Epidemiology of and risk factors for infection with extended-spectrum β-lactamase-producing carbapenem-resistant Enterobacteriaceae: results of a double case–control study

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Purpose: Carbapenem-resistant Enterobacteriaceae (CRE) have been increasingly reported worldwide and pose a serious public threat, but the clinical significance of extended-spectrum β-lactamase (ESBL) production in CRE is not well established.

Patients and methods: A retrospective case–case–control study was conducted to identify the clinical characteristics of patients with ESBL-CRE. The susceptibility of isolates obtained from these patients was assessed. The detection of ESBL and carbapenemase-related genes was performed by PCR methods. Predictors of 30-day mortality in patients with ESBL-CRE infection were also identified in our study.

Results: A total of 149 patients with CRE infection caused by Enterobacter cloacae (n=74), Escherichia coli (n=38), and Klebsiella pneumoniae (n=37) were identified in Chongqing, Southwestern China, between January 2011 and December 2014. Of the 35 isolates detected with carbapenemase-related genes, 16 isolates had New Delhi metallo-β-lactamase (NDM), nine isolates had K. pneumoniae carbapenemase (KPC), seven isolates had imipenemase (IMP), and four isolates had oxacillinase (OXA)-1. One strain of enterobacter cloacae carried both NDM-1 and IMP-8 genes. ESBL isolates included the genes CTX-M (72/149), SHV (64/149), and TEM (54/149). All ESBL-CRE isolates exhibited ertapenem resistance, and the rate of cephalosporin resistance was relatively high in general. Independent risk factors for infection with ESBL-CRE included previous exposure to β-lactam antibiotics, transfer from another hospital, and some underlying diseases. In addition, solid tumors, hypoalbuminemia, and central venous catheters were independent predictors of mortality in patients with ESBL-CRE infection.

Conclusion: Physicians should understand the peculiar predictors for the identification of these organisms among high-risk patients.

Keywords: risk factors, carbapenem, resistance, ESBL, mortality

Introduction
In recent years, the emergence and spread of extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae have posed a serious threat to public health. ESBL production is often accompanied by other resistance mechanisms that provide cross-resistance to some other antimicrobial agents, such as aminoglycosides and fluoroquinolones. Patients at high risk for ESBL-producing infections often experience greater mortality, longer hospitalization, and higher costs of treatment. Carbapenems, potent antibiotics used in treating Gram-negative bacilli infections, are frequently used for suspected or diagnosed infections caused by ESBL-producing bacteria. With the
increased utility of carbapenem driven by the dissemination of ESBL-producing Enterobacteriaceae, carbapenem-resistant Enterobacteriaceae (CRE) have emerged over the past decade. Notably, the production of ESBL by CRE has been increasingly documented worldwide in recent years. This increase is worrisome since most of these isolates harbor both ESBL and carbapenemase genes that confer a higher level of resistance to both carbapenem and cephalosporin. Therefore, the emergence and spread of ESBL-CRE leave few therapeutic options, and the issue of ESBL production in CRE deserves special attention.

Previous studies have analyzed the risk factors in patients with CRE infection, which can be classified as being related to severe comorbid conditions, extensive invasive procedures, or heavy exposure to antibiotics. However, few studies have specifically assessed the risk factors and clinical outcomes for carbapenem-resistant ESBL-producing Enterobacteriaceae (ESBL-CRE) infection. Moreover, most studies have used the traditional case-control design to identify the risk factors for CRE infection, overestimating the effect of antibiotics by comparing resistant and susceptible isolates. The aim of our study was to identify some specific risk factors associated with ESBL-CRE infection by using a case–case–control study. Moreover, predictors for mortality in patients with ESBL-CRE infection were also identified in our study.

Materials and methods
Study setting and study design
This retrospective case–case–control study was performed from January 2011 to December 2014 in the First Affiliated Hospital of Chongqing Medical University, a tertiary university hospital with 3,200 beds in Chongqing, Southwest China. Patients with isolates (including Klebsiella pneumoniae, Enterobacter cloacae, and Escherichia coli) that were resistant to at least one carbapenem were enrolled in the study. Patients admitted for <48 hours and those with duplicate isolates were excluded. The three study groups in our analysis were defined as follows: the first case group consisted of patients with ESBL-CRE infection during hospitalization; the second case group consisted of patients with a positive culture for CRE but without ESBL production (non-ESBL-CRE); and the third uninfected control group was randomly selected from among patients hospitalized during the same period of time with a 1:1 ratio to the ESBL-CRE case group, consisting of patients with no clinical cultures positive for Enterobacteriaceae during hospitalization.

