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ORIGINAL ARTICLE

Investigation of antibiotic use in patients with acute pancreatitis in a Vietnamese hospital

Vo Duy Thong,*,† Trinh Thi Hong Anh,‡ Bui Thi Huong Quynh‡,§ and Ngo Thi Thanh Quyt§

*Department of Internal Medicine, Faculty of Medicine, University of Medicine and Pharmacy at Ho Chi Minh city, †Department of Gastroenterology, Cho Ray Hospital, ‡Department of Clinical Pharmacy, Faculty of Pharmacy, University of Medicine and Pharmacy at Ho Chi Minh city and §Thong Nhat Hospital, Ho Chi Minh City, Vietnam

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Correspondence
Vo Duy Thong, Department of Internal Medicine, Faculty of Medicine, University of Medicine and Pharmacy at Ho Chi Minh city, 217 Hong Bang, Ward 11, Dis. 5, Ho Chi Minh City, Vietnam.
Email: duythong@ump.edu.vn

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Abstract

Background and Aim: The aim of this study was to investigate the antibiotics used in patients with acute pancreatitis and evaluate their appropriateness.
Methods: We conducted a descriptive cross-sectional study on 136 patients aged 18 years or older who were diagnosed with acute pancreatitis and admitted to a national hospital in Ho Chi Minh City from January 2017 to December 2018. Medical records of patients were reviewed for data analysis, including epidemiological characteristics, pathological characteristics, treatment methods, and treatment effectiveness.
Results: There were 69.9% men and 30.1% women with a median age of 49.9 years. The most common etiologies included alcohol (21.3%), gallstones (23.6%), and hypertriglyceridemia (19.9%). The proportions of mild, moderate, and severe disease were 54.4, 39.0, and 6.6%, respectively. Antibiotics were given in 52.2% of patients. Although antibiotic prophylaxis was not recommended, 23.5% of cases used prophylactic antibiotics when there were no suspicion or evidence of infection.
Conclusions: Our study suggests that it is necessary to optimize the appropriateness of antibiotic indications for patients with acute pancreatitis.

Introduction

Acute pancreatitis (AP) is one of the most common diseases of the gastrointestinal tract, leading to tremendous emotional, physical, and financial burdens.[1] In the United States alone, more than 220 000 patients are hospitalized for AP annually.[2] About 20% of AP is severe, with a high mortality rate of around 20%. For several decades, the administration of prophylactic antibiotics for the management of severe AP has been controversial.[3] Prophylactic antibiotics are not recommended in patients without evidence or suspicion of infection regardless of severity. When compared to patients with sterile necrosis, a higher mortality rate is observed for patients with infected pancreatic necrosis.[1] However, the use of prophylactic antibiotics is not recommended in sterile necrosis because there is no effect or improvement in the clinical outcome. Moreover, it can lead to antibiotic resistance and an increased risk of *Clostridium difficile* infection.[4]

Recent studies have found that the proportion of antibiotic inappropriateness was varied, ranging from 15.3 to 51.4%.[5-7] However, in Vietnam, there is a lack of available studies investigating the appropriateness of antibiotics used in AP. Therefore, the aims of this study were to determine the rate of antibiotic compliance with respect to the current guidelines.

Methods

Study design and setting. This descriptive cross-sectional study involved all adult patients who were admitted to Thong Nhat Hospital in Ho Chi Minh City in Vietnam for the treatment of AP from January 2017 to December 2018.

Study population. All adult patients aged 18 years or older who were diagnosed with AP were included in this study if they met two of the three diagnostic criteria for AP: abdominal pain, serum amylase or lipase activity three times higher than the upper limit of normal, and pancreatitis documented by computed tomography (CT). Patients with exacerbation of chronic pancreatitis were excluded.

Antibiotic use. Antibiotic use was considered appropriate when patients had signs or suspicions of infection based on one of the following standards[1]: positive bacterial culture test[2]; gas in

pancreatic/peripancreatic collections on CT[3]; extrapancreatic infection complication (pneumonia, cholangitis, bacteremia, urinary tract infections) or systemic inflammatory response syndrome (SIRS); and[4] pancreatic necrosis and organ failure that do not improve after 5–7 days, high fever, or white blood cells (WBC) > 20 K/μL. These standards were based on the guidelines of the American College of Gastroenterology Guideline (ACG) 2013,[1] Vietnam Ministry of Health guideline,[8] and Thong Nhat Hospital guideline for the treatment of AP.[9]

Statistical analysis. Descriptive statistics were used to summarize the patients' characteristics. Continuous data were presented as mean and SD, while categorical data were presented as frequencies and percentages. The Chi-square test or Fisher's exact test was used to compare categorical variables between the antibiotic and nonantibiotic groups, including elevated C-reactive protein (CRP) at admission, fever, amylase >3 ULN, and between the antibiotic adherence and nonadherence groups, including gender, faculty treatment, and severity of disease. A standard *t*-test or the Mann–Whitney *U* test was used to compare continuous variables, including WBC at admission and age. Multivariate logistic regression was used to determine the relationship between white blood count reduction efficiency and influent factors (antibiotic use and severity of disease). All statistical analyses were performed using SPSS software 20.0. *P*-value <0.05 was considered statistically significant.

