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ORIGINAL RESEARCH

Eight-Year Surveillance of Uropathogenic *Escherichia coli* in Southwest China

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Purpose: To assess antimicrobial resistance profiles change in uropathogenic *Escherichia coli* (UPEC) during an 8-year period, especially extended-spectrum β-lactamase (ESBL)-producing and carbapenem-resistant isolates.

Materials and Methods: A retrospective observational study of urinary tract infections (UTIs) was performed in a territory hospital between 2012 and 2019. Isolates were identified using matrix-assisted laser desorption/ionization time of flight mass spectrometry or the VITEK 2 Compact system. The antimicrobial susceptibility testing was performed using the VITEK 2 Compact system and the modified Kirby–Bauer disc diffusion method.

Results: Of the 7713 non-repetitive UPEC isolates, 7075 (91.7%) were from inpatients and 638 (8.3%) were from outpatients. The prevalence of ESBL declined from 62.5% to 49.7% ($P = 0.003$). Except for cefoxitin, the resistance rates of ESBL-producing isolates were mostly higher than that of non-ESBL-producing isolates ($P < 0.001$). The resistance rates of ampicillin ($P = 0.013$), ampicillin/sulbactam ($P = 0.013$), ceftriaxone ($P < 0.001$), gentamycin ($P = 0.001$), tobramycin ($P = 0.011$), and trimethoprim/sulfamethoxazole ($P = 0.028$) declined slightly, while the resistance rate of imipenem increased slightly ($P = 0.001$). The prevalence of carbapenem-resistant *Escherichia coli* was <2.0%.

Conclusion: ESBL-producing *Escherichia coli* is still the main drug-resistant bacteria causing UTIs. We should pay attention to antimicrobial resistance in high-risk inpatient areas and take effective measures to prevent and control nosocomial infections.

Keywords: UTIs, ESBL, *E. coli*, CRE, antimicrobial resistance, trends

Introduction

Urinary tract infection (UTI) is one of the most common clinical infectious diseases. In China, UTI ranks second in nosocomial infections, after respiratory tract infection.[1–3] UTIs are usually caused by bacteria originating from the digestive tract, and *Escherichia coli* (*E. coli*) is the primary pathogen.[4] Quantitative urine culture remains the gold standard for diagnosing UTIs in symptomatic patients;[5,6] However, oral antibiotics are usually prescribed empirically before the results of urine culture and antimicrobial susceptibility testing are available in healthy, non-pregnant, reproductive-age women presenting with symptomatic acute uncomplicated cystitis.

Empirical therapy should be based on local antimicrobial surveillance data from previous years. Recently, as the widespread use of broad-spectrum antibiotics, some changes have taken place in the antimicrobial resistance (AMR) profiles of uropathogens, including uropathogenic *Escherichia coli* (UPEC), which brings difficulties for clinical treatment. In England, the nonsusceptibility to third-generation

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cephalosporins for UPEC from hospital specimens from 6.3% in 2010 to 7.4% in 2013.[7] In Canadian, multidrug-resistant (MDR) phenotypes of UPEC from outpatients increased from 9.7% in 2007 to 16.5% in 2016.[8]

We present AMR data from routine laboratory-based surveillance of UPEC isolates in Southwest China for the period 2012–2019. We aimed to describe first- and second-line antimicrobial agents resistance levels and assess the changing antibiotic sensitivity profiles among *E. coli* isolated from urine, especially extended-spectrum β-lactamase (ESBL)-producing and carbapenem-resistant *Escherichia coli* (CREC) isolates.

Materials and Methods

Study Design

This retrospective study was conducted at the First Affiliated Hospital of Chongqing Medical University, a large comprehensive tertiary-care center in southwest China, with 3200 beds. The microbiological laboratory receives about 12,000 urine culture specimens per year. Urine specimens were cultured on blood agar plates and MacConkey agar plates (ThermoFisher Scientific, Shanghai, China), and Isolates were identified using matrix-assisted laser desorption/ionization time of flight mass spectrometry (MALDI-TOF MS) (VITEK®MS, bioMérieux, Marcy l'Etoile, France) or the VITEK 2 Compact system (bioMérieux, Marcy l'Etoile, France). The antimicrobial susceptibility testing (AST) was performed using the VITEK 2 Compact system and Modified Kirby–Bauer disc diffusion method. The clinical and microbiological information of isolates were separately collected from the electronic medical record system (EMRS) and the laboratory information system (LIS).

