

## Urinary Tract Infection (UTIs)s: Microflora, Microbial pathogenesis, host-pathogen interactions and new treatment strategies

Suresh Kumar, Akshay Kumar, Anirudh Gupta, Indu Sharma  
Nims Institute of Allied Medical Science and Technology  
NIMS University, Rajasthan, Jaipur 303121 (India)

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#### Correspondence:

E-mail: endusharma@gmail.com

### ABSTRACT

Recently, the world's problem has become in the spread of microbes and the extent of their impact on public health, especially the problem of urinary tract infections (UTIs). Urinary tract infections (UTIs) are among the most common bacterial infections and account for a significant part of the workload in clinical microbiology laboratories. Enteric bacteria (in particular, *Escherichia coli*) remain the most frequent cause of UTIs, although the distribution of pathogens that cause UTIs is changing. Therefore, the purpose of the study was to clarify the extent of infection of the urinary tract and the extent of development of these microbes in resistance to antibiotics (antibiotic susceptibility pattern). Bacterial identification was based on standard culture and biochemical characteristics of isolates. Antimicrobial susceptibility was tested by the disk diffusion method. Results. *E. coli* was the most frequent isolate throughout the experiment. It was followed by *Klebsiella pneumoniae* and *Proteus* sp., *Pseudomonas aeruginosa*, *Enterococcus* sp., and *Streptococcus agalactiae*. *E. coli* occurred more frequently in women (69.8%) than in men (61.4%). The lowest percentage of susceptibility of *E. coli* was manifested against piperacillin and ampicillin. The pathogens are isolated from hospitals and private medical centers. In this study, two hundred twenty-five urine samples were collected from various sources, where 126 patients were infected with bacteria while 99 patients had no infection. In Gram-negative bacteria, the most common bacteria were *E. coli* (55.5%) followed by *Klebsiella* spp (23.0%), *Proteus* spp (7.14%), *Pseudomonas* spp (6.34%), and *Acinetobacter* spp (3.96%). In the Gram-positive bacteria *Staphylococcus* spp (2.38%) and *Enterococcus* spp (1.58%) were found. Antibiotic susceptibilities for Gram-negative and positive bacteria were investigated according to clinical laboratory standard institute (CLSI 2019). In Gram-negative bacteria, Amikacin, Impinem, and levofloxacin was sensitive. However, in Gram-positive bacteria, levofloxacin, ofloxacin, and linezolid was sensitive. At the same time, most of the remaining antibiotics are 100% resistant to pathogenic-bacterial isolates. This study showed bacteria that are isolated from urine which causing urinary tract infection and showed resistance to almost all antibiotics, so UTI is difficult to treat by common antibiotics.

## 1. INTRODUCTION

Urinary tract infections (UTIs) represent one of the most common bacterial infections worldwide, affecting millions of individuals annually. Currently, they are one of the most

frequent diseases which occur at any ages from the neonate to adult. (Subramanian M, 2011) Approximately 50% of women will experience at least one episode of a UTI at some point in their lives, and nearly 20% to 40% of women will have recurring infections (den Heijer, 2010) (Subramanian, 2011). Infants, pregnant women (Subramanian M, 2011) (Emiru T, 2013) and the elderly, and patients with spinal cord injuries, diabetes mellitus, multiple sclerosis, AIDS/HIV, and urologic abnormalities or catheters are all at higher risk of UTIs.

Adults with lower urinary tract infections (UTIs) may experience the following symptoms like burning, pain, or discomfort when urinating, an intense, sudden need to urinate and murky, pungent urine that may contain blood. The impression that one's bladder is not quite empty like fatigue, aches, and discomfort. The ureters and kidneys are impacted by upper UTIs. Besides the aforementioned symptoms, they may result in a fever of 38 °C (100.4 °F) or greater confusion Anger, restlessness discomfort on the sides and back shivering and chills, nausea, and vomiting (McIntosh, 2024).

The symptoms of a person with urinary tract infections depend on the age and the location. Chronic and acute infection of urinary tract leads to high blood pressure, kidney damage and results in death. Chronic manifestations of the UTIs are acute and chronic pyelonephritis (a disease process resulting from the effect of infection of parenchyma and pelvis of the kidney), cystitis, renal carbuncle, urethritis and prostatitis. UTIs are 14 times more common in females than in males. In males the anatomical length of the urethra (20cm) provides a distance barrier that excludes microorganisms from the urinary bladder. Conversely, the short urethra (5cm) in females is more readily transverse by microorganisms. In women, the urethra is much shorter and very close to the anus, which is a constant source of fecal bacteria (Zilevià, 2005).