Ethics. The protocol of this study was approved by the Institutional Review Board of Thong Nhat Hospital, Ho Chi Minh City, Vietnam.

Results

There were 95 (69.9%) men and 41 (30.1%) women, and the median age was 49.9 ± 17.2 years. The proportion of patients aged older than 60 years was 25.7%. Alcohol (29, 21.3%), gallstones (28, 20.6%), and hypertriglyceridemia (27, 19.9%) were the most common etiologies. The proportions of mild, moderate, and severe disease were 54.4, 39.0, and 6.6%, respectively (*Table* 1).

Overall, 71 (52.2%) patients received antibiotics. Assessed by episode severity, 23 (31.1%) patients with mild AP received antibiotics in the absence of infection. In contrast, nine (100%) patients with severe AP received antibiotics. There were two patients with severe AP who had complications after hospitalization. The mean duration of admission of severe AP patients was 18 days, which was longer than that of mild AP (7 days) and moderate AP (9 days) (*Table* 2).

Overall, 71 patients received antibiotics. There was a broad range of antibiotics used, but two of the most common were ceftriaxone (25.4%) and cefoxitin (11.3%). The combination of two antibiotics and three antibiotic regimens was indicated in 25 (35.2%) and 5 (7.0%) patients, respectively. This result was different from the study of Párniczky *et al.*[4] (42.5% of patients received cephalosporin in combination with metronidazole, and 5.5% of patients received imipenem) and the study of Fabisiak *et al.*[10] (86.8% of patients used cephalosporin in combination with metronidazole, and 27.8% of patients used carbapenem). The cephalosporins used in the study included cefoxitin, ceftriaxone, cefoperazone, and cefpirome. Cefoxitin (11.3%) is a second-generation cephalosporin with poor pancreatic penetration and could not achieve adequate pancreatic tissue concentrations.[11] In addition, five patients were prescribed carbapenem (imipenem/cilastatin, meropenem) combined with metronidazole, and three patients were prescribed imipenem/cilastatin combined with quinolone (ciprofloxacin, levofloxacin) or amikacin. Metronidazole were not necessary because it acts exclusively against anaerobes and is recommended only in combination with nonanaerobic antibiotics. Moreover, one patient received ampicillin/sulbactam, and four patients received amikacin in combination with other antibiotics, although this is not recommended by the current guidelines because these antibiotics are unable to penetrate the human pancreatic tissue sufficiently to achieve bactericidal concentration.[11,12] The inconsistency of a specific recommendation for the kinds of antibiotics and the combination of antibiotics made it difficult for the researchers to evaluate. Therefore, in this study, no rationality was evaluated regarding the kind of antibiotics or combination of antibiotics (*Table* 3).

Table 1 Patient's characteristics (*n* = 136)

Characteristics	*n* (%)
Age (median ± SD)	49.9 ± 17.2
>60 years	35 (25.7)
≤60 years	101 (74.3)
Gender	
Male	95 (69.9)
Female	41 (30.1)
Etiology	
Alcohol	29 (21.3)
Gallstone	28 (20.6)
Hypertriglyceridemia	27 (19.9)
Others	13 (9.5)
Not recorded	39 (28.7)
Pancreatitis severity	
Mild	74 (54.4)
Moderate	53 (39.0)
Severe	9 (6.6)

Values are presented as mean ± SD or *n* (%).

