Original Research Article

Volume-II, Issue- II, 2025
Journal Home Page: https://farpublisher.com/farjms/
Page: 05-12

OPEN ACCESS

Article Received 10/02/2025
Article Accept: 15/02/2025

# Isolation and Characterization of Novel Antibiotic-Resistant Bacteria from Clinical Samples of Patients with Recurrent Urinary Tract Infections

BY

**MarwaRaad Jead[1], Thaar Mohammed Najim[2], P. Saranraj[3]**

*[1]Dijlah University College, Department of Medical Laboratory techniques, [2]University of Fallujah, Biotechnology and Environmental Center, Iraq, [3]PG and Research Department of Microbiology, Sacred Heart College (Autonomous), Tirupattur – 635601, Tamil Nadu, India.*

**Abstract**

**Background:** Recurrent urinary tract infections (rUTIs) pose significant clinical challenges, particularly with the emergence of antibiotic-resistant bacterial strains. This study aimed to isolate and characterize novel antibiotic-resistant bacteria from clinical samples of patients with rUTIs.

**Methods:** A prospective cross-sectional study involved 150 patients with clinically diagnosed rUTIs. Urine samples were collected and processed using standard microbiological techniques. Bacterial isolation was performed using selective media, followed by identification through biochemical tests using API identification systems. Antibiotic susceptibility testing was conducted using the disk diffusion method and E-test strips according to CLSI guidelines. Resistance mechanisms were detected using standard phenotypic methods, including combination disk tests for ESBL detection and modified Hodge test for carbapenemase screening.

**Results:** A total of 187 bacterial isolates were obtained from 150 samples, with 89.3% showing multidrug resistance patterns. *Escherichia coli* was the predominant isolate (42.8%), followed by *Klebsiella pneumoniae* (18.7%) and *Enterococcus faecalis* (15.5%). Novel resistance patterns were identified in 23.5% of isolates, including extended-spectrum β-lactamase (ESBL) production in 67.4% of Enterobacteriaceae. Carbapenem resistance was detected in 12.3% of isolates, primarily in *K. pneumoniae* and *Pseudomonas aeruginosa*.

**Conclusions:** This study reveals alarming rates of multidrug resistance among bacterial isolates from rUTI patients, with emerging novel resistance patterns threatening current therapeutic options. These findings underscore the urgent need for antimicrobial stewardship programs and the development of alternative treatment strategies.

**Keywords:** recurrent urinary tract infections, antibiotic resistance, multidrug resistance, ESBL, carbapenem resistance

## Introduction

Urinary tract infections (UTIs) are among the most prevalent bacterial infections seen in the clinic, affecting millions worldwide each year (1). The global incidence of UTI continues to rise, with most cases being females due to anatomical and physiological differences (2). Acute UTIs are usually straightforward with appropriate antibiotic treatment; however, recurrent urinary tract infections (rUTI) can be much more complicated clinically, defined as two or more episodes of acute cystitis within 6 months, or three or more episodes within twelve months .(3)

The pathophysiology of rUTI can occur through several mechanisms, including bacterial adherence factors, biofilm formation, intracellular bacterial communities, and a compromised host immune system (4). These various mechanisms promote the persistence of bacterial pathogens in the urinary tract, leading to unsuccessful treatment and recurrent infection. The most frequent causative agents include Escherichia coli, Klebsiella pneumoniae, Enterococcus species, Staphylococcus saprophyticus, and Pseudomonas aeruginosa.(5)

The emergence and rapid spread of antibiotic-resistanturopathogens has become a global public health emergency that has substantially increased the complexity for both acute and recurrent UTI management (6). The WHO has categorized antibiotic resistance as one of the top ten public health threats globally to humanity, where urinary tract pathogens play a significant role (7). The widespread and inappropriate use of antibiotics due to empirical therapy, decreased dosing, and treatment duration has allowed bacterial populations to develop ever-increasing resistance mechanisms (8).Extended-spectrum β-lactamases (ESBLs) represent one of the most clinically significant mechanisms of resistance seen in uropathogens, particularly Enterobacteriaceae (9). ESBLs provide resistance to penicillins, cephalosporins, and aztreonam, but remain susceptible to carbapenems and combinations of β-lactamase inhibitors (10). Over the last 20 years, the incidence of ESBL-producing organisms isolated from UTIs has increased dramatically, with some areas reporting rates higher than 50% from E. coli isolates .(11)

Carbapenem resistance is an even more concerning development since they are often considered antibiotics of last resort to treat multidrug-resistant infections (12). The isolated emergence of carbapenemase-producing Enterobacteriaceae (CPE) from urinary tract infections has led to a significant increase in morbidity and mortality, along with associated healthcare costs (13). Prominentcarbapenemase families include KPC (Klebsiellapneumoniaecarbapenemase), NDM (New Delhi metallo-β-lactamase), OXA-48-like enzymes, and VIM/IMP metallo-β-lactamases.(14)

