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SUPPLEMENT ARTICLE

Risk Factors and Molecular Epidemiology of Complicated Intra-Abdominal Infections With Carbapenem-Resistant *Enterobacteriaceae*: A Multicenter Study in China

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Background. Carbapenem-resistant *Enterobacteriaceae* (CRE) infections are associated with poor patient outcomes. Data on risk factors and molecular epidemiology of CRE in complicated intra-abdominal infections (cIAI) in China are limited. This study examined the risk factors of cIAI with CRE and the associated mortality based on carbapenem resistance mechanisms.

Methods. In this retrospective analysis, we identified 1024 cIAI patients hospitalized from January 1, 2013 to October 31, 2018 in 14 intensive care units in China. Thirty CRE isolates were genotyped to identify β-lactamase-encoding genes.

Results. *Escherichia coli* (34.5%) and *Klebsiella pneumoniae* (21.2%) were the leading pathogens. Patients with hospital-acquired cIAI had a lower rate of *E coli* (26.0% vs 49.1%; $P < .001$) and higher rate of carbapenem-resistant Gram-negative bacteria (31.7% vs 18.8%; $P = .002$) than those with community-acquired cIAI. Of the isolates, 16.0% and 23.4% of *Enterobacteriaceae* and *K pneumoniae*, respectively, were resistant to carbapenem. Most carbapenemase-producing (CP)-CRE isolates carried bla_{KPC} (80.9%), followed by bla_{NMD} (19.1%). The 28-day mortality was 31.1% and 9.0% in patients with CRE vs non-CRE ($P < .001$). In-hospital mortality was 4.7-fold higher for CP-CRE vs non-CP-CRE infection ($P = .049$). Carbapenem-containing combinations did not significantly influence in-hospital mortality of CP and non-CP-CRE. The risk factors for 28-day mortality in CRE-cIAI included septic shock, antibiotic exposure during the preceding 30 days, and comorbidities.

Conclusions. *Klebsiella pneumoniae* had the highest prevalence in CRE. Infection with CRE, especially CP-CRE, was associated with increased mortality in cIAI.

Keywords. carbapenem-resistant *Enterobacteriaceae* (CRE); carbapenemase-producing *Enterobacteriaceae* (CP-CRE); complicated intra-abdominal infection (cIAI); epidemiology; risk factors.

Complicated intra-abdominal infection (cIAI) is a localized or diffuse peritoneal infection associated with various conditions such as gastrointestinal perforation [1]. Severe sepsis and septic shock occur in 10%–15% of patients with cIAI and are important causes of morbidity and mortality [2].

Complicated intra-abdominal infection typically involves multiple bacteria species. The most common bacteria include *Enterobacteriaceae* (*Escherichia coli*, *Klebsiella pneumoniae*), *Enterococcus*, *Streptococcus*, and *Bacteroides* [3]. With the increasing use of a variety of antimicrobial agents, bacterial resistance to commonly used antibiotics is expanding [4]. In particular, the incidence of carbapenem-resistant *Enterobacteriaceae* (CRE) has been increasing rapidly [5]. During the last decade, CRE has caused numerous outbreaks of severe nosocomial infections, and it has become endemic in several countries [6]. The mortality rate in patients with severe CRE infections has been reported to be >50% in a study [7]. This poses a great challenge to antibiotics treatment of cIAIs [8].

Based on resistance mechanisms, CRE are classified as carbapenemase-producing (CP)-CRE and non-CP-CRE strains. Non-CP-CRE include strains that produce extended-spectrum β-lactamases (ESBLs) and/or AmpC cephalosporinases (AmpCs) with loss or alteration of outer membrane protein to alter membrane permeability. In a previous study, the 14-day mortality was 32% in patients with CP-CRE bacteremia and

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13% in non-CP-CRE bacteremia [9]. Clear difference in prognosis between CP and non-CP-CRE infection may impact antibiotics determination (eg, combination of carbapenem administration on CP or non-CP-CRE strains). However, to the best of our knowledge, no previous study has analyzed the outcomes of cIAI patients with CP-CRE versus non-CP-CRE.

