MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2018; 24: 8781-8788
DOI: 10.12659/MSM.913739

Received: 2018.10.22
Accepted: 2018.11.23
Published: 2018.12.04

Enzyme Inhibitor Antibiotics and Antibiotic-Associated Diarrhea in Critically Ill Patients

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Source of support: Departmental sources

Background: This study aimed to analyze the factors associated with the development of antibiotic-associated diarrhea (AAD) in critically ill patients receiving enzyme inhibitor antibiotics.

Material/Methods: A retrospective study of patients with and without AAD admitted to the intensive care unit (ICU) of the First Teaching Hospital of Xi'an Jiaotong University from February 1, 2014, to January 31, 2016, was undertaken. Relevant clinical data underwent univariate or multivariate regression analysis.

Results: Of 184 patients who received enzyme inhibitor antibiotic therapy, 70 patients (38.04%) developed AAD, with a mean duration of onset of 6.97±3.64 days. AAD was associated with the use of enzyme inhibitor antibiotic therapy alone (OR, 1.142; 95% CI, 1.038–1.256; P=0.007), and in combination with antifungal agents (OR, 2.449; 95% CI, 1.116–5.372; P=0.025), quinolones (OR, 5.219; 95% CI, 1.746–15.601; P=0.003), and oxazolidinones (OR 2.895; 95% CI, 1.183–7.083; P=0.020). The mean duration of ICU stay was significantly increased in patients with AAD (19.00±11.49 days *vs.* 9.60±6.76 days) (P<0.001). Mean duration of antibiotic therapy (14.09±8.82 days *vs.* 8.10±4.91 days) (P<0.001) and duration of enzyme inhibitor antibiotic therapy (9.26±5.06 days *vs.* 6.61±3.24 days) (P<0.001) were significantly increased in patients with AAD.

Conclusions: Duration of use of enzyme inhibitor antibiotic therapy and the combined use of antifungals, quinolones, and oxazolidinones increased the incidence and duration of AAD and increased the length of stay in ICU.

MeSH Keywords: Antifungal Agents • *Clostridium Difficile* • Diarrhea • Enzyme Inhibitors • Intensive Care Units

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/913739

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

The extensive use of antibiotics has led to the increased annual incidence of antibiotic-associated diarrhea (AAD) [1]. AAD is a syndrome resulting from changes in intestinal flora associated with disorders of varying severity caused by antibiotic treatment, with the primary symptom being diarrhea [1]. The reported incidence of AAD in patients treated with antibiotics varies from between 5–35% [1–3], possibly due to differences in the populations studied and the types of antibiotics used. The prevalence of AAD increases in cases of combined antibiotic treatment. AAD can occur within several hours after the start of antibiotic therapy and can also occur at up to 6–8 weeks after the antibiotic therapy has been discontinued. A delay in diagnosis can lead to serious complications and, mortality rates as that have been reported to be as high as 15–24% [4].

AAD is predominantly caused by *Clostridium difficile*, *Klebsiella* sp., and *Staphylococcus aureus*, as well as some fungi and viruses. *C. difficile* is the most common pathogen causing AAD [3,5,6]. The recent increase in the incidence of AAD has made *C. difficile* an important nosocomial infection, particularly in hospitalized patients. Therefore, AAD increases patient morbidity and mortality, the length of hospital stay, and healthcare costs [7–9]. In patients admitted to the intensive care unit (ICU), the incidence of AAD is considerably increased, and the condition is more severe [1]. Therefore, AAD is a condition that should be prevented in critically ill patients.

Previously published studies have shown that combined antibiotic treatment, parenteral nutrition, and hospital stay are associated with the occurrence of AAD [1,9,10]. Also, different types of antibiotics have different risks of causing AAD [3]. Some antibiotics inhibit the enzymes that are essential for the growth of pathogens and include commonly used antibiotics such as penicillin and vancomycin, which are more commonly used in critically ill patients because they are effective broad-spectrum antimicrobial [1]. However, enzyme inhibitor antibiotics are also associated with the development of AAD in critically ill patients [1]. A recent study showed that the incidence of AAD was significantly different between patients who treated with enzyme inhibitor antibiotics compared with non-enzyme inhibitor antibiotics (35.36% *vs.* 21.43%) (P=0.013) [1]. However, the mechanisms associated with the effects of enzyme inhibitor antibiotics and the development of AAD remain unclear. Therefore, this study aimed to analyze the factors associated with the development of AAD in critically ill patients receiving enzyme inhibitor antibiotics.

