]. Longer hospital stays and longer courses of antibiotics are also risk factors for AAD [14,17]. Many studies have investigated ordinary hospitalized patients [5,8,14,18], but there have been few studies on the factors related to AAD in critically ill patients. Therefore, this study aimed to explore the contributing and protective factors related to AAD in critically ill patients. The conclusions from this study will be applied to future clinical practice, to better guide the rational use of antibiotics in critically ill patients and to reduce the occurrence of AAD.

Material and Methods

Research object

This study was a retrospective analysis of the clinical data of patients receiving antibiotic therapy for the first time from January 1, 2015 to December 31, 2016 while staying in the Department of Critical Care Medicine of the First Affiliated Hospital of Xi'an Jiaotong University. A total of 293 patients, including 180 males and 113 females, were enrolled. Patients were divided into either the case group (AAD group) or the control group (no AAD group) according to whether AAD occurred. The inclusion criteria were: (1) antibiotic therapy was provided for the first time during the study period and (2) antibiotic treatment lasted for more than 3 days [17]. The exclusion criteria were: (1) no antibiotics were used, (2) multiple admissions to the ICU within 1 month, (3) previously diagnosed with AAD within 3 months, and (4) serious loss of case data.

Research methods

Data collection

Clinical data were collected for each patient according to the "Guidelines for Diagnosis, Treatment, and Prevention of *Clostridium difficile* Infections" [19]. The patients with AAD were assigned to the case group and the patients without AAD were assigned to the control group. Detailed records of the patients' general information and related data were collected, including gender, age, diagnosis of hypertension or diabetes, infection site, APACHE II score at admission into the ICU, albumin levels, use of proton pump inhibitors, administration of parenteral nutrition, prophylactic use of probiotics, the type antibiotics, time, AAD status, ICU stay time, and prognosis.

Statistical analysis

SPSS18.0 statistical software was used to analyze all the relevant data. The count data are expressed as the number of cases and the correlation between groups was tested by the χ^2 test. Measurement data are expressed as the mean ± standard deviation. After the data of all groups were tested for homogeneity of variance and normal distribution, independent-samples *t* tests were used to calculate the significant differences between groups and $P < 0.05$ was used as the criterion of significance. Univariate logistic regression analysis was performed for each variable. Then, each variable with $P<0.05$ in the univariate analysis was included in the non-conditional logistic regression model independent risk factors multivariate analysis to determine AAD-related factors.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Table 1. The clinic characteristics of the patients.

Variables	AAD	NO AAD	P
No. of patients	88	205	
Age, years	59.05±21.99	50.28±20.20	0.001*
Male: Female	63/25	117/88	0.026*
Use proton pump inhibitors (%)	74 (84.1)	189 (92.2)	0.056
Parenteral nutrition (%)	56 (63.6)	95 (46.3)	0.007*
Prophylactic use of probiotics (%)	34 (38.6)	121 (59.0)	0.001*
Albumin levels (g/L)	31.00±7.03	32.00±7.90	0.287
Hypertension (%)	36 (40.9)	43 (21.0)	0.001*
Diabetes (%)	15 (17.0)	17 (8.3)	0.040*
APACHE II score at admission to the ICU (points)	18.67±8.03	15.77±7.95	0.005*
Cephalosporins (%)	11 (12.5)	31 (15.1)	0.716
Carbapenem antibiotics (%)	20 (22.7)	61 (6.8)	0.255
Enzyme inhibitors antibiotics (%)**	64 (72.7)	117 (57.1)	0.013*
Quinolones (%)	13 (14.8)	28 (13.7)	0.855
Glycopeptides (%)	5 (5.7)	16 (7.8)	0.627
Oxazolidinones (%)	14 (15.9)	28 (13.7)	0.591
Antifungals (%)	31 (35.2)	53 (25.9)	0.121
Combined antibiotics (%)	69 (78.4)	136 (66.3)	0.025*

* Two groups were significantly different, p <0.05; ** The enzyme inhibitor antibiotics were piperacillin-tazobactam and sulbactam-cefoperazone.

