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# **BMJ Open**

#### Risk factors and drug resistance of adult communityacquired urinary tract infections caused by Escherichia coliproducing extended spectrum β-lactamase in the Chongqing region, China: A 5-year retrospective analysis

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1	Risk factors and drug resistance of adult community-acquired urinary
2	tract infections caused by Escherichia coli-producing extended
3	spectrum $\beta$ -lactamase in the Chongqing region, China: A 5-year
4	retrospective analysis
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10	ABSTRACT:
11	<b>Objective</b> : To evaluate the prevalence, resistance, and risk factors of community-acquired urinary
12	tract infections (CAUTIs) caused by extended-spectrum β-lactamase-producing <i>Escherichia coli</i>
13	(ESBL-EC) for providing a basis for the selection of clinical therapeutic agents
14	Methods: We retrospectively analyzed the clinical data of patients diagnosed with CAUTIs caused
15	by <i>E. coli</i> from May 2017 to December 2022 at a tertiary hospital in the Chongqing region, China,
16	and evaluated the detection rate of ESBL-EC. To assess the risk factors for CAUTIs caused by
17	ESBL-EC, a case-control design was used, focusing on the resistance of ESBL-EC.
18	Results: In total, 394 cases of CAUTIs caused by E. coli were included; 192 cases were ESBL-
19	positive, with a detection rate of 48.7% (192/394). Parenchymal tumor, history of urolithiasis stone
20	fragmentation, history of urological surgery, hospitalization within 6 months, indwelling urinary
21	catheter insertion within 6 months, and antibiotic use (mainly third-generation cephalosporins) were
22	the factors significantly associated with CAUTIs caused by ESBL-EC ( $P \le 0.05$ ) through logistic
23	regression for univariate analysis. Multivariate analysis revealed that a history of urolithiasis stone
24	fragmentation, urological surgery, indwelling urinary catheter insertion within 6 months,
25	hospitalization within 6 months, and use of third-generation cephalosporins were the independent
26	risk factors for CAUTIs caused by ESBL-EC. Analysis of resistance in ESBL-EC revealed that the
27	sensitivity of carbapenems, including imipenem, meropenem, and ertapenem; amikacin; cefotetan;
28	piperacillin/tazobactam; nitrofurantoin; and cefoperazone/sulbactam was 100%, 100%, 96.6%,
29	95.3%, 87.9%, and 76.5%, respectively. Penicillins, cephalosporins, and quinolones were associated
30	with higher antibiotic resistance rates.
31	Conclusions: Our results revealed high ESBL-EC detection rates. CAUTIs caused by ESBL-EC are
32	more likely to occur in patients with parenchymal tumor, a history of urolithiasis stone
33	fragmentation, a history of urological surgery, hospitalization within 6 months, indwelling urinary
34	catheter insertion within 6 months, and use of third-generation cephalosporins. These patients were

35 highly resistant to penicillins, cephalosporins, and quinolones.

36 Key Words: Drug Resistance; Community-acquired Urinary Tract Infections; *Escherichia Coli-*

37 producing Extended Spectrum β-Lactamase; Adult

#### 38 Strengths and limitations of this study

39 This study incorporated nearly 200 cases of community-acquired urinary tract infections (CAUTIs)

40 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 causedby ESBL-EC.

43 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  $\beta$ -lactamases to hydrolyze broad-spectrum  $\beta$ -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

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69 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 -

73 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.

#### 83 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.

90The risk factors for CAUTIs caused by ESBL-EC were evaluated using a case-control design,91defining patients who were diagnosed with UTIs and had an ESBL-positive urine culture as the case92group and patients who were diagnosed with UTIs and had an ESBL-negative urine culture as the93control group, using logistic regression for univariate analysis. Multivariate analysis was performed94for variables with significant differences (P < 0.05).

#### **2.3 Inclusion and Exclusion Criteria**

96 The inclusion criteria were as follows: (1) patients older than 18 years; (2) those with urine

97 collection done before admission or within 48 h of admission; (3) those with a positive urine culture
98 with a growth of 10<sup>5</sup> CFU/mL; (5) those with a clinical diagnosis of UTI.

99 The exclusion criteria were as follows: (1) Patients with incomplete clinical data; (2) those who did 100 not agree to provide case information for participation in the study; (3) those who were hospitalized 101 for more than 48 h before diagnosis.

#### 102 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.

#### 107 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.

#### 114 2.6 Statistical Analysis

115 Analyses were performed using SPSS 26.0 (IBM Corp., Armonk, NY, USA). Count data were 116 expressed as numbers and percentages, and chi-square tests were performed. Measurements that met 117 normal distribution were presented as mean  $\pm$  standard deviation and were subjected to a t-test. 118 Binary logistic regression was used to analyze the risk factors for CAUTIs caused by ESBL-EC, and 119 P < 0.05 was considered statistically significant.

120 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**

130 Of the 192 ESBL-positive patients, 50 were male, accounting for 26.0% (50/192). The mean patient 131 age was  $64 \pm 13$  years, and 62.0% (119/192) of the patients were aged 60 years and older. The vast 132 majority of patients had underlying comorbidities, including diabetes, hypertension, parenchymal 133 tumors, prostatic hyperplasia, and others. Enseignement Superieur (ABES) . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

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.