Material and Methods

Study design

A retrospective study reviewed the medical records of critically ill patients admitted to the intensive care unit (ICU) of the First Affiliated Hospital of Xi 'an Jiaotong University between February 1, 2014 and January 31, 2016, who received enzyme inhibitor antibiotic therapy. The patients were divided into the antibiotic-associated diarrhea (AAD) treatment group and non-AAD treatment group. The inclusion criteria were patients admitted to the ICU who had the first use of enzyme inhibitor antibiotic therapy, and treatment that lasted for more than three days [10]. The exclusion criteria included patients who were admitted to the ICU who were not treated with an enzyme inhibitor antibiotic, or multiple admissions to the ICU within one month, or a previous diagnosis of AAD within the preceding three months, and incomplete or missing case file data [1]. All study participants provided informed consent, and this study was reviewed and approved by The First Affiliated Hospital of Xi'an Jiaotong University Ethics Committee (No. XJTU1AF2018LSK-097).

Diagnosis of antibiotic-associated diarrhea (AAD)

Diagnosis of the critically ill patients recruited for this study was made according to the US 2013 guidelines for diagnosis, treatment, and prevention of *Clostridium difficile* infections [5], and the 2014 European Society of Clinical Microbiology and Infectious Diseases guidance document for the treatment of *C. difficile* infection [11].

Data collection

Baseline patient clinical and demographic data were collected from the medical records and included data on the presence of diabetes, loss of appetite exceeding 72 hours, a history of gastrointestinal surgery, medical treatment including immunosuppressive therapy, and hormone supplementation. Laboratory findings were noted, including serum albumin levels. For each patient included in the study analysis, the Acute Physiology and Chronic Health Evaluation (APACHE II) score on admission to the ICU were retrospectively collected and analyzed.

Statistical analysis

Statistical analysis was performed using SPSS version 18.0 (IBM Corp, Armonk, NY). Data were expressed as the number of cases and percentages and the chi-squared (χ^2) test was used for correlation between groups. Measurement data were expressed as the mean ± standard deviation (SD), with calculation of the odds ratio (OR) and 95% confidence interval (CI). After the data of all groups were tested for homogeneity of variance

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Table 1. The clinic characteristics of the patients.

Variables	AAD	No AAD	P-value
No. of patients	70	114	
Age (years)	61.01±21.65	52.10±19.13	0.004
Male: Female	48:22	66:48	0.162
Hypertension (%)	29 (41.43%)	27 (23.68%)	0.014
Diabetes (%)	12 (17.14%)	12 (10.53%)	0.259
Fasting time exceeding 72 hours (%)	34 (48.57%)	58 (50.88%)	0.879
Gastrointestinal surgery (%)	6 (8.57%)	5 (4.39%)	0.338
Immunosuppressants (%)	3 (4.29%)	4 (3.51%)	0.789
Use of hormones (%)	38 (54.29%)	57 (50.00%)	0.649
Albumin levels (g/L)	30.56±7.00	30.83±7.18	0.802
APACHE II score at admission into the ICU (points)	17.64±6.98	16.47±6.50	0.251
Enzyme inhibitor in combination with other antibiotics (%)	51 (72.86%)	49 (42.98%)	<0.001

AAD – antibiotic-associate diarrhea; ICU – intensive care unit; APACHE – Acute Physiology and Chronic Health Evaluation.

and normal distribution, independent sample t-tests were used to calculate the significant difference between groups, and a P-value <0.05 was considered to be statistically significant. Univariate logistic regression analysis was performed for each variable. Each variable with P <0.05 in the univariate analysis was included in the logistic regression model for independent risk factors using multivariate analysis to determine AAD-related factors. The statistical methods of this study were reviewed by Bin Yan from the Clinical Research Center of the First Affiliated Hospital of Xi'an Jiaotong University.