Results

General Information

A total of 293 patients were enrolled, with 180 males and 113 females. The average patient age was 52.91±21.11 years. The incidence of AAD was 30.03%. There were 88 cases in the case group, including 63 males and 25 females, with a mean age of 59.05±21.99 years. There were 205 individuals in the control group, including 117 males and 88 females, with a mean age of 50.28±20.20 years.

The case and control groups were significantly different in terms of age, gender, parenteral nutrition, prophylactic use of probiotics, APACHE II score at admission into the ICU, hypertension, diabetes, use of enzyme-inhibitor antibiotics, and the combined use of antibiotics (P<0.05). The case and control groups were not significantly different in terms of the use of proton pump inhibitors, albumin level at admission into the ICU, or use of other types of antibiotics (except enzyme inhibitors) (P>0.05) (Table 1).

Infection sites and the use of antibiotics

Out of the 293 patient, there were 176 (60.1%) cases of lung infection, 13 (4.4%) cases of abdominal infection, 2 (0.7%) cases of hematogenously disseminated infection, 3 (1.0%) cases of central nervous system infection, 4 (1.4%) cases of urinary tract infection, 2 (0.7%) cases of skin and soft tissue infection, 21 (7.2%) cases of mixed infections, and 72 (24.5%) cases of other types of infections, including pericarditis, pancreatitis, appendicitis, and peritonitis. Among these patients, 88 (30.0%) were administered single antibiotics, 86 (29.4%) were administered a combination of 2 antibiotics, 62 (21.2%) were administered a combination of 3 antibiotics, and 57 (19.4%) were administered a combination of 4 or more antibiotics. AAD occurred mainly in patients who had used antibiotics for 6.56±5.68 days. Among those who developed AAD, 19 (21.6%) were administered single antibiotics, 29 (33.0%) were administered a combination of 2 antibiotics, 22 (25.0%) were administered a combination of 3 antibiotics, and 18 (20.4%) were administered a combination of 4 or more antibiotics.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Table 2. Risk factors of AAD by univariate and multivariate regression analyses.

Related factors	Univariate regression analysis			Multivariate regression analysis		
	OR (95% CI)		P	OR (95% CI)		P
Age	0.980	(0.968–0.992)	0.001	0.998	(0.983–1.013)	0.798
Gender	1.895	(1.105–3.251)	0.020	1.915	(1.061–3.455)	0.031
Use of proton pump inhibitors	2.235	(1.039–4.807)	0.040	1.653	(0.680–4.018)	0.267
Parenteral nutrition	2.019	(1.213–3.360)	0.007	1.877	(1.043–3.377)	0.036
Preventive use of probiotics	0.429	(0.255–0.722)	0.001	0.497	(0.285–0.866)	0.014
Albumin levels	1.017	(0.984–1.052)	0.308			
Hypertension	2.608	(1.517–4.484)	0.001	1.523	(0.797–2.910)	0.203
Diabetes	2.272	(1.079–4.787)	0.031	1.084	(0.468–2.511)	0.851
APACHE II score at admission into the ICU	0.956	(0.926–0.987)	0.005	0.961	(0.927–0.998)	0.037
Cephalosporins	1.247	(0.596–2.609)	0.558			
Carbapenems	1.440	(0.805–2.576)	0.219			
Enzyme inhibitors	2.006	(1.163–3.458)	0.012	1.889	(1.044–3.420)	0.016
Quinolones	1.096	(0.538–2.231)	0.801			
Glycopeptides	1.405	(0.498–3.963)	0.520			
Oxazolidinones	1.196	(0.596–2.400)	0.615			
Antifungals	1.560	(0.911–2.670)	0.105			

Factors related to AAD in critically ill patients by univariate and multivariate regression analyses

A univariate regression analysis of the risk factors associated with AAD showed that age, gender, use of proton pump inhibitors, parenteral nutrition, preventive use of probiotics, hypertension, diabetes, APACHE II score at admission into the ICU, and use of enzyme-inhibitor antibiotics were associated with AAD in critically ill patients. However, albumin levels at admission to the ICU, cephalosporins, carbapenems, quinolones, glycopeptides, and oxazolidinones were not associated with AAD in critically ill patients (Table 2).

