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Clinical and Microbiological Characteristics of Patients with Complicated Intra-abdominal Infections in Intensive Care Unit*

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Summary: In order to investigate the clinical and microbiological characteristics of patients with complicated intra-abdominal infections (cIAIs) in intensive care unit (ICU), the clinical data of 612 cIAIs patients from January 2016 to December 2018 were retrospectively collected. Clinical characteristics, distribution of pathogens and drug resistance were statistically analyzed. It was found that patients with community-acquired intra-abdominal infections (CA-IAIs) made up a majority of cIAIs patients. The positive rate of abdominal drainage fluid culture was 55.56%. Gram-negative bacteria accounted for the majority, the most commonly isolated bacteria of which were *Escherichia coli* (20.96%), *Klebsiella pneumoniae* (10.20%) and *Pseudomonas aeruginosa* (5.57%). The most commonly isolated gram-positive bacteria were *Enterococcus* (16.88%) and Methicillin-resistant *staphylococcus aureus* (MRSA, 3.90%). Enterobacter isolates showed high resistance rate to most cephalosporins and low resistance rate to piperacillin/tazobactam and carbapenems. Extended spectrum beta-lactamase (ESBL) screen positive isolates from CA-IAIs patients showed an increasing trend in past three years. *Enterococcus* and MRSA showed high resistance rate to clindamycin, quinolone, erythromycin and tetracycline, while they showed high sensitivity rate to linezolid, tegacycline, teicoplanin and vancomycin. Our results indicate that isolated bacteria from abdominal drainage fluid show high resistance rates to commonly used antibiotics in ICU patients with cIAIs. The curative effects on diseases should be monitored continuously when antibiotics are used. Meanwhile, we should always keep eyes on drug-resistant bacteria, especially when the treatment efficacy is not good.
Key words: complicated intra-abdominal infection; pathogens; extended spectrum beta-lactamase screen positive isolates; resistance rate

Intra-abdominal infections (IAIs), closely associated with a poor prognosis, is a common disease in intensive cure unit (ICU)[1–3]. Large sample study[1] showed IAIs patients accounted for 19.6% of infectious diseases in ICU. The mortality rate of IAIs is as high as 29.4%, which is significantly higher than that of other infections. Most IAIs patients in ICU were those with complicated IAIs (cIAIs), which required simultaneous surgical intervention and antibiotic treatments. In 2017, with reference to the "2016 Surviving Sepsis Campaign"[4], World Society of Emergency Surgery (WSES) Guidelines[5] recommended to use broad-spectrum antibiotics for empirical anti-infective treatment within 1 h in cIAIs patients with septic shock. Improper use of antibiotics is closely related to the adverse outcome. Treatment with broad-spectrum antibiotics to cover all possible pathogens is critical. However, a series of problems, such as double infections, emergence of drug-resistant bacteria, increasing globalization of antibiotic resistance, has been caused by excessive use of antibacterial drugs. Although numerous guidelines[4, 6–8] made recommendations for antibiotics use in some patients, microbial pathogens trends, resistance characteristics and antibiotics use are still diverse in different regions.

With the widespread use of antibiotics, resistant bacteria keep emerging. However, antibiotic resistance rate of pathogens from IAIs patients reported in different regions is different. Chang[9] reported, from 2002 to 2013, culture rate of *Escherichia coli* (*E. coli*) with extended-spectrum beta-lactamases (ESBL) in IAIs patients in China mainland, Hong Kong (China), Taiwan (China) and Australia was 66.6%, 26.3%, 12.8% and 6.1%, respectively. The results indicated analysis

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of pathogenic characteristics of cIAIs patients in ICU of different regions and combined use of antibiotics with "regional characteristics" were extremely necessary. Nowadays, researches on the pathogenic differences of cIAIs patients in different cities of China were imperative. Also, no researches about pathogenic characteristics of cIAIs patients in ICU of Hubei were reported. This study aimed to analyze the pathogenic characteristics of cIAIs patients collected by the ICU of Wuhan University Zhongnan Hospital during the past three years, expecting to guide the rational clinical use of drugs in early stage.

1 SUBJECTS AND METHODS

1.1 Research Subjects

612 cases of cIAIs in ICU of Wuhan University Zhongnan Hospital were selected from January 2016 to December 2018. The diagnosis of cIAIs was made according to "diagnosis and management of complicated intra-abdominal infections in adults and children" guidelines released by Infectious Diseases Society of America (IDSA) in 2010[6].