Inclusion Criteria

Urine specimens with suspected (10^4 ~10^5 CFU/mL) or significant (>10^5 CFU/mL) growth of *E. coli* from January 2012 to December 2019; patients with at least three of the following symptoms: urgency, frequency, dysuria, hematuria, bladder or perineal discomfort, ipsilateral or bilateral low back pain, significant tenderness or throbbing pain in the costalspinal angle; routine urine test indicated that leukocyte, urinary protein or nitrite were positive.

Exclusion Criteria

Urine specimens with negative culture, no suspected or significant growth, or growth other than *E. coli*; duplicate specimens from the same patient within 3 days for the same specimen type.

Antimicrobial Susceptibility Testing

Antimicrobial susceptibility testing was performed using the Vitek Compact 2 system and disc diffusion. The antibiotic discs (Oxoid, Hampshire, UK) used for *Enterobacteriaceae* included Ampicillin (10 μg), Aztreonam (30 μg), Cefoperazone/Sulbactam (75/30 μg), Ciprofloxacin (5 μg), Gentamicin (10 μg), Meropenem (10 μg). Susceptibility interpretations were based on clinical breakpoints recommended by the Clinical Laboratory Standards Institute (CLSI).[9] ESBL production in *E. coli* was screened using the Vitek Compact 2 system and confirmatory test followed CLSI guidelines.

Statistical Analysis

Raw susceptibility test results of UPEC isolates were processed by Whonet 5.6 software (WHO, Geneva, Switzerland). Simple linear regression was used to assess the statistical significance of AMR trends over the study period. Chi-square test or Fisher's exact test was employed to compare resistance rates between groups. All statistical analyses were performed using GraphPad Prism 6 software (GraphPad, San Diego, CA, USA), and a two-tailed *P*-value of less than 0.05 was considered statistically significant.

Results

Of the total 7713 non-repetitive UPEC isolates, 7075 (91.7%) were from inpatients, 638 (8.3%) were from outpatients; males and females accounted for 26.6% and 73.4%, respectively. The ward distribution of inpatients was: 1882 of urology, 641 of gynecology, 638 of neurology, 628 of endocrinology, and 579 of intensive care unit (ICU), accounting for 24.4%, 8.3%, 8.3%, 8.1%, and 7.5%, respectively.

Overall from 2012 to 2019, UPEC isolates exhibited low resistance to carbapenems, nitrofurantoin, amikacin, cefoperazone/sulbactam, and piperacillin/tazobactam, with resistance rates <6.5%; they demonstrated high resistance to ampicillin, ampicillin/sulbactam, ceftriaxone, quinolones, and trimethoprim/sulfamethoxazole, with resistance rates ranged from 42.8% to 90.6%. Imipenem-resistant UPEC isolates showed an increasing trend (P = 0.001), while decreasing resistance trends were observed for ampicillin (P = 0.013), ampicillin/sulbactam (P = 0.013), ceftriaxone