The risk factors that maintained their association with AAD in critically ill patients after the multivariate regression analysis were gender (OR 1.915, 95% [CI] 1.061–3.455, P=0.031), parenteral nutrition (OR 1.877, 95% [CI] 1.043–3.377, P=0.036), preventive use of probiotics (OR 0.497, 95% [CI] 0.285–0.866, P=0.014), APACHE II score at admission into the ICU (OR 0.961, 95% [CI] 0.927–0.998, P=0.037), and use of enzyme-inhibitor antibiotics (OR 1.899, 95% [CI] 1.044–3.420, P=0.016) (Table 2).

Risk factors of AAD stratified by gender in univariate and multivariate regression analyses

According to the above analysis, gender is associated with AAD. Therefore, we stratified the analysis based on gender.

The results showed that while there was a significant difference in ages between the males and females (P=0.001), there was no significant differences in other aspects according to gender, and the baseline data were stable (Table 3). Univariate regression analysis of male patients with AAD showed that parenteral nutrition (OR 2.047, 95% [CI] 1.095–3.827, P=0.025), preventive use of probiotics (OR 0.347, 95% [CI] 0.182–0.661, P=0.001), hypertension (OR 2.276, 95% [CI] 1.186–4.368, P=0.013), and APACHE II score at admission into the ICU (OR 0.952, 95% [CI] 0.915–0.990, P=0.013) were associated with AAD. Risk factors that maintained their association in the multivariate regression analysis were parenteral nutrition (OR 2.144, 95% [CI] 1.064–4.322, P=0.033), preventive use of probiotics (OR 0.367, 95% [CI] 0.186–0.722, P=0.004), and APACHE II score at admission into the ICU (OR 1.055, 95% [CI] 1.011–1.101, P=0.014) (Table 4).

Univariate regression analysis of female patients with AAD showed that age (OR 0.967, 95% [CI] 0.946–0.989, P=0.004),

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Table 3. Basic information of patients stratified by gender.

Variables	Male	Female	P
No. of patients	180	113	
Age, years	56.19±21.03	47.69±20.24	0.001*
Use of proton pump inhibitors (%)	154 (85.6)	98 (86.7)	0.863
Parenteral nutrition (%)	84 (46.7)	67 (59.3)	0.054
Prophylactic use of probiotics (%)	91 (50.6)	60 (53.1)	0.719
Hypertension (%)	56 (31.1)	23 (20.4)	0.058
Diabetes (%)	25 (13.9)	7 (6.2)	0.053
APACHE II score at admission into the ICU (points)	17.07±8.03	15.96±8.12	0.25
Carbapenem antibiotics (%)	46 (25.6)	35 (31.0)	0.348
Enzyme inhibitor antibiotics (%)	113 (62.8)	68 (60.2)	0.711

* Significant difference between two groups, p<0.05.

Table 4. Risk factors of AAD by univariate and multivariate regression analysis (Male).

Related factors	Univariate regression analysis		Multivariate regression analysis	
	OR (95% CI)	P	OR (95% CI)	P
Age	0.989 (0.973–1.004)	0.142		
Use of proton pump inhibitors	1.982 (0.706–5.563)	0.194		
Parenteral nutrition	2.047 (1.095–3.827)	0.025	2.144 (1.064–4.322)	0.033
Preventive use of probiotics	0.347 (0.182–0.661)	0.001	0.367 (0.186–0.722)	0.004
Albumin levels	1.036 (0.994–1.080)	0.097		
Hypertension	2.276 (1.186–4.368)	0.013	1.460 (0.713–2.911)	0.301
Diabetes	1.651 (0.670–4.068)	0.276		
APACHE II score at admission into the ICU	0.952 (0.915–0.990)	0.013	1.055 (1.011–1.101)	0.014
Cephalosporins	1.110 (0.475–2.594)	0.810		
Carbapenem	1.067 (0.543–2.095)	0.850		
Enzyme inhibitors	1.866 (0.966–3.602)	0.063		
Quinolones	1.163 (0.512–2.646)	0.718		
Glycopeptides	1.379 (0.414–4.587)	0.601		
Oxazolidinones	1.091 (0.459–2.594)	0.844		
Antifungals	1.748 (0.914–3.341)	0.091		