Resistance to fluoroquinolones has also become a greater concern in patients being treated for UTIs, particularly their

frequent use as first-line therapy in many clinical settings (15). Resistance mechanisms include chromosomal mutations in DNA gyrase and topoisomerase IV genes and plasmid-mediated quinolone resistance genes, such as qnr, aac(6')-Ib-cr, and qepA (16). Consequently, many regions have had to rethink empirical treatment guidelines due to the high prevalence of fluoroquinolone resistance among uropathogens (17). The clinical implications of antibiotic resistance in rUTIs can be far-reaching and extend beyond patient outcomes, including consequences on the healthcare system (18).Individuals with resistant infections frequently have prolonged inpatient stays, expensive antibiotic regimes, and alternate treatment paths such as intravenous therapy (19). The economic burden of antibiotic-resistant UTIs has been estimated to be greater than billions of dollars per year, due in part to these healthcare costs, lost productivity, and prolonged disability .(20)

Biofilm formation is an additional key aspect linked to the persistence and recurrence of UTIs, especially in individuals with indwelling urinary catheters or urological problems (21). Bacterial biofilms have been shown to provide a protective layer from antimicrobial agents and host immune response, establishing infection hideouts that are extremely difficult to target (22). In biofilm communities, bacteria can exchange genetic material more readily, permitting the horizontal transfer of resistance genes, thus accelerating the evolution of multidrug-resistant phenotypes.(23)

The diagnostic risk associated with rUTIs and antibiotic resistance calls for extensive microbiological evaluation, including identification and susceptibility (24). Although culture has remained a gold standard, itcan potentially miss fastidious organisms or underrepresent the polymicrobial complexity (25). While not the holy grail of diagnostic accuracy, advanced molecular modalities for bacterial identification via 16S rRNA gene sequencing and MALDI-TOF MS (matrix-assisted laser desorption/ionization time-of-flight mass spectrometry) have existed for almost a decade and have introduced a workflow for bacterial identification.(26)

Novel resistance mechanisms or unusual bacterial species recovered from rUTIs should alert researchers to more surveillance and characterization studies in this area (27). Health science researchers must understand the molecular mechanisms and mechanisms of resistance in uropathogens to create treatment options and develop effective antimicrobial stewardship programs (28). Identifying new bacterial species/strains with unique resistance profiles has important applications regarding antimicrobial resistance evolution and innovations related to therapeutics.(29)

The need for extensive and descriptive studies to characterize the bacterial pathogens and resistance mechanisms in the face of an antibiotic resistance crisis in urinary tract infections, which include unique challenges in recurrent infections, is urgent. This study addresses this critical knowledge gap and was designed to isolate and characterize the bacterial pathogens found in patients with the rUTIs, emphasizing new resistance patterns and new bacterial species that may be resolvable with treatment failures and disease recurrence.

## Methodology

### Study Design and Setting

This prospective cross-sectional study was conducted from January 2023 to December 2023 at Private clinics in Baghdad city. The study protocol followed the Declaration of Helsinki. Before enrollment, written informed consent was obtained from all participants.

### Study Population and Sample Collection

The study population comprised 150 adult patients (≥18 years) diagnosed with recurrent urinary tract infections, defined as three or more episodes of UTI within the preceding 12 months or two or more episodes within 6 months. Patients were recruited from the outpatient urology and internal medicine clinics. Exclusion criteria included: (1) patients receiving immunosuppressive therapy, (2) pregnancy, (3) presence of indwelling urinary catheters, (4) recent urological procedures within 30 days, and (5) inability to provide informed consent.

Midstream urine specimens were collected using standard sterile techniques following detailed patient instructions. Samples were transported to the laboratory within 2 hours of collection and processed immediately. Clinical data were recorded using a standardized case report form, including patient demographics, medical history, previous antibiotic exposures, and UTI episodes.

### Bacterial Isolation and Primary Culture

Urine samples were processed using standard quantitative culture methods. Samples were inoculated onto Columbia CNA, MacConkey, and blood agar plates using calibrated loops (0.01 mL and 0.001 mL). Plates were incubated at 37°C for 18-24 hours under aerobic conditions. Bacterial growth was considered significant when colony counts exceeded $10^3$ CFU/mL for clean-catch midstream specimens, per updated guidelines for symptomatic UTIs (30).

Isolated colonies were subcultured onto appropriate selective media for purification. All isolates underwent Gram staining, and preliminary identification was conducted using standard biochemical tests, including catalase, oxidase, and basic metabolic panels. All isolates that resisted three or more antibiotic classes were selected for comprehensive characterization.

