

# Incidence of and Risk Factors for Third-Generation Cephalosporin-Resistant *Escherichia coli* Bloodstream Infections in Children

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**Objective:** Third-generation cephalosporin-resistant (3GC-R) bloodstream infection (BSI) is associated with poor prognosis. We investigated the incidence of and risk factors for 3GC-R *Escherichia coli* (*E. coli*) BSI in children.

**Methods:** Patients with *E. coli* BSIs who were hospitalized at the Children's Hospital of Chongqing Medical University were retrospectively enrolled. Univariate and multivariate logistic regression analyses were used to identify the independent risk factors for 3GC-R BSI.

**Results:** Two hundred fifty-two children with *E. coli* BSIs were enrolled. The mortality rate was 11.51% (29/252). The infection rate of 3GC-R *E. coli* was 48.81% (123/252), and the incidence of *E. coli* BSI during hospitalization was 18.58 per 1000 person-days. Approximately half (47.22%, 119/252) of the children were infected with extended-spectrum beta-lactamases (ESBLs) produced by *E. coli*. More than one-third (37.30%, 94/252) of the children were unnecessarily administered carbapenems. According to our logistic regression analysis, a history of carbapenem administration, an elevated Pediatric Sequential Organ Failure Assessment (pSOFA) score  $\geq 2$ , and antimicrobial agent administration before blood culture were independently associated with 3GC-R BSI (odds ratio [OR] 2.05, 95% confidence interval [CI] 1.08–3.94,  $P=0.029$ ; OR 2.00, 95% CI 1.10–3.71,  $P=0.025$ , OR 1.86, 95% CI 1.02–3.42,  $P=0.044$ , respectively).

**Conclusion:** In this study, the incidence of 3GC-R *E. coli* BSI among children was retrospectively evaluated. Patients with a history of carbapenem administration, an elevated pSOFA score  $\geq 2$  and who were administered antimicrobial agents before blood culture had an increased risk of 3GC-R *E. coli* BSI.

**Keywords:** third-generation cephalosporin-resistant, inappropriate use of carbapenems, *Escherichia coli*, bloodstream infection, children

## Introduction

Bloodstream infection (BSI) is responsible for more than 2 million deaths per year, and *Escherichia coli* (*E. coli*) is one of the most common pathogens causing BSIs.<sup>1</sup> The immediate administration of broad-spectrum antimicrobial agents may be crucial to avoid delayed antimicrobial therapy.<sup>2</sup> However, as the antibiotic administration time window for BSIs has been emphasized in recent years,<sup>3,4</sup> overtreatment may be also be an urgent problem for clinicians.<sup>5</sup>

Third-generation cephalosporins are among the most frequently used broad-spectrum antimicrobial agents in critical patients with gram-negative bacterial infections.<sup>6</sup> The emergence of third-generation cephalosporin-resistant (3GC-R) isolates may worsen the prognosis,<sup>7</sup> especially in areas with limited medical resources.<sup>8</sup> For *E. coli* isolates, the resistance rate to third-generation cephalosporins is approximately 40% in China,<sup>9</sup> thus, more intensive antimicrobial agents (such as carbapenems) may be a reasonable option. However, antibiotic associated adverse events should also be considered by clinicians,<sup>10</sup> because antibiotic overuse may harm patients.<sup>11</sup> Reducing antimicrobial overtreatment is an urgent problem with major challenges.<sup>12</sup> Approximately one-third of children receive antimicrobial treatment during hospitalization, and one-quarter of antimicrobial

therapy is not the optimal choice.<sup>13</sup> Both overly narrow and unnecessarily broad regimens may increase mortality.<sup>11</sup> How to balance the benefits of antimicrobial agents and their side effects has yet to be resolved. Rottier et al<sup>14</sup> constructed two prediction scoring systems for 3GC-R Enterobacteriaceae bacteraemia, and those systems were further developed by Deelen et al.<sup>15</sup> However, these two prediction systems<sup>14</sup> and their external validation study<sup>15</sup> included only adult patients, and few studies have reported any prediction models for children with 3GC-R BSIs. Choosing the adequate antimicrobial therapy for children with *E. coli* BSIs is still difficult for paediatricians, and early recognition of 3GC-R *E. coli* BSIs is urgently needed.

