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ORIGINAL RESEARCH

Socioeconomic Burden of Bloodstream Infections Caused by Carbapenem-Resistant *Enterobacteriaceae*

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Background: Although infection with carbapenem-resistant *Enterobacteriaceae* (*CRE*) has become an urgent public health threat worldwide, the socioeconomic burden of *CRE* bloodstream infection (BSI) remains to be clarified.

Methods: This retrospective study included all patients infected with *Escherichia coli* or *Klebsiella pneumoniae* who were hospitalized for BSI from 2013 to 2015. Socioeconomic burden, including direct and indirect economic burden, was compared in patients infected with carbapenem-sensitive *Enterobacteriaceae* (*CSE*) and *CRE* following 1:1 propensity score matching (PSM) to control for confounding variables.

Results: Data from 879 patients with *Enterobacteriaceae* BSI were evaluated, including 152 (17.3%) patients infected with *CRE* and 727 (82.7%) infected with *CSE*. PSM yielded 112 pairs of 224 patients. Median hospital length of stay did not differ significantly in the *CRE* and *CSE* groups (35 vs 29 days, P = 0.089), but in-hospital 28-day mortality rate was significantly higher in patients infected with *CRE* than with *CSE* (45.5% vs 32.1%, P = 0.040). Median direct economic burden was significantly greater in patients with *CRE*-BSI than with *CSE*-BSI during hospitalization ($24,940.1 vs 16,864.0, P = 0.017) but not during the period after infection ($10,403.4 vs 8498.0, P = 0.178). Drug expenditure accounted for the largest proportion of costs in both groups. The median disability-adjusted life year (DALY) was higher in *CRE*-BSI than in *CSE*-BSI patients, but the difference was not statistically significant (7.9 vs 6.7 years, P = 0.190). Median indirect economic burden did not differ significantly in these two groups ($3848.5 vs 1139.9, P = 0.304), although indirect economic burden increased significantly from 2013 to 2015 in patients with *CRE*-BSI.

Conclusion: Carbapenem resistance had a major impact on the clinical and socioeconomic burden of patients with *Enterobacteriaceae* BSI. The higher mortality rate in patients with *CRE*-BSI was associated with increased direct healthcare burden and indirect socioeconomic loss.

Keywords: carbapenem resistant, *Enterobacteriaceae*, *Escherichia coli*, *Klebsiella pneumonia*, socioeconomic burden, disability-adjusted life years

Introduction

Infections caused by antibiotic-resistant bacteria are a huge threat to modern healthcare systems and have triggered the development of comprehensive international plans to deal with them.[1] In particular, bacterial resistance to carbapenems has a deleterious effect on patient safety. Carbapenems are atypical β-lactam antibiotics characterized by potent, broad-spectrum antibacterial activity and are often used to treat infections with multidrug-resistant (MDR) *Enterobacteriaceae*, including *Escherichia coli* and *Klebsiella pneumoniae*.[2–4] However, the incidence of carbapenem-resistant *Enterobacteriaceae* (CRE) has increased worldwide with great regional variability. Previous study has shown different incidence of *CRE* BSI in three main

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adult acute-care hospitals of the metropolitan area of Italy, indicating the significance of management in different regions.[5] The emergence and dissemination of *CRE* seriously threatened world public health security.[6] Carbapenem resistance has been associated with increased length of hospital stay (LOS) and mortality in patients with *CRE* bloodstream infections (BSI).[7–9] So that particular attention should be given to the patients with *CRE* BSI, especially in China.[10] The mortality rates in patients infected with *CRE* were found to range from 26% to 44%, about 2-fold higher than in patients infected with carbapenem sensitive *Enterobacteriaceae (CSE)*.[7,8] Take *Klebsiella pneumoniae* for example, previous study revealed that the patients with bacteremia due to carbapenem-resistant *Klebsiella pneumoniae* (CRKP) had a 3-fold higher risk of death.[11] Carbapenem resistance has also been associated with increased economic burdens on patients and healthcare systems so that control measures of *CRE* were economically worthwhile.[12] For example, the cost of *CRE* infections was found to be higher than the annual costs of many chronic and acute diseases.[13] The median direct costs of a single *CRE* infection can range from $22,484 to $66,031 for hospitals, $10,440 to $31,621 for third-party payers, and $37,778 to $83,512 for society. Studies analyzing the socioeconomic burden of disease tend to focus only on direct costs while overlooking indirect economic costs.[13]