Table 1 Trends of Antimicrobial Resistance Rate (%) in UPEC Isolates

Antibiotics	2012	2013	2014	2015	2016	2017	2018	2019	P-value	Trend
ESBL	59.3	62.5	57.8	59.2	51.9	51.5	52.8	49.7	0.003	↓
Ampicillin	90.6	86.9	88.2	87.3	87.5	85.9	83.8	85.8	0.013	↓
Cefoperazone/Sulbactam	NA	NA	NA	4.8	5.6	5.7	6.3	4.4	0.973	NS
Ampicillin/Sulbactam	56.3	53.5	56.5	59.1	54.8	46.9	44.4	42.8	0.013	↓
Piperacillin/Tazobactam	1.8	2	1.1	1.6	1.9	1.8	1.9	3.4	0.129	NS
Ceftazidime	31.9	30.3	26.3	28.9	27.9	28	28.7	26.1	0.069	NS
Ceftriaxone	66.8	65.4	59.7	61.9	60.3	56.2	56.5	54	<0.001	↓
Cefepime	22.3	22	18.4	20.1	21.4	19.8	17.8	26	0.783	NS
Cefoxitin	NA	NA	NA	11.8	11.1	11.2	11.8	12.5	0.295	NS
Aztreonam	43.7	43.1	38.4	40.8	39.1	40.1	40.3	39.6	0.105	NS
Ertapenem	0.5	1.3	1.4	1.5	1.7	1.1	1.5	1	0.481	NS
Imipenem	0	0.1	0.4	0.4	0.7	0.7	0.8	0.7	0.001	↑
Meropenem	NA	NA	NA	0.4	0.6	0.7	0.8	0.7	0.079	NS
Amikacin	2.3	4	2.1	3	1.8	2.1	2.5	1.5	0.174	NS
Gentamicin	51.2	50	49.2	46.5	42	41.9	38.5	28.6	0.001	↓
Tobramycin	18.4	17.3	15.5	17.1	15.3	13.9	12.7	15	0.011	↓
Ciprofloxacin	69.3	63.8	60.9	61.9	61.5	59.7	61.1	61.8	0.061	NS
Levofloxacin	66.6	60.4	58.5	58.1	56	55.8	58.5	59.4	0.113	NS
Trimethoprim/Sulfamethoxazole	64.8	59.6	56.5	58.5	64.5	52.6	47.9	51	0.028	↓
Nitrofurantoin	3.7	4	3.1	4.2	1.9	2.2	3.2	3.6	0.404	NS

Notes: ↑, resistance rate is increasing; ↓, resistance rate is decreasing; NS, not significant at the $P < 0.05$ value by the simple linear regression.
Abbreviation: NA, not available.

($P < 0.001$), gentamicin ($P = 0.001$), tobramycin ($P = 0.011$), trimethoprim/sulfamethoxazole ($P = 0.028$) (Table 1).

The prevalence of ESBL-producing isolates decreased from the highest 62.5% in 2013 to 49.7% in 2019 ($P = 0.003$) (Table 1). Except for cefoxitin, the resistance rates of ESBL-producing isolates were mostly higher than that of non-ESBL-producing isolates ($P < 0.001$), exceeding 80% to ampicillin, ceftriaxone and ciprofloxacin (Table 2).

During the 8-year period, a total of 94 non-repetitive CREC strains (defined as resistance to any of the carbapenems) were isolated from patients with UTIs, and the top four ward sources were urology, ICU, geriatrics, neurology, accounting for 29.8%, 13.8%, 8.5%, 8.5%, respectively. CREC isolates presented high susceptibility only to amikacin (88.2%) and nitrofurantoin (71.9%), while resistance to cefoperazone/sulbactam, ampicillin/sulbactam, third- and fourth-generation cephalosporins exceeded 80%, and quinolones even reached about 95% (Table 3).

Discussion

UTI is a common infection both in community and hospital settings. *E. coli* is a major pathogen causing UTIs. In recent years, the prevalence of ESBL-producing *E. coli* stays at a high level, and CREC is also increasing year by year. AMR of *Enterobacteriaceae* bacteria has become more and more serious. This retrospective study focuses on changes in AMR of UPEC to different classes of antimicrobials, especially ESBL-producing and CREC isolates.

Many risk factors associated with UTIs have been reported, including bradyuria due to anatomical abnormality and dysfunction of urinary system, invasive operation such as urinary tract catheterization and urinary endoscopy, chronic basic diseases such as diabetes, acute or chronic kidney diseases, long-term bedridden, elderly and women[10,11] In our study, inpatients with infections caused by UPEC isolates mainly were from urology (24.4%), gynecology (8.3%), neurology (8.3%), endocrinology (8.1%) and ICU (7.5%), and females were more than males (73.4% vs 26.6%). The distributions of wards and sex are basically consistent with that the literature reported.