1.2 General Data Collection

For general data collection, the medical records of patients were reviewed through the hospital case management system, including: gender, age, APACHE-II and SOFA score when entering ICU, patient sources (operating room, emergency department, general ward or other hospitals), underlying diseases (diabetes, cancer, chronic obstructive pulmonary disease, organ transplantation, HIV), required organ support treatments (mechanical ventilation, blood purification), clinical classification [CA-IAIs, healthcare-associated IAIs (HA-IAIs)], clinical outcome (ICU hospitalization time, number of deaths, cIAIs related deaths).

CA-IAIs and HA-IAIs refer to "Abdominal Infection Management " guideline released by World Emergency Surgery Association in 2017[5]. CA-IAIs included hospital-acquired infections (infections obtained after 48 h of primary infection control), infections in patients with a history of hospitalization for nearly 3 months or long-term residence in experienced nursing institutions, invasive medical treatment at home or in hospital clinic in the past 1 month (such as intravenous medication, hemodialysis, chemotherapy, radiotherapy, etc.).

1.3 Source of Strains

The strain was obtained from the culture of the patient's peritoneal drainage fluid or puncture fluid. The cultured specimens were collected when patients were first admitted to ICU. The bacterial resistance information was collected, and if the same bacteria were cultured in different parts of the abdominal cavity, bacterial results were only recorded once. If the drug sensitivity was largely different, multiple bacterial results were simultaneously recorded.

1.4 Materials And Instruments

Materials and instruments included: Mueller-Hinton (MH) agar medium, VITEK-2 Compact Automatic Bacteria Identification and Drug Sensitivity Analyzer (French BioMerieux).

1.5 Isolation and Identification of Strains and Drug Susceptibility Test

The strains were isolated according to the "National Clinical Laboratory Procedures". French BioMerieux VITEK-2 Compact system was used for bacterial identification and drug sensitivity analysis. Susceptibility results were interpreted according to M100-S23 standard released by US Clinical and Laboratory Standards Institute (CLSI).

1.6 Statistical Analysis

SPSS 20.0 statistical software was performed for data analysis. Normally distributed measurement data were indicated as $\bar{x}\pm s$. Non-normal distribution measurement data were indicated as median (interquartile range). Count data were displayed as percentage (%), and ratio was compared by χ^2 test. The difference was statistically significant when $P<0.05$.

2 RESULTS

2.1 Clinical Characteristics of Patients

612 patients were enrolled, including 382 males (62.42%) and 230 females (37.58%) with age ranging from 24 to 89 years old (mean 68.66±12.79). The elderly patients (>60 years old) accounted for 72.39%. Average APACHE-II and SOFA scores were 18.0±9.5 and 7.3±4.0, respectively. 27.94% of hospitalization patients were given blood purification treatment, and 68.95% of patients required mechanical ventilation. The number of patients with CA-IAIs, HA-IAIs and positive abdominal fluid culture, median length of ICU stay, ICU mortality and cIAIs-related mortality were 375 (61.27%), 237 (38.73%), 340 (55.56%), 12 (4–27) days, 21.24%, and 13.89%, respectively (table 1).

2.2 Distribution and Composition Ratio of Pathogenic Bacteria

Totally, 539 strains were cultured in the peritoneal drainage fluid, about 48.42% of which were gram-negative bacteria. The first three common bacteria were *E. coli* (113 strains, 20.96%), *Klebsiella pneumoniae* (55 strains, 10.20%) and *Pseudomonas aeruginosa* (30 strains, 5.57%). Gram-positive bacteria accounted for 26.35%. The first three were *Enterococcus faecium* (54 strains, 10.02%), *Enterococcus faecalis* (37 strains, 6.86%) and Methicillin-resistant *staphylococcus aureu* (MRSA, 21 strains, 3.90%). Fungi accounted for 25.23%, nearly half of which were *Candida albicans* (61 strains, 11.32%). *Candida glabrata, Candida parapsilosis* and *Candida tropicalis* accounted for a nearly equal proportion (table 2).

Table 1 Clinical characteristics of patients

Characteristics	Inclusion in patients (*n*=612)
Age (years)	68.66±12.79
Male (*n*, %)	382 (62.42)
APACHE-II score when entering ICU	18.0±9.5
SOFA score when entering ICU	7.3±4.0
Patient source (*n*, %)	
Operating room	285 (46.57)
Emergency department	133 (21.73)
General ward	101 (16.50)
Other hospitals	93 (15.20)
Comorbidity (*n*, %)	
Diabetes	195 (31.86)
Malignant tumor	155 (25.33)
Chronic obstructive pulmonary disease	94 (15.36)
Organ transplantation	32 (5.23)
HIV	30 (4.90)
Organ support treatment (*n*, %)	
Blood purification	171 (27.94)
Mechanical ventilation	422 (68.95)
Clinical classification (*n*, %)	
CA-IAIs	375 (61.27)
HA-IAIs	237 (38.73)
Abdominal drainage culture positive rate (*n*, %)	340 (55.56)
Clinical outcome	
ICU hospital stay (days)	12 (4–27)
ICU deaths (*n*, %)	130 (21.24)
cIAIs related deaths (*n*, %)	85 (13.89)