Antimicrobial susceptibilities and ESBL identification
Bacterial cultures were processed in the clinical microbiology laboratory. Isolates were identified using the VITEK 2 Compact system or the VITEK MS system (bioMérieux, Marcy l’Etoile, Lyon, France) and antimicrobial susceptibilities were determined in vitro using a VITEK 2 Compact AST-GN13 card (bioMérieux). All the carbapenem-resistant isolates (with resistance to at least one of the carbapenems, including imipenem, meropenem, and ertapenem) were confirmed manually by the standard broth microdilution method according to Clinical and Laboratory Standards Institute (CLSI) guidelines. E. coli American Type Culture Collection (ATCC) 25922 was used as a quality control strain during the antimicrobial susceptibility testing. Additionally, VITEK 2 compact AST-GN13 cards were used to test the antibiotic susceptibilities of all isolates to ceftazidime (CAZ), ceftriaxone (CRO), cefepime (FEP), gentamicin (GM), tobramycin (TOB), ciprofloxacin (CIP), and levofloxacin (LEV).

ESBL production was measured by the double-disk synergy test and the disk diffusion method performed on Mueller-Hinton agar supplemented with cloxacillin (250 mg/L); these tests were interpreted as defined in previously described studies. Additionally, the presence of β-lactamase-encoding genes (blaCTX-M, blaTEM, and blaSHV) and carbapenemase-encoding genes (blaKPC, blaNDM, blaOXA) were determined by PCR, as previously described.

Data collection and definitions
Relevant demographics and clinical data of the enrolled patients were extracted from medical records or directly from physicians if needed. The following parameters were used: 1) demographics: age, gender, hospital transfer, intensive care unit (ICU) admission, and 21-day mortality; 2) underlying and concomitant diseases: hypertension, diabetes, solid tumor, hypoproteinemia, hypokalemia, and anemia, as well as respiratory, cardiovascular, liver, renal, and endocrine system diseases; 3) invasive operations before a positive culture: previous surgery in the past 6 months, parenteral nutrition, mechanical ventilation, urinary catheter, drainage tube, gastric tube, tracheal cannula, nasal catheter, bladder irrigation, and central venous catheter within the prior 4 weeks; and 4) source of infection determined as pneumonia, urinary tract infection (UTI), surgical site infection, intra-abdominal infection, or line-related infection using the definitions of the US Centers for Disease Control and Prevention (CDC). Patients 260 years old were defined as elderly. Severe anemia was defined as hemoglobin level <60 g/L. Hypoproteinemia was defined as serum total
protein level <60 g/L or albumin level <25 g/L. Hypokalemia was defined as serum potassium level <3.5 mmol/L.

Sample size calculations and statistical analysis
In our study, we assumed that there would be 12% CRE cases vs 88% non-CRE cases. Based on previously published data regarding the non-ESBL isolates, we estimated that non-ESBL-CRE will be 12.8% of cases and non-ESBL control will be 49.9%. To determine a difference at the 0.05 significance level with 80% power, we estimated that we would need at least 14 non-ESBL-CRE vs 114 non-ESBL control cases (EpiInfo, version 3.3.2).

All analyses were performed using SPSS version 21.0 software (SPSS, Chicago, IL, USA). Univariate analyses were performed separately for each of the variables. Categorical variables were presented as frequencies and percentages and were compared using the McNemar test. Continuous variables were presented as medians and interquartile ranges and were compared using Student’s t-test (normally distributed variables) and Wilcoxon rank-sum test (nonnormally distributed variables). ORs and 95% CIs were calculated to evaluate the strength of any association. Variables with P < 0.10 in the univariate analysis were included in the logistic regression model for the multivariate analysis.

Ethics
The study was approved by the Chongqing Medical University Institutional Review Board and Biomedical Ethics Committee. The ethics committee waived the need for written informed consent provided by participants due to the retrospective nature of the study. Because all patient data were analyzed in anonymity, no additional informed consent was required.