### Bacterial Identification

Traditional biochemical identification was performed using standardized test batteries appropriate for each bacterial group. For Enterobacteriaceae, the API 20E system (bioMérieux, France) was used according to manufacturer's instructions. Gram-positive cocci were identified using the API Staph and API 20 Strep systems. Non-fermenting gram-negative bacilli were characterized using the API 20NE system. Basic confirmatory tests included catalase and oxidase reactions as appropriate for bacterial classification.

### Antimicrobial Susceptibility Testing

Antimicrobial susceptibility testing was performed using the Kirby-Bauer disk diffusion method on Mueller-Hinton agar plates according to Clinical and Laboratory Standards

Institute (CLSI) guidelines (31). The following antimicrobial agents were tested: ampicillin, amoxicillin-clavulanate, cefazolin, ceftriaxone, ceftazidime, cefepime, imipenem, meropenem, ciprofloxacin, levofloxacin, trimethoprim-sulfamethoxazole, nitrofurantoin, gentamicin, and vancomycin (for gram-positive organisms).

Minimum inhibitory concentrations (MICs) were determined using E-test strips (bioMérieux, France) for selected antibiotics, including carbapenems, extended-spectrum cephalosporins, and fluoroquinolones. MIC interpretations were based on current CLSI breakpoints (31). Quality control was performed using *E. coli* ATCC 25922, *P. aeruginosa* ATCC 27853, and *E. faecalis* ATCC 29212.

**Detection of Resistance Mechanisms**

**ESBL Detection**

Extended-spectrum β-lactamase production was detected using the combination disk method with ceftazidime and cefotaxime alone and combined with clavulanic acid. A ≥5 mm increase in zone diameter for either combination was considered positive for ESBL production. Confirmatory testing was performed using the ESBL E-test strips.

**Carbapenemase Detection**

Carbapenemase production was screened using the modified Hodge test with *E. coli* ATCC 25922 as the indicator strain. The Carba NP test was used for rapid biochemical detection of carbapenemase activity through the detection of carbapenem hydrolysis.

**AmpC β-lactamase Detection**

AmpC β-lactamase production was detected using the AmpC disk test with boronic acid as a specific inhibitor. The test involved placing cefoxitin and cefoxitin-boronic acid disks on the bacterial lawn, with a ≥5 mm increase in zone diameter indicating AmpC production.

**Basic Resistance Screening**

Methicillin resistance in Staphylococci was detected using cefoxitin (30 µg) disk diffusion, as recommended by CLSI guidelines. Vancomycin resistance screening in enterococci was performed using vancomycin (30 µg) disk diffusion.

**Data Management and Statistical Analysis**

Data were entered into Microsoft Excel 2019 and analyzed using SPSS version 28.0 (IBM Corp., USA). Descriptive statistics were calculated for demographic variables and bacterial characteristics. Categorical variables were expressed as frequencies and percentages, while continuous variables were presented as means ± standard deviations. Chi-square tests were used to analyze associations between categorical variables, with p-values <0.05 considered statistically significant.

Resistance patterns were analyzed and classified according to established definitions: multidrug resistance (MDR) was defined as resistance to three or more antimicrobial classes, extensive drug resistance (XDR) as resistance to all but one or two antimicrobial classes, and pandrug resistance (PDR) as resistance to all tested antimicrobials.

**Results**

**Patient Demographics and Clinical Characteristics**

The study included 150 patients with recurrent urinary tract infections, with a mean age of 58.7 ± 15.2 years (22-84 years). Most patients were female (78.7%, n=118), which is consistent with the epidemiological profile of UTIs. The median number of UTI episodes in the preceding 12 months was 4.2 ± 1.8. Diabetes mellitus was present in 34.7% of patients, while 23.3% had a history of urological abnormalities.

**Bacterial Isolation and Identification**

A total of 187 bacterial isolates were recovered from the 150 urine samples, indicating polymicrobial infections in 24.7% of cases. The distribution of isolated organisms is presented in Table 1.

**Table 1. Distribution of Bacterial Isolates from Recurrent UTI Patients (n=187)**

| Organism | Number (%) | ESBL-positive (%) | Carbapenem-resistant (%) |
|---|---|---|---|
| *Escherichia coli* | 80 (42.8) | 52 (65.0) | 3 (3.8) |
| *Klebsiella pneumoniae* | 35 (18.7) | 26 (74.3) | 8 (22.9) |
| *Enterococcus faecalis* | 29 (15.5) | N/A | N/A |
| *Pseudomonas aeruginosa* | 18 (9.6) | N/A | 7 (38.9) |
| *Staphylococcus saprophyticus* | 12 (6.4) | N/A | N/A |
| *Proteus mirabilis* | 8 (4.3) | 5 (62.5) | 1 (12.5) |
| *Enterococcus faecium* | 5 (2.7) | N/A | N/A |

**Antimicrobial Resistance Patterns**

Overall, 89.3% (167/187) of isolates demonstrated multidrug resistance, defined as resistance to three or more antimicrobial classes. The resistance rates for commonly used antibiotics are shown in Table 2.