Disability-adjusted life year (DALY) is a widely used metric for estimating disease loss.[14–17] In a previous study, DALY was used to assess the harm caused by antimicrobial resistant in the European Union and European Economic Area (EU/EEA), the results showed the cumulative burden was estimated at 501 disability-adjusted life years (DALYs) per 100,000 general population each year.[18] To provide information enabling strategic decisions on infection control measures, antibiotic stewardship, and resistance containment, this study analyzed the direct medical costs and indirect socioeconomic costs by measuring DALY in patients with *CRE*-BSI.

Methods

Patients

Our study was conducted at a tertiary teaching hospital which is a 2500-bed teaching hospital in Eastern China. Clinical records, microbiological laboratory results and economic costs of patients with *Enterobacteriaceae* bacteremia (including *E. coli* and *K. pneumoniae* BSI) were reviewed between January 2013 to December 2015. All patients aged >16 years hospitalised with *Enterobacteriaceae* bacteremia were included at the time of the first episode of infection. If the same patient had more than two episodes of *Enterobacteriaceae* bacteremia within 6 months, this study only included the first bloodstream infection data. Only patients with complete clinical microbiological and cost data for analysis were included in this study.

Enterobacteriaceae were identified and their antimicrobial susceptibility was determined using the Vitek 2 system (bioMérieux, Marcy-l' Etoile, France). Patients with *CRE* were identified in accordance with Clinical and Laboratory Standards Institute (CLSI) guidelines.[19] The study protocol was approved by the Ethics Committee of the First Affiliated Hospital, Zhejiang University, which waived the requirement for informed consent due to the retrospective nature of this study.

The electronic medical records of all patients were reviewed. Data on expenditures were collected from the Hospital Information System. Medical costs were converted into US dollars ($) according to the average exchange rate (1$= 6.22 Renminbi) issued by the Bank of China from 2013 to 2015.[20]

Definition

CRE infection was defined as the first blood culture with a carbapenem non-susceptible organism (minimum inhibitory concentration (MIC) of ≥4 μg/mL for meropenem or imipenem). Disease severity was assessed by measuring the Acute Physiology and Chronic Health Evaluation (APACHE) II scores and the Pitt bacteremia scores[21,22] and comorbid conditions were determined by the Charlson comorbidity index (CCI).[23] DALY, an indicator of overall burden of disease, is a sum of 'years of life lost' (YLLs), an indicator of premature death, and 'years lived with disability' (YLDs), an indicator of loss of healthy living due to living under conditions worse than perfect health.[24]

Propensity Score Matching

To control for confounding variables, the two groups of patients infected with *CRE* and *CSE* were subjected to 1:1 propensity score matching (PSM). Variables used in PSM included patients' demographic characteristics (age and sex), transplantation during hospital stay, admission to the intensive care unit (ICU), disease severity (APACHE II and Pitt bacteremia scores), and comorbid conditions (CCI), but not clinical outcomes (LOS and mortality rates) or economic burden.

Medical Costs

The direct economic burden is the direct economic costs of disease prevention and treatment, whereas the indirect economic burden refers to the current and future loss of value to the patient's family and society caused by the reduced working time or capacity due to the disease itself or to disability or death. Direct medical costs included the costs of hospitalization (room and board), nursing care, drugs, laboratory and imaging tests, blood products, consultation with doctors, surgery, and other costs. In order to eliminate the impact of pre-infection costs, we collected overall direct medical costs and direct medical costs before/after the infection. To analyze DALYs, YLL and YLD were calculated using the equations.[25]

$$YLLs[\gamma, \mathrm{K}, \beta] = \frac{KCe^{\gamma\alpha}}{(\gamma+\beta)^2}\left\{\begin{array}{l} e^{-(\gamma+\beta)(L+\alpha)}[-(\gamma+\beta)(L+\alpha)] \\ -e^{-(\gamma+\beta)\alpha}[-(\gamma+\beta)\alpha-1] \end{array}\right\} + \frac{1-K}{\gamma}\left(1-e^{-\gamma L}\right)$$