Results
Study population
A total of 149 patients with CRE infection caused by E. cloacae (n=74), E. coli (n=38), and K. pneumoniae (n=37) were identified over the 4-year study period. These nonduplicated isolates were mainly cultured from urine (n=48), followed by respiratory tract secretion (n=39), wound exudate (n=31), and blood (n=31). Among these isolates, the numbers that possessed ESBL-related genes were as follows: 65 (43.6%) blaCTX-M genes, 54 (36.2%) blaTEM genes, and 64 (43.0%) blaSHV genes. Moreover, 35 isolates carried carbapenemase-related genes: 16 isolates possessed blaNDM, nine isolates carried blaKPC, seven isolates contained blaIMP, and four isolates had blaOXA. One strain of enterobacter cloacae carried both NDM-1 and IMP-8 genes. (Table 1). Of the enrolled patients, 117 with ESBL-CRE (Case I group) and 32 with non-ESBL-CRE (Case II group) were identified. A total of 117 patients without Enterobacteriaceae infection served as the control group and were randomly matched to ESBL-CRE (Case I group) and 32 with non-ESBL-CRE (Case II group) were identified. A total of 117 patients without Enterobacteriaceae infection served as the control group and were randomly matched to ESBL-CRE cases at a 1:1 ratio. Therefore, 266 patients were included in the final study cohort.

Antimicrobial susceptibility
As shown in Table 2, all isolates were resistant to ertapenem, while only 39.6% (59/149) and 31.5% (47/149) of the isolates were resistant to imipenem and meropenem, respectively. The proportion of isolates that were not sensitive to cephalosporins was relatively high: 91.3%, 88.6%, and 77.2% of the isolates showed no sensitivity to CAZ, CRO, and FEP, respec-

Table 1 The ESBL-related and carbapenemase-related genes of E. cloacae, E. coli, and K. pneumoniae

| Microorganism (number of strains) | ESBL types (number of isolates) | Carbapenemase types (number of isolates) |
|-----------------------------------|---------------------------------|----------------------------------------|
|                                   | CTX-M (number of isolates) | TEM | SHV | KPC | NDM | IMP | OXA |
| E. cloacae (74)                   | CTX-M-3 (3)                | TEM-1 (32) | SHV-2 (23) | KPC-2 (3) | NDM-1 (7) | IMP-4 (2) | – |
|                                  | CTX-M-9 (11)               | –   | –   | –   | –   | –   | –   |
|                                  | CTX-M-14 (5)               | –   | –   | –   | –   | –   | –   |
| E. coli (38)                     | CTX-M-1 (18)               | TEM-1 (8) | SHV-2 (6) | KPC-2 (3) | NDM-1 (1) | –   | OXA-1 (4) |
|                                  | CTX-M-3 (3)                | –   | –   | –   | –   | –   | –   |
|                                  | CTX-M-9 (5)                | –   | –   | –   | –   | –   | –   |
|                                  | CTX-M-14 (3)               | –   | –   | –   | –   | –   | –   |
|                                  | CTX-M-55 (1)               | –   | –   | –   | –   | –   | –   |
| K. pneumoniae (37)               | CTX-M-3 (2)                | TEM-1 (14) | SHV-1 (5) | KPC-2 (3) | NDM-1 (5) | IMP-8 (1) | – |
|                                  | CTX-M-15 (2)               | –   | SHV-11 (7) | –   | –   | –   | –   |
|                                  | CTX-M-24 (10)              | –   | SHV-12 (20) | –   | –   | –   | –   |
|                                  | CTX-M-52 (2)               | –   | SHV-26 (3) | –   | –   | –   | –   |

Notes: Some data were collected from our previously published studies (Yan et al.17, Zhang et al.17, and Jia et al.18). “–” indicates data not available.

Abbreviation: ESBL, extended-spectrum β-lactamase.
For fluoroquinolones, 93 (62.4%) and 92 (61.7%) isolates were resistant to CIP and LEV, respectively. Notably, the resistance rates of CIP and LEV were significantly higher in *E. coli* than in *K. pneumoniae* and *E. cloacae* (*P* < 0.05).

For aminoglycosides, 92 (61.7%) isolates were resistant to GM and 82 (55.0%) were resistant to TOB. Additionally, a total of 55.0% (82/149) of the isolates were classified as multidrug resistant (MDR), including 19 *E. coli* isolates, 22 *K. pneumoniae* isolates, and 41 *E. cloacae* isolates.