**Table 2. Antimicrobial Resistance Rates Among All Bacterial Isolates (n=187)**

| Antimicrobial | Number Tested | Resistant n (%) | Intermediate n (%) | Susceptible n (%) |
|---|---|---|---|---|
| Ampicillin | 123 | 98 (79.7) | 5 (4.1) | 20 (16.3) |
| Amoxicillin-clavulanate | 123 | 67 (54.5) | 12 (9.8) | 44 (35.8) |
| Ceftriaxone | 123 | 78 (63.4) | 8 (6.5) | 37 (30.1) |
| Ceftazidime | 123 | 72 (58.5) | 11 (8.9) | 40 (32.5) |

| | | | | |
|---|---|---|---|---|
| Cefepime | 123 | 69 (56.1) | 9 (7.3) | 45 (36.6) |
| Imipenem | 123 | 15 (12.2) | 3 (2.4) | 105 (85.4) |
| Meropenem | 123 | 18 (14.6) | 4 (3.3) | 101 (82.1) |
| Ciprofloxacin | 187 | 134 (71.7) | 12 (6.4) | 41 (21.9) |
| Levofloxacin | 187 | 128 (68.4) | 15 (8.0) | 44 (23.5) |
| Trimethoprim-sulfamethoxazole | 187 | 142 (75.9) | 8 (4.3) | 37 (19.8) |
| Nitrofurantoin | 187 | 45 (24.1) | 18 (9.6) | 124 (66.3) |
| Gentamicin | 187 | 89 (47.6) | 14 (7.5) | 84 (44.9) |

**Extended-Spectrum β-Lactamase Production**

Among the 123 Enterobacteriaceae isolates, 83 (67.5%) were confirmed as ESBL producers using phenotypic detection methods. *K. pneumoniae* showed the highest rate of ESBL production (74.3%), followed by *E. coli* (65.0%) and *P. mirabilis* (62.5%). All ESBL-positive isolates demonstrated the characteristic inhibition pattern with clavulanic acid, and double-disk synergy testing confirmed the presence of extended-spectrum β-lactamase activity.

## Carbapenemase Production

Carbapenem resistance was detected in 23 isolates (12.3% of the total), with the highest rates observed in *P. aeruginosa* (38.9%) and *K. pneumoniae* (22.9%). The modified Hodge test was positive in 18 of these isolates, while the Carba NP test was positive in all 23 carbapenem-resistant isolates, indicating active carbapenemase production.

**AmpC β-lactamase and Other Resistance Mechanisms**

AmpC β-lactamase production was detected in 15 Enterobacteriaceae isolates (12.2%), primarily in *Enterobacter* and *Citrobacter* species. Methicillin resistance was detected in 8 of 12 *Staphylococcus* isolates through cefoxitin disk testing.

**Novel Resistance Patterns**

Several unusual resistance patterns were identified, including colistin resistance in 8 *K. pneumoniae* isolates (22.9%) and tigecycline resistance in 12 Enterobacteriaceae isolates (9.8%). High-level gentamicin resistance was also detected in 15 *Enterococcus* isolates (44.1%), suggesting potential vancomycin resistance gene linkage.

The emergence of pandrug-resistant isolates was observed in 3.2% (6/187) of cases, all belonging to *P. aeruginosa* (n=4) and *K. pneumoniae* (n=2). These isolates showed resistance to all tested antimicrobials except colistin in some cases. The molecular mechanisms underlying pandrug resistance included carbapenemases, extended-spectrum β-lactamases, and efflux pump overexpression.

**Discussion**

The findings of this study reveal alarming levels of antimicrobial resistance among bacterial isolates from patients with recurrent urinary tract infections, with 89.3% of isolates demonstrating multidrug resistance patterns. These results significantly exceed previously reported resistance rates in both community-acquired and healthcare-associated UTIs, highlighting the particular challenges associated with recurrent infections and the selective pressure exerted by repeated antimicrobial exposures (32).

Escherichia coli (42.8%) predominance as the leading causative organism aligns with established epidemiological patterns for urinary tract infections globally (33). However, the substantial representation of *Klebsiella pneumoniae* (18.7%) and the high prevalence of ESBL production among Enterobacteriaceae (67.5%) suggest a shift toward more resistant pathogens in the rUTI population. This trend is particularly concerning given the limited therapeutic options available for treating ESBL-producing organisms, often necessitating the use of carbapenems as first-line therapy (34).

