

Uropathogens Causing Urinary Tract Infection in Adults in a Tertiary Care Hospital

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Abstract

Objective: To study the profile of uropathogens, causing UTI in adults in our hospital and research center, assess their pattern of antimicrobial susceptibility, the clinical course, and outcome. **Materials and Methods:** This prospective observational study included all participants with suspected UTI whose urine samples grew a positive culture of uropathogens. The study was done in the department of microbiology from July 2019 to December 2019. The urine samples were processed by standard methods, and antimicrobial susceptibility was performed using the Kirby–Bauer disk diffusion method. The details of the pathogens grown and their antimicrobial sensitivity and resistance patterns were recorded, and the participants were followed up during their course in the hospital. **Results:** A total of 549 urine samples from adult participants showed positive cultures. Ceftriaxone (33.3%; $n = 50$) and piperacillin + tazobactam (31.3%; $n = 47$) were the empirical antimicrobials used. *Escherichia coli* (37.5%; $n = 195$) was the most common uropathogen, followed by *Enterococcus spp.* (17.3%; $n = 90$) and *Klebsiella pneumoniae* (12.1%; $n = 63$). *E. coli* was resistant to amoxicillin + clavulanic acid, cephalosporins, and ciprofloxacin and sensitive to meropenem, amikacin, and piperacillin + tazobactam. **Conclusion:** The changing etiology of UTI and emergence of drug resistance is highlighted. Different uropathogens and their antimicrobial resistance are a concern for future treatment options in UTI.

Keywords: Adults, Antimicrobial drug resistance, Urinary tract infection

INTRODUCTION

Any infection of the urinary tract involving either the kidneys, ureters, urinary bladder, or the urethra is termed as urinary tract infection (UTI). Bacteria are the most common causative agents involved in UTIs, followed by fungi such as *Candida*. UTIs are responsible for nearly 35% of all the hospital-acquired infections, which contribute to significant morbidity and is a major cause for hospital visits.^[1] Most of the UTIs involve the urethra and/or the urinary bladder. UTIs are common among hospitalized patients, diabetics, and patients with anatomical abnormalities of the urinary tract and neurological abnormalities which can lead to interference of urinary flow.^[2] Major risk factors for the development of UTIs include female gender, chronic renal disease, advanced age, increased length of stay in the hospital, debilitating underlying illnesses, and repeated urinary catheterizations. UTIs may lead to serious complications such as sepsis, recurrences, and progressive renal damage.^[3] The most common bacterial pathogens causing

UTIs include Gram-negative organisms such as *Escherichia coli*, *Klebsiella spp.*, *Enterobacter spp.*, and *Proteus spp.* Common Gram-positive bacteria which can cause UTIs include *Enterococcus spp.* and *Staphylococcus aureus*.^[3] Frequent and irrational antimicrobial use can lead to the development of antimicrobial drug resistance, which is a major problem in therapeutics. Due to the increasing incidence of antimicrobial drug resistance among uropathogens, it is important to identify the organisms causing UTI and determine their sensitivity to drugs. The objective of this study was to investigate the profile of

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How to cite this article: Rezia RA, Vijendra R, Gopi A. Uropathogens causing urinary tract infection in adults in a tertiary care hospital. *J Pharmacol Pharmacother* 2020;11:119-24.

Received: 30-06-2020

Revised: 01-09-2020

Accepted: 03-10-2020

Web Publication: 23-12-2020

Access this article online

Quick Response Code:



Website:
www.jpharmacol.com

DOI:
10.4103/jpp.JPP_100_20

uropathogens causing UTI in adult individuals and to assess their antimicrobial susceptibility pattern, clinical course, and outcome in Kempegowda Institute of Medical Sciences, Bangalore, a tertiary care hospital, and research center in South India.

MATERIALS AND METHODS

This study was a prospective, observational clinical study conducted in the Department of Microbiology at Kempegowda Institute of Medical Sciences and Research Centre, Bangalore. The participants were followed up in their respective inpatient and outpatient settings. The study was conducted between July 2019 and December 2019 after approval by the Institutional ethics committee (IEC) (Approval No. KIMS/IEC/A7-2019). The study was registered with Clinical Trial Registry-India (CTRI/2019/11/022156). All the participants with suspected UTI ($n = 1445$), who required urine culture and sensitivity during the study period, underwent screening for eligibility.