Symptoms		Number	Percent(%)
	urinary frequency	65	33.9
Urinary irritation	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

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

#### **3.3 Risk Factors**

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

All patients (%)	ESBL-negative (%)	ESBL-positive (%)	P value
394	202(51.3)	192 (48.7)	
109(27.9)	59(29.2)	50(26.0)	0.483
227(57.6)	108(53.5)	119(62.0)	0.088
161(40.9)	86(42.6)	75(39.1)	0.479
	394 109(27.9) 227(57.6)	394     202(51.3)       109(27.9)     59(29.2)       227(57.6)     108(53.5)	394       202(51.3)       192 (48.7)         109(27.9)       59(29.2)       50(26.0)         227(57.6)       108(53.5)       119(62.0)

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	43(10.9)	15(7.4)	28(14.6)	0.025
fragmentation				
Urological surgery	58(14.7)	21(10.4)	37(19.3)	0.014
Hospitalization (within 6	80(20.3)	26(12.8)	54(28.1)	<0.001
months)	00(20.5)	20(12.0)	0 1(20.1)	0.001
ICU hospitalization (within 6	11(2.8)	4(2.0)	7(3.6)	0.323
	11(2.8)	4(2.0)	7(3.0)	0.323
months)				
Indwelling urinary catheter	54(13.7)	19(9.4)	35(18.2)	0.002
operation (within 6 months)				
Antibiotic use (within 6	110(27.9)	41(20.3)	69(35.9)	<0.001
months)				
Second-generation	20(5.1)	9(4.5)	11(5.7)	0.566
cephalosporins			()	
Third-generation	67(17.0)	24(11.9)	43(22.4)	0.006
-	07(17.0)	24(11.7)	43(22.4)	0.000
cephalosporins				
Quinolone antibiotics	35(8.9)	17(8.4)	18(9.4)	0.492

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

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

#### **3.4 Drug Resistance Analysis**

150 The drug resistance analysis of ESBL-EC revealed revealed that the sensitivity of carbapenems,

151 including imipenem, meropenem, and ertapenem; amikacin; cefotetan; piperacillin/tazobactam;

152 nitrofurantoin; and cefoperazone/sulbactam was 100%, 100%, 96.6%, 95.3%, 87.9%, and 76.5%,

153 respectively. The antibiotic resistance rates of ampicillin, ceftriaxone, cefixime, penicillin

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154 cefuroxime, levofloxacin, and ciprofloxacin were 100%, 100%, 100%, 98.7%, 76.5%, 73.8%, and
155 77.8%, respectively (see Table 4).

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 /	12.1	76.5	11.4
Sulbactam			
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

## **Table 4: Analysis of resistance in ESBL-positive patients**

## **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].

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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  $(64 \pm 13)$  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 

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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 

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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

#### 260 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.

#### 267 Ethical Approval

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

269 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.

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  - 275 Declaration of Competing Interest
  - 276 The authors declare that there are no competing interests.

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59 60 279 Chongqing. We thank the clinical laboratory department from The People's Hospital of Dazu 280 District, and We thank Medjaden Inc. for its assistance in the preparation of this manuscript 281 Availability of Data and Materials 282 The data can get from Jing Wu by email: 2861914532@qq.com References 283 [1] Karlowsky JA, Lob SH, DeRyke CA, et al. Prevalence of ESBL non-CRE Escherichia coli and 284 285 Klebsiella pneumoniae among clinical isolates collected by the SMART global surveillance programme from 2015 to 2019. Int J Antimicrob Agents. 2022;59(3):106535. 286 doi:10.1016/j.ijantimicag.2022.106535 287 288 [2] Pitout JD, Laupland KB. Extended-spectrum beta-lactamase-producing Enterobacteriaceae: an 289 emerging public-health concern. Lancet Infect Dis. 2008;8(3):159-166. doi:10.1016/S1473-290 3099(08)70041-0 [3] Bradford PA. Extended-spectrum beta-lactamases in the 21st century: characterization, 291 epidemiology, and detection of this important resistance threat. Clin Microbiol Rev. 2001;14(4):933-292 293 951. doi:10.1128/CMR.14.4.933-951.2001 294 [4] Shah AA, Hasan F, Ahmed S, Hameed A. Extended-spectrum beta-lactamases (ESbLs): 295 characterization, epidemiology and detection. Crit Rev Microbiol. 2004;30(1):25-32. doi:10.1080/10408410490266429 296 297 [5] Tamma PD, Aitken SL, Bonomo RA, Mathers AJ, van Duin D, Clancy CJ. Infectious Diseases 298 Society of America 2022 Guidance on the Treatment of Extended-Spectrum β-lactamase Producing 299 Enterobacterales (ESBL-E), Carbapenem-Resistant Enterobacterales (CRE), and Pseudomonas 300 aeruginosa with Difficult-to-Treat Resistance (DTR-P. aeruginosa). Clin Infect Dis. 2022;75(2):187-301 212. doi:10.1093/cid/ciac268 302 [6] CLSI Performance standards for antimicrobial susceptibility testing. CLSI Supple- ment M100. 303 28th ed. Wayne, PA: Clinical and Laboratory Standards Institute; 2018. 304 [7] J. Quan, H. Dai, W. Liao et al., Etiology and prevalence of ESBLs in adult community-onset 305 urinary tract infections in East China: A prospective multicenter study, Journal of Infection, 306 https://doi.org/10.1016/j.jinf.2021.06.004 307 [8] Ludong Q, Shan C, Lihui M.Risk factors of urinary tract infection caused by extended-spectrum 308 β-lactamase-producing escherichia coli[J]. Chinese Journal of Nosocomiolog, 2011, 21(02):247-249. 309 [9] Khanna N, Boyes J, Lansdell PM, Hamouda A, Amyes SG. Molecular epidemiology and 310 antimicrobial resistance pattern of extended-spectrum-*β*-lactamase-producing Enterobacteriaceae in 311 Glasgow, Scotland. J Antimicrob Chemother. 2012;67(3):573-577. doi:10.1093/jac/dkr523 312 [10] Calbo E, Romaní V, Xercavins M, et al. Risk factors for community-onset urinary tract 313 infections due to Escherichia coli harbouring extended-spectrum beta-lactamases. J Antimicrob 314 Chemother. 2006;57(4):780-783. doi:10.1093/jac/dkl035 315 [11] Toner L, Papa N, Aliyu SH, Dev H, Lawrentschuk N, Al-Hayek S. Extended-spectrum betalactamase-producing Enterobacteriaceae in hospital urinary tract infections: incidence and antibiotic 316 317 susceptibility profile over 9 years. World J Urol. 2016;34(7):1031-1037. doi:10.1007/s00345-015-