Nitrofurantoin, fosfomycin, trimethoprim/sulfamethoxazole (TMP/SMX), levofloxacin, and β-lactams are common drugs used to treat UTIs.[12] In the current study, cefoperazone/sulbactam, piperacillin/tazobactam, amikacin, nitrofurantoin and carbapenems were the most active agents against UPEC isolates (resistance rate <10%); ampicillin, ampicillin/sulbactam, ceftriaxone and quinolones, trimethoprim/sulfamethoxazole were less active (resistance rate ≥50%). Although quinolones have a relatively high resistance rate, they are still a choice for clinical treatment of UTIs. According to

Table 2 The Comparison of Antimicrobial Susceptibility Profile Between ESBL-Producing and Non-ESBL-Producing Isolates

Antibiotics	ESBL (+)			ESBL (-)			P-value
	No. Tested	% (R)	% (S)	No. Tested	% (R)	% (S)	
Ampicillin	4295	99.9	0.1	3418	71.0	26.6	<0.001
Cefoperazone/ Sulbactam	2433	6.5	69.2	2154	4.0	91.9	<0.001
Ampicillin/ Sulbactam	3762	69.2	11.7	2897	32.6	39.1	<0.001
Piperacillin/ Tazobactam	4295	1.2	95.3	3418	2.9	94.1	<0.001
Ceftazidime	4295	44.9	52.3	3418	7.6	91.9	<0.001
Ceftriaxone	4295	99.0	0.9	3418	11.7	88.2	<0.001
Cefepime	4295	33.6	48.8	3418	4.9	94.1	<0.001
Cefoxitin	2307	11.3	80.1	2028	12.0	85.3	0.524
Aztreonam	4170	66.8	31.7	3317	7.5	92.0	<0.001
Ertapenem	4295	0.5	98.8	3418	2.2	97.2	<0.001
Imipenem	4295	0	100	3418	1.0	98.8	<0.001
Meropenem	2425	0	100	2147	1.3	98.7	<0.001
Amikacin	4137	3.5	96	3313	1.1	98.5	<0.001
Gentamicin	4070	51.7	47.2	3219	34.6	64.5	<0.001
Tobramycin	3888	22.4	45	3022	7.1	64.7	<0.001
Ciprofloxacin	4295	82.4	14.3	3418	49.9	43.8	<0.001
Levofloxacin	4295	77.1	6.3	3418	44.5	23.4	<0.001
Trimethoprim/ Sulfamethoxazole	4012	64.4	35.6	3225	47.5	52.5	<0.001
Nitrofurantoin	3881	4.0	83.6	3018	2.1	90.7	<0.001

Abbreviations: ESBL (+), ESBL-producing isolates; ESBL (-), non-ESBL-producing isolates.

Table 3 Antimicrobial Susceptibility Profiles of 94 Uropathogenic CREC Isolates

Antibiotics	%R	%I	%S	%R 95% CI
Ampicillin	100	0	0	95.1–00
Cefoperazone/Sulbactam	81.4	13.5	5.1	68.7–89.9
Ampicillin/Sulbactam	98.8	1.2	0	92.7–99.9
Piperacillin/Tazobactam	51.1	26.6	22.3	40.6–61.5
Ceftazidime	98.9	0	1.1	93.3–99.9
Ceftriaxone	100	0	0	95.1–100
Cefepime	88.3	3.2 (SDD)	8.5	79.6–93.7
Cefoxitin	98.3	1.7	0	89.7–99.9
Aztreonam	89.3	1.1	9.6	80.9–94.5
Ertapenem	100	0	0	95.1–100
Imipenem	36.2	2.1	61.7	26.7–46.8
Meropenem	47.5	0	52.5	34.5–60.8
Amikacin	10.7	1.1	88.2	5.6–19.4
Gentamicin	62.6	3.3	34.1	51.8–72.3
Tobramycin	43.8	29.2	27	33.4–54.7
Ciprofloxacin	95.7	0	4.3	88.8–98.6
Levofloxacin	93.6	4.3	2.1	86.1–97.4
Trimethoprim/ Sulfamethoxazole	69.2	0	30.8	58.5–78.2
Nitrofurantoin	9	19.1	71.9	4.2–17.4

Abbreviations: SDD, susceptible-dose dependent; CI, confidence interval.