We conducted a multicenter, retrospective study to examine risk factors of cIAI with CRE and the associated mortality. We also compared mortality rates in cIAI patients with CP-CRE versus non-CP-CRE and the influence of carbapenem-containing combinations on mortality for CP-CRE and non-CP-CRE.

MATERIALS AND METHODS

Study Design

This was a nationwide, multicenter, retrospective, observational study conducted from January 1, 2013 to October 31, 2018. A total of 1024 adults (age, 18–80 years) with cIAI from 14 intensive care units (ICUs) at academic hospitals in China were included. Patients whose hospital stay was shorter than 48 hours or with primary peritonitis were excluded. Intensive care units from 5 provinces, mostly from the eastern area, were included in the study. Ten were mixed (medical and surgical) ICUs, 2 were surgical ICUs, and 2 ICUs belonged to emergency departments. The median bed size was 32. This study was approved by the Medicine Institutional Review Board of Shanghai Jiaotong University, School of Medicine, Ruijin Hospital North. The informed consent from patients was waived.

Data Collection

The following data were extracted from medical records: age, sex, complications, history of hospitalization and surgery within 1 year, antibiotic use within 30 days, use of glucocorticoids, etiology, Sequential Organ Failure Assessment (SOFA) score, Acute Physiology and Chronic Health Evaluation (APACHE) II score, invasive operation for source control, adequacy of source control, residue lesions, and empirical and definitive antibiotics therapy. All isolates were cultured from samples obtained from intra-abdominal body sites. In-hospital and 28-day mortality data were also extracted.

Definitions

Complicated intra-abdominal infection was defined as (1) abdominal infection extending to the peritoneal cavity and causing abscesses or (2) peritonitis, extending from an intra-abdominal organ [1]. Hospital-acquired (HA)-cIAI were defined as infections diagnosed in patients hospitalized for at least 48 hours during the preceding 90 days or acquired in chronic care settings within the previous 30 days, either postoperatively or not. Recurrence of cIAI was defined as the emergence of abdominal symptoms (eg, abdominal distension, decreased bowel sounds, peritonitis signs, abdominal abscess), infection symptoms (eg, fever, shortness of breath), and laboratory measures indicative of bacterial infection (eg, C-reactive protein, procalcitonin, white blood cell count) within 7 days after discontinuation of antibiotics, in the absence of other infection foci. Adequate source control was defined as any therapy, operative or nonoperative, that controlled the original etiology without residual generalized or localized abscess and peritonitis. Adequate empirical antibiotic therapy was defined as antibiotic administration that preceded a positive culture result and that led to improvement in laboratory measures and clinical symptoms. Adequate definitive antibiotic therapy was similar to adequate empirical antibiotic therapy, except that the choice of antibiotic was based on a positive culture result and required administration of at least 1 agent with in vitro activity against the pathogens isolates from cases of cIAI. Residual lesions were identified by computed tomography scan.

Genotyping of Carbapenem-Resistant *Enterobacteriaceae*

Resistance to imipenem or meropenem of CRE isolates was defined as a minimum inhibitory concentration (MIC) ≥2 μg/mL or MIC of ertapenem ≥1 μg/mL, based on the criteria adopted at the Clinical and Laboratory Standards Institute. The susceptibility to imipenem or meropenem and ertapenem was tested by Etest methods. The modified Hodge test (MHT) was performed to determine whether strains appeared to produce carbapenemases by phenotypic methods but were negative by genotypic methods, or vice versa.