### Analysis of ESBL-CRE infections vs controls

As shown by the univariate analysis in Table 3, risk factors for ESBL-CRE infection were significantly more frequent in patients with ICU admissions, urinary system disease, concomitant infections, gastric tubes, nasal catheters, central venous catheters, or exposure to cephalosporins and carbapenem. According to the multivariate analysis, urinary system disease (OR: 2.15, 95% CI: 1.03–4.50, *P*=0.042), concomitant infections (OR: 5.29, 95% CI: 1.52–18.41, *P*=0.009), cephalosporin exposure (OR: 7.50, 95% CI: 3.85–14.62, *P*<0.001), and carbapenem exposure (OR: 4.80, 95% CI: 1.56–14.79, *P*=0.006) were identified as independent risk factors for infection with ESBL-CRE when compared with the uninfected controls (Table 4).

### Analysis of non-ESBL-CRE infections vs controls

According to the univariate analysis, the risk factors for the acquisition of non-ESBL-CRE were found to be statistically significant for patients who underwent surgery in the past 6 months and had concomitant infections, central venous catheters, and exposure to carbapenem. According to the multivariate analysis, concomitant infections (OR: 4.73, 95% CI: 1.10–20.28, *P*=0.036), central venous catheters (OR: 3.41, 95% CI: 1.26–9.23, *P*=0.016), and exposure to carbapenem (OR: 5.90, 95% CI: 1.56–22.33, *P*=0.009) were identified to be independent risk factors for infection with non-ESBL-CRE when compared with the uninfected controls (Tables 3 and 4).

When comparing risk factors for infection with ESBL-CRE and non-ESBL-CRE relative to controls, we found that concomitant infections and exposure to carbapenem were both associated with the ESBL-CRE and non-ESBL-CRE groups. However, urinary system diseases and exposure to cephalosporins were associated solely with ESBL-CRE infection. Additionally, having a central venous catheter was identified to be a unique risk factor for non-ESBL-CRE infection.

### Clinical outcomes: predictors for mortality

During the study period, the overall 21-day mortality rate of all patients was 26.5% (31/117). The results of the univariate and multivariate analyses of risk factors for 30-day mortality are shown in Table 5. The univariate analysis revealed that the presence of solid tumors, hypoproteinemia, tracheal cannula, and central venous catheters resulted in significant differences between the survivor and nonsurvivor groups. According to the multivariate analysis, the predictors independently associated with 30-day mortality were solid tumors (OR: 16.57, 95% CI: 4.22–65.10, *P*<0.001), hypoalbuminemia (OR: 6.06, 95% CI: 1.95–18.80, *P*=0.002), and central venous catheters (OR: 4.20, 95% CI: 1.40–12.62, *P*=0.010).

### Discussion

To our knowledge, this case–case–control study is the first analysis to systematically evaluate the risk factors for ESBL-

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**Table 2 The antimicrobial susceptibility of *E. cloacae*, *E. coli*, and *K. pneumoniae***

| Antibiotics | *K. pneumoniae* (n=37) | *E. coli* (n=38) | *E. cloacae* (n=74) |
|-------------|------------------------|------------------|---------------------|
|             | S (I%) | I (R%) | S (I%) | I (R%) | S (I%) | I (R%) |
| Ceftriaxone | 7 (18.9) | 3 (8.1) | 27 (73.0) | 1 (2.6) | 36 (94.8) | 3 (4.1) | 2 (2.7) | 69 (93.2) |
| Ceftazidime | 4 (10.8) | 2 (5.4) | 31 (83.8) | 1 (2.6) | 35 (92.1) | 3 (4.1) | 1 (1.4) | 70 (94.5) |
| Cefepime | 13 (35.1) | 0 (0) | 24 (64.9) | 5 (13.2) | 1 (2.6) | 32 (84.2) | 13 (17.6) | 2 (2.7) | 59 (79.7) |
| Ciprofloxacin | 9 (24.3) | 3 (8.1) | 25 (67.6) | 4 (10.5) | 4 (10.5) | 34 (89.5) | 37 (50.0) | 4 (5.4) | 33 (44.6) |
| Gentamicin | 14 (37.8) | 1 (2.7) | 22 (59.5) | 7 (18.4) | 0 (0) | 31 (81.6) | 31 (41.9) | 4 (5.4) | 39 (52.7) |
| Tobramycin | 12 (32.4) | 1 (2.7) | 24 (64.9) | 20 (52.6) | 0 (0) | 18 (47.4) | 29 (39.1) | 5 (6.8) | 40 (54.1) |
| Imipenem | 14 (37.8) | 6 (16.2) | 17 (45.9) | 20 (52.6) | 3 (7.9) | 15 (39.5) | 42 (56.8) | 5 (6.8) | 27 (36.5) |
| Meropenem | 16 (43.2) | 7 (18.9) | 14 (37.8) | 28 (73.7) | 2 (5.3) | 8 (21.1) | 45 (60.8) | 4 (5.4) | 25 (33.8) |
| Ertapenem | 0 (0) | 0 (0) | 37 (100) | 0 (0) | 0 (0) | 38 (100) | 0 (0) | 0 (0) | 74 (100) |

