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Economic Burden of Patients with Bloodstream Infections Caused by Extended-Spectrum β-Lactamase-Producing *Escherichia coli*

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Background: The prevalence of infections with extended-spectrum β-lactamase-producing *Escherichia coli* (ESBL-EC) is increasing worldwide, but the economic impact of ESBL-EC bloodstream infection (BSI) has not been comprehensively evaluated.
Patients and Methods: A retrospective cohort including patients hospitalized at a tertiary hospital between January 2013 and December 2016 who were confirmed with a BSI of ESBL-EC or non-ESBL-EC was set. Clinical data and medical costs were collected by chart review of electronic and paper medical records. The economic burden was evaluated with disability-adjusted life years (DALYs).
Results: A total of 580 patients with *E. coli* BSI, comprising 333 patients (57.4%) with ESBL-EC BSI and 247 patients (42.6%) with non-ESBL-EC BSI, were identified. There were no significant differences in comorbidity and severity of patients between ESBL-EC and non-ESBL-EC BSI. The median length of stay (LOS) after bacteremia was 12 days for ESBL-EC (interquartile range, 7 to 21) versus 11 days for non-ESBL-EC (interquartile range, 7 to 21) (P = 0.38), and appropriate empirical antimicrobial therapy occurred in 87.4% versus 89.9% (P = 0.353). The mortalities were 20.1% versus 17.4% (P = 0.41). Patients with ESBL-EC did not have significantly different in-hospital medical costs to those with non-ESBL-EC (median, $8048.68 vs $7476.84, respectively, with a difference of $571.84, P = 0.321). In the non-ESBL-EC group, 247 patients lost 531.05 DALYs in total, with an average of 2.15 DALYs per person, while in the ESBL-EC group, 333 patients lost 692.64 DALYs in total, with an average of 2.08 DALYs per person. There is no significant difference in average DALYs (P = 0.343).
Conclusion: In conclusion, patients with BSI due to ESBL-EC did not cost more than patients with BSI due to non-ESBL-EC. This phenomenon may be attributed to timely and effective antibiotic treatment, but the initial empiric therapy with second- or third-line antibiotics in non-ESBL-EC BSI should be corrected.
Keywords: *Escherichia coli*, extended-spectrum β-lactamase, ESBL, medical cost

Introduction

Escherichia coli, a member of the Enterobacterales, is a main pathogen responsible for community and nosocomial infections, and is the leading cause of Gram-negative bloodstream infections (BSIs).[1] Extended-spectrum β-lactamase (ESBL) enzyme production is the common resistance mechanism to β-lactam antibiotics in Gram-negative bacteria. In addition, other resistance determinants, such as fluoroquinolones, aminoglycosides, trimethoprim-sulfamethoxazole resistance, are often associated with ESBLs.[2] Thus, ESBL-producing organisms commonly exhibit

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a multidrug resistance phenotype. Infections due to ESBL-producing *E. coli* (ESBL-EC) have dramatically increased worldwide, presenting a great public concern. The prevalence of infections with ESBL-producing pathogens has steadily risen since 2000.[3–5] Lately, a study showed that a high prevalence of community-acquired ESBL-producing Enterobacterales infections (46.5%, 256/550) had been reported in public county hospitals in China.[6] Consistent herewith, the presence of faecal ESBL-producing Enterobacterales from healthy individuals are also very high in China ranging from 42.0% to 82.6%.[7–9]

Although the problem of ESBL resistance has attracted a great deal of attention from the public, the magnitude of the impact of drug-resistant bacteria on clinical and economic outcomes remains largely unknown. Therefore, we aimed to quantify the potential clinical and economic impact of ESBL production. In some studies, they showed increased mortality associated with ESBL-positive infection,[10,11] while our previous study[12] had come to the opposite conclusion that patients with BSI due to ESBL-EC did not show a higher mortality and a longer hospitalization than patients with BSI due to non-ESBL-EC.