$$YLDs[\gamma, \mathrm{K}, \beta] = \mathrm{D}\left\{\begin{array}{l} \frac{KCe^{\gamma\alpha}}{(\gamma+\beta)^2}\left\{\begin{array}{l} e^{-(\gamma+\beta)(L+\alpha)}[-(\gamma+\beta)(L+\alpha)] \\ -e^{-(\gamma+\beta)\alpha}[-(\gamma+\beta)\alpha-1] \end{array}\right\} \\ +\frac{1-K}{\gamma}\left(1-e^{-\gamma L}\right) \end{array}\right\}$$

where K is the age weighting modulation factor; C is a constant; γ is the discount rate; a is age at onset of disability; β is a parameter of the age weighting function; L is the duration of disability; and D is the disability weight.

These formulas included the values recommended by the World Health Organization (WHO).[26] The international standard discount rate was set at 0.03; K-values were set at 0 when no age weights were used and 1 when age weights are used; and the standard age weights used a β of 0.04 and a constant of 0.1658.[25] According to the Global Burden of Disease (GBD) template provided by the WHO,[27–29] D ranged from 0 to 1. D was based on the severity of acute infection, with mild, moderate, and severe infections having D values of 0.006, 0.051, and 0.133, respectively.[25] Productivity weights for individuals aged 15–44, 45–59, and >60 years were 0.75, 0.80, and 0.1,[30] respectively. Per capita gross domestic product (GDP) in 2013, 2014, and 2015 in China were $7023.15, $7584.08, and $8076.69, respectively.[31]

Statistical Analysis

Categorical variables were compared by the $\chi 2$ test or two-tailed Fisher's exact test, as appropriate. Normally distributed continuous variables were expressed as mean ± standard deviation (SD) and compared using Student's t tests, whereas non-normally distributed continuous variables were expressed as median and interquartile range (IQR) and compared using Mann–Whitney *U*-tests. All statistical analyses were performed using SPSS version 23.0 software (IBM Corporation, Armonk, NY, USA), with P-values ≤0.05 considered statistically significant.

Results

Patient Characteristics and Outcomes

Between January 2013 and December 2015, 879 patients hospitalized with *Enterobacteriaceae* BSIs qualified for this study; of these, 727 (82.7%) had *CSE*-BSI and 152 (17.3%) had *CRE*-BSI. Median LOS was significantly longer (35 vs 20 days, P < 0.001) and mortality rate significantly higher (57.2% vs 18.3%, P < 0.001) in the *CRE* than in the *CSE* group. However, median LOS after BSI in two groups had no significant difference (13 vs 13 days, P = 0.979). Patients with *CRE*-BSI were also more likely to undergo organ transplantation, be admitted to the ICU while hospitalized, and have more severe disease than patients with *CSE*-BSI (Table 1). PSM yielded 112 pairs of patients with largely balanced potential confounding factors (Table 2).

Following PSM, median LOS was longer (35 vs 29 days, P = 0.089) and overall mortality rate was higher (50.1% vs 38.4%, P = 0.060) in patients with *CRE*-BSI than with *CSE*-BSI, but the differences were not statistically significant. While the median LOS after BSI in two groups had also no significant difference (12.5 vs 16.5 days, P = 0.493). However, mortality rates 7 (27.7% vs 16.1%, P = 0.036), 14 (47.5% vs 22.3%, P = 0.013), and 28 (45.5% vs 32.1%, P = 0.040) days after infection were significantly higher in the *CRE* than in the *CSE* group (Table 2).

Direct Economic Burden

Median in-hospital total direct healthcare burden was significantly higher in patients with *CRE*-BSI than with *CSE*-BSI ($24,940.1 vs 16,864.0, P = 0.017). After eliminating costs before infection, however, the direct economic burden after BSI onset was higher in the *CRE*-BSI than in the *CSE*-BSI group, but the difference was not statistically significant ($10,403.4 vs 8498.0, P = 0.178). Expenditures for medicine accounted for the largest proportion of costs in both groups. The median cost of antibiotics during the entire hospital stay was significantly higher in the *CRE*-BSI than in the *CSE*-BSI group ($5904.9 vs 3693.0, P = 0.001) but did not differ

Table 1 Demographic and Clinical Characteristics of the Patients with Bacteremia Caused by CRE or CSE