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# **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

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<ul> <li>tract infections caused by Escherichia coli-producing extended</li> <li>spectrum β-lactamase in the Chongqing region, China: A retrospective</li> <li>case-control study</li> <li>Yan-ling Zhou<sup>1*</sup>, Biao-li Long<sup>1*</sup>, He-lei Liu<sup>1</sup>, Jing Wu<sup>1#</sup>, Hong Xia<sup>1#</sup></li> <li>'Department of Infectious Disease, The People's Hospital of Dazu Chongqing, Chongqing 402360,</li> <li>China</li> <li>*Authors contributed equally</li> <li>"Correspondence: Jing Wu 2861914532@qq.com ; Hong Xia HongXiaChongqing@163.com</li> <li>ABSTRACT:</li> <li>Objective: To evaluate the prevalence, resistance, and risk factors of Community onset urinary tract infections (COUTIs) caused by extended-spectrum β-lactamase-producing <i>Escherichia coli</i> (ESBL-EC) for providing a basis for the selection of clinical therapeutic agents.</li> <li>Design: retrospective case-control study.</li> <li>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.</li> </ul>	1	Risk factors and drug resistance of adult Community onset urinary
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	16	
17 <b>Data and participants:</b> This study encompassed adult patients diagnosed with community-acquired	17	Data and participants: This study encompassed adult patients diagnosed with community-acquired
18 urinary tract infections caused by Escherichia coli between May 2017 and December 2022, with	18	urinary tract infections caused by Escherichia coli between May 2017 and December 2022, with
19 exclusion criteria including incomplete clinical data, disagreement to participate in the study,	19	exclusion criteria including incomplete clinical data, disagreement to participate in the study,
20 hospitalization duration exceeding 48 hours prior to confirmation of diagnosis, and prior history of	20	hospitalization duration exceeding 48 hours prior to confirmation of diagnosis, and prior history of
21 urinary tract infection caused by Escherichia coli.	21	urinary tract infection caused by Escherichia coli.
22 <b>Outcome measures:</b> The risk factors for COUTIs caused by ESBL-EC were evaluated using a case-	22	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		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	24	culture as the case group and patients who were diagnosed with UTIs and had an ESBL-negative
25 urine culture as the control group. Analyzing Drug Resistance of ESBL-EC.	25	urine culture as the control group. Analyzing Drug Resistance of ESBL-EC.
26 <b>Results</b> : In total, 394 cases of COUTIs caused by <i>E. coli</i> were included; 192 cases were ESBL-	26	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	27	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	28	fragmentation, history of urological surgery, hospitalization within 6 months, indwelling catheter
29 outside hospital, and antibiotic use (mainly third-generation cephalosporins) were the factors	29	outside hospital, and antibiotic use (mainly third-generation cephalosporins) were the factors
30 significantly associated with COUTIs caused by ESBL-EC ( $P < 0.05$ ) through logistic regression for	30	significantly associated with COUTIs caused by ESBL-EC ( $P < 0.05$ ) through logistic regression for
31 univariate analysis. Multivariate analysis revealed that a history of urolithiasis stone fragmentation	31	univariate analysis. Multivariate analysis revealed that a history of urolithiasis stone fragmentation
32 (OR=2.450; 95%CI: 1.342-4.473; P=0.004), urological surgery (OR=3.102; 95%CI: 1.534-6.270;	32	(OR=2.450; 95%CI: 1.342-4.473; P=0.004), urological surgery (OR=3.102; 95%CI: 1.534-6.270;

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5	33	P=0.002), indwelling catheter outside hospital (OR=2.059; 95%CI: 1.025-4.133; P=0.042),
6	34	hospitalization within 6 months (OR=2.127; 95%CI: 1.207-3.748; P=0.009), and use of third-
7 8	35	generation cephalosporins (OR=1.903; 95%CI: 1.069-3.389; P=0.029) were the independent risk
o 9	36	factors for COUTIs caused by ESBL-EC. Analysis of resistance in ESBL-EC revealed that the
10	37	sensitivity of carbapenems, including imipenem, meropenem, and ertapenem; amikacin; cefotetan;
11	38	piperacillin/tazobactam; nitrofurantoin; and cefoperazone/sulbactam was 100%, 100%, 96.6%,
12	39	95.3%, 87.9%, and 76.5%, respectively. Penicillins, cephalosporins, and quinolones were associated
13 14	40	with higher antibiotic resistance rates.
15 16	41	Conclusions: Our results revealed high ESBL-EC detection rates. COUTIs caused by ESBL-EC are
17	42	more likely to occur in patients with parenchymal tumor, a history of urolithiasis stone
18	43	fragmentation, a history of urological surgery, hospitalization within 6 months, indwelling catheter
19 20	44	outside hospital, and use of third-generation cephalosporins. These patients were highly resistant to
20	45	penicillins, cephalosporins, and quinolones.
22	10	pomoninis, copilatosporins, and quinoronos.
23	46	Key Words: Drug Resistance; Community onset urinary tract infections; Escherichia Coli-
24 25	47	producing Extended Spectrum β-Lactamase; Adult
26		
27	48	Strengths and limitations of this study
28		
29 30	49	The study focused on community-acquired UTIs in patients, 62% of whom were $\geq$ 60 years.
31	50	Results are applicable to elderly community dwellers.
32	51	
33	52	Using a case-control design, this study examined factors associated with ESBL-EC UTIs, including
34 35	53	comorbidities, surgical history, recent antibiotic usage, and indwelling catheter outside hospital.
36	54	
37	55	The study utilized the the double-disk diffusion method for confirmation of bacterial phenotypes,
38	56	without conducting genetic sequencing at the molecular level.
39	57	
40 41	58	This retrospective study relies on existing data, potentially limited by incompleteness, bias, and
42	59	confounding factors.
43	57	
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45 46	60	1 Introduction
47		
48	61	Urinary tract infections (UTIs) are characterized by high incidence rates, frequent recurrence, a
49	62	predisposition among certain populations, and bacterial resistance, among other notable features, is
50 51	63	one of the most common infections in the community, with urinary-derived <i>Escherichia coli</i> being
52	64	the most predominant pathogenic bacteria. E. coli has shown more complex changes in drug
53	65	resistance, more rapid geographic variation, and a faster transmission rate with the widespread use of
54	66	antimicrobials. The establishment of long-term surveillance and analysis of drug resistance in <i>E. coli</i>
55 56	67	are being focused on globally to find a faster treatment method for <i>E. coli</i> infections and control the
57	68	epidemic of novel drug-resistant strains [1, 2].
58	00	epidenne of nover drug-resistant suams [1, 2].
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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  $\beta$ -lactamases to hydrolyze broad-spectrum  $\beta$ -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**