pharmacokinetics/pharmacodynamics (PK/PD), quinolones have a much higher level in urine than in blood. However, the current breakpoints recommended by CLSI M100 standard for antimicrobial susceptibility testing are based on drug concentration levels in blood. Armstrong et al found that when the minimum inhibitory concentration (MIC) of *Enterobacteriaceae* to levofloxacin was 4 μg/mL, the clinical cure rate could reach 100%; when MIC was 32 μg/mL, the clinical cure rate was also above 80%.[13] During the 8-year period, the susceptibilities have changed to ampicillin, ampicillin/sulbactam, trimethoprim/sulfamethoxazole, ceftriaxone, gentamicin, imipenem, tobramycin in UPEC isolates; except for imipenem with declining susceptibility, other six antibiotics presented increasing susceptibility trends, which is roughly the same as the multi-center AMR surveillance data in China,[14,15] but different from data of other countries.[16–18] The diversity may be related to region, hospital scale, disease type, hospital medication habits such as antibiotics rotation and defined daily doses (DDDs), etc. Since high nephrotoxicity, the DDDs of aminoglycosides are low, which perhaps explained the increasing susceptibility. As the first-line drug for the simple UTIs treatment, trimethoprim/sulfamethoxazole has no obvious advantage for the therapy of serious complicated UTIs due to the only oral agents in our hospital, and it is rarely used clinically.

Patients with long-term hospitalization or invasive procedures, and unreasonable use of antibiotics, raise the risk of infection and colonization of ESBL-producing isolates.[19] Increasing ESBL-producers greatly limit therapeutic options for related infections.[20,21] In the present study, we observed a decreasing trend of ESBL prevalence, which may be attributed to the restricted use of third-generation cephalosporins; even so, the overall prevalence rate was still up to around 50%. The ESBL plasmid-bearing strains are often multi-drug resistant due to the combined carrying of resistance genes to aminoglycosides, quinolones, sulfonamides, and other antibiotics, which can reproduce and proliferate among the homologous and heterologous bacteria.[22,23]

For severe infections caused by ESBL-producing isolates, carbapenems are often the preferred empirical therapeutic choice. Unfortunately, carbapenem-resistant *Enterobacteriaceae* (CRE) is globally increasing year by year and poses an urgent public health threat. Between 2012 and 2019, imipenem-resistant UPEC isolates demonstrated an upward tendency in our study, and

ertapenem-resistant strains ranged from 0.5% to 1.7%. The climbing CREC prevalence may be attributed to the increased empirical treatment of carbapenems. Three major mechanisms are involved in *Enterobacteriaceae* resistance to carbapenems: production of carbapenemases, production of efflux pumps and porin mutations or loss.[24] CRE is usually resistant to all β-lactams and most other antibiotics, leading to a limited clinical choice of antimicrobial agents, sometimes only tigecycline and colistin are available.[25] However, the level of tigecycline in the urinary tract is not high, and the treatment should be cautious.

There were some limitations in our study. First, since it was a retrospective study and the majority of isolates were not collected, no molecular diagnostic approaches were conducted in this paper. Second, the patient-mix was not optimal, which may lead to sub-optimal results. Finally, our study was done in a single tertiary-care teaching hospital with limited data; therefore, the results could not reflect the local AMR precisely.

Conclusion

E. coli is the most common pathogenic bacteria causing UTIs, and ESBL-producing isolates were still the major drug-resistant bacteria in our settings. Carbapenem-resistant UPEC isolates were gradually increasing, which needs to be paid enough attention. Nitrofurantoin, amikacin, piperacillin/tazobactam, cefoperazone/sulbactam, and carbapenems had high susceptibility, and were the preferable choice for the empirical treatment of UTIs. Of course, some factors, such as the cost and safety of antibiotics in the target population, should also be considered when changing therapy. In a word, local timely resistance surveillance data, proper guidelines, and management of antibiotic usage can help to prevent and control antimicrobial resistance.

Ethics Approval

The study was approved by the Ethics Committee of Chongqing Medical University. Due to its retrospective design and anonymous information, the ethics committee waived the requirement for informed consent from patients.

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Disclosure

The authors report no conflicts of interest in this work.

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