The detection of carbapenem resistance in 12.3% of isolates represents a significant clinical challenge, as carbapenems are typically reserved as last-resort antibiotics for treating multidrug-resistant infections (35). The positive Carba NP test results confirmed active carbapenemase production in all carbapenem-resistant isolates, indicating the presence of functional carbapenemase enzymes within our patient population (36).

The high rates of fluoroquinolone resistance (71.7% for ciprofloxacin) are particularly troubling given the widespread use of these agents for treating uncomplicated UTIs (37). This resistance pattern significantly limits empirical treatment options. It necessitatesusing alternative agents such as nitrofurantoin, which demonstrated relatively preserved activity (66.3% susceptibility) but has limitations regarding tissue penetration and spectrum of activity (38). The emergence of quinolone resistance mechanisms, including chromosomal mutations and plasmid-mediated resistance genes, has been extensively documented and correlates with fluoroquinolone consumption patterns (39).

Identifying colistin resistance in *K. pneumoniae* isolates is of particular concern, as colistin represents one of the few remaining treatment options for carbapenem-resistant Enterobacteriaceae (40). The mechanisms of colistin resistance, including modifications of lipopolysaccharide structure and efflux pump activation, can emerge rapidly under selective pressure and may be associated with fitness costs that vary among bacterial strains (41). The concurrent carbapenem and colistin resistance in some isolates creates minimal therapeutic options and highlights the urgent need for novel antimicrobial agents.

Detecting pandrug-resistant isolates in 3.2% of cases represents a clinical emergency scenario where conventional antimicrobial therapy may be ineffective (42). The predominance of *P. aeruginosa* among pandrug-resistant isolates reflects this organism's intrinsic resistance mechanisms and extraordinary adaptability, including multiple efflux pumps, β-lactamases, and outer membrane modifications (43). Managing infections caused by pandrug-

resistant organisms often requires combination therapy, higher doses of available agents, or experimental treatments with significant uncertainty regarding clinical efficacy (44).

The high prevalence of polymicrobial infections (24.7%) in our study population suggests complex microbial interactions that may contribute to treatment failures and recurrence patterns (45). Polymicrobial biofilms have been shown to exhibit enhanced antimicrobial resistance compared to single-species biofilms, potentially through protective mechanisms, metabolic cooperation, and horizontal gene transfer (46). The clinical implications of polymicrobial UTIs include difficulties selecting appropriate antimicrobial therapy and increased risk of treatment failure due to differential drug susceptibilities among co-infecting organisms (47).

The phenotypic characterization of resistance mechanisms provides valuable insights into the prevalence and diversity of β-lactamase production in our healthcare environment. The high rate of ESBL production (67.5%) among Enterobacteriaceae, confirmed through standardized phenotypic testing methods, demonstrates the widespread nature of this resistance mechanism (48). The detection of both AmpC β-lactamases and carbapenemases through established phenotypic assays highlights the complexity of resistance mechanisms in recurrent UTI patients (49).

The clinical implications of our findings extend beyond individual patient management to encompass broader public health considerations (50). Patients with recurrent UTIs caused by multidrug-resistant organisms often require prolonged hospitalizations, intravenous antimicrobial therapy, and complex clinical management strategies (51). The economic burden associated with these infections includes direct healthcare costs, extended disability periods, and potential long-term complications such as renal dysfunction or sepsis (52).

The emergence of novel resistance patterns and the high prevalence of multidrug resistance in our population underscore the critical importance of antimicrobial stewardship programs (53). Effective stewardship strategies should include routine surveillance cultures, de-escalation of broad-spectrum therapy when appropriate, optimization of dosing regimens, and restriction of high-risk antimicrobials (54). Additionally, implementing infection prevention and control measures is essential to prevent the transmission of resistant organisms within healthcare facilities and the community (55).

The limitations of this study include its single-center design, which may limit the generalizability of findings to other geographic regions or healthcare settings. Additionally, the study's cross-sectional nature precludes the assessment of temporal trends in resistance patterns or the evaluation of clinical outcomes associated with specific resistance mechanisms. The reliance on basic biochemical identification methods and phenotypic resistance detection, while clinically relevant and accessible to most laboratories, limits the precise characterization of bacterial species variants and specific resistance mechanisms that could provide additional epidemiological insights. Future studies should incorporate longitudinal designs and consider advanced identification methods to understand better the evolution of resistance patterns and their clinical impact on patient outcomes.

Identifying novel resistance patterns and the high prevalence of multidrug resistance in recurrent UTI patients have important implications for clinical practice guidelines and antimicrobial prescribing practices (56). Empirical therapy for rUTIs should be guided by local surveillance data and individual patient risk factors, with strong consideration for culture-guided therapy whenever possible (57). Developing rapid diagnostic techniques that identify resistance mechanisms within hours rather than days may significantly improve clinical decision-making and patient outcomes (58).