hypertension (OR2.973, 95% [CI] 1.098–8.055, P=0.032), diabetes (OR4.150, 95% [CI] 1.095–15.727, P=0.036), and use of carbapenem antibiotics (OR4.823, 95% [CI] 1.059–21.956, P=0.042) were associated with AAD. Risk factors that maintained their association in the multivariate regression analysis were age (OR 0.975, 95% [CI] 0.951–0.999, P=0.041), and use of carbapenem antibiotics (OR 4.826,95% [CI] 1.011–23.030, P=0.048) (Table 5).

Prognostic evaluation

In total, 293 cases were included, of whom 181 improved, 81 abandoned treatment, and 31 died. AAD occurred in 88 cases, of whom 46 were improved, 32 abandoned treatment, and 10 died, because the primary disease was fatal. Once AAD occurred, except in 1 patient, the remaining patients were unable

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Table 5. Risk factors of AAD by univariate and multivariate regression analysis (Female).

Related factors	Univariate regression analysis		Multivariate regression analysis	
	OR (95% CI)	P	OR (95% CI)	P
Age	0.967 (0.946–0.989)	0.004	0.975 (0.951–0.999)	0.041
Use of proton pump inhibitors	3.158 (0.979–10.182)	0.054		
Parenteral nutrition	2.339 (0.933–5.865)	0.070		
Preventive use of Probiotics	0.637 (0.258–1.571)	0.328		
Albumin levels	0.995 (0.938–1.055)	0.866		
Hypertension	2.973 (1.098–8.055)	0.032	1.672 (0.534–5.237)	0.378
Diabetes	4.150 (1.095–15.727)	0.036	2.047 (0.459–9.118)	0.347
APACHE II score at admission into the ICU	0.972 (0.919–1.027)	0.312		
Cephalosporins	4.541 (0.567–36.357)	0.154		
Carbapenem	4.823 (1.059–21.956)	0.042	4.826 (1.011–23.030)	0.048
Enzyme inhibitors	2.407 (0.876–6.609)	0.088		
Quinolones	1.474 (0.301–7.214)	0.632		
Glycopeptides	1.756 (0.201–15.309)	0.610		
Oxazolidinones	1.950 (0.599–6.350)	0.268		
Antifungals	1.008 (0.356–2.852)	0.989		

Table 6. The prognosis of patients with and without AAD.

Variables	AAD	No AAD	p
ICU stay time, days	17.16±11.03	9.15±6.85	<0.001
Prognosis in ICU			
Improved (%)	46 (52.3)	135 (65.9)[1]	0.508*
Stop treatment (%)	32 (36.4)	49 (23.9)	
Death (%)	10 (11.4)	21 (10.2)[2]	

* Compare for 1 and 2.

to discontinue antibiotics. The average ICU stay time in patients with AAD was 17.16±11.03 days, while it was significantly lower in patients without AAD (9.15±6.85 days) (P <0.001). There was no significant difference in mortality in the ICU between the 2 groups. AAD did not directly cause any deaths in either group (Table 6).

Discussion

AAD is the most common nosocomial intestinal infection [20,21], often caused by *Clostridium difficile* [2]. After the use of antibiotics, most of the antibiotic-sensitive intestinal bacteria have been inhibited, and the antibiotic-resistant bacteria multiply, allowing *Clostridium difficile* to become the dominant bacteria and produce toxin A and toxin B, prompting AAD and causing diarrhea [2,7,22]. In this study, the patients selected were critically ill patients receiving antibiotics for the first time, in whom the incidence of AAD was 30.03%, which is the same incidence that has been reported in the literature [2–4,6]. In this study, we found that age, prophylactic use of probiotics, and combined use of antibiotics are associated with AAD. This is consistent with recent research in non-critically ill patients. However, gender, use of parenteral nutrition, the APACHE II score at admission into the ICU, and use of enzyme inhibitors were associated with AAD in critically ill patients, which has not been previously reported.