#### 90 2.1 Environment and Population

91 The People's Hospital of Dazu Chongqing, Dazu District, Chongqing, China, is a national tertiary 92 general hospital integrating medical, teaching, scientific research, preventive health care, first aid, 93 and rehabilitation, with a bed capacity of 1000 and receives more than 8000 patients per year. The 94 Dazu district, located in the western part of Chongqing, has a resident population of 8,56,000, and 95 the region has a high degree of population aging, with a large population suffering from common 96 diseases such as diabetes, cardiovascular disease, respiratory disease, and cancer.

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97 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.

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

105 defining patients who were diagnosed with UTIs and had an ESBL-positive urine culture as the case 106 group and patients who were diagnosed with UTIs and had an ESBL-negative urine culture as the 107 control group, using logistic regression for univariate analysis. Multivariate analysis was performed 108 for variables with significant differences (P < 0.05).

#### 109 2.3 Inclusion and Exclusion Criteria

110 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<sup>5</sup> 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).

117 2.4 Microbiological Methods

118 The strain identification was conducted using matrix-assisted laser desorption/ionization time-of-119 flight mass spectrometry (VITEK® MS IND MALDI TOF, BioMérieux, France). The isolated *E. coli* 120 were initially screened using the conventional paper chip diffusion method to detect the susceptibility 121 to broad-spectrum  $\beta$ -lactamase antibiotics. The phenotypic confirmation of ESBL-EC was performed 122 using the double-disk diffusion method according to the Clinical and Laboratory Standards Institute 123 performance standards.

#### 124 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.

131 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  $\pm$  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**

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#### 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).

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#### **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  $64 \pm 13$  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.

## Number Symptoms Percent(%)

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

	urinary frequency	65	33.9
Urinary irritation	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

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

159	Table 2: Univariate analysis of the risk factors in ESBL-positive patients
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Risk factors	All patients (%)	ESBL-negative (%)	ESBL-positive (%)	<i>P</i> value
Total	394	202(51.3)	192 (48.7)	
Gender (male)	109(27.9)	59(29.2)	50(26.0)	0.483
Advanced age ( $\geq 60$	years) 227(57.6)	108(53.5)	119(62.0)	0.088
Underlying diseases	and			
comorbidity	1(1(40.0)	$\Omega(\mathbf{A}\mathbf{D}_{\mathbf{A}})$	75(20.1)	0.470
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 carc	einoma 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 hyp	perplasia 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 (with months)	nin 6 80(20.3)	26(12.8)	54(28.1)	<0.001
ICU hospitalization months)	(within 6 11(2.8)	4(2.0)	7(3.6)	0.323
indwelling catheter of hospital	outside 54(13.7)	19(9.4)	35(18.2)	0.002
Antibiotic use (withi months)	in 6 110(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 antibiotic	es 35(8.9)	17(8.4)	18(9.4)	0.492

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

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

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

#### **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).

#### 168 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

#### 169 4 Discussion

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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 ure thrat 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 

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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  $(64 \pm 13)$  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-

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producing Enterobacteriaceae and can be the first choice of treatment for pyelonephritis and 251 252 complicated UTI caused by ESBL-producing Enterobacteriaceae [5]. In addition, piperacillin/tazobactam, a commonly used empirical therapeutic agent, demonstrated good 253 254 antibacterial activity against multiple ESBL-producing *Enterobacteriaceae* [20]. However, 255 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 256 257 carbapenem-resistant Enterobacteriaceae is also constantly increasing [21] and that repeated 258 carbapenem use is a major contributing factor to the increasing prevalence of carbapenem-resistant 259 Enterobacteriaceae [22]. Therefore, we preferentially use piperacillin/tazobactam for some patients 260 with COUTIs caused by ESBL-ECs who are less symptomatic, thus reducing the frequency of 261 carbapenem use.

262 Currently, the commonly used cephalosporins for the treatment of infections are not very effective in 263 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 264 developed obvious resistance, and the resistance for ceftriaxone and cefixime reached 100%. 265 Combined with the risk factor analysis in this study, the use of third-generation cephalosporins is an 266 independent risk factor for COUTIs caused by ESBL-EC, and we assume that there may be a 267 situation of transitional third-generation cephalosporin use in this region and that the widespread use 268 269 of third-generation cephalosporins will induce the emergence of new ESBL strains. Thus, the use of 270 third-generation cephalosporins should be reduced in response to community-acquired infections, particularly COUTIs caused by ESBL-EC to avoid inducing more ESBL-producing. 271

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.

### 277 **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.

#### 284 Ethical Approval

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

#### 287 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).

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#### 295 Declaration of Competing Interest

296 The authors declare that there are no competing interests.

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#### 303 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.