Furthermore, there are few assessments of the specific economic impact of ESBL production on patient outcomes.[10,11,13] These articles mainly studied the direct economic burden of drug-resistant bacterial infections, and did not pay attention to the indirect economic burden caused by drug-resistant bacteria infections. Disability-adjusted life years (DALYs) is a widely used metric for estimating disease burden, which was developed and used by experts from Harvard University School of Public Health and the World Health Organization (WHO) in 1993. The Global Burden of Disease (GBD) study systematically compared the magnitude of health losses caused by different diseases worldwide. DALYs was successfully used by GBD to measure health losses quantitatively. It is a summary measure that combines the time lost due to premature mortality, expressed as years of life lost (YLL), with the time lived in states worse than full health, expressed as years lived with disability (YLD).[14] One DALY can be thought of as one year of "healthy" life lost due to different diseases. The sum of these DALYs can be thought of as the gap between current health status and that of an ideal health situation, that is, a normative reference population that lives to an advanced age, free of disease and disability.[15]

To analyze the economic impact of ESBL-EC BSI, we conducted a retrospective cohort study to compare direct costs and indirect costs between inpatients with ESBL-EC and those with non-ESBL-EC.

Patients and Methods

Patients

A retrospective cohort study of adult inpatients with *E. coli* bacteremia at a 2500 bed teaching hospital (Zhejiang, China) from January 2013 to December 2016 was conducted. Inclusion criteria were as follows: (1) all patients had a positive blood culture for *E. coli*; (2) clinical manifestations of bloodstream infection; and (3) hospitalization with complete clinical microbiological and cost data for analysis. Patients were excluded if they had incomplete medical records or their age was younger than 16 years. For patients having multiple episodes of *E. coli* bacteremia during hospitalization or readmission within 6 months, data only from the first episode of *E. coli* bacteremia were included. The patients infected with ESBL-EC were referred as "cases" and patients infected with non-ESBL-EC were referred as "controls" in the study.

Microbiological Tests

These isolates were identified by the matrix-assisted laser desorption ionization-time-of-flight mass spectrometry (MALDI-TOF-MS) (Bruker, Bremen, German) and the VITEK 2 COMPACT automatic microbial identification system (bioMérieux, Marcy l'Etoile, France). Antimicrobial susceptibility of these strains was assessed by using the VITEK 2 system. According to the guidelines of the Clinical and Laboratory Standards Institute (CLSI) standards (2016),[16] ESBL production was determined by the double-disk test using a combination of ceftazidime and ceftazidime-clavulanic acid or cefotaxime and cefotaxime-clavulanic acid.[17]

Definitions

Hospital-acquired bacteremia was defined as a positive blood culture obtained at greater than or equal to 48 h after admission. Community-acquired bacteremia was defined as a positive blood culture taken on admission or less than 48 h after admission. Severity of illness at the time of BSI onset was assessed by the Acute Physiology and Chronic Health Evaluation (APACHE) II scores and Pitt scores.[18] The Charlson comorbidity index was calculated to determine the overall systemic health status of patients.[19] Initial antibiotic treatment was defined as the drugs administered empirically in culture-negative

situations. The initial antimicrobial therapy was considered effective if the empirical administration of at least one antibiotic being active against isolated microorganisms with in vitro susceptibility testing.[20]

Data Collection

For all patients enrolled in this study, clinical and laboratory data were collected from electronic medical records, including: patient demographics (sex; age), comorbid illnesses, Charlson comorbidity index, day of BSI onset, intensive care unit (ICU) stay before bacteremia, organ transplantation during hospitalization, severity of illness (APACHEII score and Pitt score), overall hospital length of stay (LOS) and LOS before/after the infection; microbiological data, susceptibility of empirical antimicrobials and targeted antimicrobial, and clinical outcome recorded as "death" or "discharged alive". The study complies with the Declaration of Helsinki; Ethics Committee approval was received from the Hospital Ethics Committee.

Cost Analysis

The cost was obtained from the hospital information system. The patient's direct costs and indirect costs (i.e. productivity losses due to absenteeism and mortality) were analyzed. All the costs were converted into US dollars ($) with an exchange rate (average: $1 = 6.33 Renminbi).

