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RISK FACTORS OF MULTIDRUG RESISTANT PATHOGENS INDUCED INFECTION IN SEVERE ACUTE PANCREATITIS

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ABSTRACT—**Purpose:** A retrospective study was first performed to assess the multidrug resistant (MDR) pathogen in severe acute pancreatitis (SAP) patients who were treated using the step-up approach. We aim to assess the risk factors between MDR pathogen and potential covariates in SAP patients. **Methods:** The clinical data of 51 SAP patients who were treated from June, 2013 to December, 2016 were retrospectively collected. A total of 23 patients in the MDR group and 28 patients in the non-MDR group were reviewed. The risk factors for MDR pathogen-induced infections in SAP patients were analyzed. **Results:** Hyperlipidemia was the leading cause of SAP in our study. The mean duration of hospital stay was significantly longer in the patients with MDR pathogen infections (P=0.0135). The hospitalization expenses of MDR group were much higher than those in non-MDR group. The mortality of MDR group (56.5%) was higher than that in non-MDR group (28.6%) (P=0.0436). Gram-negative isolates (63.8%) were commonly detected in SAP patients. *Acinetobacter baumannii* was the most common MDR pathogens. Systemic disease (P = 0.0136), initial use of carbapenem (P = 0.0438), and open necrosectomy (P = 0.0002) were the potential risk factors for MDR pathogen-induced infections in SAP. Furthermore, the logistic regression analysis revealed that open necrosectomy was the independent variable for MDR infections (OR: 15.6, 95% CI: 2.951–82.469, P = 0.0012). **Conclusions:** MDR pathogen-induced infections were common in SAP patients and *Acinetobacter baumannii* was the main pathogen. Meanwhile, open necrosectomy was the independent risk factor for the infection of MDR pathogen.

KEYWORDS—*Acinetobacter baumannii*, multidrug resistant, open necrosectomy, pathogen, severe acute pancreatitis

ABBREVIATIONS—*A baumannii*—*Acinetobacter baumannii*; MDR —multidrug resistant; PCD —percutaneous catheter drainage; SAP —severe acute pancreatitis

INTRODUCTION

Acute pancreatitis is a commonly encountered emergency disease that requires immediate hospital admission. In most cases, acute pancreatitis represents a mild, self-limited disease. However, in 15% to 25% severe acute pancreatitis (SAP) develops, manifests with pancreatic parenchymal and/or peripancreatic tissue necrosis (1). Despite the great progress in the current therapies, the mortality rate is up to 30% to 70% (2). The clinical course of SAP is divided into two phases, an early inflammatory phase (lasts 2 weeks from the onset) and a late phase (after the first 2 weeks). Nevertheless, septic complications are the main cause of death in the late phase (3).

Adequate antibiotic therapy is critical to improve the clinical outcomes of patients with life-threatening infections. However, the continuous and misuse of antibiotics has developed a strong selective pressure on microorganisms, favoring the emergence of resistant strains (4). Recently, several studies have revealed that the incidence of infections caused by multidrug resistant (MDR) pathogen was increasing and the mortality associated with MDR was high in SAP (5). In addition, MDR pathogen infection plays a vital role in prolonged hospital and intensive care unit (ICU) stay (6). MDR pathogen infection is normal and difficult to treat in the SAP. The most common last resort antibiotics in the treatment of MDR pathogen infection were polymyxins and tigecycline. However, polymyxins are uncommon in China and the minimum inhibitory concentration value of tigecycline against bacterial is gradually increasing, which reduced the sensitivity of tigecycline (7). Therefore, better methods for the prevention and optimal treatment of MDR infection are essential and could improve the outcomes of SAP patients.

Previous studies have demonstrated that MDR pathogen colonization or infection, ICU admission, invasive procedures, age, systemic disease, and early use of broad-spectrum antibiotics are the crucial risk factors for MDR pathogen infections in patients with liver cirrhosis, hemodialysis-associated pneumonia, etc. (8–12). Lee et al. (13) found the high incidence of MDR bacterial infections in transferred SAP patients. However, the MDR pathogen infection and their clinical effects have been rarely reported in SAP patients especially in China. A minimally invasive step-up approach or open necrosectomy are both considerable strategies for the treatment of SAP. Our previous studies indicated that open pancreatic necrosectomy increases

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surgical trauma for patients, and step-up approach significantly reduces the cost, shortens the hospital stay, and improves the prognosis in SAP. But, the effect of different treatments for MDR pathogen infection is unclear. Thus, this retrospective study is performed to assess the MDR pathogen in SAP patients who were treated with step-up approach. We aim to assess the risk factors between MDR pathogen and potential covariates in SAP patients.