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

Research into non-critically ill patients [15,23] has demonstrated that almost all antibiotics cause AAD. Cephalosporins, penicillin, lincomycin, and azithromycin most readily induce AAD [2,18,19,24]. Our analysis showed that cephalosporins were not associated with AAD in critically ill patients. This may be related to the condition of the ICU patients; those with severe illnesses usually receive stronger antibiotics, as reflected in the use of cephalosporins in this study, which was only 6.3%. It has not been reported that the use of enzyme-inhibitor antibiotics in critically ill patients can increase the risk of AAD [17]. This may be related to medication habits. In the treatment of critically ill patients, mostly carbapenems and enzyme inhibitors are used in the empirical or targeted application of antibiotics against gram-negative bacteria, which in this study accounted for 48% of all antibiotics, while antifungal drugs accounted for 17.7%. Studies have shown that the combined use of antibiotics and the use of antibiotics for longer than 3 days readily led to AAD [17]. Our study also showed that the combined use of antibiotics is more likely to induce AAD. In ICU patients with severe illness, even if AAD occurs, it is very difficult to discontinue antibiotics [25].

Critically ill patients who are receiving parenteral nutrition therapy usually have intestinal dysfunction, which, when coupled with the use of antibiotics, may cause imbalances in the intestinal flora, thereby promoting the occurrence of AAD. Further analysis of the association between the length of the use of parenteral nutrition and AAD is needed to provide guidelines for the cessation of parenteral nutrition as soon as possible. A higher APACHE II score upon admission into the ICU indicates that the patient is in more serious condition, which may involve chronic underlying disease and multiple organ dysfunction, which, when coupled with the use of antibiotics, may be more likely to result in AAD [10,26]. Therefore, the APACHE II score reflects a combination of multiple risk factors.

Existing research does not report the correlation between the occurrence of AAD and gender; however, studies have shown that age is a risk factor for AAD [10,26,27], with older patients being more prone to AAD [5,11]. When stratified by gender, our data revealed that there was a significant difference in the age of patients, with 56.19±21.03 years as the mean age of males and 47.69±20.24 as the mean age of females. This was related to the ICU's admission of patients during the study period and may have resulted in gender differences in the analysis of AAD risk factors. Thus, there was a need to perform subgroup analyses of the risk factors by gender.

Multivariate regression analysis showed that parenteral nutrition, preventive use of probiotics, and APACHE II scores at admission into the ICU are associated with AAD in critically ill male patients. Age and the use of carbapenem antibiotics are associated with AAD in female critically ill patients. In this study, most of the patients were elderly men. Such patients often present with immune dysfunction, poor nutrition, severe illness, and high APACHE II scores upon admission into the ICU, which may make them more likely to develop AAD. The older the female patient, the greater the likelihood of AAD. The average age of female patients with AAD was 60.64±24.68 years old. For female patients, carbapenem antibiotics were more likely to cause AAD, which may be related to the etiology of the infection and other characteristics of infected female patients.

It has been reported [28] that proton pump inhibitors and hypoproteinemia are associated with AAD and that, in particular, there is a significant correlation with the recurrence of *Clostridium difficile* colitis. In this study, univariate analysis showed that there was a correlation between proton pump inhibitors and AAD; however, multivariate analysis did not show a significant correlation. Albumin levels also did not present a significant difference, suggesting that the sample size is small. In addition, hospitalized patients in the ICU have serious illnesses, and in some, human albumin may have been infused prior to ICU admission. In the future, data on human serum albumin intervention should be recorded because it may interfere with the statistical results. Future prospective studies may further clarify the relationship between albumin levels and AAD or identify its correlation with AAD by continuously monitoring the level of albumin after the patient enters the ICU.

Probiotics seem have a role in preventing AAD in hospitalized patients who are not critically ill, although this is still controversial [10,13,20,29–32]. In this study, multivariate regression analysis of AAD in critically ill patients found that the use of probiotics is a protective factor against AAD, and the subgroup analysis by gender showed that for male patients, the prophylactic use of probiotics can reduce the incidence of AAD. Therefore, the prophylactic use of probiotics has an important clinical use in reducing the incidence of AAD. AAD patients in this study, according to intestinal flora smears and clinical manifestations, could be divided into 28 mild cases, 31 moderate cases, and 29 severe cases. Whether the use of probiotics can reduce the severity of AAD in critically ill patients also needs more in-depth study.