Direct Cost

The total direct costs comprised of room and board, nursing, medicines (including antibacterial agents, traditional chinese medicines), oxygen inhalation, mechanical ventilation, blood transfusion, operation, laboratory tests and images.

Indirect Economic Burden

The indirect economic burden of *E. coli* bacteremia was analyzed through DALYs and human capital methods, which are equal to DALYs multiplied by Gross Domestic Product (GDP) per capita multiplied by productivity weight. And the GDP per capita in China in 2013 was $6944.99, in 2014 was $7682.90, in 2015 was $8063.72 and in 2016 was $8153.46.[21] Productivity weights are different for different age groups.[22] Children aged from 0 to 14 years old did not participate in social wealth creation, with a weight of 0.15; 15–44 years old and 45–59 years old created more wealth, with a value of 0.75 and 0.80 respectively; over 60 years old, it dropped to 0.1.[22]

DALYs for *E.coli* BSI are calculated by summing the YLLs for all deaths caused by this disease and the YLDs for people living in states of less than good health caused by this disease.[15] These factors, such as life expectancy, age, future time and disability, were included in the YLLs and YLDs calculation.

The formula for YLLs is described below. The calculation YLLs [γ,K,β] is used to signify key factors (age weight and discount rate). Values were recommended and used by Murray and Lopez,[23,24] i.e. γ = 0.03, K = 1 and β = 0.04.

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

K = age weighting modulation factor; C = constant; γ = discount rate; a = age of onset of disability; β = parameter from the age weighting function; L = standard expectation of life at age a.

The difference with the formula for YLLs is that D (the disability weight) was added in the formula for YLDs [γ, K,β], as follows:

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

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

This formula uses the values recommended by the WHO,[25] constant value is 0.1658.[25] The value of disability weight (D) ranges from 0 to 1 according to the GBD template provided by the WHO.[14,26,27] Since the recent GBD studies did not mention the standard for BSI, we decided that the evaluation of D is based on the acute infection, which is divided into 0.006, 0.051 and 0.133 according to severity of the diseases in mild, moderate and severe conditons.[14] In order to calculate L (the years lost by death and discounted by disability), we used "standard expected years of life lost" (SEYLL) as a good approximation of life expectancy.[25]

Statistical Methods

Dates were expressed as mean standard deviation or median (interquartile range [IQR]) for continuous variables

and percentage n (%) for categorical variables. For statistical analysis, inter-group differences were tested using Student's *t*-test (for variables with normal distribution) or the Mann–Whitney *U*-test (for variables with non-normal distribution) for continuous variables and χ2 or two-tailed Fisher exact test for Categorical variables. P values less than 0.05 were considered statistically significant. Statistical analyses were performed using SPSS version 23.0 package (SPSS, Chicago, IL, USA).

Results
Patient Demographics and Clinical Outcomes

We identified a total of 1115 *E. coli* isolates from blood from 647 patients between January 2013 and December 2016, and excluded 468 duplicate isolates from the same patient and then 67 patients without complete information about their hospitalization. Finally, 580 non-replicate clinical isolates of *E. coli* isolated from blood from 580 patients were included in the analysis. The 580 patients comprised 333 patients (57.4%) with ESBL-EC BSI and 247 patients (42.6%) with non-ESBL-EC BSI. Half of the 580 patients were male, and the average ages were 61 and 60 years old for those with ESBL-EC BSI and non-ESBL-EC BSI, respectively. In the ESBL-EC group, the most common comorbidities were hepatobiliary disease (27.9%), hypertension (27.3%) and malignant tumor (20.4%) while being hepatobiliary disease (29.6%), hypertension (27.5%) and hematological diseases (20.6%) in the non-ESBL-EC group. There was no significant difference in the comorbidities and Charlson comorbidity index between patients with ESBL-EC and those with non-ESBL-EC. The severity of BSI (APACHEII score and Pitt score) of the ESBL-EC group showed no significant difference compared with the non-ESBL-EC group (Table 1).

For the initial therapy, β-lactam-β-lactamase inhibitors (BLBLI) and carbapenems were administered empirically in 85% of patients with non-ESBL-EC infection while in 83.4% of patients with ESBL-EC infection. Notably, 87.4% of patients with ESBL-EC BSI received effective initial antibiotic treatment, compared with 89.9% of those with non-ESBL-EC BSI (P = 0.975).