In this study, we investigated the incidence of and risk factors for the occurrence of 3GC-R *E. coli* BSIs in children, which may help clinicians predict the efficacy of third-generation cephalosporins for treating *E. coli* BSIs while avoiding the overuse of carbapenems as much as possible.

## Methods

### Study Design and Population

This was a retrospective, observational cohort study, conducted at the Children's Hospital of Chongqing Medical University, the National Clinical Research Center for Child Health and Disorders. Patients with *E. coli* BSIs were enrolled from August 2015 to October 2022. The inclusion criteria were as follows: (i) hospitalized children; (ii) aged >1 month; (iii) had an *E. coli* BSI. The exclusion criteria were as follows: (i) incomplete clinical information; (ii) polymicrobial BSI. This study was approved by the Ethics Committee of the Children's Hospital of Chongqing Medical University. (approval number (2023–423)). The requirement for informed consent was waived because this was a retrospective study. This study did not involve any human or animal experiments.

### Data Collection and Definitions

We retrospectively collected demographic characteristics, patterns of admission, underlying conditions, sources of infection, antimicrobial therapy, susceptibility test results, Paediatric Sequential Organ Failure Assessment (pSOFA) scores and mortality data. An *E. coli* BSI was defined as the presence of *E. coli* in the blood.<sup>16</sup> The unnecessary use of carbapenems was defined as the administration of carbapenems to patients with third-generation cephalosporin-sensitive (3GC-S) BSIs.<sup>15</sup> An *E. coli* BSI occurring more than 48 hours after admission was considered a hospital-acquired infection.<sup>3</sup> The sources of BSI were defined according to the Centers for Disease Control and Prevention/National Healthcare Safety Network (CDC/NHSN) surveillance guidelines.<sup>17</sup> The pSOFA score was used to evaluate the severity of illness.<sup>18</sup> Antibiotic susceptibility testing and identification of extended-spectrum beta-lactamase (ESBL) isolates were based on the Clinical and Laboratory Standards Institute guidelines.<sup>19</sup> Multidrug resistance (MDR) was defined as acquired nonsusceptibility to three or more classes of antimicrobial agents.<sup>20</sup>