Sample size calculation: During the 6-month study period, a total of 1445 participants who had symptoms of UTI and who underwent urine culture were assessed for eligibility, and 549 participants were included for analysis. This is a cross-sectional observational study, and nonprobability convenience sampling was done.

The participants were followed up during their course in the hospital. The treatment was based on the culture and sensitivity report, and the clinical outcome was assessed based on the resolution of symptoms of UTI.

Inclusion criteria included participants aged ≥ 18 years belonging to both genders whose urine culture showed significant growth of one or more organisms ($n = 549$).

Table 1: Demographic profile and case distribution

Parameters	<i>n</i> (%)
Age (years)*, #	
Adults (18- 60 years)	328 (59.74)
Elderly (>60 years)	221 (40.26)
Gender	
Male	220 (40)
Female	329 (60)
Distribution of the cases	
Total culture positive	549
MDR	29 (5.28)
<i>Candida</i> species	12 (2.19)
Mixed infections (>1 organism)	17 (3.09)
Source of the cases	
Outpatients	285 (52)
Inpatients	178 (32.4)
ICUs	54 (9.8)
Postoperative surgical wards	32 (5.8)
Source of the urine specimen	
Fresh midstream urine	452 (82.3)
Urinary catheter	97 (17.6)

*Age of the participants ranged from 21 years to 99 years, #Mean age 53.73 $\pm$ 18.66 years. MDR=Multidrug resistant, ICU=Intensive care unit

Participants whose urine samples were contaminated, urine cultures showing no growth (after 24 h), participants <18 years of age, and urine samples showing insignificant bacteriuria were excluded from the study.

Fresh midstream clean-catch urine samples and samples from the urinary catheter were collected in sterile containers under aseptic precautions from all eligible participants. The samples were streaked onto 5% sheep blood agar and MacConkey agar plates using a calibrated loop, delivering 0.01 ml of the sample. The plates were incubated at 37°C overnight and observed for growth the next day. All plates that had significant growth ($>10^5$ CFU/ml) as per the Kass count were subjected to antimicrobial sensitivity testing. For *Staphylococcus aureus*, even <10 colonies (10 CFU/ml) were subjected to antimicrobial sensitivity testing. After identification of the organisms, testing was done for the isolates using Kirby–Bauer disc diffusion methods on Mueller–Hinton agar for their antimicrobial sensitivity and results were interpreted as per the National Committee for Clinical Laboratory Standards guidelines.

RESULTS

Urine samples of 549 participants showed growth of organisms. Table 1 shows the demographic profile and case distribution. Figure 1 shows the STROBE flow diagram.

The reasons for hospitalization in the intensive care unit were for ischemic heart disease ($n = 4$), urosepsis ($n = 17$), chronic kidney disease with suspected UTI ($n = 11$), pulmonary edema ($n = 1$), acute kidney injury ($n = 19$), and pneumonia ($n = 2$).

Most inpatients were hospitalized for fever with chills and suspected UTI ($n = 152$). The other reasons were for acute gastroenteritis ($n = 1$), acute pancreatitis ($n = 5$), benign prostatic hyperplasia ($n = 10$), hematuria ($n = 7$), and diabetic foot ($n = 3$).

Urine culture for the outpatients was done in cases of suspected UTI ($n = 285$).

Table 2: Profile of culture positive uropathogens

Culture positive organisms ($n=520$)	<i>n</i> (%)
<i>Escherichia coli</i>	200 (38.5)
<i>Enterococcus</i> spp. #	91 (17.5)
<i>Klebsiella</i> spp. *	136 (26.15)
<i>Proteus</i> spp. #	7 (1.35)
<i>Acinetobacter</i> spp. †	18 (3.5)
<i>Pseudomonas aeruginosa</i>	35 (6.7)
<i>Staphylococcus aureus</i>	2 (0.4)
<i>Citrobacter</i> spp. †	2 (0.4)
<i>Enterobacter</i> spp. †	15 (2.9)
CoNS	12 (2.3)
NFGNB	2 (0.4)

**Klebsiella pneumoniae*: $n=82$, *Klebsiella oxytoca*: $n=54$; #*Proteus mirabilis*: $n=6$, *Proteus vulgaris*: $n=1$, †Speciation was not conducted. NFGNB=Nonfermenting Gram-negative bacilli, CoNS=Coagulase-negative *Staphylococcus aureus*

Urine culture testing was also done in postoperative patients with suspected UTI ($n = 32$).