Results

Patient characteristics

Retrospective clinical review identified 184 patients who were admitted to the intensive care unit (ICU) of the First Affiliated Hospital of Xi 'an Jiaotong University between February 1, 2014 and January 31, 2016, who received enzyme inhibitor antibiotic therapy, including 114 men and 70 women (mean age, 55.49±20.54 years). The incidence of antibiotic-associated diarrhea (AAD) was 38.04%, which occurred mainly in patients who had used enzyme inhibitor antibiotics for 6.97±3.64 days. The AAD group included 70 patients (48 men and 22 women) (mean age, 61.01±21.65 years). The non-AAD group included114 patients, (66 men and 48 women) (mean age, 52.10±19.13 years). (Table 1)

The mean age and incidence of hypertension were significantly different between the AAD group and non-AAD group (all P<0.05). There were no significant differences between the two groups in terms of gender, diabetes, loss of appetite exceeding 72 hours, gastrointestinal surgery, treatment with immunosuppressants or hormone supplements, albumin levels, and the Acute Physiology and Chronic Health Evaluation (APACHE II) score on admission to the ICU (P>0.05). The incidence of AAD was significantly increased in patients treated with a combination of enzyme inhibitors and other antibiotics and those who received enzyme inhibitor antibiotic monotherapy (51.00% *vs.* 22.62%) (P<0.001). (Table 1)

Correlation between AAD and the use of enzyme inhibitor antibiotics

Of the 184 patients who received enzyme inhibitor antibiotic therapy, 87 patients (47.28%) were treated with piperacillin-tazobactam, and 97 patients (52.72%) were treated with cefoperazone-sulbactam. The incidence of AAD was 34.48%, which was significantly increased in patients treated with piperacillin-tazobactam combined with other antibiotics than in those treated with piperacillin-tazobactam monotherapy (44.68% *vs.* 22.50%) (P=0.042). The incidence of AAD was 41.24% in those treated with cefoperazone-sulbactam. The incidence of AAD was significantly increased in patients treated with cefoperazone-sulbactam combined with other antibiotics compared with patients treated with cefoperazone-sulbactam monotherapy (56.60% *vs.* 22.73%) (P=0.001). There was no significant difference in the incidence of AAD between the different types of enzyme inhibitor antibiotics (P=0.365) (Table 2).

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Table 2. Correlation between antibiotic-associated diarrhea (AAD) and enzyme inhibitors.

Variables	Single antibiotics		Combined antibiotics		P-value	P-value
	AAD	No AAD	AAD	No AAD		
Piperacillin-tazobactam	9	31	21	26	0.042	0.365
Cefoperazone-sulbactam	10	34	30	23	0.001	
P-value	0.98		0.316			

Table 3. Correlation between antibiotic-associated diarrhea (AAD) and enzyme inhibitors combined with other antibiotics.

Variables	AAD	No AAD	P-value
No. of patients	70	114	
Glycopeptides* (%)	11 (15.71%)	12 (10.53%)	0.360
Oxazolidinones** (%)	25 (35.71%)	16 (14.04%)	0.001
Anti-anaerobic bacteria antibiotics# (%)	10 (14.29%)	25 (21.93%)	0.247
Antifungals (%)	41 (58.57%)	31 (27.19%)	<0.001
Carbapenems (%)	25 (35.71%)	22 (19.30%)	0.015
Quinolones (%)	18 (25.71%)	7 (6.14%)	<0.001
Azithromycins (%)	3 (4.29%)	11 (9.65%)	0.255
Cephalosporins (%)	13 (18.57%)	13 (11.40%)	0.195

* Glycopeptides (vancomycin, teicoplanin); ** oxazolidinones (linezolid); # anti-anaerobic bacteria antibiotics were metronidazole.

Correlation between AAD and treatment with enzyme inhibitor antibiotics in combination with other antibiotics

Of the 184 patients who received enzyme inhibitor antibiotic therapy, 100 patients (54.35%) were treated with combined antibiotics. The incidence of AAD was significantly increased in patients treated with enzyme inhibitor antibiotics combined with oxazolidinones compared with patients treated with enzyme inhibitor antibiotics alone (P=0.001). The incidence of AAD was significantly increased in patients treated with enzyme inhibitor antibiotics combined antifungal agents (P<0.001), with enzyme inhibitor antibiotics combined with carbapenems (P=0.015), and with enzyme inhibitor antibiotics combined with quinolones (P<0.001), compared with patients treated with enzyme inhibitor antibiotics alone (Table 3).