- 311 Availability of Data and Materials
- 312 The data can get from Jing Wu by email: 2861914532@qq.com

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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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1	Risk factors and drug resistance of adult Community onset urinary
2	tract infections caused by Escherichia coli-producing extended
3	spectrum $\beta$ -lactamase in the Chongqing region, China: A retrospective
4	case-control study
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7	China
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10	ABSTRACT:
11	<b>Objective</b> : To evaluate the prevalence, resistance, and risk factors of Community onset urinary tract
12	infections (COUTIs) caused by extended-spectrum β-lactamase-producing Escherichia coli (ESBL-
13	EC) for providing a basis for the selection of clinical therapeutic agents.
14	<b>Design:</b> a retrospective case-control study.
15	Setting: The Affiliated Dazu Hospital of Chongqing Medical University (as know as The People's
16	Hospital of Dazu Chongqing), a 1000-bed tertiary hospital in China.
17	Data and participants: This study encompassed adult patients diagnosed with community-acquired
18	urinary tract infections caused by Escherichia coli between May 2017 and December 2022, with
19	exclusion criteria including incomplete clinical data, disagreement to participate in the study,
20	hospitalization duration exceeding 48 hours prior to confirmation of diagnosis, and prior history of
21	urinary tract infection caused by Escherichia coli.
22	Outcome measures: The risk factors for COUTIs caused by ESBL-EC were evaluated using a case-
23	control design, defining patients who were diagnosed with UTIs and had an ESBL-positive urine
24	culture as the case group and patients who were diagnosed with UTIs and had an ESBL-negative
25	urine culture as the control group. Perform drug susceptibility testing and resistance analysis on
26	isolated ESBL-EC.
27	Results: In total, 394 cases of COUTIs caused by E. coli were included; 192 cases were ESBL-
28	positive, with a detection rate of 48.7% (192/394). Parenchymal tumor, history of urolithiasis stone
29	fragmentation, history of urological surgery, hospitalization within 6 months, indwelling catheter
30	outside hospital, and antibiotic use (mainly third-generation cephalosporins) were the factors
31	significantly associated with COUTIs caused by ESBL-EC ( $P < 0.05$ ) through logistic regression for
32	univariate analysis. Multivariate analysis revealed that a history of urolithiasis stone fragmentation

2 3		
4	33	(OR=2.450; 95%CI: 1.342-4.473; P=0.004), urological surgery (OR=3.102; 95%CI: 1.534-6.270;
5	33 34	P=0.002, indwelling catheter outside hospital (OR=2.059; 95%CI: 1.025-4.133; P=0.042),
6 7	35	hospitalization within 6 months (OR=2.127; 95%CI: 1.207-3.748; P=0.009), and use of third-
8	36	generation cephalosporins (OR=1.903; 95%CI: 1.069-3.389; P=0.029) were the independent risk
9	37	factors for COUTIs caused by ESBL-EC. The results of the drug susceptibility testing revealed that
10 11	38	ESBL-EC exhibited the highest resistance rates to ampicillin, ceftriaxone, and cefixime, all at 100%.
12	39	Mezlocillin followed with a resistance rate of 98.7%. On the other hand, ESBL-EC strains displayed
13	40	the highest sensitivity to carbapenem antibiotics (imipenem, meropenem, ertapenem) and amikacin,
14 15	41	all at 100%. Sensitivity rates were also high for cefotetan at 96.6%, piperacillin/tazobactam at
16	42	95.3%, and nitrofurantoin at 87.9%.
17	72	
18	43	Conclusions: Our results revealed high ESBL-EC detection rates. COUTIs caused by ESBL-EC are
19 20	44	more likely to occur in patients with parenchymal tumor, a history of urolithiasis stone
21	45	fragmentation, a history of urological surgery, hospitalization within 6 months, indwelling catheter
22	46	outside hospital, and use of third-generation cephalosporins. These patients were highly resistant to
23 24	47	penicillins, cephalosporins, and quinolones.
25		
26	48	Key Words: Drug Resistance; Community onset urinary tract infections; Escherichia Coli-
27	49	producing Extended Spectrum β-Lactamase; Adult
28 29		
30 31 32	50	Strengths and limitations of this study
32 33	51	The study focused on community-acquired UTIs in patients, 62% of whom were $\geq 60$ years.
34	52	Results are applicable to elderly community dwellers.
35 36	53	
37	54	Using a case-control design, this study examined factors associated with ESBL-EC UTIs, including
38	55	comorbidities, surgical history, recent antibiotic usage, and indwelling catheter outside hospital.
39	56	
40 41	57	The study utilized the the double-disk diffusion method for confirmation of bacterial phenotypes,
42	58	without conducting genetic sequencing at the molecular level.
43	59	
44 45	60	This retrospective study relies on existing data, potentially limited by incompleteness, bias, and
46	61	confounding factors.
47	01	
48 49	(2)	1 Introduction
49 50	62	1 Introduction
51		
52	63	Urinary tract infections (UTIs) are characterized by high incidence rates, frequent recurrence, a
53 54	64	predisposition among certain populations, and bacterial resistance, among other notable features, is
55	65	one of the most common infections in the community, with urinary-derived Escherichia coli being
56	66	the most predominant pathogenic bacteria. E. coli has shown more complex changes in drug
57	67	resistance, more rapid geographic variation, and a faster transmission rate with the widespread use of
58 59	68	antimicrobials. The establishment of long-term surveillance and analysis of drug resistance in E. coli
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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  $\beta$ -lactamases to hydrolyze broad-spectrum  $\beta$ -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.

#### 91 2 Method

92 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.

99 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

105 back visits.

106 The risk factors for COUTIs caused by ESBL-EC were evaluated using a case-control design, 107 defining patients who were diagnosed with UTIs and had an ESBL-positive urine culture as the case 108 group and patients who were diagnosed with UTIs and had an ESBL-negative urine culture as the 109 control group, using logistic regression for univariate analysis. Multivariate analysis was performed 110 for variables with significant differences (P < 0.05).