Genomic deoxyribonucleic acid (DNA) was isolated from CRE pellets with an Omega Bio-Tek Bacterial DNA Kit (Norcross, GA). Illumina HiSeq (Shanghai Biozeron, Shanghai, China) technology was applied to sequence the entire genome of each strain. Contamination and low-quality reads were identified by Trimmomatic (http://www.usadellab.org/cms/uploads/supplementary/Trimmomatic) using default parameters. Then, SPAdes-v3.13.0 (http://cab.spbu.ru/software/spades/) was used to assemble the clean reads into the draft genomes. Finally, ResFinder software from the Center for Genomic Epidemiology (http://www.genomicepidemiology.org/) was used to detect the following β-lactamase genes and other resistance genes: (1) ESBLs: $bla_{CTX\text{-}M\text{-}1\ group}$, $bla_{CTX\text{-}M\text{-}1\text{-}like}$, $bla_{CTX\text{-}M\text{-}15\text{-}like}$, $bla_{CTX\text{-}M\text{-}32\text{-}like}$, $bla_{CTX\text{-}M\text{-}2\ group}$, $bla_{CTX\text{-}M\text{-}8}$, $bla_{CTX\text{-}M\text{-}25\ group}$, $bla_{CTX\text{-}M\text{-}9\ group}$, $bla_{TEM\text{-}types}$, $bla_{SHV\text{-}types}$, bla_{VEB}, bla_{PER}, bla_{BEL}, bla_{GES}; (2) plasmid-mediated AmpCs: $bla_{CMY\ I/MOX}$, bla_{ACC}, bla_{DHA}, $bla_{ACT/MIR}$, $bla_{CMY\ II}$, bla_{FOX}; and (3) carbapenemases: bla_{KPC}, bla_{NDM}, bla_{VIM}, bla_{IMP}, bla_{GES}, bla_{GIM}, bla_{SPM}, and $bla_{OXA\text{-}48\text{-}like}$, $bla_{OXA\text{-}23\text{-}like}$, $bla_{OXA\text{-}24/40\text{-}like}$, $bla_{OXA\text{-}58\text{-}like}$ [8].

Statistical Analyses

SPSS version 22.0 (IBM, Armonk, NY) was used for data analysis. Continuous variables with normal distribution are expressed as mean ± standard deviation and analyzed using Student's *t* test. Continuous variables not following normal distribution are expressed as median (interquartile range [IQR])

and analyzed using the rank-sum test. Categorical variables are expressed as frequency or ratio and analyzed using the χ^2 test. Multivariate logistic regression was used for each of the outcomes. When appropriate, results were reported as odds ratios (ORs) with associated 95% confidence intervals (CIs). $P < .05$ was considered statistically significant.

RESULTS

During the study period, a total of 1024 patients with cIAI were hospitalized in the ICUs of the participating hospitals: 503 (49.1%) with CA-cIAI and 521 (50.9%) with HA-cIAI. The median age of patients was 67 years (IQR, 55.79), and 688 (67.2%) were male. Peritoneal fluid culture was positive in 682 (66.6%) patients.

Microbiological Results

A total of 970 pathogen strains were isolated from a total of 682 patients. At least 2 pathogens were identified in 216 (31.7%) patients. Gram-negative bacteria constituted 728 (75.1%) of the 970 strains; the remainder were Gram-positive bacteria (17.0%, 165 strains) and fungi (7.9%, 77 strains) (Table 1). Among the Gram-negative bacteria, *E coli* was the most common pathogen (n = 251; 34.5%). *Escherichia coli* infection was more common in CA-cIAI than in HA-cIAI (49.1% vs 26.0%; $P < .001$). Patients with CA-cIAI also had higher rate of *Enterobacteriaceae* with AmpC-type inducible chromosomal β-lactamases (eg, *Enterobacter* spp) (8.0% vs 2.3%; $P = .017$). Infection with nonfermentative bacteria (eg, *Pseudomonas aeruginosa*) was less common for CA-cIAI (5.2% vs 12.0%; $P = .032$).

Resistance Rate

Table 2 shows the frequency of carbapenem resistance of the Gram-negative bacteria in patients with HA-cIAI versus CA-cIAI. Among the 728 Gram-negative bacteria isolates, 196 (26.9%) were carbapenem-resistant. Carbapenem resistance in *Enterobacteriaceae* was under 20%, except for *K pneumoniae* (23.4%). The rate of carbapenem resistance among nonfermentative bacteria was relatively high (54.7% for *Acinetobacter baumannii* and 43.5% for *P aeruginosa*). Fifty (18.7%) carbapenem-resistant Gram-negative bacterial strains were isolated from patients with CA-cIAI, whereas 146 (31.7%) were found in patients with HA-cIAI ($P = .002$). With the exception of *E coli*, the rate of carbapenem resistance among Gram-negative bacteria was higher in HA-cIAI than in CA-cIAI.