PATIENTS AND METHODS

Subjects

Evaluation of bacterial and fungal infections in SAP patients who were diagnosed between June, 2013 and December, 2016 at The First Affiliated Hospital of Harbin Medical University was retrospectively performed. This study was approved by the First Affiliated Hospital Institutional Review Board. One hundred sixteen patients were included from our database, and the diagnostic criteria of SAP were based on the revised 2012 Atlanta classification (14). To identify the SAP-induced infection, all the clinical features of culture and the corresponding files were reviewed by two infectious disease pharmacists and two professional pancreatic surgeons.

Treatments and culture

In our study, all the SAP patients received oral intake, pain relief, nutritional support and restoring fluid and electrolyte losses intravenously according to the guideline (15). Intravenous antibiotics were used for all the patients for either prophylactic or therapeutic purpose. Isolation of organism was defined as a positive culture obtained from blood, fine-needle aspiration, the first drainage of the percutaneous procedure, or intraoperative fluid. Isolated organisms were tested for antimicrobial susceptibility through minimum inhibitory concentration testing using the VITEK2 compact system (bioMerieux Inc, Hazelwood, Mo) or K-B method (Thermo Fisher Oxoid) according to the recommendations of the Clinical and Laboratory Standards Institute (16).

MDR organism definition

MDR pathogen was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories. MDR includes extensive drug resistance (non-susceptibility to at least one agent in all but two or fewer antimicrobial categories) and pan drug resistance (non-susceptibility to all agents in all antimicrobial categories). Methicillin-resistant *Staphylococcus aureus,* Vancomycin-resistant *Enterococcus*, Carbapenem-resistant *Enterobacteriaceae*, MDR-*Acinetobacter baumannii,* and MDR-*Pseudomonas aeruginosa* were defined as healthcare-associated infections and prone to multidrug resistance (17,18).

Statistical analysis

The risk factors for MDR pathogen-induced infections in SAP patients were analyzed, including systemic disease (diabetes, hypertension, COPD, chronic renal insufficiency), invasive procedures (central venous catheterization, mechanical ventilation, urinary catheterization, and other invasive procedures), surgical intervention (open necrosectomy), recent antibiotic treatments (within 30 days of admission), transferred from other hospitals, admission to ICU and use of carbapenem before MDR pathogen. Numerical variables were summarized as the mean ± standard deviation (SD). Parametric and non-parametric analyses and multiple linear regression analysis were performed using the SPSS statistical package (version 20.0). Determination of the statistical differences in parameters between various groups was analyzed using either Student *t* test or Wilcoxon rank sum test. A P value of <0.05 was considered to be statistically significant.

RESULTS

Baseline characteristics

Microorganisms could not be found in 29 patients, 26 patients were excluded for death within the first 48 h from the onset of disease, six patients were excluded for giving up treatment in the first 24 h, and four patients were excluded for transferring to other hospitals. A total of 51 patients with specific infection were included, and MDR pathogens were identified in 23 patients with clinical infection (Fig. 1). The baseline demographic and clinical characteristics of the patients are shown in Table 1. No significant difference was found in age, gender, or etiology of SAP between the two groups. Hyperlipidemia was the leading cause of SAP in our study. Bacteremia was present among 11 in the MDR group and one in the non-MDR group ($P = 0.0002$). Ten patients with positive blood cultures in the MDR group were died. Neither polymicrobial infection nor concomitant fungal infection incidence has significant difference between the two groups. Sixteen patients (69.6%) received antibiotics on admission for prophylaxis in the MDR group and 19 patients (67.9%) in the non-MDR group. More patients in MDR group underwent open necrosectomy than in non-MDR group (12 patients vs. 2 patients). In both groups, the rate of receiving enteral nutrition support was significantly higher than that in parenteral