Table 2 shows the profile of culture-positive uropathogens.

Multidrug resistance (MDR) uropathogens were seen with *Klebsiella pneumoniae* ($n = 19$, 3.6%), *E. coli* ($n = 5$, 0.9%), *Klebsiella oxytoca* ($n = 2$, 0.4%), *Acinetobacter spp.*,

Enterococcus spp., and *Pseudomonas aeruginosa* in one case each (0.2%).

Mixed infections were seen with *E. coli* ($n = 7$), *K. pneumoniae* ($n = 1$), *P. aeruginosa* ($n = 1$), *Acinetobacter spp.* ($n = 1$), *Enterococcus spp.* ($n = 1$), *Enterobacter spp.* ($n = 1$), *K. oxytoca* ($n = 1$), *Citrobacter spp.* ($n = 1$), *Candida tropicalis* ($n = 2$), *Proteus mirabilis* ($n = 1$), and *Candida albicans* ($n = 2$).

Table 3 gives information about culture-positive uropathogens and the resistance pattern.

Table 4 depicts culture-positive isolates and sensitivity pattern.

Culture-positive isolates also showed candida species. *C. albicans* was seen in four (33%) and isolate was obtained from suspected UTI ($n = 1$), sepsis ($n = 1$), aspiration pneumonia ($n = 1$), and pulmonary edema ($n = 1$); *C. tropicalis* in three (25%) obtained from patients with pneumonia ($n = 1$) and suspected UTI ($n = 2$); *Candida dubliniensis* seen in 2 (17%) obtained from diabetic foot ($n = 1$) and lower respiratory tract infection ($n = 1$); *Candida nonalbicans* in two (17%) seen in patients with suspected UTI ($n = 2$); and *Candida glabrata* seen in one (8%) with chronic liver disease ($n = 1$).