Factors related to AAD in critically ill patients receiving enzyme inhibitor antibiotics

Univariate regression analysis of the risk factors associated with AAD showed that age, use proton pump inhibitors (PPIs), parenteral nutrition, preventive use of probiotics, hypertension, duration of use of enzyme inhibitor antibiotics, antifungal agents, the use of carbapenem, quinolone, and oxazolidinone antibiotics were associated with AAD in critically ill patients receiving enzyme inhibitors antibiotic therapy (Table 4).

Multivariate regression analysis showed that the duration of enzyme inhibitor antibiotic therapy (OR, 1.142; 95% CI, 1.038–1.256; P=0.007) and use of antifungals (OR, 2.449; 95% CI, 1.116–5.372; P=0.025), quinolones (OR, 5.219; 95% CI, 1.746–15.601; P=0.003), and oxazolidinones (OR 2.895; 95% CI, 1.183–7.083; P=0.020) were the risk factors for AAD in critically ill patients receiving enzyme inhibitor antibiotic therapy (Table 4).

Prognostic evaluation

Of the 184 patients who received enzyme inhibitor antibiotic therapy, 20 patients died from their primary disease during the study period, including seven patients in the AAD group and 13 patients in the non-AAD group. The duration of patient stay in the ICU was significantly increased in patients with AAD, compared with patients without AAD (19.00±11.49 days *vs.* 9.60±6.76 days) (P<0.001). The duration of antibiotic treatment (14.09±8.82 days *vs.* 8.10±4.91 days) (P<0.001), and duration of enzyme inhibitor antibiotics therapy (9.26±5.06 days *vs.* 6.61±3.24 days) (P<0.001) were significantly increased in patients with AAD, compared with patients without AAD. There was no significant difference in mortality during the stay in ICU between the two groups (P=0.813), and AAD did not directly cause any deaths in either group (Table 5).

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Table 4. Factors related to antibiotic-associated diarrhea (AAD) in critically ill patients receiving enzyme inhibitors.

Related factors	Univariate regression analysis		Multivariate regression analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age	1.022 (1.007–1.038)	0.005	1.018 (0.999–1.037)	0.068
Gender	1.587 (0.848–2.970)	0.149		
Use of proton pump inhibitors	2.917 (1.188–7.159)	0.019	1.922 (0.612–6.035)	0.263
Fasting time exceeding 72 h	1.097 (0.605–1.989)	0.761		
Parenteral nutrition	1.951 (1.048–3.632)	0.035	1.362 (0.606–3.058)	0.454
Preventive use of probiotics	0.489 (0.263–0.909)	0.024	0.892 (0.408–1.952)	0.775
Albumin levels	1.005 (0.964–1.049)	0.801		
Hypertension	2.279 (1.199–4.332)	0.012	1.979 (0.875–4.474)	0.101
Diabetes	1.759 (0.742–4.167)	0.200		
APACHE II score at admission into the ICU	1.027 (0.982–1.073)	0.250		
Use of hormones	1.187 (0.654–2.156)	0.572		
Duration of enzyme inhibitor antibiotic*	1.172 (1.081–1.270)	<0.001	1.142 (1.038-1.256)	0.007
Antifungals	3.785 (2.017–7.104)	<0.001	2.449 (1.116–5.372)	0.025
Cephalosporins	1.772 (0.769–4.082)	0.179		
Carbapenems	2.323 (1.183–4.562)	0.014	1.454 (0.601–3.518)	0.406
Quinolones	5.291 (2.080–13.462)	<0.001	5.219 (1.746–15.601)	0.003
Glycopeptides**	1.585 (0.658–3.816)	0.304		
Oxazolidinones#	3.403 (1.656–6.990)	0.001	2.895 (1.183–7.083)	0.020
Anti-anaerobic bacteria Antibiotics##	0.593 (0.266–1.325)	0.203		
Azithromycins	2.385 (0.642–8.867)	0.194		

* Enzyme inhibitors were piperacillin-tazobactam and cefoperazone-sulbactam; ** glycopeptides were Vancomycin and teicoplanin; # oxazolidinones was Linezolid; ## anti-anaerobic bacteria antibiotics was metronidazole. AAD – antibiotic-associate diarrhea; ICU – intensive care unit; APACHE – Acute Physiology and Chronic Health Evaluation; OR – odds ratio; CI – confidence interval.