Table 2 Distribution and composition ratio of pathogenic bacteria in abdominal drainage

Pathogenic bacteria	Number of strains	Composition ratio (%)
Gram-negative bacteria	261	48.42
Escherichia coli	113	20.96
Klebsiella pneumoniae	55	10.20
Pseudomonas aeruginosa	30	5.57
Proteus	19	3.53
Acinetobacter baumannii	17	3.15
Stenotrophomonas maltophilia	10	1.86
Citrobacter	10	1.86
Others	7	1.30
Gram-positive bacteria	142	26.35
Enterococcus faecium	54	10.02
Enterococcus faecalis	37	6.86
Methicillin-resistant *Staphylococcus* aureus	21	3.90
Methicillin-sensitive *Staphylococcus* aureus	19	3.53
Others	11	2.04
Fungus	136	25.23
Candida albicans	61	11.32
Candida glabrata	27	5.01
Candida parapsilosis	24	4.45
Candida tropicalis	24	4.45
Total	539	100.00

2.3 Drug Resistance Analysis of Enterobacter

Statistical analysis of drug susceptibility results showed that the resistance rate of Enterobacter to ampicillin was extremely as high as 88.24%, 44.44% to 50.00% to quinolones, high to most cephalosporins, ranging from 36.23% to 47.06%, and low to enzyme inhibitors (piperacillin/tazobactam) and carbapenems, ranging from 12.59% to 20.37%. Among them, ESBL-producing enterobacter were resistant to all quinolones, most cephalosporins, and highly sensitive to enzyme inhibitors (piperacillin/tazobactam) and carbapenems. In addition, the resistance rate of *Klebsiella pneumoniae* (*K. pneumoniae*) to ampicillin, amikacin, aztreonam, quinolones, carbapenems, piperacillin/tazobactam was significantly higher than that of *E. coli* (P<0.05, table 3).

2.4 Change Trends of Separation Rate of ESBL-producing Strains

By analyzing and comparing separation rate of ESBL-producing strains in peritoneal drainage fluid, results indicated in all cIAIs patients, no significant difference was observed in separation rate of ESBL-producing strains in 2016, 2017, 2018 (P>0.05). In CA-IAIs patients, separation rate of ESBL-producing strains during the last three years was improved statistically significantly (P<0.05); in HA-IAIs patients, separation rate of ESBL-producing strains in 2017 and 2018 was higher than that in 2016 (P<0.05). No statistically significant difference was observed in the data between 2018 and 2017 (P>0.05) (table 4).

2.5 Drug Resistance Analysis of *Enterococcus* and Methicillin-Resistant *Staphylococcus Aureus*

The first two of gram-positive bacteria in the culture strains of peritoneal drainage were *Enterococcus* and MRSA. The results of drug susceptibility analysis showed that resistance rate of *Enterococcus* to clindamycin, erythromycin, tetracycline and quinolones was extremely high, ranging from 92.31% to 100.00%. Resistance rate of MRSA against clindamycin, erythromycin, tetracycline and quinolones was 100.00%. *Enterococci* or MRSA strains resistant to linezolid, tigecycline, teicoplanin and vancomycin were not found (table 5).

3 DISCUSSION

The cIAIs are the common ICU disease and closely associated with high mortality[10, 11]. Early control of infection source is the cornerstone of the treatment. And use of empirical broad-spectrum antibiotics is the key of effective treatment of the disease. Delay in the results of bacterial culture in clinical laboratories, emergence of drug-resistant bacteria, and differences in epidemiology trends in different regions have made it a major problem for early antibiotics selectivity. Therefore, analysis of pathogenic characteristics of

Table 3 Resistance rate of Enterobacteriaceae to antimicrobial agents (%)