Table 1. Microbiological Characteristics of Peritoneal Fluid Cultures According to the Type of Infection[a]

Microbioorganisms	All (%)	HA-cIAIs (%)	CA-cIAIs (%)	*P*
Gram-Positive Bacteria	165 (17.0)	107 (17.3)	58 (16.5)	.990
Staphylococcus aureus	19 (11.5)	13 (12.2)	6 (10.3)	.989
Staphylococcus epidermidis	14 (8.50)	12 (11.2)	2 (3.50)	.403
Staphylococcus haemolyticus	10 (6.10)	4 (3.70)	6 (10.3)	.409
Enterococcus faecium	69 (41.2)	45 (42.1)	24 (41.4)	.999
Enterococcus faecalis	21 (12.7)	14 (13.1)	7 (12.1)	.998
Streptococcus spp	21 (12.7)	11 (10.3)	10 (17.2)	.650
Other Gram-positive bacteria	11 (6.70)	8 (7.50)	3 (5.20)	.956
Gram-Negative Bacteria	728 (75.1)	461 (74.6)	267 (75.9)	.979
Escherichia coli	251 (34.5)	120 (26.0)	131 (49.1)	<.001**
Klebsiella spp	154 (21.2)	106 (23.0)	48 (18.0)	.466
Enterobacter spp	43 (5.90)	37 (8.00)	6 (2.30)	.017**
Serratia spp	6 (0.80)	5 (1.10)	1 (0.30)	.791
Proteus spp	7 (1.00)	7 (1.50)	0	.252
Acinetobacter baumannii	95 (13.0)	68 (14.8)	27 (10.1)	.361
Pseudomonas aeruginosa	69 (9.50)	55 (12.0)	14 (5.20)	.032**
Stenotrophomonas maltophilia	28 (3.8)	19 (4.1)	9 (3.40)	.968
Other Gram-negative bacteria	75 (10.3)	44 (9.50)	31 (11.6)	.854
Fungi	77 (7.90)	50 (8.10)	27 (7.70)	.997
Candida albicans	44 (57.1)	27 (54.0)	17 (63.0)	.902
Candida tropicalis	12 (15.6)	6 (12.0)	6 (22.2)	.707
Candida glabrata	14 (18.2)	10 (20.0)	4 (14.8)	.957
Candida parapsilosis	3 (3.90)	3 (6.00)	0	.640
Candida krusei	2 (2.60)	2 (4.00)	0	.775
Other candida	1 (1.30)	1 (2.00)	0	.908
Other fungi	1 (1.30)	1 (2.00)	0	.908
Total	970	618	352	

Abbreviations: CA-cIAIs, community-acquired complicated intra-abdominal infections; HA-cIAIs, hospital-acquired complicated intra-abdominal infections.

[a]Data are presented as number of isolates (percentage).

**, $P < .01$ vs CA-cIAIs.

Table 2. Carbapenem Resistance Profiles of the Main Gram-Negative Bacteria According to the Type of Infection[a]

	All		HA-cIAIs		CA-cIAIs		
Microorganisms	N	CR	n	CR	n	CR	*P*
Gram-Negative Bacteria	728	196 (26.9)	461	146 (31.7)	267	50 (18.7)	.002**
Enterobacteriaceae	536	86 (16.0)	319	60 (18.8)	217	26 (12.0)	.215
Escherichia coli	251	28 (11.2)	120	12 (10.0)	131	16 (12.2)	.958
Klebsiella spp	154	36 (23.4)	106	29 (27.4)	48	7 (14.6)	.390
Enterobacter spp	43	5 (11.6)	37	5 (13.5)	6	0	.821
Other *Enterobacteriaceae*	88	17 (19.3)	56	14 (25.0)	32	3 (9.40)	.363
Nonfermenting	192	110	142	86	50	24	.496
Acinetobacter baumannii	95	52 (54.7)	68	42 (61.8)	27	10 (37.0)	.189
Pseudomonas aeruginosa	69	30 (43.5)	55	25 (45.5)	14	5 (35.7)	.934
Stenotrophomonas maltophilia	28	28 (100.0)	19	19 (100.0)	9	9 (100.0)	.968

Abbreviations: CA-cIAIs, community-acquired complicated intra-abdominal infections; CR, carbapenem-resistant; HA-cIAIs, hospital-acquired complicated intra-abdominal infections.