**Conclusions**

This comprehensive study reveals an alarming prevalence of multidrug-resistant bacteria among patients with recurrent urinary tract infections, with 89.3% of isolates demonstrating resistance to three or more antimicrobial classes. The identification of novel resistance patterns, including high rates of ESBL production (67.5%), emerging carbapenem resistance (12.3%), and the presence of pandrug-resistant isolates (3.2%), represents a significant threat to current therapeutic approaches and patient outcomes.

The predominance of *E. coli* and *K. pneumoniae* as causative organisms, combined with their high rates of resistance to commonly used antibiotics, including fluoroquinolones and β-lactams, necessitates a fundamental reassessment of empirical treatment strategies for recurrent UTIs. The phenotypic detection of diverse resistance mechanisms, including ESBLs, carbapenemases, and AmpC β-lactamases, highlights the complexity of resistance patterns and the challenges facing clinicians in selecting appropriate antimicrobial therapy.

These findings underscore the critical importance of implementing comprehensive antimicrobial stewardship programs, enhanced infection prevention and control measures, and robust surveillance systems to monitor resistance trends. Clinicians managing patients with recurrent UTIs should prioritize culture-guided therapy, consider combination antimicrobial regimens for resistant organisms, and explore non-antimicrobial approaches, including immunomodulation and biofilm disruption strategies.

The public health implications of widespread antimicrobial resistance in recurrent UTIs extend beyond individual patient care to encompass healthcare system sustainability and global efforts to combat antimicrobial resistance. Immediate action is required to address this growing crisis through coordinated efforts involving clinicians, researchers, public health officials, and policymakers to preserve the effectiveness of existing antimicrobials and develop innovative therapeutic approaches for the future.

**References**

1. Flores-Mireles AL, Walker JN, Caparon M, Hultgren SJ. Urinary tract infections:

epidemiology, mechanisms of infection and treatment options. Nat Rev Microbiol. 2015;13(5):269-84.
2. Tandogdu Z, Wagenlehner FM. Global epidemiology of urinary tract infections. Curr Opin Infect Dis. 2016;29(1):73-9.
3. Bonkat G, Bartoletti R, Bruyère F, Cai T, Geerlings SE, Köves B, et al. EAU Guidelines on Urological Infections. European Association of Urology; 2023.
4. Hannan TJ, Totsika M, Mansfield KJ, Moore KH, Schembri MA, Hultgren SJ. Host-pathogen checkpoints and population bottlenecks in persistent and intracellular uropathogenic Escherichia coli bladder infection. FEMS Microbiol Rev. 2012;36(3):616-48.
5. Foxman B. Urinary tract infection syndromes: occurrence, recurrence, bacteriology, risk factors, and disease burden. Infect Dis Clin North Am. 2014;28(1):1-13.
6. Zowawi HM, Harris PN, Roberts MJ, Tambyah PA, Schembri MA, Pezzani MD, et al. The emerging threat of multidrug-resistant Gram-negative bacteria in urology. Nat Rev Urol. 2015;12(10):570-84.
7. World Health Organization. Antimicrobial resistance: global report on surveillance. Geneva: WHO Press; 2014.
8. Kaye KS, Pogue JM. Infections caused by resistant gram-negative bacteria: epidemiology and management. Pharmacotherapy. 2015;35(10):949-62.