Table 2 Antibiotics are used in patients with acute pancreatitis (*n* = 136)

	Mild (*n* = 74)	Moderate (*n* = 53)	Severe (*n* = 9)
Antibiotics use, *n* (%)	23 (31.1)	39 (73.6)	9 (100)
Bacterial culture test			
Negative, *n* (%)	0	3 (4.2)	0
Positive, *n* (%)	0	0	2 (2.8)
Treatment outcome			
Success, *n* (%)	74 (100)	53 (100)	7 (77.8)
Duration of admission (days)	7 (5–8)	9 (7–11)	18 (11–26)

Table 3 Antibiotic regimens (n = 71)

Antibiotic 1	Antibiotic 2	Antibiotic 3	n (%)
One-antibiotic regimens			41 (57.8)
Cefoxitin	—	—	8 (11.3)
Ceftriaxone	—	—	18 (25.4)
Cefoperazone	—	—	2 (2.8)
Imipenem/cilastatin	—	—	6 (8.5)
Ertapenem	—	—	1 (1.4)
Ampicillin/sulbactam	—	—	1 (1.4)
Piperacillin/tazobactam	—	—	1 (1.4)
Levofloxacin	—	—	1 (1.4)
Ciprofloxacin	—	—	1 (1.4)
Moxifloxacin	—	—	1 (1.4)
Metronidazole	—	—	1 (1.4)
Two-antibiotic regimens			25 (35.2)
Cefoxitin	Levofloxacin	—	1 (1.4)
Cefoxitin	Amikacin	—	1 (1.4)
Cefoxitin	Metronidazole	—	1 (1.4)
Ceftriaxone	Metronidazole	—	6 (8.5)
Cefoperazone	Metronidazole	—	1 (1.4)
Cefpirome	Levofloxacin	—	2 (2.8)
Imipenem/cilastatin	Levofloxacin	—	2 (2.8)
Imipenem/cilastatin	Metronidazole	—	4 (5.7)
Ertapenem	Ciprofloxacin	—	1 (1.4)
Ertapenem	Levofloxacin	—	1 (1.4)
Ertapenem	Amikacin	—	1 (1.4)
Ertapenem	Metronidazole	—	2 (2.4)
Meropenem	Metronidazole	—	1 (1.4)
Ampicillin/sulbactam	Metronidazole	—	1 (1.4)
Three-antibiotic regimens			5 (7.0)
Ceftriaxone	Ofloxacin	Metronidazole	1 (1.4)
Ceftriaxone	Amikacin	Metronidazole	1 (1.4)
Imipenem/cilastatin	Levofloxacin	Metronidazole	1 (1.4)
Imipenem/cilastatin	Ciprofloxacin	Metronidazole	1 (1.4)
Imipenem/cilastatin	Amikacin	Metronidazole	1 (1.4)

Laboratory parameters showed no association with infection in the early phase of AP, including leukocytosis or elevated CRP, amylase, or lipase levels.[4] When examining the factors that may be related to antibiotic use, this study found that rates of leukocytosis and fever at hospitalization in the antibiotic therapy group were significantly higher than the nonantibiotic group ($P < 0.001$ and $P = 0.014$, respectively) (*Table* 4). However, leukocytosis alone might not be associated with infection, and there were no specific biomarkers to guide the decision-making. The study investigated factors that may be related to decreasing the number of WBC to normal values (4.6–10.2 K/μL). There were 107 of 136 patients with leukocytosis at the time of admission. Using a multivariate logistic regression model to analyze factors involved in WBC reduction efficiency, including antibiotic use and disease severity, the study found that using antibiotics or not was not related to this efficiency (*Table* 5).

There were 32 (23.5%) patients who indicated antibiotic use without guideline adherence (there was no suspicion or proof of infection). Examining the factors related to antibiotic

Table 4 Factors related to antibiotic indications (n = 136)

Variables	Antibiotics use		P-value
	No (n = 65)	Yes (n = 71)	
Age (years)	48.1 ± 15.7	51.6 ± 18.5	0.229
WBC at admission (K/μL)	10.8 ± 3.4	15.5 ± 5.4	**<0.001**
Elevated CRP at admission (%)	10.8	21.1	0.101
Fever (%)	3.1	15.5	**0.014**
Amylase > 3 ULN (%)	35.4	38.0	0.749

CRP, C-reactive protein; ULN upper limit of normal; WBC, white blood cells.

Table 5 Factors related to white blood cells reduction efficiency (n = 107)

Factors	OR	CI 95%	P-value
Antibiotics use	0.492	0.203–1.195	0.117
Severity			
Mild	1		
Moderate	2.265	0.945–5.426	0.067
Severe	0.750	0.125–4.496	0.812

CI, confidence interval; OR, odds ratio.