[a]Data are presented as number of isolates (percentage).

**, $P < .01$ vs CA-cIAIs.

However, this difference was not statistically significant, probably because of the relatively small sample.

Comparative Analysis Between Carbapenem-Resistant *Enterobacteriaceae* (CRE) and Non-CRE Infections

Characteristics of patients stratified by CRE or non-CRE infections are reported in Table 3. Multivariate analysis revealed the following independent risk factors for occurrence of CRE infections: abdominal surgery in the preceding 1 year (OR, 6.702; 95% CI, 1.003–44.799), increased SOFA score per point (OR, 1.183; 95% CI, 1.011–1.383), increased APACHE II score per point (OR, 1.126; 95% CI, 1.036–1.224), and residual lesions (OR, 4.786; 95% CI, 1.752–13.071) (Table 4).

In multivariate analysis, the risk of 28-day mortality was higher in CRE-cIAI than in non-CRE-cIAI (OR, 3.690; 95% CI, 1.752–7.773) (Table 5). Other significant risk factors for 28-day mortality included sepsis or septic shock (OR, 4.298; 95% CI, 1.532–12.055), antibiotic exposure during the preceding 30 days (OR, 2.709; 95% CI, 1.324–5.542), and comorbidities such as cardiovascular disease (OR, 2.678; 95% CI, 1.339–5.57) and diabetes mellitus (OR, 2.964; 95% CI, 1.229–7.148).

Identification of β-Lactamase Genes

Samples from 30 cIAI patients infected with single CRE pathogen were subjected to additional genotyping. Among the 30 CRE isolates, 26 were *K pneumoniae* strains and 4 were *E coli*.

Of the 30 CRE isolates, 21 (70.0%) were CP-CRE and 9 (30.0%) were non-CP-CRE. The MHT results from non-CP-CRE strains were also negative, indicating that they were not likely to produce carbapenemases. Most CP-CRE isolates carried bla_{KPC} (80.9%), followed by bla_{NMD} (19.1%); carrying genes of bla_{OXA} or bla_{IMP} was not detected. All *K pneumoniae* isolates harbored the bla_{SHV} gene, and more than 1 β-lactamase gene was detected in 28 isolates (93.3%) (Supplementary Table 1). The genetic relatedness of 26 *K pneumoniae* strains were analyzed. The Average Nucleotide identity values of all the strains were over 0.98, and not equal to 1. It meant that 26 strains belonged to *K pneumoniae* strain but not from the same clone (Supplementary Figure 1). Carbapenem MIC in CP-CRE isolates was generally higher than 8 μg/mL and was <4 μg/mL in most non-CP-CRE isolates ($P = .032$) (Table 6).

Mortality Between Carbapenemase-Producing (CP)- Versus Non-CP-Carbapenem-Resistant *Enterobacteriaceae* Infection

Baseline demographic and clinical characteristics were similar between cIAI patients with CP- or non-CP-CRE infections (Supplementary Table 2). In-hospital mortality was higher in patients infected with CP-CRE than in those with non-CP-CRE infection (52.4% vs 11.1%; $P = .049$); there was a trend for higher 28-day mortality for CP-CRE infection (28.6% vs 0%; $P = .393$).

Antibiotics choices were based on the in vitro drug sensitivity against the CRE isolates and contained at least 1 agent with in vitro activity. Among the patients with CRE infection, tigecycline was administered to 47.6% of CP-CRE infection and to 55.6% of non-CP-CRE infection. Polymyxin B was administered to 23.8% of patients with CP-CRE infection and 33.3% of patients with non-CP-CRE infection, respectively. Amikacin was used in 9.5% of the patients with CP-CRE infection and 55.6% of the patients with non-CP-CRE infection. Carbapenem-containing antibiotic therapy was administered to 38.1% of the patients with CP-CRE infection and 64.3% of the patients with non-CP-CRE infection. In cases with carbapenem MIC >8 μg/mL, the infusion time for carbapenem was prolonged. The in-hospital mortality did not differ between patients with different antibiotics regimens, including receiving or not receiving carbapenem, either among patients with CP-CRE infection (37.5% vs 61.5%, $P = .386$) or among patients with non-CP-CRE infection (33.3% vs 0%, $P = .333$).