		CSE (n=727)	CRE (n=152)	P-value
Species, n (%)				
K. pneumoniae		293 (40.3)	135 (88.8)	
E. coli		434 (59.7)	17 (11.2)	
Demographic				
Gender	Male, n (%)	434 (59.7)	115 (75.7)	<0.001
Age	Years, (median, IQR)	60 (49–70)	59.5 (49–67)	0.582
Transplantation while in hospital, n (%)		29 (4.0)	26 (17.1)	<0.001
ICU stay while in hospital, n (%)		135 (18.6)	98 (64.5)	<0.001
Nosocomial infection, n (%)		521 (71.7)	152 (100)	<0.001
Severity of illness at time of BSI				
APACHEII score (median, IQR)		9 (6–12)	12 (8–17)	<0.001
Pitt score (median, IQR)		1 (0–2)	2 (1–4)	<0.001
Charlson comorbidity score (median, IQR)		2 (0–2)	2 (1–3)	<0.001
Total hospital stay, days (median, IQR)		20 (11–36)	35 (17.25–67.25)	<0.001
Hospital stay after BSI, days (median, IQR)		13 (7–22)	13 (4–28.75)	0.979
Mortality, n (%)				
Total		133 (18.3)	87 (57.2)	<0.001
28 days		113 (15.5)	80 (52.6)	<0.001
14 days		80 (11.0)	60 (39.5)	<0.001
7 days		61 (8.4)	46 (30.3)	<0.001

Note: Data are expressed as numbers (%) unless otherwise stated.
Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; BSI, bloodstream infection; CCI, Charlson comorbidity index; CRE, carbapenem-resistant *Enterobacteriaceae*; CSE, carbapenem-susceptible *Enterobacteriaceae*; KP, *Klebsiella pneumoniae*; *E. coli*, *Escherichia coli*; ICU, intensive care unit; IQR, interquartile range.

during the post-infection hospital stay ($2647.5 vs 1836.3, P = 0.190) (Table 3).

Indirect Economic Loss

Median DALY was higher in patients with *CRE*-BSI than with *CSE*-BSI, but the difference was not significant (7.9 vs 6.7 years, P = 0.190). In addition, the median indirect economic loss was higher in patients infected with *CRE* than with CSE ($3848.5 vs 1139.9, P = 0.340) (Table 3). DALY and indirect economic loss were highest in patients aged 16–29 years and lowest in patients aged >74 years (Table 4). Moreover, indirect economic loss increased significantly from 2013 to 2015 in patients infected with *CRE*-BSI and *Enterobacteriaceae* (Table 5).

Discussion

Infections caused by drug resistant gram-negative bacteria, particularly *CRE*, are becoming increasingly prevalent and constitute a serious threat to public health worldwide because they are difficult to treat and are associated with higher morbidity and mortality rates.[32] The incidence of *CRE* infection in China was reported to be 4.0 per 10,000 discharges,[33] and the mortality rates from *CRE* bacteremia have ranged from approximately 19% to 70%.[34,35] Infection with carbapenem-resistant gram-negative bacteria may also increase medical costs.[13] To better understand the burden of *CRE* infection, our study explored the direct economic costs and indirect economic loss of *CRE*-BSI infection and its dynamic changes in recent years.

The most important finding of this study was that carbapenem resistance had major effects on patient outcomes and socioeconomic burden of *Enterobacteriaceae* BSI. Compared with patients in the *CSE*-BSI group, those in the *CRE*-BSI group were more likely to have nosocomial infections, undergo organ transplantation, be admitted to the ICU, and have more severe disease (APACHEII and

Table 2 Features of the Patients with Bacteremia Caused by CRE or CSE After PSM for Potential Confounding Variables