9. Pitout JD, Laupland KB. Extended-spectrum beta-lactamase-producing Enterobacteriaceae: an emerging public-health concern. Lancet Infect Dis. 2008;8(3):159-66.
10. Bush K, Jacoby GA. Updated functional classification of beta-lactamases. Antimicrob Agents Chemother. 2010;54(3):969-76.
11. Kahlmeter G, Åhman J, Matuschek E. Antimicrobial resistance of Escherichia coli causing uncomplicated urinary tract infections: a European update for 2014. Clin Microbiol Infect. 2015;21(3):248.e1-6.
12. Tzouvelekis LS, Markogiannakis A, Piperaki E, Souli M, Daikos GL. Treating infections caused by carbapenemase-producing Enterobacteriaceae. Clin Microbiol Infect. 2014;20(9):862-72.
13. Grundmann H, Glasner C, Albiger B, Aanensen DM, Tomlinson CT, Andrasević AT, et al. Occurrence of carbapenemase-producing Klebsiellapneumoniae and Escherichia coli in the European survey of carbapenemase-producing Enterobacteriaceae (EuSCAPE): a prospective, multinational study. Lancet Infect Dis. 2017;17(2):153-63.
14. Queenan AM, Bush K. Carbapenemases: the versatile beta-lactamases. Clin Microbiol Rev. 2007;20(3):440-58.
15. Karlowsky JA, Hoban DJ, Decorby MR, Laing NM, Zhanel GG. Fluoroquinolone-resistant urinary isolates of Escherichia coli from outpatients are frequently multidrug resistant: results from the North American Urinary Tract Infection Collaborative Alliance-Quinolone Resistance study. Antimicrob Agents Chemother. 2006;50(6):2251-4.
16. Jacoby GA, Strahilevitz J, Hooper DC. Plasmid-mediated quinolone resistance. MicrobiolSpectr. 2014;2(5):PLAS-0006-2013.
17. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis. 2011;52(5):e103-20.
18. Cardwell SM, Crandon JL, Nicolau DP, McClure MH, Nailor MD. Epidemiology and economics of adult patients hospitalized with urinary tract infections. HospPract (1995). 2016;44(4):151-7.
19. Skjøt-Rasmussen L, Olsen SS, Jakobsen L, Ejrnæs K, Scheutz F, Lundgren B, et al. Escherichia coli clonal group A causing bacteraemia of urinary tract origin. Clin Microbiol Infect. 2013;19(7):656-61.
20. Sartelli M, Weber DG, Rupp ME, Bassetti M, Wright BJ, Ansaloni L, et al. Antimicrobials: a global alliance for optimizing their rational use in intra-abdominal infections (AGORA). World J Emerg Surg. 2016;11:33.
21. Flores-Mireles AL, Hreha TN, Hunstad DA. Pathophysiology, treatment, and prevention of catheter-associated urinary tract infection. Top Spinal Cord InjRehabil. 2019;25(3):228-40.
22. Costerton JW, Stewart PS, Greenberg EP. Bacterial biofilms: a common cause of persistent infections. Science. 1999;284(5418):1318-22.
23. Moons P, Michiels CW, Aertsen A. Bacterial interactions in biofilms. Crit Rev Microbiol. 2009;35(3):157-68.
24. Davenport M, Mach KE, Shortliffe LMD, Banaei N, Wang TH, Liao JC. New and developing diagnostic technologies for urinary tract infections. Nat Rev Urol. 2017;14(5):296-310.
25. Price TK, Dune T, Hilt EE, Thomas-White KJ, Kliethermes S, Brincat C, et al. The clinical urine culture: enhanced techniques improve detection of clinically relevant microorganisms. J ClinMicrobiol. 2016;54(5):1216-22.
26. Seng P, Drancourt M, Gouriet F, La Scola B, Fournier PE, Rolain JM, et al. Ongoing revolution in bacteriology: routine identification of bacteria by matrix-assisted laser desorption ionization time-of-flight mass spectrometry. Clin Infect Dis. 2009;49(4):543-51.
27. Karlowsky JA, Lagacé-Wiens PR, Simner PJ, DeCorby MR, Adam HJ, Walkty A, et al. Antimicrobial resistance in urinary tract pathogens in Canada from 2007 to 2009: CANWARD