Antimicrobial agents	*E. coli*	*K. pneumoniae*	*E. coli* ESBL+	*K. pneumoniae* ESBL+	All
Ampicillin	81.42	100.00[a]	100.00	100.00	88.24
Ampicillin/sulbactam	27.43	20.37[a]	50.00	21.72[b]	29.41
Amikacin	0.00	40.74[a]	0.00	50.00[b]	11.57
Aztreonam	36.28	59.26[a]	75.00	100.00[b]	41.18
Ciprofloxacin	54.87	59.26[a]	100.00	100.00	50.00
Levofloxacin	45.13	59.26[a]	100.00	100.00	44.44
Cefoxitin	8.85	20.37[a]	17.45	26.83[b]	16.67
Cefuroxime sodium	48.67	40.74[a]	83.33	71.20[b]	45.45
Cefotaxime	46.32	39.50[a]	87.40	89.31	43.81
Ceftazidime	30.09	33.31	33.33	46.53[b]	36.23
Ceftriaxone	41.15	52.08[a]	100.00	100.00	47.06
Cefepime	18.58	40.74[a]	25.00	50.00[b]	24.38
Imipenem	8.85	20.37[a]	9.35	18.40[b]	12.59
Meropenem	18.58	25.93[a]	11.44	21.72[b]	20.37
Gentamicin	27.43	59.26[a]	25.00	100.00[b]	36.42
Compound sulfamethoxazole	36.28	59.26[a]	75.00	100.00[b]	44.44
Tobramycin	18.58	40.74[a]	50.00	50.00	23.21
Piperacillin/tazobactam	9.73	18.52[a]	9.35	17.45[b]	14.36

E. coli, *Escherichia coli*; *K. pneumoniae*, *Klebsiella pneumoniae*. [a]$P<0.05$ *vs. E. coli*; [b]$P<0.05$ *vs. E. coli* ESBL+

Table 4 Separation rate of ESBL-producing strains from year 2016–2018

Patients	2016	2017	2018	All
cIAIs	35.62	36.37	38.80	37.50
CA-IAIs	18.35	23.71[a]	29.05[ab]	24.40
HA-IAIs	56.30	64.16[a]	65.74[a]	59.08

[a]$P<0.05$ *vs.* 2016, [b]$P<0.05$ *vs.* 2017

Table 5 Resistance rate of Enterococcus and MRSA to antimicrobial agents (%)

Antimicrobial agents	*Enterococcus*	MRSA
Clindamycin	100.00	100.00
Ciprofloxacin	95.60	100.00
Ergomycin	95.60	100.00
Levofloxacin	93.41	100.00
Tetracycline	100.00	100.00
Moxifloxacin	92.31	100.00
Penicillin G	100.00	100.00
Gentamicin	87.91	66.67
Quinoline nupu ting /dalfopristin	0.00	0.00
Linezolid	0.00	0.00
Tigecycline	0.00	0.00
Koalaranin	0.00	0.00
Vancomycin	0.00	0.00

cIAIs patients in different regions is essential for the rational use of antibiotics. In our study, we analyzed the etiology of cIAIs patients in our department during the past three years. It was found that gram-negative bacteria were the main culture strains of peritoneal drainage, among which resistance rate of Enterobacter to quinolones and most cephalosporins was high. However, low resistance rate to enzyme inhibitors and carbapenems was observed. Separation rate of ESBL-producing strains was 37.50%, which was rising in CA-IAIs patients year by year. Enterococcus and MRSA in peritoneal drainage fluid were highly resistant to clindamycin, erythromycin, tetracycline and quinolones, and no resistance to linezolid, tigecycline, teicoplanin and vancomycin was found.

In this study the positive rate of peritoneal drainage culture in cIAIs patients was 55.56%, which was lower than that reported by De Waele[1], with positive rate of 67%. The reason might be the difference of inclusion patients. In the study by De Waele[1], only 63.7% of patients with abdominal infections received emergency surgery. However, most of the patients in our study underwent surgery, intravenous infusion of antibiotics before surgery, intraperitoneal lavage and so on before entering the ICU, which could result in a lower positive rate of abdominal drainage fluid culture. It suggests that, for cIAIs patients, relevant culture specimens should be taken as early as possible (before antibiotic use or before intraperitoneal lavage), which may provide a basis for the rational use or modification of antibiotics in the later stage, reducing the mortality rate.

As commonly used antibacterial drugs, drug resistance rate of quinolone and cephalosporin to abdominal infection strains cannot be ignored. In this study, resistance rates of *Enterobacter* to levofloxacin and ciprofloxacin were 44.44% and 50.00%, respectively. Similarly, resistance rate of gram-negative bacteria to levofloxacin in IAIs patients in Beijing reached 46.95%[12]. Study for Monitoring Antimicrobial Resistance Trends (SMART) data[13] in China updated in 2019 showed that resistance rate of *E. coli* to levofloxacin was about 50% in IAIs patients. Therefore, for cIAIs patients admitted in