Urinary tract infection (UTI) can be caused by Gram-negative bacteria such as *Escherichia coli*, *Klebsiella* species, *Enterobacter* species, and *Proteus* species. *E.coli* is the most common organism causing both community as well as hospital-acquired UTI, (Sobel, 2010) often leading to serious secondary health issues (Kalsoom, 2012).

*Escherichia coli* is a Gram-negative, rod-shaped bacterium that typically resides in the lower intestinal tract of humans. It is also found in hospital environments and can cause nosocomial infections (Lausch, 2013). *Escherichia coli* is one of the most frequent causes of urinary tract infection (Kashef, 2010) (Hussein, 2018) and is among the most important pathogens causing bloodstream infections (Biedenbach, 2004), otitis media, wound infections, neonatal meningitis, and nosocomial pneumonia (Khan, 2002) (Kim, 2012). *Escherichia coli* is a major cause of waterborne and foodborne human diarrhea worldwide, especially in developing countries, causing several deaths, particularly in children under five-years-old (Turner, 2006).

Different factors such as age, gender, immunosuppression, and urological instrumentation can affect prevalence of UTI (Al-Jiffri, 2011). Also risk factors for UTIs include sexual activity, difficulty fully emptying the bladder, and conditions that block the urinary tract, such as kidney stones. Additionally, certain medical procedures, such as urinary catheterization, and certain medications, such as spermicides, can increase the risk of UTIs.

Detection of UTI causing pathogens and analyzing resistance pattern of these pathogens to commonly prescribed antibiotics in the clinical practice is essential and helpful in improving the efficacy of empirical treatment (Gupta, 2002).

The treatment of UTIs typically involves antibiotics, but the choice of antibiotic and duration of treatment depend on the severity and location of the infection. Resistance to antibiotics is a growing concern, and understanding the antibiotic susceptibility patterns of UTI-causing bacteria is crucial for effective treatment and prevention of complications. UTI caused by multidrug-resistant (MDR) *E. coli* increases the cost of treatment, morbidity, and mortality, especially in developing countries like India (Iqbal T, 2010) (Fink, 2012). The resistance rate of uropathogenic *E. coli* to various antibiotics has been reported as beta-lactams (57.4%), co-trimoxazole (48.5%), quinolones (74.5%), gentamicin (58.2%), amikacin (33.4%), cefuroxime (56%), and nalidixic acid (77.7%) (Afzal S, 2008) (Ramanath, 2011). However, these antibiotic sensitivity patterns may vary in different geographical locations.

UTI is the most frequent nosocomial infection and has been suffering a shift in the etiology and antimicrobial susceptibility, as common as other infection in the last decade. It is important to know the etiology and antibiotic susceptibility of infectious agents to guide the initial empirical treatment (Neto, 2003).

Distribution of urinary pathogens and their susceptibility to antibiotics varies regionally so it becomes necessary to have knowledge of distribution of these pathogens and their susceptibility to antibiotics in a particular setting (Farrell, 2003).

This thesis endeavours to comprehensively investigate the isolation, identification, and antibiotic susceptibility patterns of bacterial isolates obtained from urine samples in patients with UTIs. Through the utilization of advanced microbiological techniques and bioinformatic analyses, this research aims to elucidate the spectrum of bacterial pathogens implicated in UTIs and their associated resistance mechanisms. Moreover, by exploring potential correlations between patient characteristics, clinical outcomes, and microbial profiles, this study seeks to enhance our understanding of UTI pathogenesis and inform personalized treatment strategies.

By shedding light on the intricate dynamics of bacterial infections in the urinary tract and their response to antibiotic therapy, this thesis strives to contribute to the development of evidence-based guidelines for UTI management. Ultimately, the insights gleaned from this research have the potential to improve clinical outcomes, mitigate the emergence of antimicrobial resistance, and optimize the use of antimicrobial agents in the management of UTIs.

## Urinary Tract Infections

A urinary tract infection (UTI) is an infection of your urinary system. This type of infection can involve your:

- Urethra (urethritis).
- Kidneys (pyelonephritis).
- Bladder (cystitis).