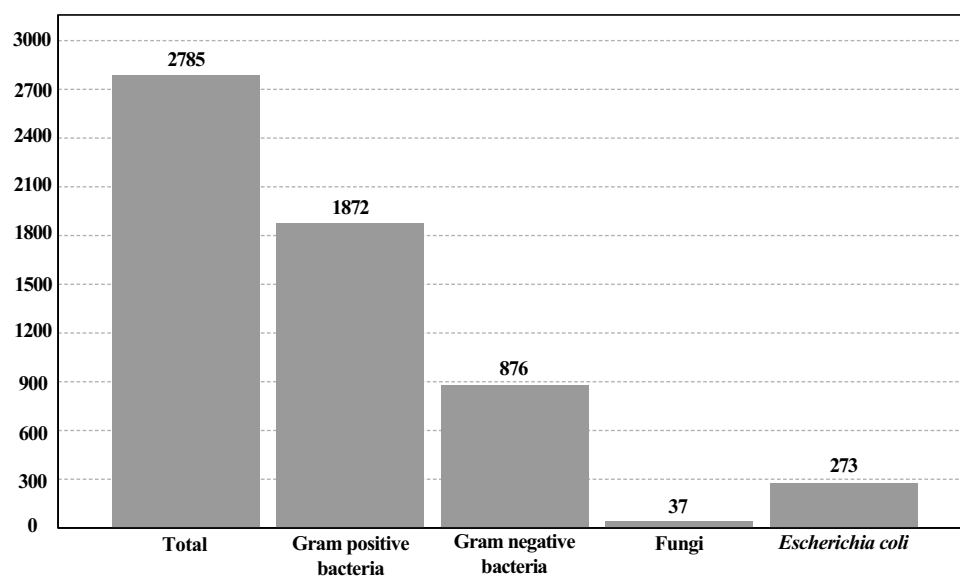
### Statistical Analysis

The categorical variables are expressed as numbers (n) and percentages (%) and were compared by using Pearson's  $\chi^2$  test or Fisher's exact test. Continuous variables are expressed as medians and interquartile ranges (IQRs), and were compared by using the Mann–Whitney *U*-test or the Student's *t* test. Variables with *P* values  $\geq 0.10$  in univariate logistic regression analysis were included in univariate analysis. Odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were calculated. All significance tests used a *P*-value < 0.05 (2-sided). Analyses were conducted using R software (version 4.3.0, R Foundation for Statistical Computing Platform, China).

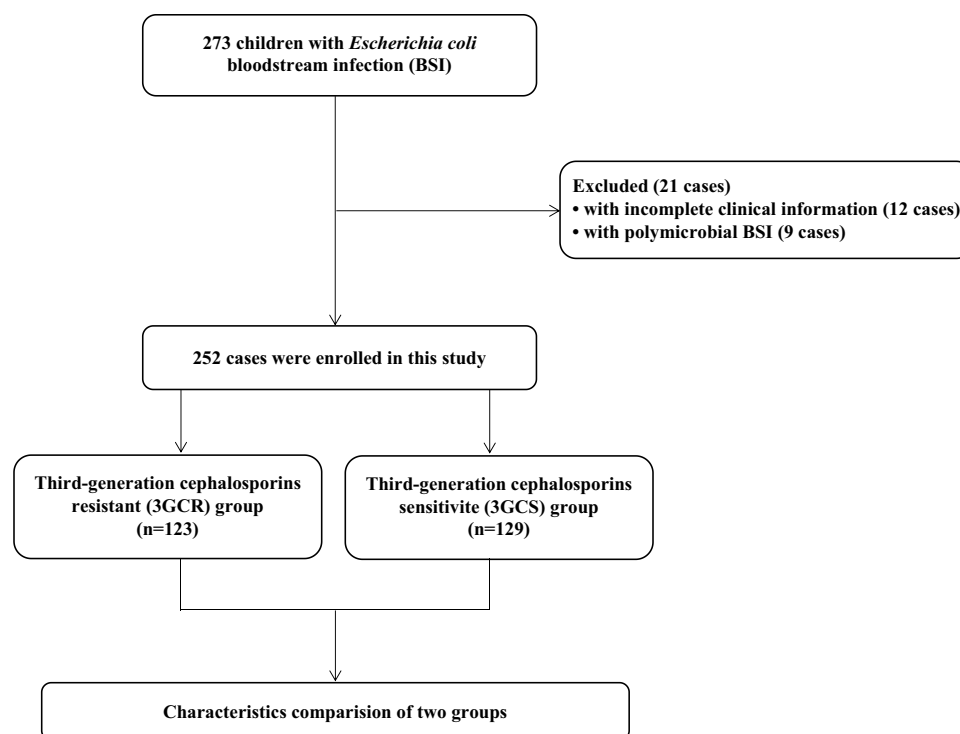
## Results

### Study Population

A total of 2785 pathogenic strains were isolated from blood cultures of patients hospitalized at the Children's Hospital of Chongqing Medical University from August 2015 to October 2022. All the details are presented in Figure 1. There were 273 children with *E. coli* BSIs. Twenty-one patients were excluded: twelve patients with incomplete clinical information and nine patients with polymicrobial BSIs. Finally, two hundred fifty-two patients were enrolled in our study (Figure 2).