The total LOS of patients with ESBL-EC BSI and non-ESBL-EC BSI was 19 (IQR, 11–36.5) and 20 (IQR, 11–31) days, respectively (P = 0.809). The LOS after bacteremia with ESBL-EC were longer (but without statistical

Table 1 Characteristics of Patients with *Escherichia coli* Bloodstream Infection (BSI) Stratified by Extended-Spectrum-Lactamase (ESBL) Production[a]

Parameter/Category	Non-SBL (n = 247)	ESBL (n=333)	P
Male sex, n (%)	138 (55.9)	184 (55.3)	0.883
Age in years, (median, IQR)	60 (47–71)	61 (49.5–70.5)	0.967
Organ transplantation during hospitalization, n (%)	11 (4.5)	18 (5.4)	0.603
LOS in days			
Total LOS in days, (median, IQR)	20 (11–31)	19 (11–36.5)	0.809
LOS after the bacteremia in days, (median, IQR)	11 (7–21)	12 (7–21)	0.38
Combined with other bacterial infections, n (%)	13 (5.3)	20 (6.0)	0.703
Admission to ICU before bacteremia, n (%)	18 (7.3)	29 (8.7)	0.535
APACHEII score, (median, IQR)	9 (6–13)	9 (6–13)	0.951
Pitt score, (median, IQR)	1 (0–2)	0 (0–2)	0.364
Comorbid illnesses (%)			
Hepatobiliary disease, n (%)	73 (29.6)	93 (27.9)	0.668
Hypertension, n (%)	68 (27.5)	91 (27.3)	0.957
Malignant tumor, n (%)	49 (19.8)	68 (20.4)	0.863
Hematological diseases, n (%)	51 (20.6)	48 (14.4)	0.049
Other, n (%)	49 (19.8)	66 (19.8)	0.996
Charlson comorbidity index, (median, IQR)	2 (0–2)	2 (0–2)	0.229
Empirical antimicrobial			
Cephalosporins, n (%)	16 (6.5)	26 (7.8)	0.541
BLBLI, n (%)	89 (36.0)	120 (36.0)	0.999
Carbapenems, n (%)	121 (49.0)	158 (47.4)	0.714
Tigecycline, n (%)	6 (2.4)	7 (2.1)	0.792
Aminoglycosides, n (%)	5 (2.0)	5 (1.5)	0.867
Fluoroquinolone, n (%)	43 (17.4)	43 (12.9)	0.132
Other, n (%)	5 (2.0)	9 (2.7)	0.599
Effective empirical antimicrobial therapy, n (%)	222 (89.9)	291 (87.4)	0.353
Mortality			
Total mortality, n (%)	43 (17.4)	67 (20.1)	0.41
28-day mortality, n (%)	38 (15.4)	54 (16.2)	0.786
14-day mortality, n (%)	31 (12.6)	37 (11.1)	0.594
7-day mortality, n (%)	21 (8.5)	31 (9.3)	0.736

Note: [a]Categorical variables are presented as n (%) and continuous variables as median (interquartile range).
Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; BSI, bloodstream infection; CCI, Charlson comorbidity index; ESBL, extended-spectrum -lactamase; BLBLI, β-lactam-β-lactamase inhibitors; E. coli, Escherichia coli.

significance) than those with non-ESBL-EC (median, 12 days vs 11 days, respectively, with a difference of 1 day, P > 0.05). 67 patients (20.1%) with ESBL-EC BSI and 43 patients (17.4%) with non-ESBL-EC BSI died (P = 0.41)

during hospitalization. No statistical differences were observed in the 28-day mortality in patients with BSI caused by ESBL-EC or non-ESBL-EC (16.2% vs. 15.4%; P = 0.786).

Cost Analysis
Direct Costs
The median cost for patients with ESBL-EC was $8048.68 and for patients with non-ESBL-EC was $7476.84, respectively (P > 0.05) (Table 2). The direct cost after *E. coli* BSI also did not show significant difference between the two groups.

In both groups, the cost of antibiotics accounted for 19.79% and 19.13% of the medicine, respectively. The median cost of antibiotics for patients with ESBL-EC BSI during hospitalization was $1592.50, which was higher than that for patients with non-ESBL-EC BSI (median, $1430.06, P = 0.252). To exclude the effects of antibiotic costs before infection, we also compared the cost of antibiotics after infection between the two groups, no significant difference between the two groups was evident (Table 1). BLBLI and carbapenems were the main antibiotics used in the two groups.

Indirect Loss
In the non-ESBL-EC group, 247 patients lost 531.05 DALYs in total, with an average of 2.15 DALYs per person. While in the ESBL-EC group, 333 patients lost 692.64 DALYs in total, with an average of 2.08 DALYs per person (P>0.05). The total indirect economic loss was $3349.32 for 247 patients with non-ESBL-EC and $6616.71 for 333 patients with ESBL-EC. No significant increase of the average indirect loss in the ESBL-EC group was found compared with the non-ESBL-EC group (median, $19.87 vs. $13.56, P=0.361) (Table 2). Among all patients with *E. coli* bloodstream, the heaviest total DALYs and indirect economic loss were in the age group 45–69, and the least total DALYs and indirect economic loss were in the age group >74 years (Figure 1).

Discussions
The information on the economic burden of infections caused by antibiotic-resistant pathogens can only be obtained from observational cohort studies, which are highly susceptible to bias and confoundings.[28] So, in the process of assessing the economic impact of the production of ESBL, the first thing we need to do is to eliminate the effects of intergroup differences on patients'

characteristics. Therefore, it is crucial to adjust for the relevant confounders when investigating the link between drug resistance and economic burden.[29] In our study, no significant differences in the baseline characteristics of patients (including patient demographics, comorbidity status, severity of illness, overall LOS and LOS before/after the infection, susceptibility of empirical antimicrobials demographics, and mortality) between the ESBL-EC and non-ESBL-EC groups were found. Therefore, we can directly compare the economic burden of the two groups without considering the confounding.

Our study found that the production of ESBL did not lead to a significant increase in direct costs. The direct cost of an ESBL-EC infection was $8048.68 and a non-ESBL-EC infection was $7476.84, with a difference of $571.84. However, Schwaber et al.[11] found that the average medic cost due to the production of ESBL was $9,620. Tumbarello et al.[10] found that ESBL BSIs were associated with more cost (+EUR 5,026.00). This difference may be caused by the following reasons: first, in order to control the confounding factors, the previous studies may not have included a large enough sample size to evaluate the economic impact of ESBL infection. Next, there are differences in the inpatient environment, treatment level and test devices, and price of drugs in different regions and hospitals. Last but not least, whether the patient infected by *E. coli* bacteremia had received rapid and effective empirical antibiotic treatment. In our study, before in vitro susceptibility test results were available, BLBLI and carbapenems were administered empirically in 85% of patients with non-ESBL-EC infection while in 83.4% of patients with ESBL-EC infection. It shows that whether ESBL or not, BLBLI and carbapenems are mainly used in clinical patients with *E. coli* bloodstream infection, which makes no significant difference in the direct economic burden between the two groups. While other studies[10,11] showed that higher hospital costs and longer hospitalization for patients infected with *E. coli* BSIs are associated with ESBL production and delay in appropriate therapy.

Clinicians should take the risk factor for ESBL production into consideration when choosing empirical antimicrobials before in vitro susceptibility test results were available. For patients with low risk of ESBL-EC infection, the third cephalosporins, fluoroquinolones and aminoglycosides were recommended as the treatment choice. And in some studies BLBLI[30,31] and carbapenem[32] were the most powerful antibiotics for the treatment of patients with high risk of ESBL-EC infection.

Table 2 Costs of Patients with *Escherichia coli* Bloodstream Infection (BSI) Stratified by Extended-Spectrum-Lactamase (ESBL) Production[a]

Costs (Median, IQR, $)	Non-ESBL (n = 247)	ESBL (n = 333)	P
Total direct economic burden	7476.84 (3470.47–16,658.55)	8048.68 (3688.81–19,358.91)	0.321
Room and board	148.50 (78.99–284.36)	148.50 (76.62–346.29)	0.769
Nursing	112.16 (44.87–215.17)	96.84 (36.73–214.22)	0.553
Medicine	3591.59 (1610.72–9019.65)	4269.80 (1600.03–10,109.30)	0.387
Antimicrobial	1430.06 (660.33–4219.78)	1592.50 (747.20–4198.98)	0.252
Cephalosporins	0 (0–5.48)	0 (0–26.84)	0.029
β-lactam-β-lactamase inhibitors	19.38 (0–372.38)	80.22 (0–516.04)	0.181
Carbapenems	406.14 (0–940.54)	525.03 (0–1100.59)	0.049
Tigecycline	0 (0–0)	0 (0–0)	0.452
Aminoglycosides	0 (0–0)	0 (0–0)	0.882
Fluoroquinolone	0 (0–538.2)	0 (0–425.25)	0.767
Anti-positive bacteria drug	0 (0–500.88)	0 (0–51.5)	0.426
Other	585.90 (187.82–2277.39)	594.17 (203.60–2168.80)	0.776
Traditional Chinese medicines	0 (0–25.75)	0 (0–25.70)	0.591
Laboratory tests	661.14 (380.25–1282.62)	705.85 (411.30–1457.03)	0.538
Ventilation	91.23 (2.49–316.63)	111.45 (27.29–318.01)	0.117
Blood transfusion	0 (0–454.98)	0 (0–280.81)	0.583
Registration fee	35.55 (16.59–66.35)	33.18 (16.51–61.61)	0.253
Surgery	0 (0–170.70)	0 (0–406.60)	0.109
Other tests	273.93 (141.71–538.07)	288.31 (134.44–584.12)	0.486
Direct economic burden after BSI	4812.31 (1900.76–10,016.93)	5106.20 (2343.98–11,680.89)	0.272
Room and board	92.42 (43.44–206.16)	96.37 (47.40–230.25)	0.398
Nursing	65.72 (21.48–132.73)	59.65 (21.95–133.79)	0.858
Medicine	2421.4 (976.78–5459.31)	2751.48 (1104.92–6336.05)	0.335
Antimicrobial	1096.41 (444.16–2547.19)	1098.90 (566.64–3014.46)	0.367
Cephalosporins	0 (0–5.48)	0 (0–11.36)	0.412
β-lactam-β-lactamase inhibitors	0(0–247.87)	0 (0–306.55)	0.322
Carbapenems	361.93 (0–812.29)	465.60 (0–985.24)	0.052
Tigecycline	0 (0–0)	0 (0–0)	0.341
Aminoglycosides	0 (0–0)	0 (0–0)	0.972
Fluoroquinolone	0 (0–23.91)	0 (0–23.91)	0.696
Anti-positive bacteria drug	0 (0–52.43)	0 (0–8.14)	0.631
Other	355.97 (77.73–1374.89)	355.97 (85.16–1332.94)	0.941
Traditional Chinese medicines	0 (0–15.47)	0 (0–15.98)	0.982
Laboratory tests	380.25 (191.63–820.22)	422.12 (215.09–877.09)	0.334
Ventilation	61.06 (0–232.43)	74.41 (13.98–243.29)	0.201
Blood transfusion	0 (0–259.08)	0 (0–206.75)	0.898
Registration fee	21.33 (9.48–40.28)	21.33 (8.53–37.91)	0.883
Surgery	0 (0–48.97)	0 (0–48.97)	0.374
Other tests	131.75 (43.60–319.74)	127.64 (57.42–344.39)	0.375
DALY			
Average DALY	2.15 (1.21–3.60)	2.08 (1.38–4.07)	0.343
Total DALY	531.05 (298.87–889.2)	692.64 (459.54–1355.31)	0.343
Indirect economic burden			
Average indirect economic burden	13.56 (2.56–70.79)	19.87 (2.54–85.37)	0.361
Total indirect economic burden	3349.32 (632.32–17,485.13)	6616.71 (845.82–28,428.21)	0.361

Note: [a]Categorical variables are presented as n (%) and continuous variables as median (interquartile range).
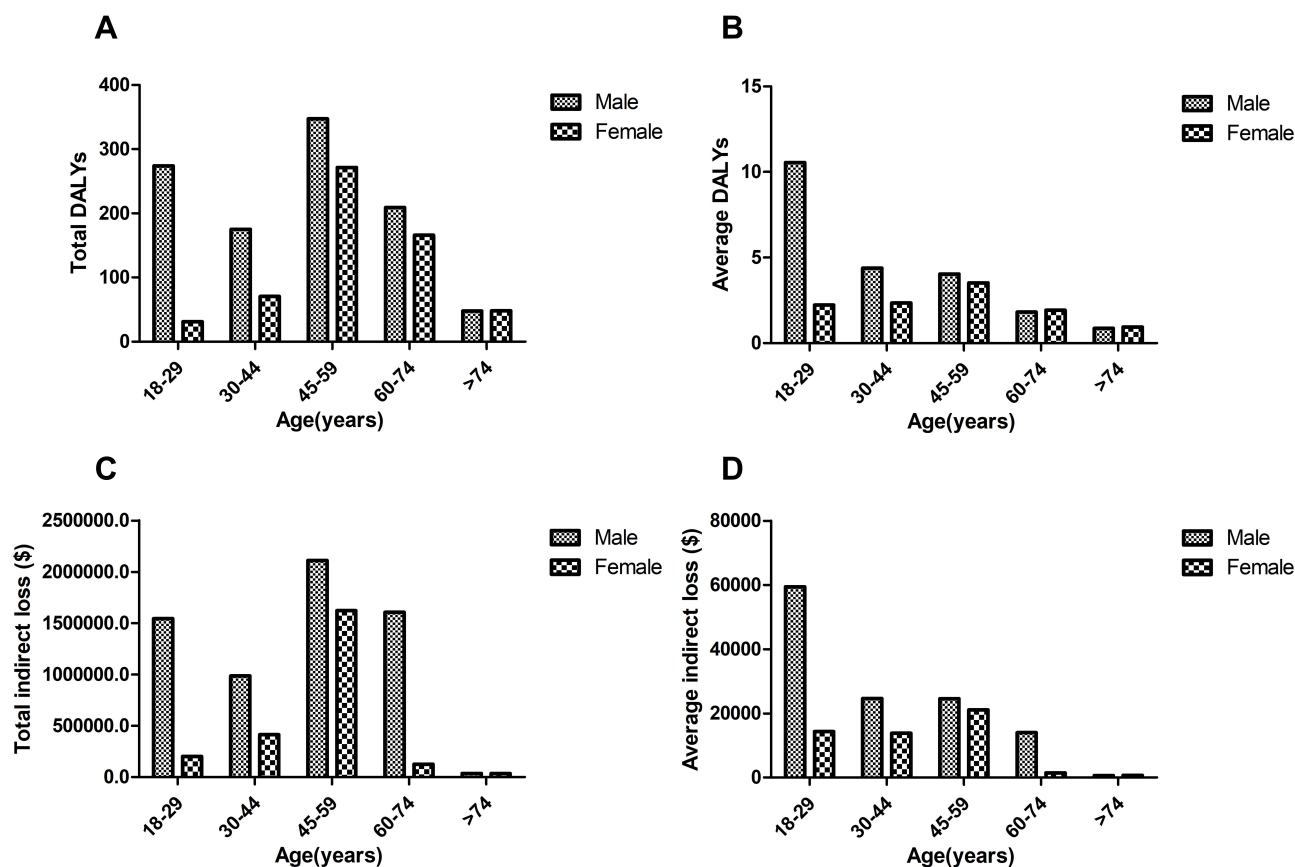**Abbreviations:** ESBL, extended-spectrum-lactamase; *E. coli, Escherichia coli.*

Figure 1 Total DALYs (**A**), average DALYs (**B**), total indirect loss (**C**) and average indirect loss (**D**) of patients with *E. coli* BSI by age group and sex.

However, in our study, for non-ESBL-EC infection group, only 26% of patients used recommended antimicrobials (cephalosporins, fluoroquinolones and aminoglycosides), 85% of patients used BLBLI and carbapenems. The reason why second-line and third-line antibiotics are chosen as empirical treatment drugs can be explained in our previous study,[12] older age, the presence of comorbidities, ICU stay, recurrent urinary tract infections (UTI), previous use of antibiotics, previous colonization with ESBL-producing commensal bacteria, and higher ESBL prevalence were identified as risk factors for acquisition of BSI caused by ESBL-producing Enterobacterales.[33–36] There are many risk factors for ESBL infection in patients with non-ESBL-EC BSI, so clinicians tend to choose antimicrobial agents covering ESBL-producing bacteria as empirical antibiotic therapy.[37] In the short term, the use of second- and third-line antibiotics can improve the cure rate, reduce the direct and indirect costs for individual and society, but in the long term, the use of antibiotics across the ladder will lead to the increase and

spread of resistance of advanced antibiotics, so for the rational application of antibiotics, clinics need to balance individual and societal needs.[38]

In our study, the per case burden of ESBL-EC BSI and non-ESBL-EC BSI was 2.15 DALYs and 2.08 DALYs respectively. And *E. coli* bacteremia had a higher burden in women. Initially, DALYs was often used to calculate the indirect burden of chronic disease. However, in the current study, DALYs was a powerful tool to provide quantitative information on communicable diseases. In 2018, in order to evaluate the burden of communicable diseases, Alessandro Cassini et al[39] used DALYs to calculate the burden of several selected infectious diseases. For viral infections, the per case burden of influenza, human immunodeficiency virus infection, and hepatitis B was 0.01 DALYs, 6.03 DALYs and 2.79 DALYs respectively. For bacterial infections, the per case burden of invasive pneumococcal disease, tuberculosis, and invasive *Haemophilus influenzae* disease was 2.74 DALYs, 3.58 DALYs, 3.43 DALYs respectively. Rabies had the highest per case burden (52.1 DALYs) compared to other infectious illness

discussed in this study.[39] In our study, *E. coli* bloodstream had a significantly lower burden compared to the infectious diseases discussed above (except influenza). We can also infer from these data that the duration of *E. coli* bloodstream is not as long as that of pneumococcal disease, hepatitis B, *Haemophilus influenzae* disease, etc. For *E. coli* bloodstream, 0.07 DALYs were produced due to the production of ESBL, which is seven times the burden of influenza. Hence using DALYs can quantify and compare the burden of different diseases. especially using DALYs to evaluate the burden of antimicrobial resistant pathogens can help decision makers to measure how much resources and energy should be invested to track and control the spread of antimicrobial-resistant organisms.

However, there are still some limitations in our study. First, this was a retrospective single-center study with inherent biases. The disease prevalence and treatment options in this hospital might have had an impact on the results. The situation in other medical institutions or healthcare systems might be different. Secondly, this was an observational study, not a randomized controlled trial, so our findings are susceptible to unmeasured confounding at both the hospital and patient levels. Thirdly, due to difficulties about statistic measurement and calculation, our study ignored direct non-medical costs and intangible economic burden including transportation costs, food costs and others, which may lead the results to not fully represent the economic burden of disease.

In conclusion, patients with BSI due to ESBL-EC did not cost more than patients with BSI due to non-ESBL-EC. This phenomenon may be attributed to timely and effective antibiotic treatment. But the antimicrobial stewardship should be implemented to avoid overaggressive use of second- and third-line antibiotics in sensitive bacterial infections.

Data Sharing Statement

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request. All patient data accessed complied with relevant data protection and privacy regulations.

Ethics Approval and Consent to Participate

Ethics approval for this study was submitted and approved through Research Ethics Committee of the First Affiliated Hospital, College of Medicine, Zhejiang University

(Reference number 2,016,605). The consent to participate was waived by our institutional review board since this study was retrospective data collection.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed on the journal to which the article will be submitted; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

None of the authors report conflicts of interest for this work.

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