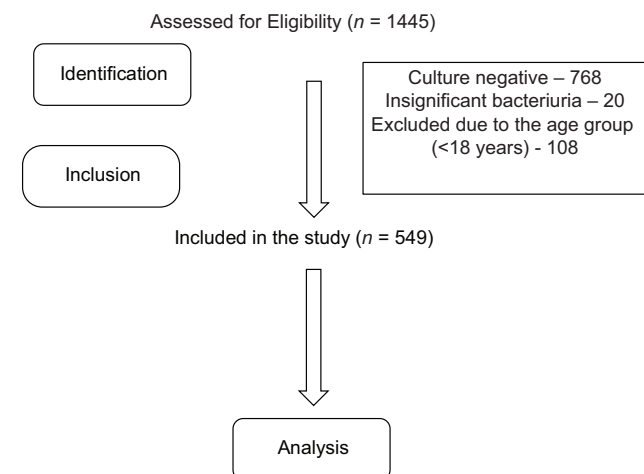


Figure 1: STROBE flow diagram

Table 3: Culture-positive uropathogens and resistance pattern

Organisms	Resistance shown to antimicrobial agents
<i>Escherichia coli</i> ($n=200$)	β -lactam antibiotics* ($n=139$) Fluoroquinolones [#] ($n=61$)
<i>Enterococcus spp.</i> ($n=91$)	β -lactam antibiotics* ($n=52$) Lincosamide [†] ($n=7$) Aminoglycoside [‡] ($n=32$)
<i>Klebsiella spp.</i> ($n=136$)	β -lactam antibiotics* ($n=98$) Fluoroquinolones [#] ($n=38$)
<i>Proteus spp.</i> ($n=7$)	β -lactam antibiotics* ($n=3$) Urinary antiseptics [§] ($n=4$)
<i>Acinetobacter spp.</i> ($n=18$)	β -lactam antibiotics* ($n=11$) Urinary antiseptics [§] ($n=7$)
<i>Pseudomonas aeruginosa</i> ($n=35$)	β -lactam antibiotics* ($n=21$) Aminoglycoside [‡] ($n=14$)
<i>Staphylococcus aureus</i> ($n=2$)	β -lactam antibiotics* ($n=1$) Macrolides [¶] ($n=1$)
<i>Citrobacter spp.</i> ($n=2$)	β -lactam antibiotics* ($n=1$) Urinary antiseptics [§] ($n=1$)
<i>Enterobacter spp.</i> ($n=15$)	β -lactam antibiotics* ($n=9$) Urinary antiseptics [§] ($n=6$)
CONS ($n=12$)	β -lactam antibiotics* ($n=6$) Fluoroquinolones [#] ($n=3$) Macrolides [¶] ($n=3$)
NFGNB ($n=2$)	β -lactam antibiotics* ($n=2$)

*Amoxicillin, ampicillin, cefoperazone, cefepime, cefoxitin, cefuroxime, ceftriaxone, cefexime, ceftazidime, piperacillin + tazobactam,

[#]Ciprofloxacin, levofloxacin, [†]Clindamycin, [‡]Gentamicin, amikacin,

[§]Nitrofurantoin, nalidixic acid, [¶]Erythromycin. NFGNB=Nonfermenting Gram-negative bacilli, CoNS=Coagulase-negative *Staphylococcus aureus*

Table 4: Culture-positive isolates and sensitivity pattern

Organisms	Sensitive AMAs
<i>Escherichia coli</i> ($n=200$)	Piperacillin + tazobactam ($n=110$) Meropenem ($n=50$) Amikacin ($n=25$) Netilmicin ($n=15$)
<i>Enterococcus spp.</i> ($n=91$)	Amoxicillin + clavulanic acid ($n=58$) Levofloxacin ($n=18$) Vancomycin ($n=15$)
<i>Klebsiella spp.</i> ($n=136$)	Meropenem ($n=88$) Amikacin ($n=48$)
<i>Proteus spp.</i> ($n=7$)	Piperacillin + tazobactam ($n=3$) Meropenem ($n=2$) Amikacin ($n=1$) Ciprofloxacin ($n=1$)
<i>Acinetobacter spp.</i> ($n=18$)	Tobramycin ($n=3$) Meropenem ($n=5$) Piperacillin + tazobactam ($n=10$)
<i>Pseudomonas aeruginosa</i> ($n=35$)	Tobramycin ($n=15$) Meropenem ($n=20$)
<i>Staphylococcus aureus</i> ($n=2$)	Gentamicin ($n=1$) Ciprofloxacin ($n=1$)
<i>Citrobacter spp.</i> ($n=2$)	Meropenem ($n=1$) Netilmicin ($n=1$)
<i>Enterobacter spp.</i> ($n=15$)	Meropenem ($n=8$) Tobramycin ($n=7$)
CONS ($n=12$)	Gentamicin ($n=6$) Vancomycin ($n=3$) Levofloxacin ($n=3$)
NFGNB ($n=2$)	Piperacillin + tazobactam ($n=1$) Tobramycin ($n=1$)

NFGNB=Nonfermenting Gram-negative bacilli, CoNS=Coagulase negative *Staphylococcus aureus*, AMA=Anti-mitochondrial anti-bodies

Table 5 gives information about the empirical antimicrobials used.

Empirical antimicrobials were used in 27.3% ($n = 150$), and all the empirical antimicrobials were administered through the intravenous route.

Clinical outcome

The participants responded to treatment with piperacillin + tazobactam ($n = 124$), meropenem ($n = 203$), gentamicin ($n = 7$), amoxicillin + clavulanic acid ($n = 58$), levofloxacin ($n = 21$), vancomycin ($n = 18$), amikacin ($n = 74$), tobramycin ($n = 26$), netilmicin ($n = 16$), and ciprofloxacin ($n = 2$).