**Figure 1** Distribution of pathogens isolated from blood cultures.



**Figure 2** Flowchart of the study population selection process.

## Clinical Characteristics of Children with *E. Coli* BSIs

The median age was 1.84 (IQR 0.22–8.52) years, and males accounted for 62.30% (157/252) of the population. The median length of stay before blood culture was 0.02 (IQR 0.00–0.58) days, and the overall median length of stay was 21.94 (IQR 12.75–34.92) days. The overall mortality was 11.51% (29/252). A total of 14.29% (36/252) of the patients were admitted from the emergency department, and 12.70% (32/252) of the patients were transferred from other medical institutions.

Many patients had bone marrow inhibition after chemotherapy (126/252, 50.00%) or after carbapenem administration (78/252, 30.95%). Approximately one sixth of patients had a history of BSI (40/252, 15.87%) or congenital heart disease

(39/252, 15.48%). Nearly half of the *E. coli* BSIs occurred in the hospital (115/252, 45.63%) and more than half of the *E. coli* BSIs were with no specific source of infection (132/252, 52.38%). More than one-quarter (64/252, 25.40%) of patients had an elevated pSOFA score  $\geq 2$ . The ESBL isolates accounted for 47.22% (119/252) of the isolates, and the third-generation cephalosporin resistance rate reached 48.81% (123/252). The incidence of 3GC-R *E. coli* BSI during hospitalization was 18.58 per 1000 person-days. A total of 28.17% (71/252) of patients were administrated with antimicrobial agents before blood culture, but only 9.92% (25/252) of patients received adequate antimicrobial agents before blood culture. Most of the children were administrated carbapenems or third-generation cephalosporins (182/252, 72.22%; 49/252, 19.44%; respectively). However, approximately one-third (94/252, 37.30%) of patients received unnecessary carbapenem treatment. All the detailed characteristics are shown in Table 1.

**Table 1** Characteristics of 252 Children with *E. Coli* Bloodstream Infection (BSI)

Characteristics	Total (n=252)
Demographic data	
Age (years) (median, IQR)	1.84 (0.22–8.52)
Sex (male) (n, %)	157 (62.30%)
Patterns of admission	
Emergency admission (n, %)	36 (14.29%)
Transferred to wards from other medical institutions (n, %)	32 (12.70%)
Underlying condition	
Bone marrow inhibition after chemotherapy (n, %)	126 (50.00%)
Carbapenem administration history (n, %)	78 (30.95%)
Congenital heart disease (n, %)	39 (15.48%)
Malnutrition (n, %)	4 (1.59%)
Albumin level (g/L) (median, IQR)	35.80 (30.88–40.80)
History	
BSI history (n, %)	40 (15.87%)
History of surgery within one year (n, %)	22 (8.73%)
Susceptibility test	
ESBLs (n, %)	119 (47.22%)
MDR due to ESBLs (n, %)	4 (1.59%)
Sulbactam resistant (n, %)	176 (69.84%)
Third-generation cephalosporin resistant (n, %)	123 (48.81%)
Fourth-generation cephalosporin resistant (n, %)	54 (21.43%)
Tazobactam resistant (n, %)	15 (5.95%)
Antimicrobial therapy after blood culture	
Carbapenems (n, %)	182 (72.22%)
Third-generation cephalosporins (n, %)	49 (19.44%)
Fourth-generation cephalosporins (n, %)	7 (2.78%)
Latamoxef (n, %)	5 (1.98%)
Tazobactam (n, %)	5 (1.98%)
Sulbactam (n, %)	2 (0.79%)
Clindamycin (n, %)	1 (0.40%)
Second-generation cephalosporins (n, %)	1 (0.40%)
Unknown source of bloodstream infection (n, %)	132 (52.38%)
Nosocomial infection (n, %)	115 (45.63%)
Antimicrobial agents administrated before blood culture (n, %)	71 (28.17%)
Susceptible antimicrobial agents administrated before blood culture (n, %)	25 (9.92%)
Unnecessary use of carbapenems (n, %)	94 (37.30%)
Elevated pSOFA score $\geq 2$ (n, %)	64 (25.40%)
Length of stay before blood culture (days) (median, IQR)	0.02 (0.00–0.58)
Length of stay (days) (median, IQR)	21.94 (12.75–34.92)
Mortality (n, %)	29 (11.51%)