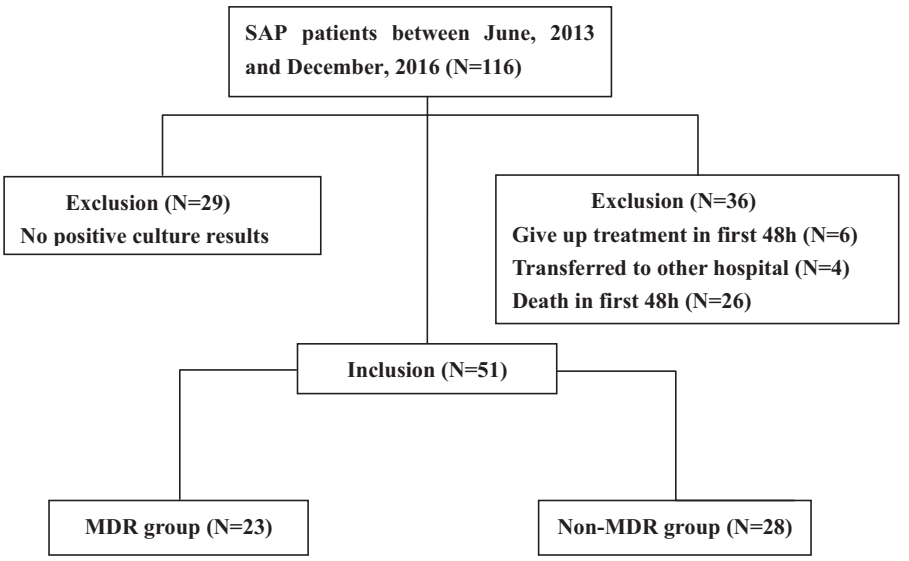

Fig. 1. **Inclusion and classification of the study patients.** SAP indicates severe acute pancreatitis; MDR, multidrug resistant.

TABLE 1. **Comparison of demographics and clinical characteristics between MDR and non-MDR groups**

Characteristics	MDR n = 23	Non-MDR n = 28	*P* value
Gender			0.279
Male	14	21	–
Female	9	7	–
Age	44.82 ± 14.51	45.68 ± 14.03	0.833
Etiology, n (%)			0.9023
Biliary	7 (30.5)	9 (32.1)	–
Hyperlipidemia	13 (56.5)	17 (60.7)	–
Alcohol-related	1 (4.3)	1 (3.6)	–
Other	2 (8.7)	1 (3.6)	–
Bacteremia	11	1	0.0002*
Mortality (%)	13	8	0.044*
Fungal infection	2	0	0.111
Polymicrobial infection	7	1	0.016*
ICU admission	16	21	0.665
Open necrosectomy	12	2	
Application of antibiotics, n (%)			0.899
Prophylaxis (on admission)	16 (69.6%)	19 (67.9%)	–
Treatment (on admission)	7 (30.4%)	9 (32.1%)	–
Nutrition support, n (%)			0.934
Enteral nutrition	19 (82.6%)	24 (85.7%)	–
Parenteral nutrition	4 (17.4%)	4 (14.3%)	–
Duration of antibiotics (days)	19 (7-29)	10 (4.5-12.5)	0.016*
Hospital stay	27.39 ± 20.54	15.12 ± 9.63	0.014*
Hospitalization costs (dollar)	22844.54 (9249.72–39555.76)	7900.62 (3409.51–13391.07)	0.039*

*$P < 0.05$.
MDR indicates multidrug resistant.

TABLE 2. **Total microorganisms and multidrug resistant microorganisms in 51 patients**

Total microorganisms	Isolates, no. (%) (n = 69)
Isolated gram-positive bacteria	22 (31.9)
Staphylococcus aureus	2 (2.9)
Enterococci species	11 (15.9)
Coagulase-negative staphylococci	5 (7.3)
Others	4 (5.8)
Isolated gram-negative bacteria	44 (63.8)
Acinetobacter baumanii	13 (18.8)
Klebsiella pneumonia	9 (13.0)
Escherichia coli	7 (10.2)
Burkholderia cepacia	5 (7.3)
Enterobacter cloacae	6 (8.7)
Pseudomonas aeruginosa	1 (1.4)
Others	3 (4.4)
Fungus	3 (4.3)
Candida albicans	2 (2.9)
Candida glabrata	1 (1.4)
MDR bacteria	N = 39
Isolated gram-positive bacteria	14 (35.9)
Staphylococcus aureus	1 (2.6)
Enterococci species	7 (17.9)
Coagulase-negative staphylococci	3 (7.7)
Others	3 (7.7)
Isolated gram-negative bacteria	25 (64.1)
Acinetobacter baumanii	9 (23.1)
Klebsiella pneumonia	5 (12.8)
Escherichia coli	4 (10.2)
Burkholderia cepacia	1 (2.6)
Enterobacter cloacae	4 (10.3)
Serratia marcescens	2 (5.1)