MDR cases are resistant to three or more groups of antimicrobials. These cases were treated with the following antimicrobial agents – vancomycin ($n = 14$), ciprofloxacin ($n = 4$), clindamycin ($n = 5$), nitrofurantoin ($n = 3$), and co-trimoxazole ($n = 3$). Repeat urine culture was negative in all the participants, and they were discharged after they fully recovered from the UTI.

Table 6 shows the WHO priority pathogens. None of these organisms were encountered in our study.

Discussion

In developing countries, UTI contributes to the most common infection, and urine culture is needed to make a

confirmed diagnosis. Urine is the most common sample to be received in a microbiology laboratory. The pattern of antimicrobial resistance varies with different regions. Isolated uropathogens and their antimicrobial resistance are highlighted in this study. The gender distribution in our study shows a female preponderance 60% ($n = 329$) of the positive cultures, which is similar to those of other reported studies.^[5] Incidence of UTI is more in females due to the anatomy of the genitourinary system and the microflora that are present.^[6] *E. coli* (37.5%) causing UTI is seen in highest numbers in this study, followed by *Enterococcus* (17.3%), *K. pneumoniae* (12.1%), and *K. oxytoca* (10%). This is in accordance with earlier study Ranjbar *et al.* and Amin *et al.*^[7,8] *E. coli* was resistant to amoxicillin + clavulanic acid, cephalosporins, and ciprofloxacin and sensitive to meropenem, piperacillin + tazobactam, and amikacin. In a study done in Beijing during 1997–1999, around 60% of *E. coli* were resistant to ciprofloxacin.^[9] Resistance to ciprofloxacin and levofloxacin in *E. coli* reached 21.6% and 20.4%, respectively, in 2005. The resistance to antimicrobials is due to higher rate of antibiotic usage, even in the absence of a prescription. A study done in King Fahd Hospital, Saudi Arabia, showed that meropenem was 95.8% sensitive, followed by amikacin (93.7%) against extended-spectrum β -lactamase-producing *E. coli*.^[10] A study done in Kuwait showed that *Klebsiella* was responsible for 12.2% of the organisms isolated.^[11] In a study done in

Table 5: Use of empirical antimicrobials

Organism	Empirical antimicrobials ($n=150$)	Indication for use of the AMA
<i>Acinetobacter</i> spp. ($n=11$)	Ceftriaxone ($n=6$) Piperacillin + tazobactam* ($n=1$) Cefexime + ofloxacin* ($n=4$)	CKD with suspected UTI ($n=3$), diabetic foot ($n=3$) Sepsis ($n=1$) CKD with suspected UTI ($n=4$)
<i>Citrobacter</i> spp. ($n=3$)	Piperacillin + tazobactam* ($n=3$)	CKD with suspected UTI ($n=3$)
Coagulase negative <i>Staphylococcus aureus</i> (CONS) ($n=2$)	Ceftriaxone ($n=1$) Metronidazole ($n=1$)	RTA with head injury ($n=1$) Pelvic infection ($n=1$)
<i>Escherichia coli</i> ($n=51$)	Ceftriaxone ($n=13$) Cefoperazone + sulbactam* ($n=2$) Cefepime ($n=1$) Ceftazidime ($n=1$) Ciprofloxacin ($n=2$)	CKD with suspected UTI ($n=13$) Diabetes mellitus with cystitis ($n=2$) Benign prostatic hyperplasia ($n=1$) Suspected UTI ($n=1$) Sub-acute intestinal obstruction with infection ($n=2$)
	Piperacillin + tazobactam* ($n=30$) Cefotaxime ($n=2$)	CKD with suspected UTI ($n=30$) Suspected UTI ($n=2$)
<i>Enterococcus</i> spp. ($n=15$)	Ceftriaxone ($n=11$) Cefoperazone + sulbactam* ($n=3$) Cefotaxime ($n=1$)	Suspected UTI ($n=11$) Chronic liver disease ($n=3$) Fever with suspected UTI ($n=1$)
<i>Klebsiella</i> spp. ($n=66$)	Ceftriaxone ($n=33$) Levofloxacin ($n=2$) Linezolid ($n=1$) Meropenem ($n=1$) Ciprofloxacin ($n=1$) Piperacillin + tazobactam* ($n=27$) Cefoperazone + sulbactam* ($n=1$)	Fever with suspected UTI ($n=33$) COPD ($n=2$) Gluteal abscess ($n=1$) Chronic kidney disease ($n=1$) Acute pancreatitis ($n=1$) Fever with suspected UTI ($n=27$) Chronic liver disease ($n=1$)
<i>Pseudomonas aeruginosa</i> ($n=2$)	Cefotaxime ($n=1$) Piperacillin + tazobactam* ($n=1$)	Chronic liver disease ($n=1$) Chronic liver disease ($n=1$)