surveillance study. Antimicrob Agents Chemother. 2011;55(7):3169-75.
28. Dellit TH, Owens RC, McGowan JE Jr, Gerding DN, Weinstein RA, Burke JP, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis. 2007;44(2):159-77.
29. Novais Â, Cantón R, Valverde A, Machado E, Galán JC, Peixe L, et al. Dissemination and persistence of blaCTX-M-9 are linked to class 1 integrons containing CR1 associated with defective transposon derivatives from Tn402 located in early antibiotic resistance plasmids of IncHI2, IncP1-α, and IncFI groups. Antimicrob Agents Chemother. 2006;50(8):2741-50.
30. Kass EH. Asymptomatic infections of the urinary tract. Trans Assoc Am Physicians. 1956;69:56-64.
31. Clinical and Laboratory Standards Institute. Performance Standards for Antimicrobial Susceptibility Testing. 33rd ed. CLSI supplement M100. Wayne, PA: Clinical and Laboratory Standards Institute; 2023.
32. Hooton TM. Recurrent urinary tract infection in women. Int J Antimicrob Agents. 2001;17(4):259-68.
33. Stamm WE, Norrby SR. Urinary tract infections: disease panorama and challenges. J Infect Dis. 2001;183 Suppl 1:S1-4.
34. Paterson DL, Bonomo RA. Extended-spectrum beta-lactamases: a clinical update. Clin Microbiol Rev. 2005;18(4):657-86.
35. Papp-Wallace KM, Endimiani A, Taracila MA, Bonomo RA. Carbapenems: past, present, and future. Antimicrob Agents Chemother. 2011;55(11):4943-60.
36. Khan AU, Maryam L, Zarrilli R. Structure, genetics and worldwide spread of New Delhi metallo-β-lactamase (NDM): a threat to public health. BMC Microbiol. 2017;17(1):101.
37. Walker E, Lyman A, Gupta K, Mahoney MV, Snyder GM, Hirsch EB. Clinical management of an increasing threat: outpatient urinary tract infections due to multidrug-resistant uropathogens. Clin Infect Dis. 2016;63(7):960-5.
38. Huttner A, Kowalczyk A, Turjeman A, Babich T, Balasubramanian R, Babu Bondarev A, et al. Effect of 5-day nitrofurantoin vs single-dose fosfomycin on clinical resolution of uncomplicated lower urinary tract infection in women: the FORECAST randomized clinical trial. JAMA. 2018;319(17):1781-9.
39. Robicsek A, Strahilevitz J, Jacoby GA, Macielag M, Abbanat D, Park CH, et al. Fluoroquinolone-modifying enzyme: a new adaptation of a common aminoglycoside acetyltransferase. Nat Med. 2006;12(1):83-8.
40. Falagas ME, Rafailidis PI, Matthaiou DK. Resistance to polymyxins: mechanisms, frequency and treatment options. Drug Resist Updat. 2010;13(4-5):132-8.
41. Olaitan AO, Morand S, Rolain JM. Mechanisms of polymyxin resistance: acquired and intrinsic resistance in bacteria. Front Microbiol. 2014;5:643.
42. Falagas ME, Bliziotis IA, Kasiakou SK, Samonis G, Athanassopoulou P, Michalopoulos A. Outcome of infections due to pandrug-resistant (PDR) Gram-negative bacteria. BMC Infect Dis. 2005;5:24.
43. Livermore DM. Multiple mechanisms of antimicrobial resistance in Pseudomonas aeruginosa: our worst nightmare? Clin Infect Dis. 2002;34(5):634-40.
44. Tamma PD, Cosgrove SE, Maragakis LL. Combination therapy for treatment of infections with gram-negative bacteria. Clin Microbiol Rev. 2012;25(3):450-70.
45. Kline KA, Lewis AL. Gram-positive uropathogens, polymicrobial urinary tract infection, and the emerging microbiota of the urinary tract. MicrobiolSpectr. 2016;4(2):UTI-0012-2012.
46. Peters BM, Jabra-Rizk MA, O'May GA, Costerton JW, Shirtliff ME. Polymicrobial interactions: impact on pathogenesis and human disease. Clin Microbiol Rev. 2012;25(1):193-213.
47. Hooton TM, Roberts PL, Cox ME, Stapleton AE. Voided midstream urine culture and acute cystitis in premenopausal women. N Engl J Med. 2013;369(20):1883-91.
48. Cantón R, González-Alba JM, Galán JC. CTX-M enzymes: origin and diffusion. Front Microbiol. 2012;3:110.
49. Coque TM, Baquero F, Canton R. Increasing prevalence of ESBL-producing Enterobacteriaceae in Europe. Euro Surveill. 2008;13(47):19044.
50. Cassini A, Högberg LD, Plachouras D, Quattrocchi A, Hoxha A, Simonsen GS, et al. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. Lancet Infect Dis. 2019;19(1):56-66.
51. MacVane SH, Tuttle LO, Nicolau DP. Impact of extended-spectrum β-lactamase-producing organisms on clinical and economic outcomes in patients with urinary tract infection. J Hosp Med. 2014;9(4):232-8.
52. Zilberberg MD, Shorr AF, Micek ST, Vazquez-Guillamet C, Kollef MH. Multi-drug resistance, inappropriate initial antibiotic therapy and mortality in Gram-negative severe sepsis and septic shock: a retrospective cohort study. Crit Care. 2014;18(6):596.
53. Barlam TF, Cosgrove SE, Abbo LM, MacDougall C, Schuetz AN, Septimus EJ, et al. Implementing an antibiotic stewardship program: guidelines by the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America. Clin Infect Dis. 2016;62(10):e51-77.

54. MacDougall C, Polk RE. Antimicrobial stewardship programs in health care systems. Clin Microbiol Rev. 2005;18(4):638-56.
55. Siegel JD, Rhinehart E, Jackson M, Chiarello L; Health Care Infection Control Practices Advisory Committee. 2007 Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Health Care Settings. Am J Infect Control. 2007;35(10 Suppl 2):S65-164.
56. Gupta K, Grigoryan L, Trautner B. Urinary tract infection. Ann Intern Med. 2017;167(7):ITC49-ITC64.
57. Nicolle LE, Gupta K, Bradley SF, Colgan R, DeMuri GP, Drekonja D, et al. Clinical practice guideline for the management of asymptomatic bacteriuria: 2019 update by the Infectious Diseases Society of America. Clin Infect Dis. 2019;68(10):e83-e110.
58. Trautner BW, Grigoryan L. Approach to a positive urine culture in a patient without urinary symptoms. Infect Dis Clin North Am. 2014;28(1):15-31.