nutrition support group. The mean duration of hospital stay was longer in the patients with MDR pathogen infections ($P = 0.0135$). The hospitalization expenses of MDR group were much higher than that in non-MDR group (22844.54 vs. 7900.62, $P = 0.039$). The overall mortality among these patients was 41.1% (21 out of 51 patients) and the mortality of MDR group was higher than that in non-MDR group (56.5% vs. 28.6%, $P = 0.0436$) (Table 1).

MDR pathogen infection

In total, 69 bacterial (97.2%) and two fungal (2.8%) pathogens were detected in 51 patients. The microorganisms are summarized in Table 2. Our data indicated that gram-negative isolates (63.8%) were commonly identified in SAP patients. *Acinetobacter baumannii* (*A baumannii*) (18.8%) and *Enterococcus* species (15.9%) were mainly identified and followed by *Klebsiella pneumoniae* (13.0%). MDR pathogens were confirmed in 39 episodes, of which 25(64.1%) were gram-negative bacteria and 14 (35.9%) were gram-positive bacteria. The top two MDR pathogens were *A baumannii* (n = 9) and *Enterococcus* species (n = 7). Thirty-nine MDR isolates were examined in 23 patients, including four specimens from surgical drainage, one from percutaneous drainage, 18 from blood specimens, and 16 specimens from pus.

Risk factor analysis of MDR pathogen infection

The relationship between MDR pathogens and potential risk factors was screened by correlation analysis, and the results are presented in Table 3. Our data suggested that there was no difference in invasive procedures, recently received antibiotics treatments, transferred from other institution, and ICU admission between the two groups ($P<0.05$), and systemic disease

TABLE 3. **Correlation analysis between MDR pathogen infection and potential risk factors.**

Risk factors	*C*	*P* value
Systemic disease	0.3295	0.014*
Invasive procedures	0.2303	0.104
Open necrosectomy	0.5241	0.0002*
Recently received antibiotics treatments	0.0035	0.981
Transferred	0.0898	0.525
ICU admission	0.0817	0.564
Initial use of carbapenem	0.2835	0.044*

*$P < 0.05$.
MDR indicates multidrug resistant.

($P = 0.0136$), initial use of carbapenem ($P = 0.0438$), and open necrosectomy ($P = 0.0002$) were the risk factors for MDR pathogen infection in SAP. To further explore the independent risk factor of MDR pathogen infection, the logistic analysis was performed. The multivariable analysis revealed that surgical intervention was the independent risk factor for MDR in SAP patients (OR: 15.6, 95%, 95% CI: 2.951–82.469, $P = 0.0012$) (Table 4).