Urine (pee) is a byproduct of your blood-filtering system, which your kidneys perform. Your kidneys create pee when they remove waste products and excess water from your blood. Pee usually moves through your urinary system without any contamination. However, bacteria can get into your urinary system, which can cause UTIs.

## What is the urinary tract?

The urinary tract makes and stores pee. It includes your:

- Kidneys. Kidneys are small, bean-shaped organs on the back of your body, above your hips. Most people have two kidneys. They filter water and waste products from your blood, which becomes pee. Common wastes include urea and creatinine.
- Ureters. Your ureters are thin tubes that carry pee from your kidneys to your bladder.
- Bladder. Your bladder is a balloon-like organ that stores pee before it leaves your body.
- Urethra. The urethra is a tube that carries pee from your bladder to the outside of your body.

## History

Urinary tract infections have been described since ancient times with the first documented description in the Ebers Papyrus dated to c. 1550 BC (Al-Achi, 2008). It was described by the Egyptians as "sending forth heat from the bladder" (Whiteman W, 1990). Effective treatment

did not occur until the development and availability of antibiotics in the 1930s before which time herbs, bloodletting and rest were recommended (Al-Achi, 2008).

### Pathophysiology

The bacteria that cause urinary tract infections typically enter the bladder via the urethra. However, infection may also occur via the blood or lymph. It is believed that the bacteria are usually transmitted to the urethra from the bowel, with females at greater risk due to their anatomy. After gaining entry to the bladder, *E. coli* are able to attach to the bladder wall and form a biofilm that resists the body's immune response (Salvatore, 2011).

*Escherichia coli* is the single most common microorganism, followed by *Klebsiella* and *Proteus* spp., to cause urinary tract infection. *Klebsiella* and *Proteus* spp., are frequently associated with stone disease. The presence of Gram-positive bacteria such as *Enterococcus* and *Staphylococcus* is increased (J, 2011).

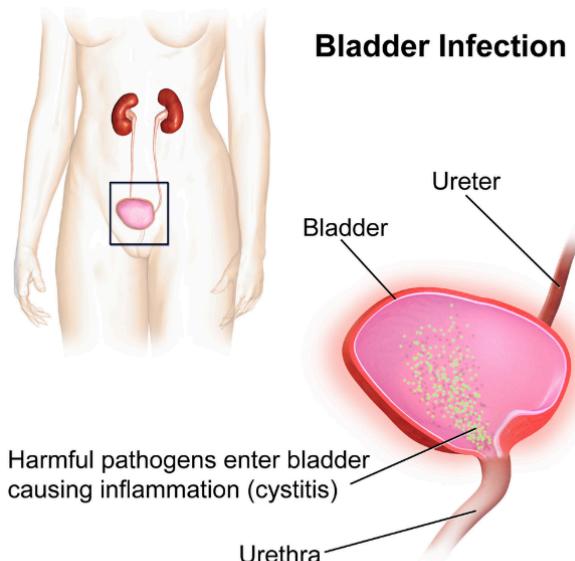


Figure 1: -Bladder Infection

The increased resistance of urinary pathogens to quinolone antibiotics has been reported worldwide and might be the consequence of overuse and misuse of quinolones. (J, 2011)

### Symptoms and Causes

Lower urinary tract infection is also referred to as a bladder infection. The most common symptoms are burning with urination and having to urinate frequently (or an urge to urinate) in the absence of vaginal discharge and significant pain (LE, 2008). These symptoms may vary from mild to severe and in healthy women last an average of six days (Colgan,

2011). Some pain above the pubic bone or in the lower back may be present. People experiencing an upper urinary tract infection, or pyelonephritis, may experience flank pain, fever, or nausea and vomiting in addition to the classic symptoms of a lower urinary tract infection (Lane DR, Diagnosis and management of urinary tract infection and pyelonephritis, 2011). Rarely, the urine may appear bloody or contain visible pus in the urine.