#### 111 2.3 Inclusion and Exclusion Criteria

112 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<sup>5</sup> 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).

119 2.4 Microbiological Methods

120 The strain identification was conducted using matrix-assisted laser desorption/ionization time-of-121 flight mass spectrometry (VITEK® MS IND MALDI TOF, BioMérieux, France). The isolated *E. coli* 122 were initially screened using the conventional paper chip diffusion method to detect the susceptibility 123 to broad-spectrum  $\beta$ -lactamase antibiotics. The phenotypic confirmation of ESBL-EC was performed 124 using the double-disk diffusion method according to the Clinical and Laboratory Standards Institute 125 performance standards.

126 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.

- - 133 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  $\pm$  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  $64 \pm 13$  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.

148 The main clinical symptoms included urinary tract irritation signs (urinary frequency: 65, urinary

149 urgencies: 56, and odynuria: 49), dysuria (11), hematuria (19), lumbago (28), pain with percussion in

150 the renal area (21), and fever (35); the detailed results are shown in Table 1.

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

Symptoms		Number	Percent(%)	
	urinary frequency	65	33.9	
Urinary irritation	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**

55 153 Univariate analysis showed that parenchymal tumor, history of urolithiasis stone fragmentation, 56 154 Littee for heited and the state of the little state of t

history of urological surgery, hospitalization within 6 months, indwelling catheter outside hospital,

and antibiotic use (mainly third-generation cephalosporins) within 6 months were factors

59 156 significantly associated with COUTIs caused by ESBL-EC (P < 0.05, see Table 2). 

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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).

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

Risk	factors	All patients (%)	ESBL-negative (%)	ESBL-positive (%)	P value
Tota	1	394	202(51.3)	192 (48.7)	
Gen	der (male)	109(27.9)	59(29.2)	50(26.0)	0.483
Adv	anced age ( $\geq 60$ years)	227(57.6)	108(53.5)	119(62.0)	0.088
Und	erlying diseases and				
com	orbidity				
Diab	oetes	161(40.9)	86(42.6)	75(39.1)	0.479
Нур	ertension	142(36.0)	68(33.7)	74(38.5)	0.314
Pare	nchymal tumor	43(10.9)	17(8.4)	26(13.5)	0.025
Urin	ary bladder carcinoma	13(3.3)	4(2.0)	9(4.7)	0.144
Pros	tatic cancer	4(1.0)	0(0.0)	4(2.1)	0.999
Beni	gn prostatic hyperplasia	29(7.4)	10(5.0)	19(9.9)	0.065
	ithiasis stone agmentation	43(10.9)	15(7.4)	28(14.6)	0.025
Urol	ogical surgery	58(14.7)	21(10.4)	37(19.3)	0.014
Hosj mon	pitalization (within 6 ths)	80(20.3)	26(12.8)	54(28.1)	<0.001
ICU mon	hospitalization (within 6 ths)	11(2.8)	4(2.0)	7(3.6)	0.323
indw hosp	velling catheter outside	54(13.7)	19(9.4)	35(18.2)	0.002
Anti mon	biotic use (within 6 ths)	110(27.9)	41(20.3)	69(35.9)	<0.001
	alosporins	20(5.1)	9(4.5)	11(5.7)	0.566
	d-generation alosporins	67(17.0)	24(11.9)	43(22.4)	0.006
Ouir	olone antibiotics	35(8.9)	17(8.4)	18(9.4)	0.492