		CSE (n=112)	CRE (n=112)	P-value
Species, n (%)				
K. pneumoniae		69 (61.6)	96 (85.7)	
E. coli		43 (38.4)	16 (14.3)	
Demographic				
Gender	Male, n (%)	84 (75)	84 (75)	1.000
Age	Years, (median, IQR)	62 (47.8–70)	58.5 (48.8–67)	0.979
Transplantation while in hospital, n (%)		17 (15.2)	17 (15.2)	1.000
ICU stay while in hospital, n (%)		65 (58.0)	66 (58.9)	0.892
Nosocomial infection, n (%)		111 (99.2)	112 (100)	0.317
Severity of illness at time of BSI				
APACHEII score (median, IQR)		11 (8–15)	12 (8.8–30.3)	0.450
Pitt score (median, IQR)		2 (0–3.3)	2 (0.8–4)	0.517
Charlson comorbidity score (median, IQR)		2 (1–3)	2 (1–3)	0.581
Total hospital stay, days (median, IQR)		29 (17–43.5)	35 (18–66)	0.089
Hospital stay after BSI, days (median, IQR)		16.5 (8–28)	12.5 (4.8–30.3)	0.493
Mortality, n (%)				
Total		43 (38.4)	57 (50.1)	0.060
28 days		36 (32.1)	51 (45.5)	0.040
14 days		25 (22.3)	42 (47.5)	0.013
7 days		18 (16.1)	31 (27.7)	0.036

Note: Data are expressed as numbers (%) unless otherwise stated.
Abbreviations: CRE, carbapenem-resistant *Enterobacteriaceae*; CSE, carbapenem-susceptible *Enterobacteriaceae*; KP, *Klebsiella pneumoniae*; *E. coli*, *Escherichia coli*; IQR, interquartile range.

Pitt scores) and more comorbidities (Charlson score). To eliminate potential confounding factors for outcomes, the two groups of patients were subjected to PSM, minimizing possible sources of bias, such as demographic characteristics and disease severity. After eliminating confounding factors, the poorest clinical outcomes were also observed in this study. Patients with *CRE*-BSI had higher mortality than patients with *CSE*-BSI at 7, 14 or 28 days after infection ($P < 0.05$), which was similar to previous study[13] and underscored the magnitude of the damage carbapenems did. This study found that the median per capita total direct medical costs ($24,940.1 vs 16,864.0, $P = 0.017$) and indirect economic loss ($3848.5 vs 1139.9, $P = 0.304$) were higher in patients with *CRE*-BSI than with *CSE*-BSI, confirming that carbapenem resistance increased the economic burden of disease. This finding was consistent with studies showing that carbapenem resistance was associated with higher medical costs in patients infected with *K. pneumoniae*[36] and *E. coli*.[37] In addition, the median economic burden for hospitals of a single patient infected with *CRE* was about $59,366.2, far more than the average person in China can afford.

The differences in direct economic burden between the two groups were caused primarily by the higher costs of antibiotics in the *CRE* group. Similarly, the cost of antibiotics, especially broad-spectrum antibiotics, has been reported to contribute to the high direct medical expenses in patients with CRE.[38] Another study, however, reported that the cost of antibacterial drugs accounted for a small part of the total cost of hospitalization.[39] However, we found that the cost of medicine was the largest single direct medical cost, with antibiotics accounting for 23.7% ($5904.9/$24,940.1) of all direct medical costs in *CRE* infected patients. Thus, although other factors were more responsible for direct medical costs in these patients, the contribution of antibiotics to all costs should not be

Table 3 Socioeconomic Burden of the Patients with BSI Caused by CRE or CSE After PSM for Potential Confounding Variables