DISCUSSION

The spectrum and resistance characteristics of pathogens in cIAI had an obvious regional difference and changed over time

Table 3. Clinical Characteristics of Patients With Complicated Intra-Abdominal Infections According to the Presence/Absence of Carbapenem-Resistant *Enterobacteriaceae* in Peritoneal Fluid[a]

Variable	All Patients (n = 1024)	CRE-cIAIs (n = 74)	non-CRE-cIAIs (n = 388)	*P*
Patient Characteristics				
Male sex	688 (67.2)	53 (71.6)	248 (63.9)	.202
Age, year, median (IQR)	67 (55–79)	70 (62–78)	68 (57–78)	.169
Comorbidities				
Charlson comorbidity index, median (IQR)	1 (0–3)	2 (1–4)	2 (0–3)	.012**
Cardiovascular disease	315 (30.8)	30 (40.5)	123 (31.7)	.139
Cerebrovascular disease	79 (7.7)	8 (10.8)	28 (7.2)	.290
Dementia	18 (1.8)	0	11 (2.8)	.143
Chronic pulmonary disease	72 (7.0)	5 (6.8)	26 (6.7)	.986
Chronic liver disease	93 (9.1)	6 (8.1)	46 (11.9)	.350
Diabetes mellitus	138 (13.5)	12 (16.2)	56 (14.4)	.692
Chronic kidney disease	53 (5.2)	8 (10.8)	13 (3.4)	.005**
Solid tumor	256 (25.0)	27 (36.5)	104 (26.8)	.090
Hematological malignancies	11 (1.1)	0	4 (1.0)	.380
Epidemiological Risks				
Hospitalized in the preceding 1 year	347 (33.9)	38 (51.4)	136 (35.1)	.008**
Abdominal surgery in the preceding 1 year	214 (20.9)	34 (46.0)	90 (23.3)	.000**
Antibiotic exposure in the preceding 30 days	696 (68.0)	59 (79.7)	279 (71.9)	.164
Time from hospital admission to pathogen confirmation (days)	6 (2–15)	10 (4–19)	5 (2–12)	.003**
Source of Infection				
Hospital-acquired	521 (50.9)	51 (68.9)	224 (57.7)	.072
Community-acquired	503 (49.1)	23 (31.1)	164 (42.3)	
Etiology				
Intestinal perforation	436 (42.6)	32 (43.2)	158 (40.7)	.686
Biliary tract disease	273 (26.7)	21 (28.4)	135 (34.8)	.285
Acute pancreatitis	97 (9.5)	6 (8.1)	30 (7.7)	.912
Complicated appendicitis	26 (2.5)	0	11 (2.8)	.143
Postoperative infection	64 (6.3)	9 (12.2)	20 (5.2)	.023**
Intestinal obstruction	50 (4.9)	1 (1.4)	12 (3.1)	.406
Others	78 (7.6)	5 (6.8)	22 (5.7)	.715
Clinical Status at the Time of ICU Admission				
SOFA score, median (IQR)	4 (2–8)	6 (4–10)	4 (2–8)	.002**
APACHE II score, median (IQR)	13 (8–18)	16 (11–22)	12 (7–16)	<.001**
Sepsis or septic shock	585 (57.1)	60 (81.1)	215 (55.4)	<.001**
Glucocorticoid	110 (10.7)	15 (20.3)	53 (13.7)	.141
Bacteremia	159 (15.5)	25 (33.8)	62 (16.0)	<.001**
Polymicrobial	216 (21.1)	35 (47.3)	144 (37.1)	.099
Invasive Device				
Indwelling urinary devices	464 (45.3)	44 (59.5)	187 (48.2)	.076
Central venous catheter	270 (26.4)	28 (37.8)	118 (30.4)	.208
Ventilation	152 (14.8)	23 (31.1)	62 (16.0)	.002**
Treatment Variables				
Management for source control	918 (89.7)	65 (87.8)	356 (92.0)	.245
Residual lesions	272 (26.6)	42 (56.8)	80 (20.7)	<.001**
Adequate empiric antibiotics	388 (37.9)	29 (39.2)	136 (35.1)	.496
Adequate definitive antibiotics	420 (41.0)	36 (48.7)	144 (37.1)	.062
Outcomes				
Length of hospitalization, median (IQR)	20 (12–33)	25 (14–47)	20 (13–35)	.613
28-day mortality	136 (13.3)	23 (31.1)	35 (9.0)	<.001**
In-hospital mortality	160 (15.6)	33 (44.6)	40 (10.3)	<.001**
Infection recurrence	42 (4.1)	5 (6.8)	12 (3.1)	.125