### **Microflora**

Microflora or the microbiota provides us with different structures and populations of microorganisms (bacteria, fungi, and archaea) inhabiting particular habitats such as soil, water, animals, plants and even humans. These organisms are firmly embedded in the functioning of an ecosystem and they enhance the stability and health of their host environment. These microorganisms dwell in diverse places including the stomach, skin surfaces and mucosal membranes of humans where they assist in digestion, immune regulation and protection against germs. In the case of human bodies for instance, the gut microflora (or gut microbiomes) is a large community of germs that assists in the digestion of food particles, synthesis of certain vitamins, and influence of immune reactions. Much in the same way, soil microflora has its roles in the decomposition of organic substances, nitrogen fixation and nutrient cycles and helps improve crop productivity and soil health too. Microflora has lately gained more interest because of its relevance in managing health as well as agriculture and environmental-related matters.

Disturbances in these microbial populations are referred to as dysbiosis, which may result in diseases and weakened stability of ecosystems hence restoration and study of microflora is an important undertaking.

Microflora in urine has been defined to be the organisms which include the bacteria.

#### **Types of Microflora in Urine.**

1. **Commensals:** Nonpathogenic bacteria inhabiting the human urinary tract. Typical examples include *Lactobacillus*, *Corynebacterium*, and *Staphylococcus* species.
2. **Pathogen In Acidic Environments:** These microorganisms are capable of affecting parts of the urinary system, such as the urinary bladder or kidneys, and causing infections. Common pathogens include *Escherichia coli* (the main cause of urinary tract infections), *Proteus*, *Klebsiella*, *Enterococcus*, *Pseudomonas* species, and some others.
3. **Yeast and Fungi:** Infection with fungal cells is not common in the urinary tract, but it can occur in patients with immunity deficiency and diabetes. *Candida* species constitute the predominant etiologic agents of infections.

4. Viruses: UTIs that are instigated by viruses are uncommon, Yet, it does happen. Of such cases, the adenovirus is a common cause.

Urine Culture and Microflora:

A urine culture is performed to establish the range of bacteria or other microbes in the urine. In the event of finding microorganisms, their pathogenicity is assessed, and suitable therapeutic measures, like antibiotic treatment, are recommended.

Normal Microflora: It could signify a state of being due to the presence of low numbers of commensal bacteria, which includes typical bacterial colonization of the lower urinary tract.

Urinary tract infections and microflora interactions:

1. Hydration: Urine becomes highly concentrated due to a lack of appropriate water intake which in turn could lead to microorganism growth.
2. Hygiene: Deficient cleanliness practices can result in contamination during urine collection thereby introducing several other types of microflora that are deemed abnormal in the urine.
3. Urinary tract infections: These infective diseases are due to incoming pathogenic bacteria in the urinary tract and such bacteria would show up in positive urine cultures.
4. Antibiotic use: The normal microbial flora composition is disrupted by antibiotics substances which cause beneficial bacteria to decrease in number and thus giving an opportunity for certain pathogens to colonize.

As such whilst the normal circumstances would see urine to be free of mf, the presence of mf in urine cushions most pathological organisms and thus points to an evidence of infection or contamination.

### **Current Treatment Regimen for Drug-Sensitive (DS) UTIs**

The current treatment regimen for drug-sensitive (DS) urinary tract infections (UTIs) involves the use of antibiotics based on local sensitivity patterns of the organisms. For adult males with UTIs, a 10- to 14-day course of antibiotics is recommended, with outpatient regimens typically including fluoroquinolones or trimethoprim-sulfamethoxazole (TMP-SMZ)

TMP-SMZ can be used for uncomplicated cystitis in areas where resistant *E. coli* numbers are less than 20%, or alternatively, a fluoroquinolone can be used for a 7–10-day treatment period. (Urinary Tract Infection (UTI) in Males Treatment & Management, n.d.)

Antibiotic prophylaxis is another approach for controlling recurrent UTIs, especially in cases of multiple rapid recurrences or when other conservative measures fail (Aggarwal, Leslie, & Lotfollahzadeh., 2024)

Various methods of antibiotic prophylaxis can be employed, such as post-coital prophylaxis for women with cystitis associated with sexual activity, self-directed therapy where patients start antibiotics at the first sign of a UTI, and long-term low-dose antibiotic prophylaxis for intractable cases (Aggarwal, Leslie, & Lotfollahzadeh., 2024)

In summary, the current treatment regimen for drug-sensitive UTIs involves the use of antibiotics like fluoroquinolones or TMP-SMZ for adult males, based on local sensitivity patterns. Antibiotic prophylaxis can also be considered for recurrent UTIs, with options like post-coital prophylaxis, self-directed therapy, and long-term low-dose prophylaxis for prevention.

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