	CSE (n=112)	CRE (n=112)	P-value
Total direct medical expenses while in hospital, $US (median, IQR)	16,864.0 (8353.7–36,556.2)	24,940.1 (11,117.1–60,442.7)	0.017
Hospitalizing	211.8 (115.6–524.5)	266.5 (133.4–705.6)	0.184
Nursing	156.6 (54.0–308.6)	209.5 (90.7–445.7)	0.050
Medicine	8102.9 (3298.7–17,891.2)	13,498.3 (6702.7–31,056.7)	0.001
Traditional Chinese medicines	2.0 (0.0–38.5)	0.0 (0.0–32.4)	0.678
Laboratory and imaging examinations	1995.3 (940.8–4352.2)	3010.4 (1157.3–6427.6)	0.049
Oxygen	329.0 (121.4–697.4)	555.4 (216.4–1132.1)	0.005
Blood transfusion	121.8 (0.0–613.9)	337.2 (32.8–1606.7)	0.003
Consultation	47.0 (87.0–19.8)	57.9 (21.4–109.6)	0.197
Surgery	77.8 (0.0–710.9)	77.8 (0.0–854.5)	0.669
Others	499.5 (268.5–1119.5)	671.3 (336.2–1430.2)	0.127
Direct medical expenses after BSI onset, $US (median, IQR)	8498.0 (3136.8–20,150.2)	10,403.4 (4967.1–24,995.0)	0.178
Hospitalizing	135.9 (56.9–289.4)	112.5 (39.2–288.4)	0.586
Nursing	103.7 (21.2–244.9)	87.8 (20.7–205.5)	0.836
Medicine	4342.8 (1794.3–10,396.9)	5892.6 (2668.8–15,299.3)	0.107
Traditional Chinese medicines	0.0 (0.0–14.2)	0.0 (0.0–7.0)	0.224
Laboratory and imaging examinations tests	1109.6 (376.5–2690.5)	1253.1 (441.6–2936.6)	0.376
Oxygen	178.9 (41.6–519.5)	253.1 (64.1–608.9)	0.145
Blood transfusion	0.0 (0.0–362.9)	162.8 (0.0–607.7)	0.037
Consultation	26.5 (10.3–57.9)	21.7 (6.8–53.7)	0.437
Surgery	0.0 (0.0–99.7)	0.0 (0.0–120.2)	0.782
Others	269.5 (68.1–631.7)	226.4 (73.9–589.3)	0.662
Total antibiotic costs while in hospital, $US (median, IQR)	3693.0 (1194.4–7179.9)	5904.9 (2705.5–11,726.1)	0.001
Antibiotic costs after infection, $US (median, IQR)	1836.3 (727.4–4952.4)	2647.5 (969.1–6390.7)	0.190
Total indirect loss $US (median, IQR)	1139.9 (41.8–14,893.5)	3848.5 (69.4–90,752.1)	0.304
Median DALY, yr	6.7	7.9	0.190

Note: Data are expressed as $(US dollars) unless otherwise stated.
Abbreviations: CRE, carbapenem-resistant *Enterobacteriaceae*; CSE, carbapenem-susceptible *Enterobacteriaceae;* KP, *Klebsiella pneumoniae*; DALY, disability-adjusted life year; IQR, interquartile range; $, US dollars.

Table 4 Indirect Economic Loss to Patients Caused by *Enterobacteriaceae* Bacteremia in Different Age Groups

	CSE (n=112)			CRE (n=112)			*Enterobacteriaceae* (n=224)		
Age Group, Year	**Number, n**	**Average DALY, Year**	**Average Indirect Economic Loss, $**	**Number, n**	**Average DALY, Year**	**Average Indirect Economic Loss, $**	**Number, n**	**Average DALY, Year**	**Average Indirect Economic Loss, $**
16~29	7	15.7	88,611.3	4	16.6	97,214.8	11	16.0	91,739.8
30~44	15	12.6	70,570.1	13	9.8	58,374.2	28	11.3	64,907.7
45~59	30	8.2	50,263.9	44	10.9	67,912.3	74	9.8	60,757.5
60~74	45	3.9	2969.9	36	4.8	3747.1	81	4.3	3315.3
>74	15	1.8	1327.1	15	2.6	1937.9	30	2.2	1632.5
Total	112	6.7	29,824.1	112	7.9	38,391.3	224	7.3	34,107.7

Abbreviations: *CRE*, carbapenem-resistant *Enterobacteriaceae*; *CSE*, carbapenems susceptible *Enterobacteriaceae*; $, US dollars.

Table 5 Yearly Socioeconomic Burden per Patient in Patients with Bacteremia from 2013 to 2015

Year		*CSE*			*CRE*			*Enterobacteriaceae*		
	GDP	Direct Economic Burden	Indirect Economic Burden	Social Economic Burden	Direct Economic Burden	Indirect Economic Burden	Social Economic Burden	Direct Economic Burden	Indirect Economic Burden	Social Economic Burden
2013	7023.2	25,144.9	29,663.2	54,808.1	42,624.6	21,279.3	63,903.9	32,948.4	25,920.4	58,868.8
2014	7584.1	34,747.7	29,352.5	64,100.2	60,490.7	35,038.6	95,529.3	46,032.3	31,845.0	77,877.4
2015	8076.7	31,082.3	31,017.9	62,100.2	45,219.5	48,120.2	93,339.7	39,267.0	40,919.2	80,186.2