Studies indicate that hospital stays ≥2 weeks are associated with AAD [14,17]. The ICU stay time (17.16±11.03 *vs.* 9.15±6.85 days) between the 2 groups was found to be significantly different ($P<0.001$). Therefore, the occurrence of AAD can extend the ICU stay time of critically ill patients. However, the difference in the mortality rate of the 2 groups was not statistically significant, which is inconsistent with previous reports. This is likely related to the traditional customs in some parts of China, particularly in the rural areas around Shaanxi Province, where most people still follow the custom of taking patients back to their homes to die. These patients are recorded as having

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]

abandoned treatment in our study and cannot be classified in either the group who survived or the group who died. This may explain the lack of a difference in mortality.

Conclusions

There are many factors associated with AAD in critically ill patients, such as parenteral nutrition, the prophylactic use of probiotics, and the use of enzyme-inhibitor antibiotics and combinations of antibiotics. It is necessary to strictly control the combination of antibiotics used, and the rational use of antibiotics is the key to preventing AAD. Risk factors related to AAD in critically ill patients still need to be clarified through more research, and many issues still need to be explored in depth. Further research will be able to better guide clinical treatment.

Conflict of interests

None.

References:

1. Bartlett JG: Clinical practice. Antibiotic-associated diarrhea. N Engl J Med, 2002; 346: 334–39
2. Tian CF, Su BY, Li YJ et al: Management of antibiotic-associated pseudomembranous colitis in Non-hospitalized and hospitalized patients. Pak J Pharm Sci, 2016; 29: 1805–10
3. Viswanathan V, Magliozzi M, Vedanta G: *Clostridium difficile* infection: An overview of the disease and its pathogenesis, epidemiology and interventions. Gut Microbes, 2010; 1: 234–42
4. Walbrown MA, Aspinall SL, Bayliss NK et al: Evaluation of *Clostridium difficile*-associated diarrhea with a drug formulary change in preferred fluoroquinolones. J Manag Care Pharm, 2008; 14: 34–40
5. Huang H, Wu S, Wang M et al: Molecular and clinical characteristics of *Clostridium difficile* infection in a university hospital in Shanghai, China. Clin Infect Dis, 2008; 47: 1606-8
6. Oughton MT, Miller MA: Clinical and epidemiological aspects of *Clostridium difficile*. Clin Microbiol Newsl, 2008; 30: 87–95
7. Roberts T, Kokaikun J F, Coughlin O et al: Tolerability and pharmacokinetics of SYN-004, an orally administered β-Lactamase for the prevention of *Clostridium difficile*-associated disease and antibiotic-associated diarrhea, in two phase 1 studies. Clin Drug Investig, 2016; 36: 725–34
8. Plummer S, Weaver M A, Harris JC et al: *Clostridium difficile* pilot study: Effects of probiotic supplementation on the incidence of *C. difficile* diarrhoea. Int Microbiol, 2004; 7: 59–62
9. Schroeder MS: *Clostridium difficile*-associated diarrhea. Am Fam Physician, 2005; 71: 921–28
10. Shen NT, Maw A, Tmanova LL et al: Timely use of probiotics in hospitalized adults prevents *Clostridium difficile* infection: A systematic review with meta-regression analysis. Gastroenterology, 2017; 152: 1889–900
11. Kelly CP: A 76-year-old man with recurrent *Clostridium difficile*-associated diarrhea: Review of *Clostridium difficile* infection. JAMA, 2009; 301: 954–62
12. Dubberke ER, Mejia-Chew C: *Clostridium difficile* control measures: Current and future methods for prevention. Expert Rev Anti Infect Ther, 2018; 16: 121–31