Table 6 Factors related to compliance with antibiotic indications

Factors	Adherence (n = 104)	Nonadherence (n = 32)	P-value
Age (year)	50.5 ± 17.4	48.1 ± 16.8	0.501
Gender, n (%)			
Male	69 (72.6)	26 (27.4)	0.108
Female	35 (85.4)	6 (14.6)	
Faculty treatment, n (%)			
ICU	7 (100)	0	0.269
Pancreatic hepatobiliary surgery	28 (71.8)	11 (28.2)	
Gastroenterology	69 (76.7)	21 (23.3)	
Severity, n (%)			
Mild	51 (68.9)	23 (31.1)	**0.038**
Moderate	44 (83.0)	9 (17.0)	
Severe	9 (100)	0	

Values are presented as mean ± SD or n (%).
ICU, intensive care unit.

compliance, this study found that the proportion of appropriate antibiotic treatment was significantly different based on episode severity (P = 0.038) (*Table* 6) in that patients with mild pancreatitis had lower compliance rates than those with moderate and severe pancreatitis (68.9 *vs* 83.0% and 100%, respectively).

Discussion

The ACG and Vietnam guidelines all advocate that the routine use of prophylactic antibiotics in patients with AP is not recommended. In our study, the practice of antibiotic therapy was widespread. In the group receiving antibiotics, the median number of WBCs was higher than the group without antibiotics, which showed that leukocytosis might be linked with antibiotic indication in patients. However, in AP, elevated WBCs may not be associated with bacterial infection and may decrease in the first few days for mild AP.[13] Moreover, when analyzing factors involved in WBC reduction efficiency, the study found that using antibiotics or not was not related to this efficiency. It could be seen that elevated WBCs alone might not be associated with infection, and this was also not a specific biological marker for infection in AP.[4] In addition, the majority of patients hospitalized with fever were prescribed antibiotics, but transient fever at admission was not a specific sign of infection in AP. Patients with suspected infection because of fever did not benefit from antibiotic therapy.[4] Regarding the study of Sun *et al.*,[14] antibiotic indications were also based on fever (54.2%) and elevated WBCs (15.0%). Other factors, moreover, included prophylaxis against infection (17.5%), extensive peripancreatitis edema (7.2%), persistent elevation of amylase/lipase (1.7%), and persistent pain (1.4%).

While there is no role for antibiotics in the management of AP, the role of antibiotics in treating severe AP is a far more controversial. Early clinical trials seemed to demonstrate a benefit of prophylactic antibiotics to prevent infection in severe AP. Subsequently, better-designed trials have consistently failed to confirm an advantage with regard to the prevention of infected necrosis, the need for surgery, and mortality.[15-17] As such, current ACG guidelines recommend against the usage of prophylactic antibiotics in patients with severe AP.[1] However, Vietnam guideline advocates for the use of antibiotics in patients with pancreatic necrosis or organ failure with suspicions like high fever and elevated WBCs. In this study, antibiotic nonadherence was observed in 32 (23.5%) patients based on ACG and two guidelines in Vietnam. This result was lower than the result of the study by Tan *et al.*[6] (38.7% patients were administered antibiotics with no suspicion or proven infection) or that of Párniczky *et al.*[5] (51.4% patients were administered prophylactic antibiotics) but higher than 15.3% reported by Nesvaderani *et al.*[7] The main reason was the difference in sample sizes and evaluation criteria among these studies. Specifically, Tan *et al.* evaluated antibiotic compliance based on the IAP/APA guideline and Japanese guideline, including two main criteria of cholangitis and infected pancreatic necrosis.[6] In the Párniczky *et al.* study, the evaluation criteria were not specified.[5] In the study of Nesvaderani *et al.*, patients were classified as having infected pancreatic necrosis if there was evidence of gas in peripancreatic or pancreatic tissue or if there were positive microbiology results from pancreatic tissue culture.[7]

The proportion of antibiotic adherence was significantly different based on episode severity. Mild AP had the lowest percentage of appropriateness, which was 68.9%, compared to 83.0% in moderate patients and 100% in severe patients. This was because infectious complication in patients with mild AP was very low, so there was no requirement to use prophylactic antibiotics. The case–control study of Mandal *et al.*[18] showed that the use of prophylactic antibiotics in mild and moderate AP did not improve treatment efficacy. In addition, the misuse of antibiotics had been associated with fungal infection, *C. difficile* infection, and increased costs.[4] This result was similar to that of the study by Baltatzis *et al.*,[19] where the high rates of patients with mild AP who received antibiotics in the absence of any recorded infection showed that this use was not in compliance with the current guidelines.

In summary, our study observed and investigated antibiotic use in AP, a very common issue in clinical management. According to this study, there was evidence of overuse of antibiotics in patients with mild AP. It is necessary to optimize the appropriateness of these drugs indications for patients with AP.

Limitations. Our study had some limitations. First, the kind of antibiotics or their combination in the treatment of AP has not

been evaluated. Second, data were collected from medical records, so subclinical results and clinical responses might not be fully documented, which could reduce reliability. Therefore, a longer prospective study may be necessary to overcome this issue.

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