## Comparisons of Clinical Characteristics Between the 3GC-R and 3GC-S Groups

Table 2 shows the differences in clinical characteristics between the 3GC-R and 3GC-S groups. The patients with 3GC-R *E. coli* BSIs had significantly greater proportions of carbapenem administration history and BSI history than did those with 3GC-S *E. coli* BSIs (39.02% vs 23.26%,  $P=0.010$ ; 21.95% vs 10.08%,  $P=0.016$ ; respectively). There were significantly more 3GC-R *E. coli* BSI patients with an elevated pSOFA score  $\geq 2$  than 3GC-S *E. coli* BSI patients (33.33% vs 17.83%,  $P=0.007$ ). Patients in the 3GC-S group had a remarkably greater rate of unnecessary carbapenem administration than did those in the 3GC-R group (72.87% vs 0.00%,  $P<0.001$ ). The demographic data, patterns of admission, sources of infection, incidence of nosocomial infection, antimicrobial therapy, susceptibility test results, length of stay, length of stay before blood culture and mortality were not significantly different between the 3GC-R group and the 3GC-S group.

## Risk Factors for 3GC-R *E. Coli* BSI

Table 3 presents the logistic analysis of 3GC-R *E. coli* BSI in children. According to the univariate analysis, a history of carbapenems administration, an elevated pSOFA score  $\geq 2$ , antimicrobial agent administration before blood culture,

**Table 2** Comparisons of Clinical Characteristics of 252 Children with *E. Coli* BSI Between Third-Generation Cephalosporin-Resistant (3GC-R) and Third-Generation Cephalosporin-Sensitive (3GC-S) Groups

Characteristics	3GC-R (n=123)	3GC-S (n=129)	P-value
Demographic data			
Age (years) (median, IQR)	1.50 (0.24–6.92)	2.50 (0.19–10.00)	0.353
Sex (male) (n, %)	83 (67.48%)	74 (57.36%)	0.127
Patterns of admission			
Emergency admission (n, %)	15 (12.20%)	21 (16.28%)	0.456
Transferred to wards from other medical institutions (n, %)	18 (14.63%)	14 (10.85%)	0.477
Underlying condition			
Bone marrow inhibition after chemotherapy (n, %)	60 (48.78%)	66 (51.16%)	0.801
Carbapenem administration history (n, %)	48 (39.02%)	30 (23.26%)	0.010*
Congenital heart disease (n, %)	20 (16.26%)	19 (14.73%)	0.871
Malnutrition (n, %)	1 (0.81%)	3 (2.33%)	0.622
Albumin level (g/L) (median, IQR)	35.60 (29.35–40.20)	36.10 (31.60–41.40)	0.105
History			
BSI history (n, %)	27 (21.95%)	13 (10.08%)	0.016*
History of surgery within one year (n, %)	15 (12.20%)	7 (5.43%)	0.093
Antimicrobial therapy after blood culture			
Carbapenems (n, %)	88 (71.54%)	94 (72.87%)	0.925
Third-generation cephalosporins (n, %)	23 (18.70%)	26 (20.16%)	0.894
Fourth-generation cephalosporins (n, %)	4 (3.25%)	3 (2.33%)	0.717
Latamoxef (n, %)	3 (2.44%)	2 (1.55%)	0.678
Tazobactam (n, %)	3 (2.44%)	2 (1.55%)	0.678
Sulbactam (n, %)	1 (0.81%)	1 (0.78%)	1.000
Clindamycin (n, %)	1 (0.81%)	0 (0.00%)	0.488
Second-generation cephalosporins (n, %)	0 (0.00%)	1 (0.78%)	1.000
Unknown source of bloodstream infection (n, %)	61 (49.59%)	71 (55.04%)	0.460
Nosocomial infection (n, %)	56 (45.53%)	59 (45.74%)	1.000
Antimicrobial agents administrated before blood culture (n, %)	42 (34.15%)	29 (22.48%)	0.055
Susceptible antimicrobial agents administrated before blood culture (n, %)	10 (8.13%)	15 (11.63%)	0.473
Unnecessary use of carbapenems (n, %)	0 (0.00%)	94 (72.87%)	<0.001*
Elevated pSOFA score $\geq 2$ (n, %)	41 (33.33%)	23 (17.83%)	0.007*
Length of stay before blood culture (days) (median, IQR)	0.00 (0.00–0.60)	0.03 (0.00–0.55)	0.947
Length of stay (days) (median, IQR)	23.92 (13.29–37.50)	20.21 (12.21–32.67)	0.387
Mortality (n, %)	18 (14.6341%)	11 (8.5271%)	0.186