Table 5. The prognosis of patients with and without antibiotic-associated diarrhea (AAD).

Variables	AAD	No AAD	P-value
No. of patients	70	114	
ICU stay, days	19.00±11.49	9.60±6.76	<0.001
Duration of antibiotic, days	14.09±8.82	8.10±4.91	<0.001
Duration of enzyme inhibitor antibiotic, days	9.26±5.06	6.61±3.24	<0.001
ICU mortality (%)	7 (10.0%)	13 (11.4%)	0.813

AAD – antibiotic-associate diarrhea; ICU – intensive care unit.

Discussion

The microflora in the human gastrointestinal tract is not usually associated with disease or abnormalities of function. However, certain antibiotics may disrupt the balance of the normal intestinal microbiota. As a result, antibiotic-sensitive bacteria are eliminated or reduced in number, while drug-resistant bacteria can multiply. For example, *Clostridium difficile* may become the dominant gut bacteria, producing toxins A and B, and cause enteritis and antibiotic-associated diarrhea (AAD) [3,12–14].

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Because of the recent increased use of antibiotics, AAD has become increasingly common [15,16]. The main clinical manifestations of AAD are diarrhea, mainly presenting with watery stool, sometimes with pus, mucus, or blood, fever, and increased white blood cell count, abdominal distension, abdominal pain, and sometimes more serious associations, including multiple organ dysfunction, and toxic mega colon. A characteristic feature of AAD is the appearance of a large amount of intestinal mucus (pseudomembranous colitis). Among patients with AAD, more than 20% experience initial treatment failure and 40–60% experience a relapse of their symptoms [7,17].

Recent studies have shown that almost all antibiotics can cause AAD [18,19], particularly broad-spectrum antibiotics [20], such as lincomycin, azithromycin, cephalosporin, and penicillin [3,5,21,22]. Also, combined antibiotic treatment is most likely to cause AAD [1]. We previously reported that the incidence of AAD was significantly increased when an enzyme inhibitor antibiotic was used in combination with other antibiotics when compared with enzyme inhibitor antibiotic monotherapy [1]. Subgroup analysis of the type of enzyme inhibitor antibiotics showed that the incidence of AAD was significantly increased in patients treated with enzyme inhibitor antibiotics, regardless of whether it was piperacillin-tazobactam or cefoperazone-sulbactam [1]. The findings of this previously reported study support those of the present study that the incidence of AAD was increased in patients treated with combined antibiotics, with no significant difference in the incidence of AAD between different enzyme inhibitor antibiotics [1].

The findings of the present study showed that the incidence of AAD was significantly increased with the use of enzyme inhibitor antibiotics used in combination with antifungal agents, oxazolidinones, carbapenems, and quinolones. Also, the duration of use of enzyme inhibitor antibiotic therapy and use of antifungals, quinolones, and oxazolidinones and the association with AAD in critically ill patients has not been previously reported [1,10]. The reasons for the increased incidence of AAD in patients treated with enzyme inhibitor antibiotics in combined with antifungal agents may be due to the fact that these patients had more severe disease, reduced immunity, and longer antibiotic use, thus making them vulnerable to developing AAD, and also, the number of patients treated with combined enzyme inhibitor antibiotics and antifungal agents were high in this study population. Further studies with a larger sample size are needed to confirm these findings. However, it is useful to know that for critically ill patients in the intensive care unit (ICU), the use of enzyme inhibitor antibiotics combined with antifungal therapy may increase the risk of AAD.

Treatment with quinolone antibiotics is recognized to be associated with a high risk of the development of drug-resistant bacteria [23]. In particular, combining quinolones with enzyme inhibitor antibiotics has been reported to increase the risk of imbalance in the intestinal flora and increase the risk of AAD, especially in critically ill patients [23]. Studies have also shown that patients treated with cephalosporins are susceptible to AAD [5,22]. However, these previously reported findings were not confirmed in the present study, which may have been due to the relatively small study population. Also, relatively high grades of broad-spectrum antibiotics are selected more often for the patients in the ICU due to their critical condition, while cephalosporins are rarely used in the ICU setting as they are associated with the development of antimicrobial resistant strains of bacteria [24,25].