*FDCs. FDCs=Fixed dose combinations, COPD=Chronic obstructive pulmonary disease, CKD=Chronic kidney disease, UTI=Urinary tract infection

Table 6: World Health Organization priority pathogens^[4]

Priority 1: Critical

Acinetobacter baumannii, carbapenam-resistant
Pseudomonas aeruginosa, carbapenam-resistant
Enterobacteriaceae, carbapenam-resistant, ESBL-producing

Priority 2: High

Enterococcus faecium, vancomycin-resistant
Staphylococcus aureus, methicillin-resistant, vancomycin-intermediate and resistant
Helicobacter pylori, clarithromycin-resistant
Campylobacter spp., fluoroquinolone resistant
Salmonellae, fluoroquinolone resistant
Neisseria gonorrhoeae, cephalosporin-resistant, fluoroquinolone-resistant

Priority 3: Medium

Streptococcus pneumoniae, penicillin-nonsusceptible
Haemophilus influenzae, ampicillin-resistant
Shigella spp., fluoroquinolone-resistant

WHO lists the following organisms as priority pathogens. WHO=World Health Organization

Aligarh, India, *Klebsiella* was isolated in 22% of cultures of 920 patients with UTI.^[12] In our study, *Klebsiella* was only the third most common uropathogen, the second being *Enterococcus species*. *Klebsiella* was resistant to amoxicillin + clavulanic acid and cephalosporins and sensitive to aminoglycosides and meropenem. *Staphylococcus aureus* is a relatively infrequent urinary tract isolate in the general population. Here, *Staphylococcus* accounted for 0.4% ($n = 2$) of UTI. This is comparable to a finding obtained from a multicenter, community-based study conducted in Great Britain, where *Staphylococcus aureus* accounted for 0.5% of the isolates.^[13] A laboratory-based study conducted in France found that *Staphylococcus aureus* contributed for only 1.3% of the isolates from urine specimens submitted from the community.^[14] *S. aureus* isolated from urine was due to staphylococcal bacteremia.^[15] In our study, *S. aureus* was found sensitive to gentamicin, cefepime, and ciprofloxacin and resistant to amoxicillin + clavulanic acid, co-trimoxazole, and erythromycin. A study by Onanuga reported higher resistance of *S. aureus* to gentamicin and vancomycin.^[16]

CONCLUSION

Our study highlights the changing etiology of UTI and emergence of drug resistance. Rational use of antibiotics and improving hygienic measures helps to prevent the spread of resistant bacteria.^[17] This study shows resistance to commonly prescribed empirical antimicrobials such as amoxicillin, ampicillin, nitrofurantoin, nalidixic acid, cefepime, cefuroxime, and cefoperazone. This is due to the widespread and prolonged use of these drugs for empirical therapy. Hence, we should refrain from using these drugs as first-line empirical agents. The results of our study do not represent the general population. Treatment of UTIs is usually empirical, and urine culture is done when the patient does not respond to one or more courses of antibiotics. Hence, this study

will help to determine the emerging trends in the resistance, to formulate local antimicrobial policies, and to assist clinicians in rational choice of antibiotic therapy, thereby to prevent misuse or overuse of antimicrobials. It will also help in infection control measures and other necessary strategies to be followed. A unified antibiotic protocol is, therefore, necessary to restrict the use of antimicrobials injudiciously, to prevent resistance, and reduce the complications of UTI arising from the use of resistant drugs. A periodical study helps to know the changing susceptibility patterns of the uropathogens and to decide empirical therapy before the actual culture and sensitivity report comes.

Financial support and sponsorship

No financial support or sponsorship was obtained.

Conflicts of interest

There are no conflicts of interest.

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