Not: \*Statistically significant at  $P < 0.05$ .

**Table 3** Logistic Regression Analysis of Risk Factors for 3GC-R *E. coli* BSI in Children

Variables	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	P	OR	95% CI	P
Carbapenem administration history	2.11	1.23–3.67	0.007*	2.05	1.08–3.94	0.029*
Elevated pSOFA score $\geq 2$	2.30	1.29–4.19	0.005*	2.00	1.10–3.71	0.025*
Antimicrobial agents administrated before blood culture	1.79	1.03–3.14	0.041*	1.86	1.02–3.42	0.044*
BSI history	2.51	1.25–5.27	0.012*			
History of surgery within one year	2.42	0.98–6.54	0.064			

Note: \*Statistically significant at  $P < 0.05$ .

a history of BSI and a history of surgery within one year were associated with an increased risk of 3GC-R *E. coli* BSI ( $P < 0.1$ ). According to multivariate logistic analysis, carbapenem administration history, an elevated of pSOFA score  $\geq 2$  and antimicrobial agents administrated before blood culture were independently correlated with the presence of 3GC-R *E. coli* BSI (OR 2.05, 95% CI 1.08–3.94,  $P = 0.029$ ; OR 2.04, 95% CI 1.10–3.71,  $P = 0.025$ ; OR 1.86, 95% CI 1.02–3.42,  $P = 0.044$ , respectively).

## Discussion

*E. coli* was the most common pathogen isolated from blood culture, and approximately 40% of the isolates were resistant to third-generation cephalosporins.<sup>9</sup> However, few studies have reported the incidence of 3GC-R *E. coli* BSI. In this study, the incidence of 3GC-R *E. coli* BSI during hospitalization was 18.58 per 1000 person-days. These findings may help clinicians evaluate the medical burden of 3GC-R *E. coli* BSIs in children.

Intensive antimicrobial treatment is sometimes a double-edged sword. Although timely treatment can save lives,<sup>3,4</sup> antimicrobial therapy that is too aggressive may also increase the risk of mortality.<sup>11</sup> Furthermore, several broad-spectrum antibiotics (eg, carbapenems) are scarce medical resources in developing areas. When administrating the antimicrobial therapy, clinicians must balance the risks of overprescribing carbapenems and inappropriate empiric antibiotics. Tauzin et al reported that the extensive administration of a broad-spectrum antibiotic was associated with the emergence of drug-resistant bacteria.<sup>21</sup> The presence of drug-resistant bacteria may be attributed to the antibiotic-related sequelae, similar to the selection pressure for resistant organisms or changes in the microbiome leading to dysbiosis and increased susceptibility to colonization.<sup>22</sup> In our study, we also found that a history of carbapenem administration increased the risk of 3GC-R *E. coli* BSI 2.05-fold, and for patients who received antimicrobial agents before blood culture, the risk increased 1.86-fold. Although receiving extended-spectrum antimicrobial agents may increase the incidence of 3GC-R *E. coli*, 1-hour or 3-hour regimens are still recommended for patients with severe BSIs.<sup>2</sup> Appropriate antimicrobial de-escalation may also help to decrease the unnecessary use of carbapenems.