ICU, treatment response should be monitored closely when quinolones are part of the initial treatment. Also, drug resistance should be taken into account while the treatment efficacy is not good. Compared with quinolones, resistance rate of *Enterobacter* to most cephalosporins was slightly lower, ranging from 36.23% to 47.06%, which was significantly lower than that in Beijing[12]. It is worth that, the present study found that *Enterobacter*, even ESBL-producing *E. coli*, had a relatively lower resistance rate to cefoxitin than other cephalosporins. This result was consistent with that reported by Zhang[14]. Bouxom[15] analyzed the drug sensitivity of 100 ESBL-producing *E. coli* strains and found that the sensitivity rate to cefoxitin was 83%. However, current clinical studies[16–18] on the efficacy of cefoxitin on ESBL-producing *E. coli* infection are mostly confined to patients with urinary tract infections, and further clinical studies are demanded to confirm the therapeutic effects in cIAIs patients admitted to ICU.

ESBL is a bacterial plasmid-mediated protein that hydrolyzes and extinguishes many beta-lactam antibiotics, such as third-generation cephalosporins, penicillin, and aztreonam. In this study, ESBL-producing *E. coli* and *K. pneumoniae* cultured in peritoneal drainage fluid accounted for 36.28% and 40.00% respectively, which were similar to that in Guangzhou (31.5% and 30.8%)[19]. However, the separation rate of ESBL-producing *E. coli* strains was significantly lower than that (66.6%) of Shanghai and Beijing in China[9]. This difference may be related to the different economic development levels and broad-spectrum antibiotics use in the general population between regions. These ESBL-producing strains are highly sensitive to meropenem and imipenem. The drug susceptibility results show that piperacillin/tazobactam has good antibacterial activity *in vitro*. Therefore, it provides us with a new thought that, considering globalization of increased resistance rate of carbapenem year by year, piperacillin/tazobactam might be a good choice for cIAIs caused by ESBL-producing *Enterobacter*. However, the antibacterial activity of piperacillin/tazobactam in patients with ESBL-producing *E. coli* and its prognosis are still controversial. Rodriguez-Bano[20] reported there was no significant difference between piperacillin/tazobactam and carbapenems in mortality and hospitalization time in patients with ESBL-producing *E. coli* infection. However, reverse results were obtained by Tamma *et al*[21]. They reported that patients with ESBL-producing bacteremia with treatment of piperacillin/tazobactam had a higher mortality rate than carbapenems. Currently, large-scale clinical study on the effectiveness of piperacillin/tazobactam for ESBL-producing *Enterobacter* infection in cIAIs patients were imperative, and its application in these patients needs further investigation.

During the past three years, the separation rate of ESBL-producing strains in peritoneal drainage fluid of cIAIs patients was about 37.50%. In HA-cIAIs patients, the separation rate of ESBL-producing strains stabilized in 2017 and 2018. This result may be attributed to the hospitals' strict supervision of clinical antibiotic use and physician awareness of the rational use of antibiotics. However, it is worth noting that the separation rate in CA-cIAIs patients was increasing year by year. This indicates that the regulation of antibiotics use by community or township medical units and the monitoring of antibiotics sale in pharmacies by the Ministry of Health may need to be further strengthened. Meanwhile, the possibility of ESBL-producing strains infection should be taken into consideration in respect of antibiotics selectivity for CA-cIAIs patients.

This study had some shortcomings: (1) Compared with other studies, the sample size of this study was less, but the cIAIs patients admitted to the comprehensive ICU of Wuhan University Zhongnan Hospital were more diverse and could more effectively reflect clinical features and etiological characteristics of cIAIs patients in ICU, resulting in more instructive guide for rational drug use in ICU patients. Population of large sample study by Zhang[12] were abdominal infections, and less ICU patients were included in their study. (2) Most of the pathogen specimens in this study were derived from peritoneal drainage fluid or puncture fluid. Fewer specimens were taken directly from the infected site during surgery, leading to some deviations in the research results. (3) Due to less fungal susceptibility testing, it was pity that no drug resistance data of peritoneal drainage culture fungi in cIAIs patients were recorded. (4) In clinical practice, antibiotics selectivity relates to not only possibly infected strains but also patients' basic conditions such as immune status, organ function. This study didn't make relevant analysis because of lack of clinical data.

To sum up, the peritoneal drainage culture strains of cIAIs patients admitted to ICU had high resistance rate to commonly used clinical antibiotics (most cephalosporins and quinolones). Furthermore, separation rate of ESBL-producing strains was increasing in patients with CA-cIAIs year by year. Therefore, in the process of antibiotic selection and treatment, it is necessary to pay more attention to the possible drug resistance of pathogenic bacteria, especially when the treatment efficacy is not good.

Conflict of Interest Statement

The authors declare that they have no competing interest.

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