The findings of the present study showed that the duration of enzyme inhibitor antibiotic therapy was associated with AAD in critically ill patients. Long-term enzyme inhibitor antibiotic therapy may also be related to changes in intestinal flora, resulting in an increased incidence of AAD. In this study, AAD occurred after an average of 6.97±3.64 days following treatment initiation, particularly in patients who were treated with combined antibiotics; the earliest time that AAD developed was after approximately 24 hours from the start of treatment. Despite the development of AAD, these antibiotics cannot be discontinued as they are crucial in the treatment of the patients in the ICU. When patients in ICU with AAD and without AAD were compared, there was a significant difference between the two groups in the duration of antibiotic treatment (14.09±8.82 *vs.* 8.10±4.91 days) ($P<0.001$) and the duration of treatment with enzyme inhibitor antibiotics (9.26±5.06 *vs.* 6.61±3.24 days) ($P<0.001$). Therefore, clinicians should be made aware of the occurrence of AAD in critically ill patients who require long-term enzyme inhibitor antibiotic therapy.

Treatment with proton pump inhibitors (PPIs) and the presence of hypoproteinemia have been reported to be associated with AAD [26,27], and are significantly correlated with the recurrence of *C. difficile* colitis. In the present study, the associations between AAD and the use of PPIs and serum albumin levels were not assessed but should be investigated in future studies. Also, human albumin may have been infused in some patients prior to admission to the ICU. Prospective studies are also needed to further clarify the relationship between albumin levels and PPIs and the development of AAD.

Critically ill patients who are fasting usually have intestinal dysfunction, which when combined with the use of antibiotics may cause an imbalance in the intestinal flora, promoting the occurrence of AAD. However, this study did not show an association between fasting (loss of appetite) and AAD. Further studies on the association between the length of the fasting time, antibiotic treatment, and AAD are needed. Patients with chronic underlying diseases and multiple organ dysfunction, who are on antibiotic treatment may be more prone to AAD [7,28].

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This study showed that the incidence of AAD in critically ill patients with hypertension who were treated with enzyme inhibitor antibiotics was increased when compared with patients without hypertension. However, although univariate regression analysis showed that hypertension was associated with AAD, no correlation was found in multivariate regression analysis.

Previously published studies have shown that increased age is a risk factor for AAD [7,28,29], with older patients being more prone to AAD [2,17]. This study also found that the average age of critically ill patients with AAD was higher than that of patients without AAD. Although univariate regression analysis showed that increased age was associated with AAD, multivariate regression analysis did not show any correlation.

There have been previous studies that have shown that admission to hospital for more than two weeks is correlated with the occurrence of AAD [9,10]. In this study, when compared with patients with combined antibiotic treatment, the duration of stay in the ICU was found to be significantly lower in the monotherapy group (19.00±11.49 days *vs.* 9.60±6.76 days) ($P<0.001$), indicating that the occurrence of AAD could prolong the duration of ICU stay for critically ill patients. However, there was no significant difference in mortality between the two groups, which is consistent with our previous study on risk factors associated with AAD in critically ill patients [1], but inconsistent with the findings of some other studies.

The study findings by our group may be influenced by cultural factors as, for example, in rural areas around Shaanxi, in China, many families request discharge home for critically ill patients when they are still alive. These patients are classified as cases of 'automatic discharge' in the health statistics data, and would not be identifiable from the hospital records as cases of survival or death, which might explain the differences in mortality associated with AAD reported in the literature [1].

Conclusions

The use of enzyme inhibitor antibiotics is associated with the occurrence of antibiotic-associated diarrhea (AAD) in critically ill patients, particularly for those patients who require long-term antibiotic therapy. Their combined use with antifungal agents, quinolones, and oxazolidinones increases the incidence of AAD in critically ill patients receiving enzyme inhibitor antibiotic therapy. Therefore, to prevent the occurrence of AAD in critically ill patients, antibiotics should be administered conservatively according to their established indications. Combined antibiotic therapy and long-term antibiotic therapy should be avoided if possible. It is hoped that the findings from this study will provide a valuable basis for future prospective, large-scale, controlled, multinational studies to provide an evidence base for the rational use of antibiotics in critically ill patients and to reduce the occurrence of AAD.

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