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

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

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	indwelling catheter outside	2.059	1.025-4.133	0.042
	hospital	2.037	1.025 4.155	0.042
	Hospitalization (within 6	2.127	1.207-3.748	0.009
	months )			
	Third-generation	1.903	1.069-3.389	0.029
	cephalosporins			
163	3.4 Drug Resistance Analysis			
164	The results of drug sensitivity to	esting reveale	d high resistance rates of	f ESBL-EC to the
165	drugs ampicillin and mezlocillin	•	•	
66	considerable variation in the res			
67	rates to ceftriaxone and cefixim		1 1	1 5,
68	0%, with a sensitivity rate of 96			
69	of infections caused by ESBL-I		- F	
70	ESBL-EC showed the highest s		arbapenems, with sensit	ivity rates of 100
71	imipenem, meropenem, and erta	-	•	•
72	piperacillin/tazobactam, and nit	-		
73	respectively (see Table 4).		•	
	Table 4: Analysis of resistance	e in ESPE-h	usitive patients	
	Antibiotics	Resistance		%) Interm
				%) Interm
	Antibiotics	Resistanc	ce (%) Sensitivity (	
	Antibiotics Ampicillin	Resistance 100	ce (%) Sensitivity ( 0	0
	Antibiotics Ampicillin Ampicillin/sulbactam	Resistanc 100 65.1	ee (%) Sensitivity (9 0 23.5	0 11.4
	Antibiotics Ampicillin Ampicillin/sulbactam Piperacillin/tazobactam	Resistance 100 65.1 2.7	ce (%) Sensitivity ( 0 23.5 95.3	0 11.4 2
	Antibiotics Ampicillin Ampicillin/sulbactam Piperacillin/tazobactam Mezlocillin	Resistanc 100 65.1 2.7 98.7	ce (%) Sensitivity (9 0 23.5 95.3 1.3	0 11.4 2 0
	Antibiotics Ampicillin Ampicillin/sulbactam Piperacillin/tazobactam Mezlocillin Cefuroxime	Resistance 100 65.1 2.7 98.7 76.5	ce (%) Sensitivity ( 0 23.5 95.3 1.3 23.5	0 11.4 2 0 0
	Antibiotics Ampicillin Ampicillin/sulbactam Piperacillin/tazobactam Mezlocillin Cefuroxime Cefoperazone / Sulbactam	Resistance 100 65.1 2.7 98.7 76.5 12.1	28 (%) Sensitivity (% 0 23.5 95.3 1.3 23.5 76.5	0 11.4 2 0 0 11.4
	Antibiotics Ampicillin Ampicillin/sulbactam Piperacillin/tazobactam Mezlocillin Cefuroxime Cefoperazone / Sulbactam Cefotetan	Resistant 100 65.1 2.7 98.7 76.5 12.1 0	2e (%) Sensitivity ( 0 23.5 95.3 1.3 23.5 76.5 96.6	0 11.4 2 0 0 11.4 3.4
	Antibiotics Ampicillin Ampicillin/sulbactam Piperacillin/tazobactam Mezlocillin Cefuroxime Cefoperazone / Sulbactam Cefotetan Ceftazidime	Resistance 100 65.1 2.7 98.7 76.5 12.1 0 44.3	2e (%) Sensitivity (% 0 23.5 95.3 1.3 23.5 76.5 96.6 52.3	0 11.4 2 0 0 11.4 3.4 4.6
	Antibiotics Ampicillin Ampicillin/sulbactam Piperacillin/tazobactam Mezlocillin Cefuroxime Cefoperazone / Sulbactam Cefotetan Ceftazidime Ceftriaxone Cefixime	Resistance 100 65.1 2.7 98.7 76.5 12.1 0 44.3 100 100	Sensitivity (%)         0         23.5         95.3         1.3         23.5         76.5         96.6         52.3         0         0         0         0	0 11.4 2 0 0 11.4 3.4 4.6 0 0
	Antibiotics Ampicillin Ampicillin/sulbactam Piperacillin/tazobactam Mezlocillin Cefuroxime Cefoperazone / Sulbactam Cefotetan Ceftazidime Ceftriaxone Ceftriaxone Cefixime Cefepime	Resistance 100 65.1 2.7 98.7 76.5 12.1 0 44.3 100 100 41.6	Sensitivity (%)         0         23.5         95.3         1.3         23.5         76.5         96.6         52.3         0         0         58.4	0 11.4 2 0 0 11.4 3.4 4.6 0 0 0
	AntibioticsAmpicillinAmpicillin/sulbactamPiperacillin/tazobactamMezlocillinCefuroximeCefoperazone / SulbactamCefotetanCeftazidimeCeftriaxoneCefiximeCefopimeCefopimeCefotaxime	Resistance 100 65.1 2.7 98.7 76.5 12.1 0 44.3 100 100 41.6 64.4	Sensitivity (%)         0         23.5         95.3         1.3         23.5         76.5         96.6         52.3         0         0         58.4         35.6	0 11.4 2 0 0 11.4 3.4 4.6 0 0 0 0
	AntibioticsAmpicillinAmpicillin/sulbactamPiperacillin/tazobactamMezlocillinCefuroximeCefoperazone / SulbactamCefotetanCeftazidimeCeftriaxoneCefiximeCefepimeCefotaximeCefotaximeAztreonam	Resistant 100 65.1 2.7 98.7 76.5 12.1 0 44.3 100 100 41.6 64.4 66.4	Sensitivity (%)         0         23.5         95.3         1.3         23.5         76.5         96.6         52.3         0         0         58.4         35.6         33.6	0 11.4 2 0 0 11.4 3.4 4.6 0 0 0 0 0 0
	AntibioticsAmpicillinAmpicillin/sulbactamPiperacillin/tazobactamMezlocillinCefuroximeCefoperazone / SulbactamCefotetanCeftazidimeCeftriaxoneCefiximeCefepimeCefotaximeAztreonamImipenem	Resistance 100 65.1 2.7 98.7 76.5 12.1 0 44.3 100 100 41.6 64.4 66.4 0	Sensitivity (%)         0         23.5         95.3         1.3         23.5         76.5         96.6         52.3         0         0         58.4         35.6         33.6         100	0 11.4 2 0 0 11.4 3.4 4.6 0 0 0 0 0 0 0 0
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174	AntibioticsAmpicillinAmpicillin/sulbactamPiperacillin/tazobactamMezlocillinCefuroximeCefoperazone / SulbactamCefotetanCeftazidimeCeftriaxoneCeftriaxoneCefopimeCefopimeCefotaximeAztreonamImipenemMeropenemErtapenem	Resistance 100 65.1 2.7 98.7 76.5 12.1 0 44.3 100 100 41.6 64.4 66.4 0 0 0 0	Sensitivity (%)         0         23.5         95.3         1.3         23.5         95.3         1.3         23.5         96.6         52.3         0         0         58.4         35.6         33.6         100         100         100         100	0 11.4 2 0 0 11.4 3.4 4.6 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0
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Ciprofloxacin	77.8	18.8	3.4
Furadantin	3.4	87.9	8.7
trimethoprim/sulfamethoxazole	62.4	37.6	0

#### 175 **4 Discussion**

176 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 177 encoded to produce ESBL, and degraded  $\beta$ -lactamase antibiotics are widely used in the clinic, 178 179 making the bacteria resistant to these antibiotics [3]. Furthermore, it is also possible to spread drug-180 resistant genes to other bacteria by transfer nature plasmid vectors or by mechanisms such as 181 homologous recombination, leading to multidrug resistance [4]. Over the past 20 years, ESBL-EC 182 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]. 183