*Note: S, susceptible; I, intermediate-resistant; R, resistant.*
CRE infection and the predictors of mortality. In this work, we identified several particularly important findings. First, the most frequent ESBL-CRE species observed in our study was *E. coli*, followed by *K. pneumoniae* and *E. cloacae*, revealing that CTX-M was the most prevalent type in *E. coli*, indicating that CTX-M *E. coli* isolates are widely spread among ESBL-CRE isolates in our region.

Second, we reported for the first time that urinary system disease is an independent predictor associated with the isolation of ESBL-CRE. One explanation for this finding is that many patients with urinary obstruction or incontinence...
require some implanted medical devices, such as a urinary catheter, or suprapubic cystostomy, increasing the possibility of bacterial adherence, biofilm formation, and some morphological changes.\textsuperscript{22} Furthermore, patients with symptomatic UTIs are usually treated with prolonged or multiple antibiotic exposures, which may lead to long-term changes in the normal microbiota of the gastrointestinal tract and the development of MDR microorganisms.\textsuperscript{23}

Third, we observed that central venous catheters were identified to be independently associated with non-ESBL-CRE, and this association was well established by a previous study on CRE.\textsuperscript{24} Compared with previous observations, our results revealed that carbapenem exposure and concomitant infections are common risk factors for infection with ESBL-CRE and non-ESBL-CRE, demonstrating that these factors may be associated with CRE infection in general. First, possibly due to the increased and inappropriate use of carbapenem, selective pressure exerted by these agents could potentially promote the emergence and spread of CRE in China. Second, dysbacteriosis induced by large doses of antibiotics could stimulate the development of secondary infections, namely, concomitant infections. Third, most of these patients with concomitant infections have more severe underlying diseases and lower immunity, which may make them more vulnerable to acquiring CRE infection.

Fourth, solid tumors, hypoalbuminemia, and central venous catheters were linked to a significantly increased risk of mortality. Many cancer patients infected with resistant bacteria often receive inappropriate initial antimicrobial therapy, which may impair outcomes, prolong hospitalization,
and increase mortality. Moreover, hypoalbuminemia, as an acute phase response, may have a strong predictive value for the severity of underlying conditions, as it is the main cause of increased mortality in some malnourished patients. In addition, some invasive devices that patients receive may destroy intestinal barrier functions, promote formation of microbial biofilms, and possibly lead to catheter-related bloodstream infections, thus increasing mortality in these patients.

Our study has several limitations. First, this retrospective study was conducted at a single medical center, and our sample size was relatively small. Therefore, our findings might not be generalizable to other multicenter studies. Second, the clonality of the resistant isolates at the molecular level was not examined in our study. Therefore, potential outbreaks might not be ruled out. Finally, our study focused only on clinically significant ESBL-CRE strains, which underestimates the burden of colonizing CRE isolates with ESBL production.

Conclusion
This case–case–control study was conducted retrospectively to assess the clinical predictors associated with ESBL-CRE and non-ESBL-CRE. Our findings differed from those of previous studies, showing that urinary system disease could be independently associated with the isolation of ESBL-CRE. Moreover, another important finding of this study is that carbapenem exposure and concomitant infections are common risk factors for infection with both ESBL-CRE and non-ESBL-CRE. We also identified some peculiar factors that could have deleterious effects on clinical outcomes. Therefore, effective control measures and standard antibiotic stewardship efforts should be taken up to prevent the further spread of ESBL-CRE strains within different hospitals.

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Author contributions
All authors contributed toward data analysis, drafting, and revising the paper and agree to be accountable for all aspects of the work.

Disclosure
The authors report no conflicts of interest in this work.

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