Note: All results reported as US $.
Abbreviations: GDP, gross domestic product; *CRE*, carbapenem-resistant *Enterobacteriaceae*; *CSE*, carbapenem-susceptible *Enterobacteriaceae*.

underestimated. Implementation of antibiotic stewardship practices may therefore reduce the economic burden on individuals, hospitals, and society. Besides, we indeed found that *CRE* infections were associated with higher medicine cost, but increased cost mainly occurred before the infection. This may be related to delayed correct diagnosis or premature antibiotic intervention or some underlying condition such as other kinds of infection. On the other hand, unlike the United States or other developed countries, the cost of room and board in China was very cheap. So that the cost of room and board played a trivial role in all total direct medical expenses, which was inseparable from Chinese national conditions.

The indirect loss analyzed in this study consisted primarily of reduced working time and socially creative productivity resulting from a patient's illness, disability, or death. Although these costs are frequently determined using a capital- or output-accounting approach, this method has certain limitations.[40] The indirect economic loss due to disease in this study was analyzed by determining DALY, a new disease burden index. The present study found that DALY and indirect economic loss were higher in patients infected with *CRE* than with *CSE*, but the differences were not statistically significant. Analysis of indirect economic loss in different age groups showed that this loss was highest in patients aged 16–29 years, which may be related to different productivity weights. However, the results remained uncertain due to smaller sample sizes in some age groups (eg, 16–29 years group) and there were little data based on the distribution of indirect burdens by age groups worldwide. And it was important to note that these burdens were mainly paid by individuals but did not reduced by the healthcare provision. Therefore, healthcare providers may be able to reduce the economic burden of society to the greatest extent by changing the proportion of medical reimbursements for different age groups. Notably, indirect economic loss in this group increased yearly. Combined with the increasing incidence of *CRE*, these findings suggest that the indirect economic loss caused by *CRE* infection may continue to increase over time.

Similar to previous findings,[14] the present study found that mortality rates were significantly higher in patients with *CRE*-BSI than with *CSE*-BSI ($P < 0.05$), emphasizing the clinical effects of carbapenem resistance. Although hospital LOS was greater in the *CRE*-BSI than in the *CSE*-BSI group, the difference was not statistically significant. PSM that included LOS as a potential confounding variable resulted in a similar median LOS in the two groups, indicating that the effect of carbapenem-resistance on hospital LOS was due to longer hospital LOS before infection.[36] These findings suggest that hospital LOS was unrelated to the increase in medical costs.

This study had several limitations. First, this study was a retrospective analysis, which has certain selection and recall biases. Although PSM was performed to control for potential confounding factors, some unmeasured confounders remained present. Second, the socioeconomic burden of disease also includes indirect medical expenses and intangible economic burdens such as psychosocial costs. Because these costs are difficult to estimate, they were omitted from the cost estimates in this study. Finally, this single-center study only included patients infected with *K. pneumoniae* and *E. coli*. Thus, our findings may not represent the economic burden of infection with other types of *Enterobacteriaceae.*

In conclusion, infection with carbapenem-resistant bacteria resulted in higher direct and indirect economic costs. Although *CRE*-BSI did not significantly affect hospital LOS, mortality rates were higher in patients with *CRE*-BSI than with *CSE*-BSI. Medicines accounted for the largest proportion of direct medical expenses in both groups, suggesting the need for stricter regulation of antibiotic use. But the fundamental thing was that we could

spend more effort to prevent the occurrence of nosocomial infection, which may reduce the cost of infection effectively.

Ethics

This study protected relevant data of all patients and received approval from the Research Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University (Reference number 2019693) in accordance with the Declaration of Helsinki. All data in relation to transplantations performed in the People's Republic of China were obtained after the modification of the transplant law banning the use of organs from executed prisoners (year 2015) which was conducted in accordance with the Declaration of Istanbul. All organs were donated voluntarily with written informed consent. The study was registered at http://www.ClinicalTrials.gov (ID: ChiCTR1900025064).

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work. These authors contributed equally to this work and should be considered co-first authors: Yunying Zhu and Tingting Xiao.

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Disclosure

None of the authors reports any conflicts of interest for this work.

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