184 Epidemiological studies have shown marked differences in the transmission of ESBL-EC, mainly 185 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 186 by ESBL-EC in various regions in the last two decades, we referred to a large and reliable literature. 187 188 Two studies in China reported the prevalence of ESBL-EC in COUTIS [6, 7]. In 2021, a prospective 189 multicenter study in East China [6] reported the prevalence of ESBL-EC in communities in detail, 190 comprising 1760 UTI cases from 19 hospitals; the detection rate of ESBL Enterobacteriaceae was 191 37.2%. The detection rate of community-acquired ESBL-EC cases was 22% in a retrospective study 192 from Tongren Hospital, Beijing, China [7]. A similar pattern has been reported in several European 193 countries, with a study from the Glasgow region of Scotland, UK, published in 2011 indicating a 194 detection rate of ESBL Enterobacteriaceae of 7.5% in urine samples [8]. The detection rate of 195 ESBL-EC in COUTIs increased from 0.47% in 2000 to 1.7% in 2014 in Spain [9]. A 9-year 196 retrospective Australian study revealed a 44% increase in the proportion of ESBL-EC in individuals 197 with UTIs caused by E. coli from 4.6% in 2006 to 6.6% in 2014 [10]. The prevalence of ESBL-EC 198 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 199 Amman in Jordan reported a detection rate as high as 62% [12]. A multicenter study from North 200 201 America reported a 3.9% detection rate of ESBL-EC in patients with community-associated 202 infections [13], and another study from California reported a 5.9% detection rate in patients with 203 UTIs [14]. In the present study, we reviewed all cases of COUTIs caused by E. coli in the 204 Chongqing region over the past 5 years and found that the detection rate of ESBL-EC was 48.7%, 205 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. 206

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

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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 ure thrat 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  $(64 \pm 13)$  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%

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3 4	0.51	
5	251	sensitivity. Aminoglycoside antimicrobials showed a wide variation in the antimicrobial activity; the
6 7	252	sensitivity of amikacin was excellent, reaching 100%, and that of gentamicin and tobramycin was
8	253	64.4% and 54.4%, respectively. Nitrofurantoin, a nitrofuran, had a sensitivity of 87.9%. The
9	254	sensitivity of piperacillin/tazobactam was 95.3%.
10	255	The treatment guidelines on multidrug-resistant bacteria issued by the Infectious Diseases Society of
11 12	256	America in 2022 indicated that carbapenems have strong antibacterial activity against ESBL-
13	250	producing <i>Enterobacteriaceae</i> and can be the first choice of treatment for pyelonephritis and
14	258	complicated UTI caused by ESBL-producing <i>Enterobacteriaceae</i> [5]. In addition,
15 16	259	piperacillin/tazobactam, a commonly used empirical therapeutic agent, demonstrated good
17	260	antibacterial activity against multiple ESBL-producing <i>Enterobacteriaceae</i> [20]. However,
18	260	compared with the in vitro efficacy of carbapenems, piperacillin/tazobactam is slightly less effective
19 20	262	[5], which is consistent with the results of our study. It is important to note that the prevalence of
20 21	262	carbapenem-resistant <i>Enterobacteriaceae</i> is also constantly increasing [21] and that repeated
22	264	carbapenem use is a major contributing factor to the increasing prevalence of carbapenem-resistant
23	265	<i>Enterobacteriaceae</i> [22]. Therefore, we preferentially use piperacillin/tazobactam for some patients
24 25	266	with COUTIs caused by ESBL-ECs who are less symptomatic, thus reducing the frequency of
26	267	carbapenem use.
27	207	
28 29	268	Currently, the commonly used cephalosporins for the treatment of infections are not very effective in
30	269	treating infections caused by ESBL-EC. In the present study, only the second-generation
31	270	cephalosporin cefotetan had a high sensitivity (96.6%); third-generation cephalosporins have
32 33	271	developed obvious resistance, and the resistance for ceftriaxone and cefixime reached 100%.
34	272	Combined with the risk factor analysis in this study, the use of third-generation cephalosporins is an
35	273	independent risk factor for COUTIs caused by ESBL-EC, and we assume that there may be a
36 27	274	situation of transitional third-generation cephalosporin use in this region and that the widespread use
37 38	275	of third-generation cephalosporins will induce the emergence of new ESBL strains. Thus, the use of
39	276	third-generation cephalosporins should be reduced in response to community-acquired infections,
40	277	particularly COUTIs caused by ESBL-EC, to avoid inducing more ESBL-producing $_{\circ}$
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43	278	The study has some limitations. Firstly, our investigation focused on patients with COUTIs,
44	279	excluding those with hospital-acquired urinary tract infections. Therefore, we could not compare the
45 46	280	difference of epidemiological data between COUTIs and hospital acquired UTIs. Secondly, we only
40 47	281	compiled statistics and analyzed the drug resistance in the ESBL-positive group without comparing
48	282	the differences in drug resistance between the ESBL-positive and ESBL-negative groups. Thirdly, we
49 50	283	employed the double-disk synergy test to confirm the phenotype of ESBL-producing Escherichia coli
50 51	284	strains without conducting gene sequencing at the molecular level. Consequently, the resistance genes
52	285	and virulence genes of ESBL-producing Escherichia coli, as well as the correlation between them,
53	286	were not identified. Fourthly, this study is retrospective and relies on existing data, which may be
54 55	287	subject to issues such as data quality, selection bias, and confounding factors. Additionally, due to
56	288	limitations in sample size, we did not perform a prior sample size calculation. Instead, we simply
57	289	included all eligible samples from the past five years, which may have reduced the statistical power
58 59	290	of our findings.

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#### **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.

#### 299 Ethical Approval

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

#### 302 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).

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#### 310 Declaration of Competing Interest

311 The authors declare that there are no competing interests.

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#### 318 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,

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4	322	telephone interviews, and face-to-face communication. We plan to write popular science articles
5	323	based on the findings of this study and disseminate them to patients and the public through official
6 7	324	channels of hospitals and regional CDCs, as well as by conducting educational lectures in infectious
8	325	disease departments.
9	525	disease departments.
10 11	326	Availability of Data and Materials
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13	327	The data is available upon reasonable request from the corresponding author Jing Wu
14 15	328	(2861914532@qq.com).
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