Abbreviations: APACHE, Acute Physiology and Chronic Health Disease Classification System; CRE-cIAI, complicated intra-abdominal infection caused by carbapenem-resistant *Enterobacteriaceae*; ICU, intensive care unit; IQR, interquartile range; SOFA, Sequential Organ Failure Assessment score.

[a]Data are expressed in n (%) unless otherwise stated.

**, $P < .01$ vs non-CRE-cIAIs.

Table 4. Multivariate Analysis of Risk Factors for the Occurrence of Carbapenem-Resistant *Enterobacteriaceae*

Risk factors	OR	95% CI	*P*
Abdominal surgery in the preceding 1 year	6.702	1.003–44.799	.05
SOFA score (per point)	1.183	1.011–1.383	.035
APACHE II score (per point)	1.126	1.036–1.224	.035
Residual lesions	4.786	1.752–13.071	.002

Abbreviations: APACHE, Acute Physiology and Chronic Health Disease Classification System; CI, confidence interval; OR, odds ratio; SOFA, Sequential Organ Failure Assessment.

[10–12]. In order to provide carbapenem resistance mechanical information for the outcome and the selection of combined antibiotic strategy to Chinese intensivists, we retrospectively collected data from 1024 cIAI patients between 2013 and 2018 in China. Infection with CRE was associated with increased mortality in cIAI. The CP-CRE isolates were more virulent than non-CP-CRE, which were related with poorer outcome.

In the study, Gram-negative bacteria are consistent with recent epidemiological studies in Europe [12]. The rate of CRE out of *Enterobacteriaceae* was 16.0%, which varied by years (2013, 14.3%; 2014, 16.1%; 2015, 15.0%; 2016, 12.6%; 2017, 15.1%; 2018, 21.7%). Furthermore, the distribution of CRE was imbalanced between different areas in China. Our data showed that rates of CRE in the eastern area was higher than in other areas (16.3% vs 11.6%). We observed higher proportions of non-*Candida albicans* species in cIAI (20.0% *Candida glabrata* and 12.0% *Candida tropicalis*) than previous worldwide studies [13, 14]. This result was consistent with a study from Spain, which demonstrated that *C albicans* remained the most frequent yeast causing intra-abdominal infection. Non-*C albicans* species has been observed more frequently than before, and some of them had a reduced susceptibility to antifungal drugs [15].

The carbapenem resistance rate among CA-cIAI patients in our study was relatively high (18.7%). One plausible reason might be that antibiotics have been used in the cultivation of livestock and sea food [17], which are the daily diet in China. The bla_{VIM}, bla_{VIM}, and bla_{NDM} genes could be detected in the livestock and sea food [17]. It is possible that Carbapenem-resistant genes would be integrated to the epithelial cells in the gut. This might be the main cause of CA-CRE occurrence, which may spread more widely into the community in recent years in China. Multivariate analysis of CRE infections indicates that adequacy of source control with appropriate drainage and/or debridement and effective antimicrobial intervention policies are important in preventing severe drug resistance and decreasing mortality.

The incidence of CRE infections has been increasing in China in recent years [18], with production of carbapenemases as the major contributing mechanism [19]. Three dominant carbapenemase genes have been reported [20], with varying distribution across geographical regions and ethnicities [3]. The *K pneumoniae* carbapenemase (KPC)-2 gene is frequent in North and South America, Italy, Poland, and some parts of China, whereas carbapenem-hydrolyzing OXA genes have spread throughout Canada and Europe [21]. The interesting finding in our study suggests that KPC-carried CRE are the most frequent CRE in China. All of the non-CP-CRE isolates in our study carried ESBLs genes, and over 90% harbored more than 1 ESBL gene, which may lead to multidrug resistance. Consistent with previous results [22], carbapenem resistance (MIC >4 μg/mL) was more common in CP-CRE isolates than in non-CP-CRE isolates (86.3% vs 11.1%, $P = .032$). Non-CP-CRE isolates have been shown to carry ESBLs and AmpC genes, often together with loss or alteration of outer membrane proteins (eg, Ompk35 and Ompk36 of *K pneumoniae*) [23].