13. Hempel S, Newberry SJ, Maher AR et al: Probiotics for the prevention and treatment of antibiotic-associated diarrhea: A systematic review and meta-analysis. JAMA, 2012; 307: 1959–69
14. Ruiter-Ligeti J, Vincent S, Czuzoj-Shulman N et al: Risk factors, incidence, and morbidity associated with obstetric *Clostridium difficile* infection. Obstet Gynecol, 2018; 131: 387–91
15. Owens RC, Donskey CJ, Gaynes RP et al: Antimicrobial-associated risk factors for *Clostridium difficile* infection. Clin Infect Dis, 2008; 46: S19–31
16. Rodríguez-Varón A, Muñoz OM, Pulido-Arenas J et al: Antibiotic-associated diarrhea: Clinical characteristics and the presence of *Clostridium difficile*. Rev Gastroenterol Mex, 2017; 82(2): 129–33
17. Videlock EJ, Cremonini F: Meta-analysis: Probiotics in antibiotic-associated diarrhea. Aliment Pharmacol Ther, 2012; 35: 1355–69
18. Surawicz CM, Brandt LJ, Binion DG et al. Guidelines for diagnosis, treatment, and prevention of *Clostridium difficile* infections. Am J Gastroenterol, 2013; 108: 478–98
19. Lau CS, Chamberlain RS: Probiotics are effective at preventing *Clostridium difficile*-associated diarrhea: A systematic review and meta-analysis. Int J Gen Med, 2016; 9: 27–37
20. Yoldaş Ö, Altindis M, Cufali D et al: A diagnostic algorithm for the detection of *Clostridium difficile*-associated diarrhea. Balkan Med J, 2016; 33: 80–86
21. Leal JR, Heitman SJ, Conly JM: Cost-effectiveness analysis of the use of probiotics for the prevention of *Clostridium difficile*-associated diarrhea in a Provincial Healthcare System-ERRATUM. Infect Control Hosp Epidemiol, 2016; 37: 1079–86
22. Wilcox M, Minton J: Role of antibody response in outcome of antibiotic associated diarrhea. Lancet, 2001; 357: 158–59
23. Dubberke ER, Reske KA, Olsen MA et al: Evaluation of *Clostridium difficile*-associated disease pressure as a risk factor for *C. difficile*-associated disease. Arch Intern Med, 2007; 167: 1092–97
24. Bauer MP, van Dissel JT: Alternative strategies for *Clostridium difficile* infection. Int J Antimicrob Agents, 2009; 33: S51–56
25. Debast SB, Bauer MP, Kuijper EJ et al: European Society of Clinical Microbiology and Infectious Diseases: Update of the treatment guidance document for *Clostridium difficile* infection. Clin Microbiol Infect, 2014; 20: 1067–79
26. Evans CT, Safdar N: Current trends in the epidemiology and outcomes of *Clostridium difficile* infection. Clin Infect Dis, 2015; 60: S66–71
27. Giannelli FR: Antibiotic-associated diarrhea. JAAPA, 2017; 30: 46–47
28. Rotramel A, Poritz LS, Messaris E et al: PPI therapy and albumin are better predictors of recurrent *Clostridium difficile* colitis than choice of antibiotics. Gastrointest Surg, 2012; 16: 2267–73
29. Johnston BC, Ma SS, Goldenberg JZ et al: Probiotics for the prevention of *Clostridium difficile*-associated diarrhea: A systematic review and meta-analysis. Ann Intern Med, 2012; 157: 878-88
30. Dubberke ER, Carling P, Carrico R et al: Strategies to prevent *Clostridium difficile* infections in acute care hospitals: 2014 update. Infect Control Hosp Epidemiol, 2014; 35: 628–45
31. Allen SJ, Wareham K, Wang D et al: Lactobacilli and bifidobacteria in the prevention of antibiotic-associated diarrhea and *Clostridium difficile* diarrhea in older inpatients (PLACIDE): A randomised, double-blind, placebo-controlled, multicentre trial. Lancet, 2013; 382: 1249-57
32. Blaabjerg S, Artzi DM, Aabenhus R: Probiotics for the prevention of antibiotic-associated diarrhea in outpatients-a systematic review and meta-analysis. Antibiotics, 2017; 6: 21–37

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS]