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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-090665
Article Type:	Original research
Date Submitted by the Author:	01-Jul-2024
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Keywords:	Urinary tract infections < UROLOGY, PUBLIC HEALTH, Adult urology < UROLOGY

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Risk factors and drug resistance of adult community-acquired urinary tract infections caused by *Escherichia coli*-producing extended spectrum β-lactamase in the Chongqing region, China: A 5-year retrospective analysis

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ABSTRACT:

Objective: To evaluate the prevalence, resistance, and risk factors of community-acquired urinary tract infections (CAUTIs) caused by extended-spectrum β-lactamase-producing *Escherichia coli* (ESBL-EC) for providing a basis for the selection of clinical therapeutic agents

Methods: We retrospectively analyzed the clinical data of patients diagnosed with CAUTIs caused by *E. coli* from May 2017 to December 2022 at a tertiary hospital in the Chongqing region, China, and evaluated the detection rate of ESBL-EC. To assess the risk factors for CAUTIs caused by ESBL-EC, a case-control design was used, focusing on the resistance of ESBL-EC.

Results: In total, 394 cases of CAUTIs caused by *E. coli* were included; 192 cases were ESBL-positive, with a detection rate of 48.7% (192/394). Parenchymal tumor, history of urolithiasis stone fragmentation, history of urological surgery, hospitalization within 6 months, indwelling urinary catheter insertion within 6 months, and antibiotic use (mainly third-generation cephalosporins) were the factors significantly associated with CAUTIs caused by ESBL-EC ($P < 0.05$) through logistic regression for univariate analysis. Multivariate analysis revealed that a history of urolithiasis stone fragmentation, urological surgery, indwelling urinary catheter insertion within 6 months, hospitalization within 6 months, and use of third-generation cephalosporins were the independent risk factors for CAUTIs caused by ESBL-EC. Analysis of resistance in ESBL-EC revealed that the sensitivity of carbapenems, including imipenem, meropenem, and ertapenem; amikacin; cefotetan; piperacillin/tazobactam; nitrofurantoin; and cefoperazone/sulbactam was 100%, 100%, 96.6%, 95.3%, 87.9%, and 76.5%, respectively. Penicillins, cephalosporins, and quinolones were associated with higher antibiotic resistance rates.

Conclusions: Our results revealed high ESBL-EC detection rates. CAUTIs caused by ESBL-EC are more likely to occur in patients with parenchymal tumor, a history of urolithiasis stone fragmentation, a history of urological surgery, hospitalization within 6 months, indwelling urinary catheter insertion within 6 months, and use of third-generation cephalosporins. These patients were

highly resistant to penicillins, cephalosporins, and quinolones.

Key Words: Drug Resistance; Community-acquired Urinary Tract Infections; *Escherichia Coli*-producing Extended Spectrum β-Lactamase; Adult

Strengths and limitations of this study

This study incorporated nearly 200 cases of community-acquired urinary tract infections (CAUTIs) caused by extended-spectrum β-lactamase-producing *Escherichia coli* (ESBL-EC) .

The study employed a case-control design to analyze the risk factors o urinary tract infections caused by ESBL-EC.

This study analyzed the drug resistance of ESBL-EC.

The study utilized the disk diffusion method for confirmation of bacterial phenotypes, without conducting genetic sequencing at the molecular level.

1 Introduction

Urinary tract infection (UTI), characterized by bacterial resistance and recurrence, is one of the most common infections in the community, with urinary-derived *Escherichia coli* being the most predominant pathogenic bacteria. *E. coli* has shown more complex changes in drug resistance, more rapid geographic variation, and a faster transmission rate with the widespread use of antimicrobials. The establishment of long-term surveillance and analysis of drug resistance in *E. coli* are being focused on globally to find a faster treatment method for *E. coli* infections and control the epidemic of novel drug-resistant strains [1, 2].

The current worldwide prevalence of extended-spectrum β-lactamase-producing *Escherichia coli* (ESBL-EC) in the community is increasing, causing a significant issue in clinical diagnosis and treatment [1, 2]. Laboratory studies have reported that ESBL-producing *Enterobacteriaceae* can produce several β-lactamases to hydrolyze broad-spectrum β-lactamase antibiotics, thus leading to resistance to penicillins and cephalosporins [3]. Moreover, genes encoding ESBL can be transferred in different species of plasmid-mediated *Enterobacteriaceae* [4]; therefore, bacteria carrying ESBL genes usually comprise additional genes or gene mutations that mediate resistance to multiple antibiotics [5].

Reviewing the literature over the past 20 years approximately, we found reports about the genetic and epidemic characteristics, drug resistance patterns, and susceptibility factors of *E. coli* from China, the United States, the United Kingdom, Australia, Spain, Turkey, Jordan, and other countries [7-15]; the results from these studies have been used in the empirical treatment and development of related drugs in the clinic. In China, a well-established surveillance system for drug-resistant bacteria was formed quite late; therefore, relatively few reports about the bacteria are available, and more surveillance data and laboratory studies are still required to help doctors choose the appropriate

treatment. Thus, we herein retrospectively analyzed cases of community-acquired urinary tract infections (CAUTIs) caused by *E. coli* within the past 5 years in the Chongqing region, China, evaluated the drug resistance and clinical characteristics of ESBL-EC and analyzed the risk factors for CAUTIs caused by ESBL-EC by performing a case-control study in ESBL-positive and -negative patients.

2 Method

2.1 Environment and Population

The Dazu Affiliated Hospital of Chongqing Medical University, Dazu District, Chongqing, China, is a national tertiary general hospital integrating medical, teaching, scientific research, preventive health care, first aid, and rehabilitation, with a bed capacity of 1000 and receives more than 8000 patients per year. The Dazu district, located in the western part of Chongqing, has a resident population of 8,56,000, and the region has a high degree of population aging, with a large population suffering from common diseases such as diabetes, cardiovascular disease, respiratory disease, and cancer.

2.2 Study Design and Materials

We herein retrospectively reviewed patients diagnosed with CAUTIs caused by *E. coli* diagnosed from May 2017 to December 2022. We collected data including sex, age, admission time, sample collection time, clinical manifestations, and risk factors (including underlying disease, history of urologic surgery, hospitalization within 6 months, antibiotic use within 6 months, and indwelling urinary catheter insertion within 6 months) through electronic medical records, examination reports, and telephone call back visits.

The risk factors for CAUTIs caused by ESBL-EC were evaluated using a case-control design, defining patients who were diagnosed with UTIs and had an ESBL-positive urine culture as the case group and patients who were diagnosed with UTIs and had an ESBL-negative urine culture as the control group, using logistic regression for univariate analysis. Multivariate analysis was performed for variables with significant differences ($P < 0.05$).

2.3 Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) patients older than 18 years; (2) those with urine collection done before admission or within 48 h of admission; (3) those with a positive urine culture with a growth of 10^5 CFU/mL; (5) those with a clinical diagnosis of UTI.

The exclusion criteria were as follows: (1) Patients with incomplete clinical data; (2) those who did not agree to provide case information for participation in the study; (3) those who were hospitalized for more than 48 h before diagnosis.

2.4 Microbiological Methods

The isolated *E. coli* were initially screened using the conventional paper chip diffusion method to detect the susceptibility to broad-spectrum β-lactamase antibiotics. The phenotypic confirmation of ESBL-EC was performed using the two-paper diffusion method according to the Clinical and Laboratory Standards Institute performance standards.

2.5 Antimicrobial Susceptibility Testing

The minimum inhibitory concentration was determined according to the Clinical and Laboratory Standards Institute guidelines [6], and the standard strain *E. coli* ATCC25922 was used as the control strain. Drugs including, ampicillin, ampicillin/sulbactam, piperacillin/tazobactam, meloxicillin, cefuroxime, cefoperazone/sulbactam, cefotetan, ceftazidime, ceftriaxone, cefixime, cefepime, cefotaxime, aztreonam, imipenem, meropenem, ertapenem, gentamicin, tobramycin, amikacin, levofloxacin, ciprofloxacin, nitrofurantoin, and cotrimoxazole, were tested.

2.6 Statistical Analysis

Analyses were performed using SPSS 26.0 (IBM Corp., Armonk, NY, USA). Count data were expressed as numbers and percentages, and chi-square tests were performed. Measurements that met normal distribution were presented as mean ± standard deviation and were subjected to a t-test. Binary logistic regression was used to analyze the risk factors for CAUTIs caused by ESBL-EC, and $P < 0.05$ was considered statistically significant.

2.7 Patient and public involvement

Patients and their guardians were not involved in the design and implementation of our study. Patients were not invited to contribute to the writing or editing of this manuscript. The main results of this study will be disseminated to patients and the public in an appropriate manner and seek their participation in the future.

3 Results

3.1 Detection Rate

A total of 394 cases diagnosed with CAUTIs caused by *E. coli* were included. Among them, 192 cases were ESBL-positive, with a detection rate of 48.7% (192/394).

3.2 Clinical Characteristics of ESBL-Positive Patients

Of the 192 ESBL-positive patients, 50 were male, accounting for 26.0% (50/192). The mean patient age was 64 ± 13 years, and 62.0% (119/192) of the patients were aged 60 years and older. The vast majority of patients had underlying comorbidities, including diabetes, hypertension, parenchymal tumors, prostatic hyperplasia, and others.

The main clinical symptoms included urinary tract irritation signs (urinary frequency: 65, urinary urgencies: 56, and odynuria: 49), dysuria (11), hematuria (19), lumbago (28), pain with percussion in the renal area (21), and fever (35); the detailed results are shown in Table 1.

Table 1: Clinical presentation and proportion of ESBL-positive patients

Symptoms		Number	Percent(%)
Urinary irritation	urinary frequency	65	33.9
	urinary urgency	56	29.2
	Odynuria	49	25.5
Dysuria		11	5.7
Hematuresis		19	9.9
Lumbago		28	14.6
Renal buckle pain		21	10.9
Fever		35	18.2
Chilly		16	8.3
Shiver		6	3.1
Dizzy		12	6.3
Headache		18	9.4
Nausea		11	5.7
Vomit		17	8.9
Belly distention		14	7.3
Diarrhea		2	1.0

3.3 Risk Factors

Univariate analysis showed that parenchymal tumor, history of urolithiasis stone fragmentation, history of urological surgery, hospitalization within 6 months, indwelling urinary catheter insertion within 6 months, and antibiotic use (mainly third-generation cephalosporins) within 6 months were factors significantly associated with CAUTIs caused by ESBL-EC ($P < 0.05$, see Table 2).

Multivariate analysis of these factors revealed that a history of urolithiasis stone fragmentation, urological surgery, indwelling urinary catheter insertion within 6 months, hospitalization within 6 months, and use of third-generation cephalosporins were independent risk factors for CAUTIs caused by ESBL-EC (see Table 3).

Table 2: Univariate analysis of the risk factors in ESBL-positive patients

Risk factors	All patients (%)	ESBL-negative (%)	ESBL-positive (%)	*P* value
Total	394	202(51.3)	192（48.7)	
Gender (male)	109(27.9)	59(29.2)	50(26.0)	0.483
Advanced age (⩾60 years)	227(57.6)	108(53.5)	119(62.0)	0.088
Underlying diseases and comorbidity				
Diabetes	161(40.9)	86(42.6)	75(39.1)	0.479

Hypertension	142(36.0)	68(33.7)	74(38.5)	0.314
Parenchymal tumor	43(10.9)	17(8.4)	26(13.5)	**0.025**
Urinary bladder carcinoma	13(3.3)	4(2.0)	9(4.7)	0.144
Prostatic cancer	4(1.0)	0(0.0)	4(2.1)	0.999
Benign prostatic hyperplasia	29(7.4)	10(5.0)	19(9.9)	0.065
Urolithiasis stone fragmentation	43(10.9)	15(7.4)	28(14.6)	**0.025**
Urological surgery	58(14.7)	21(10.4)	37(19.3)	**0.014**
Hospitalization (within 6 months)	80(20.3)	26(12.8)	54(28.1)	**<0.001**
ICU hospitalization (within 6 months)	11(2.8)	4(2.0)	7(3.6)	0.323
Indwelling urinary catheter operation (within 6 months)	54(13.7)	19(9.4)	35(18.2)	**0.002**
Antibiotic use (within 6 months)	110(27.9)	41(20.3)	69(35.9)	**<0.001**
Second-generation cephalosporins	20(5.1)	9(4.5)	11(5.7)	0.566
Third-generation cephalosporins	67(17.0)	24(11.9)	43(22.4)	**0.006**
Quinolone antibiotics	35(8.9)	17(8.4)	18(9.4)	0.492

Table 3: Multivariate analysis of the risk factors in ESBL-positive patients

	OR	95% confidence interval	*P* value
Parenchymal tumor	1.801	0.882–3.678	0.107
Urolithiasis stone fragmentation	2.450	1.342–4.473	**0.004**
Urological surgery	3.102	1.534–6.270	**0.002**
Indwelling urinary catheter operation (within 6 months)	2.059	1.025–4.133	**0.042**
Hospitalization (within 6 months)	2.127	1.207–3.748	**0.009**
Third-generation cephalosporins	1.903	1.069–3.389	**0.029**

3.4 Drug Resistance Analysis

The drug resistance analysis of ESBL-EC revealed revealed that the sensitivity of carbapenems, including imipenem, meropenem, and ertapenem; amikacin; cefotetan; piperacillin/tazobactam; nitrofurantoin; and cefoperazone/sulbactam was 100%, 100%, 96.6%, 95.3%, 87.9%, and 76.5%, respectively. The antibiotic resistance rates of ampicillin, ceftriaxone, cefixime, penicillin

cefuroxime, levofloxacin, and ciprofloxacin were 100%, 100%, 100%, 98.7%, 76.5%, 73.8%, and 77.8%, respectively (see Table 4).

Table 4: Analysis of resistance in ESBL-positive patients

Antibiotics	Resistance (%)	Sensitivity (%)	Intermediate (%)
Ampicillin	100	0	0
Ampicillin/sulbactam	65.1	23.5	11.4
Piperacillin/tazobactam	2.7	95.3	2
Mezlocillin	98.7	1.3	0
Cefuroxime	76.5	23.5	0
Cefoperazone / Sulbactam	12.1	76.5	11.4
Cefotetan	0	96.6	3.4
Ceftazidime	44.3	52.3	4.6
Ceftriaxone	100	0	0
Cefminox	100	0	0
Cefepime	41.6	58.4	0
Cefotaxime	64.4	35.6	0
Aztreonam	66.4	33.6	0
Imipenem	0	100	0
Meropenem	0	100	0
Ertapenem	0	100	0
Gentamicin	43.6	56.4	0
Tobramycin	16.1	64.4	19.5
Amikacin	0	100	0
Levofloxacin	73.8	10.7	15.5
Ciprofloxacin	77.8	18.8	3.4
Furadantin	3.4	87.9	8.7
Bactrim	62.4	37.6	0

4 Discussion

UTI caused by ESBL-EC, characterized by bacterial resistance and recurrence, is one of the most common infections in the community; it has a high treatment difficulty. ESBL-EC can be genetically encoded to produce ESBL, and degraded β-lactamase antibiotics widely used in the clinic, making the bacteria resistant to these antibiotics [3]. Furthermore, it is also possible to spread drug-resistant genes to other bacteria by transfer nature plasmid vectors or by mechanisms such as homologous recombination, leading to multidrug resistance [4]. Over the past 20 years, ESBL-EC has widely spread worldwide and is no longer restricted to infections in hospital wards, and the prevalence of CAUTIs caused by ESBL-EC is continuously increasing [1, 2].

Epidemiological studies have shown marked differences in the transmission of ESBL-EC, mainly because ESBL-EC has a high genetic diversity and diverse resistant strains may dominate in different regions and populations [1]. To understand the spread and differences of CAUTIs caused by ESBL-EC in various regions in the last two decades, we referred to a large and reliable literature. Two studies in China reported the prevalence of ESBL-EC in CAUTIs [7, 8]. In 2021, a prospective multicenter study in East China [7] reported the prevalence of ESBL-EC in communities in detail, comprising 1760 UTI cases from 19 hospitals; the detection rate of ESBL *Enterobacteriaceae* was 37.2%. The detection rate of community-acquired ESBL-EC cases was 22% in a retrospective study from Tongren Hospital, Beijing, China [8]. A similar pattern has been reported in several European countries, with a study from the Glasgow region of Scotland, UK, published in 2011 indicating a detection rate of ESBL *Enterobacteriaceae* of 7.5% in urine samples [9]. The detection rate of ESBL-EC in CAUTIs increased from 0.47% in 2000 to 1.7% in 2014 in Spain [10]. A 9-year retrospective Australian study revealed a 44% increase in the proportion of ESBL-EC in individuals with UTIs caused by *E. coli* from 4.6% in 2006 to 6.6% in 2014 [11]. The prevalence of ESBL-EC has also been reported in countries in West Asia, with a report from Turkey in 2019 revealing a 50.5% detection rate of ESBL-EC in UTIs [12]. In 2018, a two-center cross-sectional study from Amman in Jordan reported a detection rate as high as 62% [13]. A multicenter study from North America reported a 3.9% detection rate of ESBL-EC in patients with community-associated infections [14], and another study from California reported a 5.9% detection rate in patients with UTIs [15]. In the present study, we reviewed all cases of CAUTIs caused by *E. coli* in the Chongqing region over the past 5 years and found that the detection rate of ESBL-EC was 48.7%, which was higher than that in East China and Beijing; much higher than that in the United Kingdom, Spain, Australia, and the United States; and lower than that in Turkey and Jordan.

The high detection rate of ESBL-EC in the community may be associated with the clinical characteristics of the local infected population and the previous healthcare and antibiotic usage patterns of patients. In the present study, the proportion of ESBL-positive female patients was 74%, which was much higher than that of male patients. This finding is consistent with those of two reports from East China and Beijing, wherein the number of ESBL-positive female patients was more than 80% [7, 8]. Moreover, women are more susceptible to UTIs for reasons associated with the physiological anatomy and estrogen levels of women [16, 17]. In terms of anatomy, the female urethra is relatively shorter than that of males and closer to the anus, increasing the chance of bacterial migration from the intestine to the urinary tract. Postmenopausal women are more susceptible to ascending UTIs due to changes in the urinary and vaginal microbiota because of reduced estrogen levels, with blooms of enterobacterial flora [17]. Oral or topical estrogen preparations are used to prevent recurrent UTIs in postmenopausal women [17, 18]. In the present study, most women were infected with CAUTIs caused by ESBL-EC, and the patients' age was mainly over 60 years old, which is consistent with the fact that menopausal women are more susceptible to UTIs.

In the present study, the mean age of the patients was (64 ± 13) years, and 62.0% (119/192) of the patients were aged 60 years and older. The vast majority of patients had underlying comorbidities, including diabetes, hypertension, urinary stones, parenchymal tumors, and others. Regarding the risk

factors, 19.3% of patients had a history of urologic surgery, 18.2% had an indwelling urinary catheter inserted within 6 months, 28.1% were hospitalized within 6 months, and 35.9% used antibiotics within 6 months.

Univariate analysis revealed that parenchymal tumor, history of urolithiasis stone fragmentation, history of urological surgery, hospitalization within 6 months, indwelling urinary catheter insertion within 6 months, and antibiotic use (mainly third-generation cephalosporins) within 6 months were factors significantly associated with CAUTIs caused by ESBL-EC ($P < 0.05$). Multivariate analysis revealed that a history of urolithiasis stone fragmentation, urological surgery, indwelling urinary catheter insertion within 6 months, hospitalization within 6 months, and use of third-generation cephalosporins were independent risk factors for CAUTIs caused by ESBL-EC. Although these findings are similar to those of previous studies [7, 8, 11-14, 19], there are still some differences. Furthermore, age is one of the possible risk factors [11, 12], and ESBL-positive patients were older than ESBL-negative patients in our study; however, the age difference was not statistically significant in the regression analysis ($P = 0.088$). Prostatic hyperplasia is one of the possible risk factors [7], and more patients with prostatic hyperplasia were ESBL-positive than ESBL-negative; however, the difference was not significant in the regression analysis ($P = 0.065$). Clinically, patients with prostatic hyperplasia present with urinary tract obstruction and urine retention and need more frequent catheterization maneuvers, which undoubtedly increases the risk of ESBL-EC infection. Nonetheless, our findings did not include prostatic hyperplasia as one of the independent risk factors, possibly due to the low sample size of male patients and a smaller number of patients with prostatic hyperplasia. This led to some deviation in the statistical results.

The most difficult part of UTI treatment is the increase in bacterial resistance, and the multidrug resistance of ESBL-EC makes the choice of therapeutic agents narrower and limited, in turn, increases the difficulty of treatment. In the present study, we statistically evaluated the results of susceptibility testing in 192 ESBL-positive patients. The results showed that carbapenems, including imipenem, meropenem, and ertapenem, had very strong antimicrobial activity in vitro, with 100% sensitivity. Aminoglycoside antimicrobials showed a wide variation in the antimicrobial activity; the sensitivity of amikacin was excellent, reaching 100%, and that of gentamicin and tobramycin was 64.4% and 54.4%, respectively. Nitrofurantoin, a nitrofuran, had a sensitivity of 87.9%. The sensitivity of piperacillin/tazobactam was 95.3%.

The treatment guidelines on multidrug-resistant bacteria issued by the Infectious Disease Society of America in 2022 indicated that carbapenems have strong antibacterial activity against ESBL-producing *Enterobacteriaceae* and can be the first choice of treatment for pyelonephritis and complicated UTI caused by ESBL-producing *Enterobacteriaceae* [5]. In addition, piperacillin/tazobactam, a commonly used empirical therapeutic agent, demonstrated good antibacterial activity against multiple ESBL-producing *Enterobacteriaceae* [20]. However, compared with the in vitro efficacy of carbapenems, piperacillin/tazobactam is slightly less effective [5], which is consistent with the results of our study. It is important to note that the prevalence of carbapenem-resistant *Enterobacteriaceae* is also constantly increasing [21] and that repeated carbapenem use is a major contributing factor to the increasing prevalence of carbapenem-resistant

Enterobacteriaceae [22]. Therefore, we preferentially use piperacillin/tazobactam for some patients with CAUTIs caused by ESBL-ECs who are less symptomatic, thus reducing the frequency of carbapenem use.

Currently, the commonly used cephalosporins for the treatment of infections are not very effective in treating infections caused by ESBL-EC. In the present study, only the second-generation cephalosporin cefotetan had a high sensitivity (96.6%); third-generation cephalosporins have developed obvious resistance, and the resistance for ceftriaxone and cefixime reached 100%. Combined with the risk factor analysis in this study, the use of third-generation cephalosporins is an independent risk factor for CAUTIs caused by ESBL-EC, and we assume that there may be a situation of transitional third-generation cephalosporin use in this region and that the widespread use of third-generation cephalosporins will induce the emergence of new ESBL strains. Thus, the use of third-generation cephalosporins should be reduced in response to community-acquired infections, particularly CAUTIs caused by ESBL-EC to avoid inducing more ESBL-producing

5 Conclusions

The positive detection rate of CAUTIs caused by ESBL-EC in this study was high; history of urolithiasis stone fragmentation, urological surgery, indwelling urinary catheter insertion within 6 months, hospitalization within 6 months, and use of third-generation cephalosporins were independent risk factors for CAUTIs caused by ESBL-EC. The susceptibility profile suggested significant resistance to penicillins, cephalosporins, and quinolones; however, carbapenems and amikacin showed 100% sensitivity.

Ethical Approval

This study was approved by the Ethics Commission of The People's Hospital of Dazu District.

Authors' contributions

YLZ and BLL conceived the study. HLL and YLZ collected the data. LHL and JW analyzed the data. BLL and YLZ wrote this article. JW and HX revised it. HX supervised study conduct. All the authors have read and approved the final version of this manuscript.

Funding

The study was supported by *The Chongqing Key Specialty Construction of Public Health.*

Declaration of Competing Interest

The authors declare that there are no competing interests.

Acknowledgments

We acknowledge all health-care workers involved in the diagnosis and treatment of patients in Dazu

Chongqing. We thank the clinical laboratory department from The People's Hospital of Dazu District,and We thank Medjaden Inc. for its assistance in the preparation of this manuscript

Availability of Data and Materials

The data can get from Jing Wu by email: 2861914532@qq.com

References

[1] Karlowsky JA, Lob SH, DeRyke CA, et al. Prevalence of ESBL non-CRE Escherichia coli and Klebsiella pneumoniae among clinical isolates collected by the SMART global surveillance programme from 2015 to 2019. *Int J Antimicrob Agents*. 2022;59(3):106535. doi:10.1016/j.ijantimicag.2022.106535

[2] Pitout JD, Laupland KB. Extended-spectrum beta-lactamase-producing Enterobacteriaceae: an emerging public-health concern. *Lancet Infect Dis*. 2008;8(3):159-166. doi:10.1016/S1473-3099(08)70041-0

[3] Bradford PA. Extended-spectrum beta-lactamases in the 21st century: characterization, epidemiology, and detection of this important resistance threat. *Clin Microbiol Rev*. 2001;14(4):933-951. doi:10.1128/CMR.14.4.933-951.2001

[4] Shah AA, Hasan F, Ahmed S, Hameed A. Extended-spectrum beta-lactamases (ESbLs): characterization, epidemiology and detection. *Crit Rev Microbiol*. 2004;30(1):25-32. doi:10.1080/10408410490266429

[5] Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America 2022 Guidance on the Treatment of Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and Pseudomonas aeruginosa with Difficult-to-Treat Resistance (DTR-P. aeruginosa). *Clin Infect Dis*. 2022;75(2):187-212. doi:10.1093/cid/ciac268

[6] CLSI Performance standards for antimicrobial susceptibility testing. CLSI Supple- ment M100. 28th ed. Wayne, PA: Clinical and Laboratory Standards Institute; 2018.

[7] J. Quan, H. Dai, W. Liao et al., Etiology and prevalence of ESBLs in adult community-onset urinary tract infections in East China: A prospective multicenter study, Journal of Infection, https://doi.org/10.1016/j.jinf.2021.06.004

[8] Ludong Q, Shan C,Lihui M.Risk factors of urinary tract infection caused by extended-spectrum β-lactamase-producing escherichia coli[J].Chinese Journal of Nosocomiolog,2011,21(02):247-249.

[9] Khanna N, Boyes J, Lansdell PM, Hamouda A, Amyes SG. Molecular epidemiology and antimicrobial resistance pattern of extended-spectrum-β-lactamase-producing Enterobacteriaceae in Glasgow, Scotland. *J Antimicrob Chemother*. 2012;67(3):573-577. doi:10.1093/jac/dkr523

[10] Calbo E, Romaní V, Xercavins M, et al. Risk factors for community-onset urinary tract infections due to Escherichia coli harbouring extended-spectrum beta-lactamases. *J Antimicrob Chemother*. 2006;57(4):780-783. doi:10.1093/jac/dkl035

[11] Toner L, Papa N, Aliyu SH, Dev H, Lawrentschuk N, Al-Hayek S. Extended-spectrum beta-lactamase-producing Enterobacteriaceae in hospital urinary tract infections: incidence and antibiotic susceptibility profile over 9 years. *World J Urol*. 2016;34(7):1031-1037. doi:10.1007/s00345-015-

1718-x
[12] Tüzün T, Sayın Kutlu S, Kutlu M, Kaleli İ. Risk factors for community-onset urinary tract infections caused by extended-spectrum β-lactamase-producing Escherichia coli. *Turk J Med Sci*. 2019;49(4):1206-1211. Published 2019 Aug 8. doi:10.3906/sag-1902-24
[13] Al-Jamei SA, Albsoul AY, Bakri FG, Al-Bakri AG. Extended-spectrum β-lactamase producing E. coli in urinary tract infections: A two-center, cross-sectional study of prevalence, genotypes and risk factors in Amman, Jordan. *J Infect Public Health*. 2019;12(1):21-25. doi:10.1016/j.jiph.2018.07.011
[14] Doi Y, Park YS, Rivera JI, et al. Community-associated extended-spectrum be- ta-lactamase-producing Escherichia coli infection in the United States. Clin Infect Dis 2013;56:641–8.
[15] Frazee BW, Trivedi T, Montgomery M, Petrovic DF, Yamaji R, Riley L. Emergency Department Urinary Tract Infections Caused by Extended-Spectrum β-Lactamase-Producing Enterobacteriaceae: Many Patients Have No Identifiable Risk Factor and Discordant Empiric Therapy Is Common. *Ann Emerg Med*. 2018;72(4):449-456. doi:10.1016/j.annemergmed.2018.05.006
[16] Geerlings SE. Clinical Presentations and Epidemiology of Urinary Tract Infections. *Microbiol Spectr*. 2016;4(5):10.1128/microbiolspec.UTI-0002-2012. doi:10.1128/microbiolspec.UTI-0002-2012
[17] Stamm WE. Estrogens and urinary-tract infection. *J Infect Dis*. 2007;195(5):623-624. doi:10.1086/511526
[18] Perrotta C, Aznar M, Mejia R, Albert X, Ng CW. Oestrogens for preventing recurrent urinary tract infection in postmenopausal women. *Cochrane Database Syst Rev*. 2008;(2):CD005131. Published 2008 Apr 16. doi:10.1002/14651858.CD005131.pub2
[19] Søgaard M, Heide-Jørgensen U, Vandenbroucke JP, Schønheyder HC, Vandenbroucke-Grauls CMJE. Risk factors for extended-spectrum β-lactamase-producing Escherichia coli urinary tract infection in the community in Denmark: a case-control study. *Clin Microbiol Infect*. 2017;23(12):952-960. doi:10.1016/j.cmi.2017.03.026
[20] Bush K, Macalintal C, Rasmussen BA, Lee VJ, Yang Y. Kinetic interactions of tazobactam with beta-lactamases from all major structural classes. *Antimicrob Agents Chemother*. 1993;37(4):851-858. doi:10.1128/AAC.37.4.851
[21] Zhang R, Liu L, Zhou H, et al. Nationwide Surveillance of Clinical Carbapenem-resistant Enterobacteriaceae (CRE) Strains in China. *EBioMedicine*. 2017;19:98-106. doi:10.1016/j.ebiom.2017.04.032
[22] Sun Q, Yang X, Huang Y, et al. Risk factors and clinical impact associated with infections caused by different types of carbapenem-resistant Klebsiella pneumoniae in China: A clinical study from 2014 to 2017. *J Infect*. 2022;85(4):436-480. doi:10.1016/j.jinf.2022.05.045

BMJ Open

Risk factors and drug resistance of adult Community onset urinary tract infections caused by Escherichia coli-producing extended spectrum β-lactamase in the Chongqing region, China: A retrospective case-control study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-090665.R1
Article Type:	Original research
Date Submitted by the Author:	10-Sep-2024
Complete List of Authors:	Zhou, yan-ling; The People's Hospital of Dazu Chongqing, Department of Infectious Disease Long, Biao-li; The People's Hospital of Dazu Chongqing, Department of Infectious Disease Liu, He-Lei; The People's Hospital of Dazu Chongqing, Department of Infectious Disease Wu, Jing; The People's Hospital of Dazu Chongqing, Department of Infectious Disease Xia, Hong; The People's Hospital of Dazu Chongqing, Department of Infectious Disease
Primary Subject Heading:	Public health
Secondary Subject Heading:	Urology, Epidemiology
Keywords:	Urinary tract infections < UROLOGY, PUBLIC HEALTH, Adult urology < UROLOGY, Case-Control Studies, Community Participation

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Risk factors and drug resistance of adult Community onset urinary tract infections caused by *Escherichia coli*-producing extended spectrum β-lactamase in the Chongqing region, China: A retrospective case-control study

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ABSTRACT:

Objective: To evaluate the prevalence, resistance, and risk factors of Community onset urinary tract infections (COUTIs) caused by extended-spectrum β-lactamase-producing *Escherichia coli* (ESBL-EC) for providing a basis for the selection of clinical therapeutic agents.

Design: retrospective case-control study.

Setting: The Affiliated Dazu Hospital of Chongqing Medical University (as konw as The People's Hospital of Dazu Chongqing), a 1000-bed tertiary hospital, in China.

Data and participants: This study encompassed adult patients diagnosed with community-acquired urinary tract infections caused by Escherichia coli between May 2017 and December 2022, with exclusion criteria including incomplete clinical data, disagreement to participate in the study, hospitalization duration exceeding 48 hours prior to confirmation of diagnosis, and prior history of urinary tract infection caused by Escherichia coli.

Outcome measures: The risk factors for COUTIs caused by ESBL-EC were evaluated using a case-control design, defining patients who were diagnosed with UTIs and had an ESBL-positive urine culture as the case group and patients who were diagnosed with UTIs and had an ESBL-negative urine culture as the control group. Analyzing Drug Resistance of ESBL-EC.

Results: In total, 394 cases of COUTIs caused by *E. coli* were included; 192 cases were ESBL-positive, with a detection rate of 48.7% (192/394). Parenchymal tumor, history of urolithiasis stone fragmentation, history of urological surgery, hospitalization within 6 months, indwelling catheter outside hospital, and antibiotic use (mainly third-generation cephalosporins) were the factors significantly associated with COUTIs caused by ESBL-EC ($P < 0.05$) through logistic regression for univariate analysis. Multivariate analysis revealed that a history of urolithiasis stone fragmentation (OR=2.450; 95%CI: 1.342-4.473; P=0.004), urological surgery (OR=3.102; 95%CI: 1.534-6.270;

P=0.002), indwelling catheter outside hospital (OR=2.059; 95%CI: 1.025-4.133; P=0.042), hospitalization within 6 months (OR=2.127; 95%CI: 1.207-3.748; P=0.009), and use of third-generation cephalosporins (OR=1.903; 95%CI: 1.069-3.389; P=0.029) were the independent risk factors for COUTIs caused by ESBL-EC. Analysis of resistance in ESBL-EC revealed that the sensitivity of carbapenems, including imipenem, meropenem, and ertapenem; amikacin; cefotetan; piperacillin/tazobactam; nitrofurantoin; and cefoperazone/sulbactam was 100%, 100%, 96.6%, 95.3%, 87.9%, and 76.5%, respectively. Penicillins, cephalosporins, and quinolones were associated with higher antibiotic resistance rates.

Conclusions: Our results revealed high ESBL-EC detection rates. COUTIs caused by ESBL-EC are more likely to occur in patients with parenchymal tumor, a history of urolithiasis stone fragmentation, a history of urological surgery, hospitalization within 6 months, indwelling catheter outside hospital, and use of third-generation cephalosporins. These patients were highly resistant to penicillins, cephalosporins, and quinolones.

Key Words: Drug Resistance; Community onset urinary tract infections; *Escherichia Coli*-producing Extended Spectrum β-Lactamase; Adult

Strengths and limitations of this study

- The study focused on community-acquired UTIs in patients, 62% of whom were ⩾60 years. Results are applicable to elderly community dwellers.
- Using a case-control design, this study examined factors associated with ESBL-EC UTIs, including comorbidities, surgical history, recent antibiotic usage, and indwelling catheter outside hospital.
- The study utilized the the double-disk diffusion method for confirmation of bacterial phenotypes, without conducting genetic sequencing at the molecular level.
- This retrospective study relies on existing data, potentially limited by incompleteness, bias, and confounding factors.

1 Introduction

Urinary tract infections (UTIs) are characterized by high incidence rates, frequent recurrence, a predisposition among certain populations, and bacterial resistance, among other notable features, is one of the most common infections in the community, with urinary-derived *Escherichia coli* being the most predominant pathogenic bacteria. *E. coli* has shown more complex changes in drug resistance, more rapid geographic variation, and a faster transmission rate with the widespread use of antimicrobials. The establishment of long-term surveillance and analysis of drug resistance in *E. coli* are being focused on globally to find a faster treatment method for *E. coli* infections and control the epidemic of novel drug-resistant strains [1, 2].

The current worldwide prevalence of extended-spectrum β-lactamase-producing *Escherichia coli* (ESBL-EC) in the community is increasing, causing a significant issue in clinical diagnosis and treatment [1, 2]. Laboratory studies have reported that ESBL-producing *Enterobacteriaceae* can produce several β-lactamases to hydrolyze broad-spectrum β-lactamase antibiotics, thus leading to resistance to penicillins and cephalosporins [3]. Moreover, genes encoding ESBL can be transferred in different species of plasmid-mediated *Enterobacteriaceae* [4]; therefore, bacteria carrying ESBL genes usually comprise additional genes or gene mutations that mediate resistance to multiple antibiotics [5].

Reviewing the literature over the past 20 years approximately, we found reports about the genetic and epidemic characteristics, drug resistance patterns, and susceptibility factors of *E. coli* from China, the United States, the United Kingdom, Australia, Spain, Turkey, Jordan, and other countries [6-14]; the results from these studies have been used in the empirical treatment and development of related drugs in the clinic. In China, a well-established surveillance system for drug-resistant bacteria was formed quite late; therefore, relatively few reports about the bacteria are available, and more surveillance data and laboratory studies are still required to help doctors choose the appropriate treatment. Thus, we herein retrospectively analyzed cases of Community onset urinary tract infections (COUTIs) caused by *E. coli* within the past 5 years in the Chongqing region, China, evaluated the drug resistance and clinical characteristics of ESBL-EC and analyzed the risk factors for COUTIs caused by ESBL-EC by performing a case-control study in ESBL-positive and -negative patients.

2 Method

2.1 Environment and Population

The People's Hospital of Dazu Chongqing, Dazu District, Chongqing, China, is a national tertiary general hospital integrating medical, teaching, scientific research, preventive health care, first aid, and rehabilitation, with a bed capacity of 1000 and receives more than 8000 patients per year. The Dazu district, located in the western part of Chongqing, has a resident population of 8,56,000, and the region has a high degree of population aging, with a large population suffering from common diseases such as diabetes, cardiovascular disease, respiratory disease, and cancer.

2.2 Study Design and Materials

We herein retrospectively reviewed patients diagnosed with COUTIs caused by *E. coli* diagnosed from May 2017 to December 2022. We collected data including sex, age, admission time, sample collection time, clinical manifestations, and risk factors (including underlying disease, history of urologic surgery, hospitalization within 6 months, antibiotic use within 6 months, and indwelling catheter outside hospital) through electronic medical records, examination reports, and telephone call back visits.

The risk factors for COUTIs caused by ESBL-EC were evaluated using a case-control design,

defining patients who were diagnosed with UTIs and had an ESBL-positive urine culture as the case group and patients who were diagnosed with UTIs and had an ESBL-negative urine culture as the control group, using logistic regression for univariate analysis. Multivariate analysis was performed for variables with significant differences ($P < 0.05$).

2.3 Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) patients older than 18 years; (2) those with urine collection done before admission or within 48 h of admission; (3) those with a positive urine culture with a growth of 10^5 CFU/mL; (5) those with a clinical diagnosis of UTI.

The exclusion criteria were as follows: (1) Patients with incomplete clinical data; (2) those who did not agree to provide case information for participation in the study; (3) those who were hospitalized for more than 48 h before diagnosis; (4) Patients with a history of recurrent urinary tract infections caused by Escherichia coli (only the sample data from the first episode of infection was included).

2.4 Microbiological Methods

The strain identification was conducted using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (VITEK® MS IND MALDI TOF, BioMérieux, France). The isolated *E. coli* were initially screened using the conventional paper chip diffusion method to detect the susceptibility to broad-spectrum β-lactamase antibiotics. The phenotypic confirmation of ESBL-EC was performed using the double-disk diffusion method according to the Clinical and Laboratory Standards Institute performance standards.

2.5 Antimicrobial Susceptibility Testing

The minimum inhibitory concentration was determined according to the Clinical and Laboratory Standards Institute guidelines [15], and the standard strain *E. coli* ATCC25922 was used as the control strain. Drugs including, ampicillin, ampicillin/sulbactam, piperacillin/tazobactam, meloxicillin, cefuroxime, cefoperazone/sulbactam, cefotetan, ceftazidime, ceftriaxone, cefixime, cefepime, cefotaxime, aztreonam, imipenem, meropenem, ertapenem, gentamicin, tobramycin, amikacin, levofloxacin, ciprofloxacin, nitrofurantoin, and cotrimoxazole, were tested.

2.6 Statistical Analysis

Analyses were performed using SPSS 26.0 (IBM Corp., Armonk, NY, USA). Count data were expressed as numbers and percentages, and chi-square tests were performed. Measurements that met normal distribution were presented as mean ± standard deviation and were subjected to a t-test. Binary logistic regression was used to analyze the risk factors for COUTIs caused by ESBL-EC, and $P < 0.05$ was considered statistically significant.

3 Results

3.1 Detection Rate

A total of 394 cases diagnosed with COUTIs caused by *E. coli* were included. Among them, 192 cases were ESBL-positive, with a detection rate of 48.7% (192/394).

3.2 Clinical Characteristics of ESBL-Positive Patients

Of the 192 ESBL-positive patients, 50 were male, accounting for 26.0% (50/192). The mean patient age was 64 ± 13 years, and 62.0% (119/192) of the patients were aged 60 years and older. The vast majority of patients had underlying comorbidities, including diabetes, hypertension, parenchymal tumors, prostatic hyperplasia, and others.

The main clinical symptoms included urinary tract irritation signs (urinary frequency: 65, urinary urgencies: 56, and odynuria: 49), dysuria (11), hematuria (19), lumbago (28), pain with percussion in the renal area (21), and fever (35); the detailed results are shown in Table 1.

Table 1: Clinical presentation and proportion of ESBL-positive patients

Symptoms		Number	Percent(%)
Urinary irritation	urinary frequency	65	33.9
	urinary urgency	56	29.2
	Odynuria	49	25.5
Dysuria		11	5.7
Hematuresis		19	9.9
Lumbago		28	14.6
Renal buckle pain		21	10.9
Fever		35	18.2
Chilly		16	8.3
Shiver		6	3.1
Dizzy		12	6.3
Headache		18	9.4
Nausea		11	5.7
Vomit		17	8.9
Belly distention		14	7.3
Diarrhea		2	1.0

3.3 Risk Factors

Univariate analysis showed that parenchymal tumor, history of urolithiasis stone fragmentation, history of urological surgery, hospitalization within 6 months, indwelling catheter outside hospital, and antibiotic use (mainly third-generation cephalosporins) within 6 months were factors significantly associated with COUTIs caused by ESBL-EC ($P < 0.05$, see Table 2).

Multivariate analysis of these factors revealed that a history of urolithiasis stone fragmentation, urological surgery, indwelling catheter outside hospital, hospitalization within 6 months, and use of

third-generation cephalosporins were independent risk factors for COUTIs caused by ESBL-EC (see Table 3).

Table 2: Univariate analysis of the risk factors in ESBL-positive patients

Risk factors	All patients (%)	ESBL-negative (%)	ESBL-positive (%)	*P* value
Total	394	202(51.3)	192（48.7)	
Gender (male)	109(27.9)	59(29.2)	50(26.0)	0.483
Advanced age (⩾60 years)	227(57.6)	108(53.5)	119(62.0)	0.088
Underlying diseases and comorbidity				
Diabetes	161(40.9)	86(42.6)	75(39.1)	0.479
Hypertension	142(36.0)	68(33.7)	74(38.5)	0.314
Parenchymal tumor	43(10.9)	17(8.4)	26(13.5)	**0.025**
Urinary bladder carcinoma	13(3.3)	4(2.0)	9(4.7)	0.144
Prostatic cancer	4(1.0)	0(0.0)	4(2.1)	0.999
Benign prostatic hyperplasia	29(7.4)	10(5.0)	19(9.9)	0.065
Urolithiasis stone fragmentation	43(10.9)	15(7.4)	28(14.6)	**0.025**
Urological surgery	58(14.7)	21(10.4)	37(19.3)	**0.014**
Hospitalization (within 6 months)	80(20.3)	26(12.8)	54(28.1)	**<0.001**
ICU hospitalization (within 6 months)	11(2.8)	4(2.0)	7(3.6)	0.323
indwelling catheter outside hospital	54(13.7)	19(9.4)	35(18.2)	**0.002**
Antibiotic use (within 6 months)	110(27.9)	41(20.3)	69(35.9)	**<0.001**
Second-generation cephalosporins	20(5.1)	9(4.5)	11(5.7)	0.566
Third-generation cephalosporins	67(17.0)	24(11.9)	43(22.4)	**0.006**
Quinolone antibiotics	35(8.9)	17(8.4)	18(9.4)	0.492

Table 3: Multivariate analysis of the risk factors in ESBL-positive patients

	OR	95% confidence interval	*P* value
Parenchymal tumor	1.801	0.882–3.678	0.107
Urolithiasis stone fragmentation	2.450	1.342–4.473	**0.004**
Urological surgery	3.102	1.534–6.270	**0.002**
indwelling catheter outside hospital	2.059	1.025–4.133	**0.042**

Hospitalization (within 6 months)	2.127	1.207–3.748	**0.009**
Third-generation cephalosporins	1.903	1.069–3.389	**0.029**

3.4 Drug Resistance Analysis

The drug resistance analysis of ESBL-EC revealed revealed that the sensitivity of carbapenems, including imipenem, meropenem, and ertapenem; amikacin; cefotetan; piperacillin/tazobactam; nitrofurantoin; and cefoperazone/sulbactam was 100%, 100%, 96.6%, 95.3%, 87.9%, and 76.5%, respectively. The antibiotic resistance rates of ampicillin, ceftriaxone, cefixime, penicillin cefuroxime, levofloxacin, and ciprofloxacin were 100%, 100%, 100%, 98.7%, 76.5%, 73.8%, and 77.8%, respectively (see Table 4).

Table 4: Analysis of resistance in ESBL-positive patients

Antibiotics	Resistance (%)	Sensitivity (%)	Intermediate (%)
Ampicillin	100	0	0
Ampicillin/sulbactam	65.1	23.5	11.4
Piperacillin/tazobactam	2.7	95.3	2
Mezlocillin	98.7	1.3	0
Cefuroxime	76.5	23.5	0
Cefoperazone / Sulbactam	12.1	76.5	11.4
Cefotetan	0	96.6	3.4
Ceftazidime	44.3	52.3	4.6
Ceftriaxone	100	0	0
Cefminox	100	0	0
Cefepime	41.6	58.4	0
Cefotaxime	64.4	35.6	0
Aztreonam	66.4	33.6	0
Imipenem	0	100	0
Meropenem	0	100	0
Ertapenem	0	100	0
Gentamicin	43.6	56.4	0
Tobramycin	16.1	64.4	19.5
Amikacin	0	100	0
Levofloxacin	73.8	10.7	15.5
Ciprofloxacin	77.8	18.8	3.4
Furadantin	3.4	87.9	8.7
trimethoprim/sulfamethoxazole	62.4	37.6	0

4 Discussion

UTI caused by ESBL-EC, characterized by bacterial resistance and recurrence, is one of the most common infections in the community; it has a high treatment difficulty. ESBL-EC can be genetically encoded to produce ESBL, and degraded β-lactamase antibiotics widely used in the clinic, making the bacteria resistant to these antibiotics [3]. Furthermore, it is also possible to spread drug-resistant genes to other bacteria by transfer nature plasmid vectors or by mechanisms such as homologous recombination, leading to multidrug resistance [4]. Over the past 20 years, ESBL-EC has widely spread worldwide and is no longer restricted to infections in hospital wards, and the prevalence of COUTIs caused by ESBL-EC is continuously increasing [1, 2].

Epidemiological studies have shown marked differences in the transmission of ESBL-EC, mainly because ESBL-EC has a high genetic diversity and diverse resistant strains may dominate in different regions and populations [1]. To understand the spread and differences of COUTIs caused by ESBL-EC in various regions in the last two decades, we referred to a large and reliable literature. Two studies in China reported the prevalence of ESBL-EC in COUTIs [6, 7]. In 2021, a prospective multicenter study in East China [6] reported the prevalence of ESBL-EC in communities in detail, comprising 1760 UTI cases from 19 hospitals; the detection rate of ESBL *Enterobacteriaceae* was 37.2%. The detection rate of community-acquired ESBL-EC cases was 22% in a retrospective study from Tongren Hospital, Beijing, China [7]. A similar pattern has been reported in several European countries, with a study from the Glasgow region of Scotland, UK, published in 2011 indicating a detection rate of ESBL *Enterobacteriaceae* of 7.5% in urine samples [8]. The detection rate of ESBL-EC in COUTIs increased from 0.47% in 2000 to 1.7% in 2014 in Spain [9]. A 9-year retrospective Australian study revealed a 44% increase in the proportion of ESBL-EC in individuals with UTIs caused by *E. coli* from 4.6% in 2006 to 6.6% in 2014 [10]. The prevalence of ESBL-EC has also been reported in countries in West Asia, with a report from Turkey in 2019 revealing a 50.5% detection rate of ESBL-EC in UTIs [11]. In 2018, a two-center cross-sectional study from Amman in Jordan reported a detection rate as high as 62% [12]. A multicenter study from North America reported a 3.9% detection rate of ESBL-EC in patients with community-associated infections [13], and another study from California reported a 5.9% detection rate in patients with UTIs [14]. In the present study, we reviewed all cases of COUTIs caused by *E. coli* in the Chongqing region over the past 5 years and found that the detection rate of ESBL-EC was 48.7%, which was higher than that in East China and Beijing; much higher than that in the United Kingdom, Spain, Australia, and the United States; and lower than that in Turkey and Jordan.

The high detection rate of ESBL-EC in the community may be associated with the clinical characteristics of the local infected population and the previous healthcare and antibiotic usage patterns of patients. In the present study, the proportion of ESBL-positive female patients was 74%, which was much higher than that of male patients. This finding is consistent with those of two reports from East China and Beijing, wherein the number of ESBL-positive female patients was more than 80% [6, 7]. Moreover, women are more susceptible to UTIs for reasons associated with the physiological anatomy and estrogen levels of women [16, 17]. In terms of anatomy, the female urethra is relatively shorter than that of males and closer to the anus, increasing the chance of bacterial migration from the intestine to the urinary tract. Postmenopausal women are more susceptible to ascending UTIs due to changes in the urinary and vaginal microbiota because of

reduced estrogen levels, with blooms of enterobacterial flora [17]. Oral or topical estrogen preparations are used to prevent recurrent UTIs in postmenopausal women [17, 18]. In the present study, most women were infected with COUTIs caused by ESBL-EC, and the patients' age was mainly over 60 years old, which is consistent with the fact that menopausal women are more susceptible to UTIs.

In the present study, the mean age of the patients was (64 ± 13) years, and 62.0% (119/192) of the patients were aged 60 years and older. The vast majority of patients had underlying comorbidities, including diabetes, hypertension, urinary stones, parenchymal tumors, and others. Regarding the risk factors, 19.3% of patients had a history of urologic surgery, 18.2% had an iindwelling catheter outside hospital, 28.1% were hospitalized within 6 months, and 35.9% used antibiotics within 6 months.

Univariate analysis revealed that parenchymal tumor, history of urolithiasis stone fragmentation, history of urological surgery, hospitalization within 6 months, indwelling catheter outside hospital, and antibiotic use (mainly third-generation cephalosporins) within 6 months were factors significantly associated with COUTIs caused by ESBL-EC ($P < 0.05$). Multivariate analysis revealed that a history of urolithiasis stone fragmentation, urological surgery, indwelling catheter outside hospital, hospitalization within 6 months, and use of third-generation cephalosporins were independent risk factors for COUTIs caused by ESBL-EC. Although these findings are similar to those of previous studies [6, 7, 10-13, 19], there are still some differences. Furthermore, age is one of the possible risk factors [10, 11], and ESBL-positive patients were older than ESBL-negative patients in our study; however, the age difference was not statistically significant in the regression analysis ($P = 0.088$). Prostatic hyperplasia is one of the possible risk factors [6], and more patients with prostatic hyperplasia were ESBL-positive than ESBL-negative; however, the difference was not significant in the regression analysis ($P = 0.065$). Clinically, patients with prostatic hyperplasia present with urinary tract obstruction and urine retention and need more frequent catheterization maneuvers, which undoubtedly increases the risk of ESBL-EC infection. Nonetheless, our findings did not include prostatic hyperplasia as one of the independent risk factors, possibly due to the low sample size of male patients and a smaller number of patients with prostatic hyperplasia. This led to some deviation in the statistical results.

The most difficult part of UTI treatment is the increase in bacterial resistance, and the multidrug resistance of ESBL-EC makes the choice of therapeutic agents narrower and limited, in turn, increases the difficulty of treatment. In the present study, we statistically evaluated the results of susceptibility testing in 192 ESBL-positive patients. The results showed that carbapenems, including imipenem, meropenem, and ertapenem, had very strong antimicrobial activity in vitro, with 100% sensitivity. Aminoglycoside antimicrobials showed a wide variation in the antimicrobial activity; the sensitivity of amikacin was excellent, reaching 100%, and that of gentamicin and tobramycin was 64.4% and 54.4%, respectively. Nitrofurantoin, a nitrofuran, had a sensitivity of 87.9%. The sensitivity of piperacillin/tazobactam was 95.3%.

The treatment guidelines on multidrug-resistant bacteria issued by the Infectious Disease Society of America in 2022 indicated that carbapenems have strong antibacterial activity against ESBL-

producing *Enterobacteriaceae* and can be the first choice of treatment for pyelonephritis and complicated UTI caused by ESBL-producing *Enterobacteriaceae* [5]. In addition, piperacillin/tazobactam, a commonly used empirical therapeutic agent, demonstrated good antibacterial activity against multiple ESBL-producing *Enterobacteriaceae* [20]. However, compared with the in vitro efficacy of carbapenems, piperacillin/tazobactam is slightly less effective [5], which is consistent with the results of our study. It is important to note that the prevalence of carbapenem-resistant *Enterobacteriaceae* is also constantly increasing [21] and that repeated carbapenem use is a major contributing factor to the increasing prevalence of carbapenem-resistant *Enterobacteriaceae* [22]. Therefore, we preferentially use piperacillin/tazobactam for some patients with COUTIs caused by ESBL-ECs who are less symptomatic, thus reducing the frequency of carbapenem use.

Currently, the commonly used cephalosporins for the treatment of infections are not very effective in treating infections caused by ESBL-EC. In the present study, only the second-generation cephalosporin cefotetan had a high sensitivity (96.6%); third-generation cephalosporins have developed obvious resistance, and the resistance for ceftriaxone and cefixime reached 100%. Combined with the risk factor analysis in this study, the use of third-generation cephalosporins is an independent risk factor for COUTIs caused by ESBL-EC, and we assume that there may be a situation of transitional third-generation cephalosporin use in this region and that the widespread use of third-generation cephalosporins will induce the emergence of new ESBL strains. Thus, the use of third-generation cephalosporins should be reduced in response to community-acquired infections, particularly COUTIs caused by ESBL-EC to avoid inducing more ESBL-producing。

The study has some limitations. Firstly, our investigation focused on patients with COUTIs, excluding those with hospital-acquired urinary tract infections.Therefore, we could not compare the difference of epidemiological data between COUTIs and hospital acquired UTIs. secondly, we only compiled statistics and analyzed the drug resistance in the ESBL-positive group, without comparing the differences in drug resistance between the ESBL-positive and ESBL-negative groups.

5 Conclusions

The positive detection rate of COUTIs caused by ESBL-EC in this study was high; history of urolithiasis stone fragmentation, urological surgery, indwelling catheter outside hospital, hospitalization within 6 months, and use of third-generation cephalosporins were independent risk factors for COUTIs caused by ESBL-EC. The susceptibility profile suggested significant resistance to penicillins, cephalosporins, and quinolones; however, carbapenems and amikacin showed 100% sensitivity.

Ethical Approval

This study was approved by the Ethics Commission of The People's Hospital of Dazu District (No. 2023LLSC0309).

Authors' contributions

YLZ and BLL conceived the study. HLL and YLZ collected the data. LHL and JW analyzed the data. BLL and YLZ wrote this article. JW and HX revised it. HX supervised study conduct. All the authors have read and approved the final version of this manuscript. JW are responsible for the overall content (as guarantor).

Funding

The study was supported by *The First batch of key Disciplines On Public Health in Chongqing (YWBF2022072).*

Declaration of Competing Interest

The authors declare that there are no competing interests.

Acknowledgments

We acknowledge to all members of the public and patients who have shown interest in and participated in this research. We acknowledge all health-care workers involved in the diagnosis and treatment of patients in Dazu Chongqing. We thank the clinical laboratory department from The People's Hospital of Dazu District,and We thank Medjaden Inc. for its assistance in the preparation of this manuscript.

Patient and Public Involvement

Patients and their guardians were not involved in the design and implementation of our study. Patients were not invited to contribute to the writing or editing of this manuscript. We recruited patients who were willing to participate in this study through various methods, including email, telephone interviews, and face-to-face communication. we plan to write popular science articles based on the findings of this study and disseminate them to patients and the public through official channels of hospitals and regional CDCs, as well as by conducting educational lectures in infectious disease departments.

Availability of Data and Materials

The data can get from Jing Wu by email: 2861914532@qq.com

References

[1] Karlowsky JA, Lob SH, DeRyke CA, et al. Prevalence of ESBL non-CRE Escherichia coli and Klebsiella pneumoniae among clinical isolates collected by the SMART global surveillance programme from 2015 to 2019. *Int J Antimicrob Agents*. 2022;59(3):106535. doi:10.1016/j.ijantimicag.2022.106535

[2] Pitout JD, Laupland KB. Extended-spectrum beta-lactamase-producing Enterobacteriaceae: an

emerging public-health concern. *Lancet Infect Dis*. 2008;8(3):159-166. doi:10.1016/S1473-3099(08)70041-0

[3] Bradford PA. Extended-spectrum beta-lactamases in the 21st century: characterization, epidemiology, and detection of this important resistance threat. *Clin Microbiol Rev*. 2001;14(4):933-951. doi:10.1128/CMR.14.4.933-951.2001

[4] Shah AA, Hasan F, Ahmed S, Hameed A. Extended-spectrum beta-lactamases (ESbLs): characterization, epidemiology and detection. *Crit Rev Microbiol*. 2004;30(1):25-32. doi:10.1080/10408410490266429

[5] Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America 2022 Guidance on the Treatment of Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and Pseudomonas aeruginosa with Difficult-to-Treat Resistance (DTR-P. aeruginosa). *Clin Infect Dis*. 2022;75(2):187-212. doi:10.1093/cid/ciac268

[6] J. Quan, H. Dai, W. Liao et al., Etiology and prevalence of ESBLs in adult community-onset urinary tract infections in East China: A prospective multicenter study, Journal of Infection, https://doi.org/10.1016/j.jinf.2021.06.004

[7] Ludong Q, Shan C,Lihui M.Risk factors of urinary tract infection caused by extended-spectrum β-lactamase-producing escherichia coli[J].Chinese Journal of Nosocomiolog,2011,21(02):247-249.

[8] Khanna N, Boyes J, Lansdell PM, Hamouda A, Amyes SG. Molecular epidemiology and antimicrobial resistance pattern of extended-spectrum-β-lactamase-producing Enterobacteriaceae in Glasgow, Scotland. *J Antimicrob Chemother*. 2012;67(3):573-577. doi:10.1093/jac/dkr523

[9] Calbo E, Romaní V, Xercavins M, et al. Risk factors for community-onset urinary tract infections due to Escherichia coli harbouring extended-spectrum beta-lactamases. *J Antimicrob Chemother*. 2006;57(4):780-783. doi:10.1093/jac/dkl035

[10] Toner L, Papa N, Aliyu SH, Dev H, Lawrentschuk N, Al-Hayek S. Extended-spectrum beta-lactamase-producing Enterobacteriaceae in hospital urinary tract infections: incidence and antibiotic susceptibility profile over 9 years. *World J Urol*. 2016;34(7):1031-1037. doi:10.1007/s00345-015-1718-x

[11] Tüzün T, Sayın Kutlu S, Kutlu M, Kaleli İ. Risk factors for community-onset urinary tract infections caused by extended-spectrum β-lactamase-producing Escherichia coli. *Turk J Med Sci*. 2019;49(4):1206-1211. Published 2019 Aug 8. doi:10.3906/sag-1902-24

[12] Al-Jamei SA, Albsoul AY, Bakri FG, Al-Bakri AG. Extended-spectrum β-lactamase producing E. coli in urinary tract infections: A two-center, cross-sectional study of prevalence, genotypes and risk factors in Amman, Jordan. *J Infect Public Health*. 2019;12(1):21-25. doi:10.1016/j.jiph.2018.07.011

[13] Doi Y, Park YS, Rivera JI, et al. Community-associated extended-spectrum be- ta-lactamase-producing Escherichia coli infection in the United States. Clin Infect Dis 2013;56:641–8.

[14] Frazee BW, Trivedi T, Montgomery M, Petrovic DF, Yamaji R, Riley L. Emergency Department Urinary Tract Infections Caused by Extended-Spectrum β-Lactamase-Producing Enterobacteriaceae: Many Patients Have No Identifiable Risk Factor and Discordant Empiric Therapy Is Common. *Ann Emerg Med*. 2018;72(4):449-456. doi:10.1016/j.annemergmed.2018.05.006

[15] CLSI Performance standards for antimicrobial susceptibility testing. CLSI Supple- ment M100.

28th ed. Wayne, PA: Clinical and Laboratory Standards Institute; 2018.

[16] Geerlings SE. Clinical Presentations and Epidemiology of Urinary Tract Infections. *Microbiol Spectr*. 2016;4(5):10.1128/microbiolspec.UTI-0002-2012. doi:10.1128/microbiolspec.UTI-0002-2012

[17] Stamm WE. Estrogens and urinary-tract infection. *J Infect Dis*. 2007;195(5):623-624. doi:10.1086/511526

[18] Perrotta C, Aznar M, Mejia R, Albert X, Ng CW. Oestrogens for preventing recurrent urinary tract infection in postmenopausal women. *Cochrane Database Syst Rev*. 2008;(2):CD005131. Published 2008 Apr 16. doi:10.1002/14651858.CD005131.pub2

[19] Søgaard M, Heide-Jørgensen U, Vandenbroucke JP, Schønheyder HC, Vandenbroucke-Grauls CMJE. Risk factors for extended-spectrum β-lactamase-producing Escherichia coli urinary tract infection in the community in Denmark: a case-control study. *Clin Microbiol Infect*. 2017;23(12):952-960. doi:10.1016/j.cmi.2017.03.026

[20] Bush K, Macalintal C, Rasmussen BA, Lee VJ, Yang Y. Kinetic interactions of tazobactam with beta-lactamases from all major structural classes. *Antimicrob Agents Chemother*. 1993;37(4):851-858. doi:10.1128/AAC.37.4.851

[21] Zhang R, Liu L, Zhou H, et al. Nationwide Surveillance of Clinical Carbapenem-resistant Enterobacteriaceae (CRE) Strains in China. *EBioMedicine*. 2017;19:98-106. doi:10.1016/j.ebiom.2017.04.032

[22] Sun Q, Yang X, Huang Y, et al. Risk factors and clinical impact associated with infections caused by different types of carbapenem-resistant Klebsiella pneumoniae in China: A clinical study from 2014 to 2017. *J Infect*. 2022;85(4):436-480. doi:10.1016/j.jinf.2022.05.045

BMJ Open

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2024-090665.R2
Article Type:	Original research
Date Submitted by the Author:	11-Oct-2024
Complete List of Authors:	Zhou, yan-ling; The People's Hospital of Dazu Chongqing, Department of Infectious Disease Long, Biao-li; The People's Hospital of Dazu Chongqing, Department of Infectious Disease Liu, He-Lei; The People's Hospital of Dazu Chongqing, Department of Infectious Disease Wu, Jing; The People's Hospital of Dazu Chongqing, Department of Infectious Disease Xia, Hong; The People's Hospital of Dazu Chongqing, Department of Infectious Disease
Primary Subject Heading:	Public health
Secondary Subject Heading:	Urology, Epidemiology
Keywords:	Urinary tract infections < UROLOGY, PUBLIC HEALTH, Adult urology < UROLOGY, Case-Control Studies, Community Participation

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Risk factors and drug resistance of adult Community onset urinary tract infections caused by *Escherichia coli*-producing extended spectrum β-lactamase in the Chongqing region, China: A retrospective case-control study

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ABSTRACT:

Objective: To evaluate the prevalence, resistance, and risk factors of Community onset urinary tract infections (COUTIs) caused by extended-spectrum β-lactamase-producing *Escherichia coli* (ESBL-EC) for providing a basis for the selection of clinical therapeutic agents.

Design: a retrospective case-control study.

Setting: The Affiliated Dazu Hospital of Chongqing Medical University (as know as The People's Hospital of Dazu Chongqing), a 1000-bed tertiary hospital in China.

Data and participants: This study encompassed adult patients diagnosed with community-acquired urinary tract infections caused by Escherichia coli between May 2017 and December 2022, with exclusion criteria including incomplete clinical data, disagreement to participate in the study, hospitalization duration exceeding 48 hours prior to confirmation of diagnosis, and prior history of urinary tract infection caused by Escherichia coli.

Outcome measures: The risk factors for COUTIs caused by ESBL-EC were evaluated using a case-control design, defining patients who were diagnosed with UTIs and had an ESBL-positive urine culture as the case group and patients who were diagnosed with UTIs and had an ESBL-negative urine culture as the control group. Perform drug susceptibility testing and resistance analysis on isolated ESBL-EC.

Results: In total, 394 cases of COUTIs caused by *E. coli* were included; 192 cases were ESBL-positive, with a detection rate of 48.7% (192/394). Parenchymal tumor, history of urolithiasis stone fragmentation, history of urological surgery, hospitalization within 6 months, indwelling catheter outside hospital, and antibiotic use (mainly third-generation cephalosporins) were the factors significantly associated with COUTIs caused by ESBL-EC ($P < 0.05$) through logistic regression for univariate analysis. Multivariate analysis revealed that a history of urolithiasis stone fragmentation

(OR=2.450; 95%CI: 1.342-4.473; P=0.004), urological surgery (OR=3.102; 95%CI: 1.534-6.270; P=0.002), indwelling catheter outside hospital (OR=2.059; 95%CI: 1.025-4.133; P=0.042), hospitalization within 6 months (OR=2.127; 95%CI: 1.207-3.748; P=0.009), and use of third-generation cephalosporins (OR=1.903; 95%CI: 1.069-3.389; P=0.029) were the independent risk factors for COUTIs caused by ESBL-EC. The results of the drug susceptibility testing revealed that ESBL-EC exhibited the highest resistance rates to ampicillin, ceftriaxone, and cefixime, all at 100%. Mezlocillin followed with a resistance rate of 98.7%. On the other hand, ESBL-EC strains displayed the highest sensitivity to carbapenem antibiotics (imipenem, meropenem, ertapenem) and amikacin, all at 100%. Sensitivity rates were also high for cefotetan at 96.6%, piperacillin/tazobactam at 95.3%, and nitrofurantoin at 87.9%.

Conclusions: Our results revealed high ESBL-EC detection rates. COUTIs caused by ESBL-EC are more likely to occur in patients with parenchymal tumor, a history of urolithiasis stone fragmentation, a history of urological surgery, hospitalization within 6 months, indwelling catheter outside hospital, and use of third-generation cephalosporins. These patients were highly resistant to penicillins, cephalosporins, and quinolones.

Key Words: Drug Resistance; Community onset urinary tract infections; *Escherichia Coli*-producing Extended Spectrum β-Lactamase; Adult

Strengths and limitations of this study

The study focused on community-acquired UTIs in patients, 62% of whom were ⩾60 years. Results are applicable to elderly community dwellers.

Using a case-control design, this study examined factors associated with ESBL-EC UTIs, including comorbidities, surgical history, recent antibiotic usage, and indwelling catheter outside hospital.

The study utilized the the double-disk diffusion method for confirmation of bacterial phenotypes, without conducting genetic sequencing at the molecular level.

This retrospective study relies on existing data, potentially limited by incompleteness, bias, and confounding factors.

1 Introduction

Urinary tract infections (UTIs) are characterized by high incidence rates, frequent recurrence, a predisposition among certain populations, and bacterial resistance, among other notable features, is one of the most common infections in the community, with urinary-derived *Escherichia coli* being the most predominant pathogenic bacteria. *E. coli* has shown more complex changes in drug resistance, more rapid geographic variation, and a faster transmission rate with the widespread use of antimicrobials. The establishment of long-term surveillance and analysis of drug resistance in *E. coli*

are being focused on globally to find a faster treatment method for *E. coli* infections and control the epidemic of novel drug-resistant strains [1, 2].

The current worldwide prevalence of extended-spectrum β-lactamase-producing *Escherichia coli* (ESBL-EC) in the community is increasing, causing a significant issue in clinical diagnosis and treatment [1, 2]. Laboratory studies have reported that ESBL-producing *Enterobacteriaceae* can produce several β-lactamases to hydrolyze broad-spectrum β-lactamase antibiotics, thus leading to resistance to penicillins and cephalosporins [3]. Moreover, genes encoding ESBL can be transferred in different species of plasmid-mediated *Enterobacteriaceae* [4]; therefore, bacteria carrying ESBL genes usually comprise additional genes or gene mutations that mediate resistance to multiple antibiotics [5].

Reviewing the literature over the past 20 years approximately, we found reports about the genetic and epidemic characteristics, drug resistance patterns, and susceptibility factors of *E. coli* from China, the United States, the United Kingdom, Australia, Spain, Turkey, Jordan, and other countries [6-14]; the results from these studies have been used in the empirical treatment and development of related drugs in the clinic. In China, a well-established surveillance system for drug-resistant bacteria was formed quite late; therefore, relatively few reports about the bacteria are available, and more surveillance data and laboratory studies are still required to help doctors choose the appropriate treatment. Thus, we herein retrospectively analyzed cases of Community onset urinary tract infections (COUTIs) caused by *E. coli* within the past 5 years in the Chongqing region, China, evaluated the drug resistance and clinical characteristics of ESBL-EC and analyzed the risk factors for COUTIs caused by ESBL-EC by performing a case-control study in ESBL-positive and -negative patients.

2 Method

2.1 Environment and Population

The People's Hospital of Dazu Chongqing, Dazu District, Chongqing, China, is a national tertiary general hospital integrating medical, teaching, scientific research, preventive health care, first aid, and rehabilitation, with a bed capacity of 1000 and receives more than 8000 patients per year. The Dazu district, located in the western part of Chongqing, has a resident population of 8,56,000, and the region has a high degree of population aging, with a large population suffering from common diseases such as diabetes, cardiovascular disease, respiratory disease, and cancer.

2.2 Study Design and Materials

We herein retrospectively reviewed patients diagnosed with COUTIs caused by *E. coli* diagnosed from May 2017 to December 2022. We collected data including sex, age, admission time, sample collection time, clinical manifestations, and risk factors (including underlying disease, history of urologic surgery, hospitalization within 6 months, antibiotic use within 6 months, and indwelling catheter outside hospital) through electronic medical records, examination reports, and telephone call

back visits.

The risk factors for COUTIs caused by ESBL-EC were evaluated using a case-control design, defining patients who were diagnosed with UTIs and had an ESBL-positive urine culture as the case group and patients who were diagnosed with UTIs and had an ESBL-negative urine culture as the control group, using logistic regression for univariate analysis. Multivariate analysis was performed for variables with significant differences ($P < 0.05$).

2.3 Inclusion and Exclusion Criteria

The inclusion criteria were as follows: (1) patients older than 18 years; (2) those with urine collection done before admission or within 48 h of admission; (3) those with a positive urine culture with a growth of 10^5 CFU/mL; (5) those with a clinical diagnosis of UTI.

The exclusion criteria were as follows: (1) Patients with incomplete clinical data; (2) those who did not agree to provide case information for participation in the study; (3) those who were hospitalized for more than 48 h before diagnosis; (4) Patients with a history of recurrent urinary tract infections caused by Escherichia coli (only the sample data from the first episode of infection was included).

2.4 Microbiological Methods

The strain identification was conducted using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (VITEK® MS IND MALDI TOF, BioMérieux, France). The isolated *E. coli* were initially screened using the conventional paper chip diffusion method to detect the susceptibility to broad-spectrum β-lactamase antibiotics. The phenotypic confirmation of ESBL-EC was performed using the double-disk diffusion method according to the Clinical and Laboratory Standards Institute performance standards.

2.5 Antimicrobial Susceptibility Testing

The minimum inhibitory concentration was determined according to the Clinical and Laboratory Standards Institute guidelines [15], and the standard strain *E. coli* ATCC25922 was used as the control strain. Drugs including ampicillin, ampicillin/sulbactam, piperacillin/tazobactam, meloxicillin, cefuroxime, cefoperazone/sulbactam, cefotetan, ceftazidime, ceftriaxone, cefixime, cefepime, cefotaxime, aztreonam, imipenem, meropenem, ertapenem, gentamicin, tobramycin, amikacin, levofloxacin, ciprofloxacin, nitrofurantoin, and cotrimoxazole, were tested.

2.6 Statistical Analysis

Analyses were performed using SPSS 26.0 (IBM Corp., Armonk, NY, USA). Count data were expressed as numbers and percentages, and chi-square tests were performed. Measurements that met normal distribution were presented as mean ± standard deviation and were subjected to a t-test. Binary logistic regression was used to analyze the risk factors for COUTIs caused by ESBL-EC, and $P < 0.05$ was considered statistically significant.

3 Results

3.1 Detection Rate

A total of 394 cases diagnosed with COUTIs caused by *E. coli* were included. Among them, 192 cases were ESBL-positive, with a detection rate of 48.7% (192/394).

3.2 Clinical Characteristics of ESBL-Positive Patients

Of the 192 ESBL-positive patients, 50 were male, accounting for 26.0% (50/192). The mean patient age was 64 ± 13 years, and 62.0% (119/192) of the patients were 60 years and older. The vast majority of patients had underlying comorbidities, including diabetes, hypertension, parenchymal tumors, prostatic hyperplasia, and others.

The main clinical symptoms included urinary tract irritation signs (urinary frequency: 65, urinary urgencies: 56, and odynuria: 49), dysuria (11), hematuria (19), lumbago (28), pain with percussion in the renal area (21), and fever (35); the detailed results are shown in Table 1.

Table 1: Clinical presentation and proportion of ESBL-positive patients

Symptoms		Number	Percent(%)
Urinary irritation	urinary frequency	65	33.9
	urinary urgency	56	29.2
	Odynuria	49	25.5
Dysuria		11	5.7
Hematuresis		19	9.9
Lumbago		28	14.6
Renal buckle pain		21	10.9
Fever		35	18.2
Chilly		16	8.3
Shiver		6	3.1
Dizzy		12	6.3
Headache		18	9.4
Nausea		11	5.7
Vomit		17	8.9
Belly distention		14	7.3
Diarrhea		2	1.0

3.3 Risk Factors

Univariate analysis showed that parenchymal tumor, history of urolithiasis stone fragmentation, history of urological surgery, hospitalization within 6 months, indwelling catheter outside hospital, and antibiotic use (mainly third-generation cephalosporins) within 6 months were factors significantly associated with COUTIs caused by ESBL-EC ($P < 0.05$, see Table 2).

Multivariate analysis of these factors revealed that a history of urolithiasis stone fragmentation, urological surgery, indwelling catheter outside hospital, hospitalization within 6 months, and use of third-generation cephalosporins were independent risk factors for COUTIs caused by ESBL-EC (see Table 3).

Table 2: Univariate analysis of the risk factors in ESBL-positive patients

Risk factors	All patients (%)	ESBL-negative (%)	ESBL-positive (%)	*P* value
Total	394	202(51.3)	192（48.7)	
Gender (male)	109(27.9)	59(29.2)	50(26.0)	0.483
Advanced age (⩾60 years)	227(57.6)	108(53.5)	119(62.0)	0.088
Underlying diseases and comorbidity				
Diabetes	161(40.9)	86(42.6)	75(39.1)	0.479
Hypertension	142(36.0)	68(33.7)	74(38.5)	0.314
Parenchymal tumor	43(10.9)	17(8.4)	26(13.5)	**0.025**
Urinary bladder carcinoma	13(3.3)	4(2.0)	9(4.7)	0.144
Prostatic cancer	4(1.0)	0(0.0)	4(2.1)	0.999
Benign prostatic hyperplasia	29(7.4)	10(5.0)	19(9.9)	0.065
Urolithiasis stone fragmentation	43(10.9)	15(7.4)	28(14.6)	**0.025**
Urological surgery	58(14.7)	21(10.4)	37(19.3)	**0.014**
Hospitalization (within 6 months)	80(20.3)	26(12.8)	54(28.1)	**<0.001**
ICU hospitalization (within 6 months)	11(2.8)	4(2.0)	7(3.6)	0.323
indwelling catheter outside hospital	54(13.7)	19(9.4)	35(18.2)	**0.002**
Antibiotic use (within 6 months)	110(27.9)	41(20.3)	69(35.9)	**<0.001**
Second-generation cephalosporins	20(5.1)	9(4.5)	11(5.7)	0.566
Third-generation cephalosporins	67(17.0)	24(11.9)	43(22.4)	**0.006**
Quinolone antibiotics	35(8.9)	17(8.4)	18(9.4)	0.492

Table 3: Multivariate analysis of the risk factors in ESBL-positive patients

	OR	95% confidence interval	*P* value
Parenchymal tumor	1.801	0.882–3.678	0.107
Urolithiasis stone fragmentation	2.450	1.342–4.473	**0.004**
Urological surgery	3.102	1.534–6.270	**0.002**

indwelling catheter outside hospital	2.059	1.025–4.133	**0.042**
Hospitalization (within 6 months)	2.127	1.207–3.748	**0.009**
Third-generation cephalosporins	1.903	1.069–3.389	**0.029**

3.4 Drug Resistance Analysis

The results of drug sensitivity testing revealed high resistance rates of ESBL-EC to the penicillin drugs ampicillin and mezlocillin, with resistance rates of 100% and 98.7%, respectively. There was considerable variation in the resistance of ESBL-EC to cephalosporins. Specifically, the resistance rates to ceftriaxone and cefixime both reached 100%, whereas the resistance rate to cefotetan was 0%, with a sensitivity rate of 96.6%. This indicates the potential value of cefotetan in the treatment of infections caused by ESBL-EC.

ESBL-EC showed the highest sensitivity to carbapenems, with sensitivity rates of 100% for imipenem, meropenem, and ertapenem, following the carbapenems, cefotetan, piperacillin/tazobactam, and nitrofurantoin exhibited sensitivity rates of 96.6%, 95.3%, and 87.9%, respectively (see Table 4).

Table 4: Analysis of resistance in ESBL-positive patients

Antibiotics	Resistance (%)	Sensitivity (%)	Intermediate (%)
Ampicillin	100	0	0
Ampicillin/sulbactam	65.1	23.5	11.4
Piperacillin/tazobactam	2.7	95.3	2
Mezlocillin	98.7	1.3	0
Cefuroxime	76.5	23.5	0
Cefoperazone / Sulbactam	12.1	76.5	11.4
Cefotetan	0	96.6	3.4
Ceftazidime	44.3	52.3	4.6
Ceftriaxone	100	0	0
Cefixime	100	0	0
Cefepime	41.6	58.4	0
Cefotaxime	64.4	35.6	0
Aztreonam	66.4	33.6	0
Imipenem	0	100	0
Meropenem	0	100	0
Ertapenem	0	100	0
Gentamicin	43.6	56.4	0
Tobramycin	16.1	64.4	19.5
Amikacin	0	100	0
Levofloxacin	73.8	10.7	15.5

Ciprofloxacin	77.8	18.8	3.4
Furadantin	3.4	87.9	8.7
trimethoprim/sulfamethoxazole	62.4	37.6	0

4 Discussion

UTI caused by ESBL-EC, characterized by bacterial resistance and recurrence, is one of the most common infections in the community; it has a high treatment difficulty. ESBL-EC can be genetically encoded to produce ESBL, and degraded β-lactamase antibiotics are widely used in the clinic, making the bacteria resistant to these antibiotics [3]. Furthermore, it is also possible to spread drug-resistant genes to other bacteria by transfer nature plasmid vectors or by mechanisms such as homologous recombination, leading to multidrug resistance [4]. Over the past 20 years, ESBL-EC has widely spread worldwide and is no longer restricted to infections in hospital wards, and the prevalence of COUTIs caused by ESBL-EC is continuously increasing [1, 2].

Epidemiological studies have shown marked differences in the transmission of ESBL-EC, mainly because ESBL-EC has a high genetic diversity and diverse resistant strains may dominate in different regions and populations [1]. To understand the spread and differences of COUTIs caused by ESBL-EC in various regions in the last two decades, we referred to a large and reliable literature. Two studies in China reported the prevalence of ESBL-EC in COUTIs [6, 7]. In 2021, a prospective multicenter study in East China [6] reported the prevalence of ESBL-EC in communities in detail, comprising 1760 UTI cases from 19 hospitals; the detection rate of ESBL *Enterobacteriaceae* was 37.2%. The detection rate of community-acquired ESBL-EC cases was 22% in a retrospective study from Tongren Hospital, Beijing, China [7]. A similar pattern has been reported in several European countries, with a study from the Glasgow region of Scotland, UK, published in 2011 indicating a detection rate of ESBL *Enterobacteriaceae* of 7.5% in urine samples [8]. The detection rate of ESBL-EC in COUTIs increased from 0.47% in 2000 to 1.7% in 2014 in Spain [9]. A 9-year retrospective Australian study revealed a 44% increase in the proportion of ESBL-EC in individuals with UTIs caused by *E. coli* from 4.6% in 2006 to 6.6% in 2014 [10]. The prevalence of ESBL-EC has also been reported in countries in West Asia, with a report from Turkey in 2019 revealing a 50.5% detection rate of ESBL-EC in UTIs [11]. In 2018, a two-center cross-sectional study from Amman in Jordan reported a detection rate as high as 62% [12]. A multicenter study from North America reported a 3.9% detection rate of ESBL-EC in patients with community-associated infections [13], and another study from California reported a 5.9% detection rate in patients with UTIs [14]. In the present study, we reviewed all cases of COUTIs caused by *E. coli* in the Chongqing region over the past 5 years and found that the detection rate of ESBL-EC was 48.7%, which was higher than that in East China and Beijing, much higher than that in the United Kingdom, Spain, Australia, and the United States; and lower than that in Turkey and Jordan.

The high detection rate of ESBL-EC in the community may be associated with the clinical characteristics of the local infected population and the previous healthcare and antibiotic usage patterns of patients. In the present study, the proportion of ESBL-positive female patients was 74%, which was much higher than that of male patients. This finding is consistent with those of two

reports from East China and Beijing, wherein the number of ESBL-positive female patients was more than 80% [6, 7]. Moreover, women are more susceptible to UTIs for reasons associated with the physiological anatomy and estrogen levels of women [16, 17]. In terms of anatomy, the female urethra is relatively shorter than that of males and closer to the anus, increasing the chance of bacterial migration from the intestine to the urinary tract. Postmenopausal women are more susceptible to ascending UTIs due to changes in the urinary and vaginal microbiota because of reduced estrogen levels, with blooms of enterobacterial flora [17]. Oral or topical estrogen preparations are used to prevent recurrent UTIs in postmenopausal women [17, 18]. In the present study, most women were infected with COUTIs caused by ESBL-EC, and the patients' age was mainly over 60 years old, which is consistent with the fact that menopausal women are more susceptible to UTIs.

In the present study, the mean age of the patients was (64 ± 13) years, and 62.0% (119/192) of the patients were aged 60 years and older. The vast majority of patients had underlying comorbidities, including diabetes, hypertension, urinary stones, parenchymal tumors, and others. Regarding the risk factors, 19.3% of patients had a history of urologic surgery, 18.2% had an indwelling catheter outside hospital, 28.1% were hospitalized within 6 months, and 35.9% used antibiotics within 6 months.

Univariate analysis revealed that parenchymal tumor, history of urolithiasis stone fragmentation, history of urological surgery, hospitalization within 6 months, indwelling catheter outside hospital, and antibiotic use (mainly third-generation cephalosporins) within 6 months were factors significantly associated with COUTIs caused by ESBL-EC ($P < 0.05$). Multivariate analysis revealed that a history of urolithiasis stone fragmentation, urological surgery, indwelling catheter outside hospital, hospitalization within 6 months, and use of third-generation cephalosporins were independent risk factors for COUTIs caused by ESBL-EC. Although these findings are similar to those of previous studies [6, 7, 10-13, 19], there are still some differences. Furthermore, age is one of the possible risk factors [10, 11], and ESBL-positive patients were older than ESBL-negative patients in our study; however, the age difference was not statistically significant in the regression analysis ($P = 0.088$). Prostatic hyperplasia is one of the possible risk factors [6], and more patients with prostatic hyperplasia were ESBL-positive than ESBL-negative; however, the difference was not significant in the regression analysis ($P = 0.065$). Clinically, patients with prostatic hyperplasia present with urinary tract obstruction and urine retention and need more frequent catheterization maneuvers, which undoubtedly increases the risk of ESBL-EC infection. Nonetheless, our findings did not include prostatic hyperplasia as one of the independent risk factors, possibly due to the low sample size of male patients and a smaller number of patients with prostatic hyperplasia. This led to some deviation in the statistical results.

The most difficult part of UTI treatment is the increase in bacterial resistance, and the multidrug resistance of ESBL-EC makes the choice of therapeutic agents narrower and limited,which, in turn, increases the difficulty of treatment. In the present study, we statistically evaluated the results of susceptibility testing in 192 ESBL-positive patients. The results showed that carbapenems, including imipenem, meropenem, and ertapenem, had very strong antimicrobial activity in vitro, with 100%

sensitivity. Aminoglycoside antimicrobials showed a wide variation in the antimicrobial activity; the sensitivity of amikacin was excellent, reaching 100%, and that of gentamicin and tobramycin was 64.4% and 54.4%, respectively. Nitrofurantoin, a nitrofuran, had a sensitivity of 87.9%. The sensitivity of piperacillin/tazobactam was 95.3%.

The treatment guidelines on multidrug-resistant bacteria issued by the Infectious Diseases Society of America in 2022 indicated that carbapenems have strong antibacterial activity against ESBL-producing *Enterobacteriaceae* and can be the first choice of treatment for pyelonephritis and complicated UTI caused by ESBL-producing *Enterobacteriaceae* [5]. In addition, piperacillin/tazobactam, a commonly used empirical therapeutic agent, demonstrated good antibacterial activity against multiple ESBL-producing *Enterobacteriaceae* [20]. However, compared with the in vitro efficacy of carbapenems, piperacillin/tazobactam is slightly less effective [5], which is consistent with the results of our study. It is important to note that the prevalence of carbapenem-resistant *Enterobacteriaceae* is also constantly increasing [21] and that repeated carbapenem use is a major contributing factor to the increasing prevalence of carbapenem-resistant *Enterobacteriaceae* [22]. Therefore, we preferentially use piperacillin/tazobactam for some patients with COUTIs caused by ESBL-ECs who are less symptomatic, thus reducing the frequency of carbapenem use.

Currently, the commonly used cephalosporins for the treatment of infections are not very effective in treating infections caused by ESBL-EC. In the present study, only the second-generation cephalosporin cefotetan had a high sensitivity (96.6%); third-generation cephalosporins have developed obvious resistance, and the resistance for ceftriaxone and cefixime reached 100%. Combined with the risk factor analysis in this study, the use of third-generation cephalosporins is an independent risk factor for COUTIs caused by ESBL-EC, and we assume that there may be a situation of transitional third-generation cephalosporin use in this region and that the widespread use of third-generation cephalosporins will induce the emergence of new ESBL strains. Thus, the use of third-generation cephalosporins should be reduced in response to community-acquired infections, particularly COUTIs caused by ESBL-EC, to avoid inducing more ESBL-producing。

The study has some limitations. Firstly, our investigation focused on patients with COUTIs, excluding those with hospital-acquired urinary tract infections. Therefore, we could not compare the difference of epidemiological data between COUTIs and hospital acquired UTIs. Secondly, we only compiled statistics and analyzed the drug resistance in the ESBL-positive group without comparing the differences in drug resistance between the ESBL-positive and ESBL-negative groups. Thirdly, we employed the double-disk synergy test to confirm the phenotype of ESBL-producing Escherichia coli strains without conducting gene sequencing at the molecular level. Consequently, the resistance genes and virulence genes of ESBL-producing Escherichia coli, as well as the correlation between them, were not identified. Fourthly, this study is retrospective and relies on existing data, which may be subject to issues such as data quality, selection bias, and confounding factors. Additionally, due to limitations in sample size, we did not perform a prior sample size calculation. Instead, we simply included all eligible samples from the past five years, which may have reduced the statistical power of our findings.

5 Conclusions

The positive detection rate of COUTIs caused by ESBL-EC in this study was high; history of urolithiasis stone fragmentation, urological surgery, indwelling catheter outside hospital, hospitalization within 6 months, and use of third-generation cephalosporins were independent risk factors for COUTIs caused by ESBL-EC. The susceptibility profile suggested significant resistance to penicillins, cephalosporins, and quinolones; however, carbapenems and amikacin showed 100% sensitivity.

Ethical Approval

This study was approved by the Ethics Commission of The People's Hospital of Dazu District (No. 2023LLSC0309).

Authors' contributions

YLZ and BLL conceived the study. HLL and YLZ collected the data. LHL and JW analyzed the data. BLL and YLZ wrote this article. JW and HX revised it. HX supervised study conduct. All the authors have read and approved the final version of this manuscript. JW are responsible for the overall content (as guarantor).

Funding

The study was supported by The First batch of key Disciplines On Public Health in Chongqing (YWBF2022072).

Declaration of Competing Interest

The authors declare that there are no competing interests.

Acknowledgments

We acknowledge to all members of the public and patients who have shown interest in and participated in this research. We acknowledge all health-care workers involved in the diagnosis and treatment of patients in Dazu Chongqing. We thank the clinical laboratory department from The People's Hospital of Dazu District,and We thank Medjaden Inc. for its assistance in the preparation of this manuscript.

Patient and Public Involvement

Patients and their guardians were not involved in the design and implementation of our study. Patients were not invited to contribute to the writing or editing of this manuscript. We recruited patients who were willing to participate in this study through various methods, including email,

telephone interviews, and face-to-face communication. We plan to write popular science articles based on the findings of this study and disseminate them to patients and the public through official channels of hospitals and regional CDCs, as well as by conducting educational lectures in infectious disease departments.

Availability of Data and Materials

The data is available upon reasonable request from the corresponding author Jing Wu (2861914532@qq.com).

References

[1] Karlowsky JA, Lob SH, DeRyke CA, et al. Prevalence of ESBL non-CRE Escherichia coli and Klebsiella pneumoniae among clinical isolates collected by the SMART global surveillance programme from 2015 to 2019. *Int J Antimicrob Agents*. 2022;59(3):106535. doi:10.1016/j.ijantimicag.2022.106535

[2] Pitout JD, Laupland KB. Extended-spectrum beta-lactamase-producing Enterobacteriaceae: an emerging public-health concern. *Lancet Infect Dis*. 2008;8(3):159-166. doi:10.1016/S1473-3099(08)70041-0

[3] Bradford PA. Extended-spectrum beta-lactamases in the 21st century: characterization, epidemiology, and detection of this important resistance threat. *Clin Microbiol Rev*. 2001;14(4):933-951. doi:10.1128/CMR.14.4.933-951.2001

[4] Shah AA, Hasan F, Ahmed S, Hameed A. Extended-spectrum beta-lactamases (ESbLs): characterization, epidemiology and detection. *Crit Rev Microbiol*. 2004;30(1):25-32. doi:10.1080/10408410490266429

[5] Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases Society of America 2022 Guidance on the Treatment of Extended-Spectrum β-lactamase Producing Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and Pseudomonas aeruginosa with Difficult-to-Treat Resistance (DTR-P. aeruginosa). *Clin Infect Dis*. 2022;75(2):187-212. doi:10.1093/cid/ciac268

[6] J. Quan, H. Dai, W. Liao et al., Etiology and prevalence of ESBLs in adult community-onset urinary tract infections in East China: A prospective multicenter study, Journal of Infection, https://doi.org/10.1016/j.jinf.2021.06.004

[7] Ludong Q, Shan C,Lihui M.Risk factors of urinary tract infection caused by extended-spectrum β-lactamase-producing escherichia coli[J].Chinese Journal of Nosocomiolog,2011,21(02):247-249.

[8] Khanna N, Boyes J, Lansdell PM, Hamouda A, Amyes SG. Molecular epidemiology and antimicrobial resistance pattern of extended-spectrum-β-lactamase-producing Enterobacteriaceae in Glasgow, Scotland. *J Antimicrob Chemother*. 2012;67(3):573-577. doi:10.1093/jac/dkr523

[9] Calbo E, Romaní V, Xercavins M, et al. Risk factors for community-onset urinary tract infections due to Escherichia coli harbouring extended-spectrum beta-lactamases. *J Antimicrob Chemother*. 2006;57(4):780-783. doi:10.1093/jac/dkl035

[10] Toner L, Papa N, Aliyu SH, Dev H, Lawrentschuk N, Al-Hayek S. Extended-spectrum beta-lactamase-producing Enterobacteriaceae in hospital urinary tract infections: incidence and antibiotic susceptibility profile over 9 years. *World J Urol*. 2016;34(7):1031-1037. doi:10.1007/s00345-015-

1718-x

[11] Tüzün T, Sayın Kutlu S, Kutlu M, Kaleli İ. Risk factors for community-onset urinary tract infections caused by extended-spectrum β-lactamase-producing Escherichia coli. *Turk J Med Sci*. 2019;49(4):1206-1211. Published 2019 Aug 8. doi:10.3906/sag-1902-24

[12] Al-Jamei SA, Albsoul AY, Bakri FG, Al-Bakri AG. Extended-spectrum β-lactamase producing E. coli in urinary tract infections: A two-center, cross-sectional study of prevalence, genotypes and risk factors in Amman, Jordan. *J Infect Public Health*. 2019;12(1):21-25. doi:10.1016/j.jiph.2018.07.011

[13] Doi Y, Park YS, Rivera JI, et al. Community-associated extended-spectrum be- ta-lactamase-producing Escherichia coli infection in the United States. Clin Infect Dis 2013;56:641–8.

[14] Frazee BW, Trivedi T, Montgomery M, Petrovic DF, Yamaji R, Riley L. Emergency Department Urinary Tract Infections Caused by Extended-Spectrum β-Lactamase-Producing Enterobacteriaceae: Many Patients Have No Identifiable Risk Factor and Discordant Empiric Therapy Is Common. *Ann Emerg Med*. 2018;72(4):449-456. doi:10.1016/j.annemergmed.2018.05.006

[15] CLSI Performance standards for antimicrobial susceptibility testing. CLSI Supple- ment M100. 28th ed. Wayne, PA: Clinical and Laboratory Standards Institute; 2018.

[16] Geerlings SE. Clinical Presentations and Epidemiology of Urinary Tract Infections. *Microbiol Spectr*. 2016;4(5):10.1128/microbiolspec.UTI-0002-2012. doi:10.1128/microbiolspec.UTI-0002-2012

[17] Stamm WE. Estrogens and urinary-tract infection. *J Infect Dis*. 2007;195(5):623-624. doi:10.1086/511526

[18] Perrotta C, Aznar M, Mejia R, Albert X, Ng CW. Oestrogens for preventing recurrent urinary tract infection in postmenopausal women. *Cochrane Database Syst Rev*. 2008;(2):CD005131. Published 2008 Apr 16. doi:10.1002/14651858.CD005131.pub2

[19] Søgaard M, Heide-Jørgensen U, Vandenbroucke JP, Schønheyder HC, Vandenbroucke-Grauls CMJE. Risk factors for extended-spectrum β-lactamase-producing Escherichia coli urinary tract infection in the community in Denmark: a case-control study. *Clin Microbiol Infect*. 2017;23(12):952-960. doi:10.1016/j.cmi.2017.03.026

[20] Bush K, Macalintal C, Rasmussen BA, Lee VJ, Yang Y. Kinetic interactions of tazobactam with beta-lactamases from all major structural classes. *Antimicrob Agents Chemother*. 1993;37(4):851-858. doi:10.1128/AAC.37.4.851

[21] Zhang R, Liu L, Zhou H, et al. Nationwide Surveillance of Clinical Carbapenem-resistant Enterobacteriaceae (CRE) Strains in China. *EBioMedicine*. 2017;19:98-106. doi:10.1016/j.ebiom.2017.04.032

[22] Sun Q, Yang X, Huang Y, et al. Risk factors and clinical impact associated with infections caused by different types of carbapenem-resistant Klebsiella pneumoniae in China: A clinical study from 2014 to 2017. *J Infect*. 2022;85(4):436-480. doi:10.1016/j.jinf.2022.05.045