A multicenter study in Latin American countries showed that 28-day mortality was 4-fold higher in patients with CP-CRE bacteremia than in those with non-CP-CRE bacteremia [24].

Table 5. Multivariate Analysis to Identify Predictors of Mortality in Patients With CRE-cIAIs Versus Non-CRE-cIAIs

	28-Day Mortality			In-Hospital Mortality		
Risk factors	OR	95% CI	*P*	OR	95% CI	*P*
CRE infection	3.690	1.752–7.773	.001	6.038	2.923–12.475	.000
Sepsis or septic shock	4.298	1.532–12.055	.006	2.624	1.106–6.225	.029
Antibiotic exposure in the preceding 30 days	2.709	1.324–5.542	.006	3.278	1.534–7.007	.002
Cardiovascular disease	2.678	1.339–5.357	.005	2.740	1.382–5.432	.004
Diabetes mellitus	2.964	1.229–7.148	.016	-	-	-
Chronic pulmonary disease	-	-	-	4.291	1.374–13.398	.012
Hospital-acquired	-	-	-	2.547	1.176–5.517	.018
Residual lesions	-	-	-	2.861	1.420–5.761	.003

Abbreviations: CI, confidence interval; cIAI, complicated intra-abdominal infection; CRE, carbapenem-resistant *Enterobacteriaceae*; OR, odds ratio.

The higher mortality with CP-CRE infection has been attributed to higher resistance to more antibiotics [25]. In the current study, the 28-day mortality in cIAI patients infected with CRE was 12.2%, with only a nonsignificant trend in patients infected with CP-CRE versus non-CP-CRE, most likely due to the small sample size. However, in-hospital mortality was higher in patients infected with CP-CRE than non-CP-CRE. The reason may be related to the prolonged in-hospital duration due to refractory CRE infection in cIAI.

Klebsiella *pneumoniae* carbapenemase-contained bacteria have increased resistance to all β-lactam antibiotics. A previous study has reported that carbapenem-containing combination therapy for patients with CP-CRE bloodstream infection (imipenem and meropenem MIC >8 μg/mL) was associated with improved survival [26]. However, another study found that combination antibiotic therapy was associated with 27% lower risk of 14-day mortality than monotherapy in patients with CP-CRE or non-CP-CRE bloodstream infections, but that the use of carbapenem was not associated with decreased mortality for CP-CRE [9]. In the present study, a similar result was observed: significant difference of in-hospital mortality was observed between cIAI patients with CP-CRE or non-CP-CRE infection, regardless of whether their antibiotic regimen included carbapenem.

The present study has some limitations. First, most of the study sites in the current study were academic hospitals, and thus they may not be completely representative of the epidemiology of CRE in China. Second, the sample size of cIAI patients with CRE (n = 86) was relatively small. Studies of larger sample size are needed to verify the preliminary findings in the current study. Third, only 30 CRE strains were used to analyze the difference and the effect of different antibiotic regimens on 28-day mortality between CP-CRE and non-CP-CRE infections.

CONCLUSIONS

In conclusion, the current study showed that *Enterobacteriaceae*, especially *E coli*, are the predominant bacteria causing cIAI in ICUs in China. Carbapenem-resistant *K pneumoniae* is most common in CRE-cIAI. Infection with CRE, and particularly CP-CRE, was associated with increased in-hospital mortality. Our findings of the study suggest that adequacy of source control with appropriate drainage and/or debridement was important in preventing CRE occurrence. This could have important implications in the development or update of relevant guidelines for care. The presence or absence of carbapenem in antibiotic regimens did not significantly influence mortality rates of cIAI patients infected with CP-CRE or non-CP-CRE. The present results represent a first step toward further investigations in the empirical and precise antibiotics strategies of CRE infection in patients with cIAIs to improve patients' outcomes.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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