DISCUSSION

Previous studies showed that cholelithiasis was the most common etiological factors for MDR resistance in China (19,20). In our study, hyperlipidemia (n = 30, 58.9%) was the primary etiology, which was different from the studies performed in other regions and countries (21,22). The cold climate and unhealthy lifestyle such as high-fat diet and deficiency of movement result in higher incidence of hyperlipidemia pancreatitis in the northeast of China. Despite that, several studies have documented a shift from gram-negative to gram-positive isolates, and we found that the gram-negative pathogens were the dominating bacteria in SAP (23–25). Our data was consistent with the previous studies. The cultured *Enterococci* species were generally sensitive to vancomycin (only one isolate showed vancomycin resistant) compared with other studies (26–28). *A baumannii* was the main MDR pathogen in our study, and there are several explanations for its higher incidence. Prior antibiotic use was the most important risk factor for the acquisition of MDR *A baumannii* (29). Carbapenems, third-generation cephalosporins, and/or fluoroquinolones are the independent risk factors for the acquisition of MDR *A baumannii* (30,31). In this study, we observed that the above-mentioned antibiotics were used either for prophylactic or therapeutic purpose in all patients. Third-generation cephalosporins and/or fluoroquinolones were intravenously used for either prophylactic or therapeutic purpose, although antibiotic prophylaxis is not recommended for the prevention of infective complications in AP (32,33). Carbapenem was considered a first-line treatment for patients who were suspected with infected pancreatic necrosis, and the clinical symptoms were obvious. In addition, conventional treatments of SAP, including mechanical ventilation and nasogastric tube use, may result in *A baumannii* infection (34). Besides, 16 out of 23 patients were admitted to ICU, which may improve the high rate of MDR *A baumannii.* MDR pathogens may be caused by unrestricted antibiotic use (35–37). Adequate antibiotic therapy including optimal dosage has a significant impact on clinical outcome in patients with life-threatening infections such as those occurring in SAP patients. Inappropriate antibiotics dose and duration lead to MDR pathogens. SAP can also affect the pharmacokinetics of antibiotics. He et al. (38) found that plasma trough concentration of vancomycin was significantly reduced in SAP patients. The most probable cause was that SAP-related SIRS affected the distribution and excretion of vancomycin. Higher dosage regimens (exceed instruction recommended dosage) are needed to enhance the clinical effect and avoid MDR pathogen. Thus, surgeons should use antibiotics appropriately at the next stage to avoid overprescription.

Our data suggested a strong correlation between MDR pathogen and systemic disease, initial use of carbapenem and open necrosectomy. Further data showed that open necrosectomy was the independent risk factor for producing MDR. van Santvoort et al. (39,40) found that the step-up approach for SAP was superior to open necrosectomy because of its relatively lower incidence of postoperative complications and long-term pancreatic function deficiency. In our study, the step-up approach (percutaneous catheter drainage (PCD) would be performed initially) was first carried out, and open necrosectomy was then selectively performed for patients who cannot be treated via PCD 4 weeks after the onset of pancreatitis (41). However, the over enthusiasm for PCD might yield the SAP patient a longer use of broad-spectrum antibiotics, which may delay the open necrosectomy time, damage the microbial ecology, and produce MDR pathogen. In addition, open necrosectomy brought more therapeutic interventions, such as peritoneal cavity drainage tube and usage of suctioning equipment. These may increase the incidence of MDR pathogen. Our data suggested that the hospital stay was longer, and hospitalization expenses and mortality were much higher in patients who had MDR pathogen infections. Thus, preventing the production of MDR and improving SAP patient outcome are the issues for further study. The multidisciplinary team (MDT) has shown to ameliorate the outcomes of various diseases (42,43). MDT management may probably provide practical recommendations and prevent MDR pathogen production in SAP patients.

There were some limitations in our study. First, this study was a retrospective analysis, and the samples size was limited

TABLE 4. **Multivariate analyses of explanatory variables for MDR pathogen infection.**

Characteristic	β	*SE*	*Wald*χ2	*P*	OR	95% CI
Open necrosectomy	2.747	0.850	10.457	0.001*	15.600	2.951–82.469

*$P < 0.05$.
MDR indicates multidrug resistant.

(116 patients met the criteria for SAP while only 51 patients were included). Second, the results were derived from a single-center experience in the northeast of China which could not be generalized to other hospitals. Third, the empirical treatment for SAP patients was different and hence yielded different results, including therapeutic strategies (PCD or PCD plus open necrosectomy), nutrition support method (i.e., enteral nutrition and parenteral nutrition), and the use of equipment (i.e., naso-enteric tube placement). Moreover, several studies have demonstrated that selective decontamination may decrease the complications and reduce the mortality in SAP (44,45). In our study, selective decontamination, which could influence the ratio of MDR organisms and the mortality of SAP patients, was avoided.

CONCLUSION

In summary, MDR pathogen infections were common in SAP patients and gram-negative bacteria were the major pathogen. Systemic disease, initial use of carbapenem, and surgical intervention were the risk factors for MDR pathogen infections in SAP. Furthermore, surgical intervention was the independent risk factor for the infection of MDR pathogen. Clinicians should be aware of the high incidence of MDR pathogen infections, and accurate use of antibiotics could prevent MDR pathogen infections.

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