Patients in more critical conditions are recommended to receive more intensive antimicrobial therapy.<sup>2</sup> In this study, many patients were had bone marrow inhibition after chemotherapy (126/252, 50.00%) and a history of BSI (40/252, 15.87%) or congenital heart disease (39/252, 15.48%), and up to 72.22% (182/252) for whom carbapenem was used in our study seemed reasonable. However, 37.30% (94/252) of the children in this study did not need to be treated with carbapenems. The pSOFA is one of the most common prognostic scoring systems for children.<sup>18</sup> Aleidan et al<sup>23</sup> reported that a higher SOFA score indicated an increased risk of resistant infection. In this study, we found that patients with an elevated pSOFA score  $\geq 2$  had a 2.00-fold increased risk of 3GC-R *E. coli* BSI. To avoid overtreatment, patients without an elevated of pSOFA score  $\geq 2$  may not need treatment with carbapenem.

Aggressive antimicrobial therapy may save lives, but antibiotic associated adverse events should also be considered.<sup>10</sup> Tribble et al reported that treating one-quarter of hospitalized children was not the optimal choice.<sup>13</sup> Early recognition of 3GC-R *E. coli* BSI is urgently needed. Rottier et al<sup>14</sup> constructed two prediction scoring systems for 3GC-R Enterobacteriaceae bacteraemia, however, they<sup>14</sup> did not include the children in their study. It is widely known that the disease spectrum, pathophysiological process and the antimicrobial therapy used in children are different from those used in adult patients. Moreover, there are no reported prediction criteria for 3GC-R BSI in children. In this study, we identified three risk factors for



3GC-R *E. coli* BSI in children. These risk factors are clinical predictors that are readily available before the initiation of empirical antimicrobial treatment. These findings may help clinicians predict the efficacy of third-generation cephalosporins for treating *E. coli* BSIs, and avoid unnecessary use of carbapenems as much as possible.

There were several limitations in our study. First, this was a retrospective, small sample, single-centre study, which may limit the generalizability of our results, and a prospective, large-sample, multicentre study is expected to strengthen our conclusions. Second, we focused only on children in our study, therefore, our results may not be generalizable to newborns or adult patients. Third, the risk factors found in our study were applied to predict the possibility of 3GC-R in patients with *E. coli* BSI, and these risk factors may not be applicable for other infections.

## Conclusion

The incidence of 3GC-R *E. coli* BSI in children was retrospectively evaluated in this study. A history of carbapenem administration, an elevated pSOFA score  $\geq 2$  and antimicrobial agent administration before blood culture were associated with 3GC-R *E. coli* BSI. When these conditions are met, third-generation cephalosporins may be avoided, and carbapenems may be a reasonable option.

## Abbreviations

BSI, Bloodstream infection; CI, Confidence interval; ESBL, Extended spectrum beta-lactamase; IQR, Interquartile range; MDR, Multidrug resistance; OR, Odds ratio; pSOFA, Paediatric Sequential Organ Failure Assessment; 3GC-R, Third-generation cephalosporin resistant; 3GC-S, Third-generation cephalosporin sensitive.

## Data Sharing Statement

The data from this study can be obtained from the corresponding author upon reasonable request.

## Ethics Approval and Consent to Participate

The requirement for informed consent was waived by the Ethics Committee of the Children's Hospital of Chongqing Medical University, as only anonymized data were utilized in this retrospective study to protect individuals. This study was approved by the Ethics Committee of the Children's Hospital of Chongqing Medical University. (approval number (2023-423)). All the authors declare that this study did not involve any human or animal experiments. All methods were carried out in accordance with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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## Author Contributions

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

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## Disclosure

The authors have no competing interests to declare for this work.

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