



Bacterial diversity associated with urinary tract infections in humans

Sharma S.; Gupta V.; Yadav M.; Sain D.; Rahi R.K.; Neelam D.K.*

Department of Microbiology, JECRC University, Jaipur, Rajasthan, 303905 India

*Corresponding author E-mail: deepesh40neelam@gmail.com; deepesh.neelam@jecrcu.edu.in



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Abstract

The present study aimed to evaluate the concepts of epidemiology, uropathogenic, diagnosis, prevention, and treatment of urinary tract infections (UTI) in humans. One of the most frequent infections that affect people is UTIs. During childhood they are equally common in boys and girls, and after that, they are more common in girls. In both of the general population and hospital environment, women frequently experienced at least one UTI in their lifetime. The existence of bacteriuria and pyuria are the 2 most significant signs of UTIs. Frequent urination, pain during urination, and soreness in the side or lower back are among the main symptoms of UTI. These infections are classified into 3 primary types: asymptomatic bacteriuria, lower UTI (cystitis), and febrile upper UTI (acute pyelonephritis), because such classification supports understanding of the infection's etiology. UTI can be diagnosed through a combination of positive urine tests and/or culture and symptoms. Dipstick urinalysis is widely used due to its ease of availability and utility; however, the outcomes must be evaluated by considering the patient's pretest probability depending on the characteristics and symptoms. Most UTIs can be treated with antibiotics such as Amoxicillin, cephalexin, and doxycycline. But the Gram-positive bacterium (*Enterobacter faecalis*) exhibited great resistance to erythromycin, while the Gram-negative bacterium (*Escherichia coli*) displayed great resistance to ampicillin. So, there is an urgent need for a combination between organic treatments and antibiotics to treat the complicated UTI. For example, the plant-based treatments, such as cranberry juice, are efficient in treating the UTI and can be used as an alternative to combating the bacteria that cause UTI.

Keywords: Bacteriuria, Pyuria, *Escherichia coli*, *Enterobacter faecalis*, Dipstick urinalysis



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1. Introduction

Nowadays, UTIs are still fairly common. Up to 50 % of women claim to have experienced at least one UTI throughout their lives ([Al-Shaheen *et al.*, 2022](#)), and 30-40 % will have recurring UTIs (rUTIs) ([Kwok *et al.*, 2022](#)). Cystitis (lower UTI) and pyelonephritis (upper UTI) are the two possible manifestations of UTI, and both can be categorized as complicated or uncomplicated ([Kodner and Gupton, 2010](#)). An underlying disease and/or the structural abnormalities of the urinary tract that is connected to a complicated UTI can both increase the risk of infection and treatments failure. Uncomplicated UTIs are rare; however, the community-acquired cases of cystitis and pyelonephritis in those people who are otherwise fit or healthy people but have the potential to develop into more serious conditions, need extra care ([Aydin *et al.*, 2015](#)). More than two uncomplicated UTI episodes in the previous six months or greater than three in the previous twelve months, as confirmed by culture, are the general definitions of recurrent UTIs ([Epp *et al.*, 2010](#); [Nosseir *et al.*, 2012](#)). By the age of thirty, one in every two women is expected to have a UTI, where 30 % of them will experience an infection recurrence within 6 months, despite of antibiotic therapy ([Morris *et al.*, 2023](#)). The recurrent UTIs are linked to severe morbidity, a decline in quality of life, and a subsequent financial burden in the healthcare system ([Renard *et al.*, 2015](#)). UTI is an inflammatory reaction at the urothelium level. Bacteriuria, or the presence of bacteria in the urine, and pyuria, or the presence of white blood cells in the urine, are virtually invariably linked to UTI. Bacteriuria can exist without pyuria, which may be caused by contamination from bacteria or due to aseptic urine collection techniques. On the other hand, pyuria, which can signify an inflammatory process of the urothelium such as a urinary stone or cancer, can exist without bacteriuria ([Abou-Heidar *et al.*, 2019](#)).

Due to its ability to connect to the uroepithelium through the utilization of adhesins, the

Enterobacterales order is the most frequent etiological factor of UTIs ([Nas *et al.*, 2019](#)). In many countries, *E. coli* is the most prevalent bacterium linked to UTIs in both community-acquired and hospital-acquired ([Gajdacs *et al.*, 2019](#)). Additionally, there may be other pathogens, including *Enterococcus* sp., *Klebsiella* sp., *Enterobacter* sp., *Citrobacter* sp., *Proteus* sp., *Morganella* sp., *Providencia* sp., and *Staphylococcus saprophyticus* ([Gajdacs and Urban, 2019](#)). One of the biggest threats to public health is the spread and growth of antibiotic-resistant bacteria. The *Enterobacteriaceae* in particular are resistant to antibiotics, which can be fatal at high dosages and have different chemical structures and modes of action ([Gajdacs, 2019](#); [Odongo *et al.*, 2020](#)).

Cranberry supplements can help prevent UTIs that produce symptoms in children who have UTIs, women who have UTIs and persons who have undergone a bladder intervention ([Williams *et al.*, 2023](#)). One technique that has been suggested to reduce UTI is urinary alkalization ([Abou-Heidar *et al.*, 2019](#)). Probiotic *Lactobacillus* strains are both safe and effective in protecting the adult females from UTIs. However, because a small number of patients provided information for this meta-analysis, additional randomized clinical trials (RCTs) are necessary before a firm recommendation can be given ([Grin *et al.*, 2013](#)). UTIs have a severe negative impact on the person's physical and mental health. More than half of UTI patients experiences clinical depressions, and 38.5 % expresses anxiety; with a significant improvement in the quality of life after appropriate prophylaxis and treatment ([Renard *et al.*, 2015](#)). The objective of the study was to provide information related to the epidemiology, uropathogenic, diagnosis, prevention, and treatments of UTIs.

2. Types and symptoms of UTIs

UTIs are characterized as lower (bladder) and upper (pyelonephritis), as well as uncomplicated and

complicated, respectively. The results of urine culture and urinary symptoms have shown quantities of a recognized uropathogen above the specific threshold level “often >1,000 cfu/ ml of urine” ([Rubin *et al.*, 1992](#)), “but threshold as low as 100 cfu/ ml and as high as 100,000 cfu/ ml have been also employed” ([Warren *et al.*, 1999](#)), which are combined to diagnose UTI.

2.1. Asymptomatic bacteriuria: is defined as the presence of 100,000 cfu/ ml in a female patient without symptoms; however, if a person has expressed symptoms, about 100 cfu/ ml is all that is required to make the diagnosis. Asymptomatic bacteriuria is more likely to occur after sexual activity and as the people age ([Foxman, 2010](#)).

2.2. Acute urethral syndrome: is characterized by symptoms of dysuria, frequency, or pyuria without a considerable amount of bacteriuria, frequently associated with urethritis or vaginitis ([Salvatore *et al.*, 2011](#)). Acute urethral syndrome commonly occurs in female patients who have UTI symptoms but have negative urine cultures, and don't improve even after treatment with antibiotics.

2.3. Cystitis: is the most typical type of UTI, which is an infection of the bladder. Urgency, dysuria, frequency, occasionally suprapubic discomfort, haematuria, and cloudy or offensive urine are typical symptoms ([Salvatore *et al.*, 2011](#)). Clinical analysis of UTI provides few challenges when these typical signs are present. Systemic symptoms including nausea, fever, and vomiting may also be observed ([Sheerin, 2011](#)).

2.4. Urethritis: Dysuria and urethral discharge are the typical symptoms of urethritis, though it is frequently asymptomatic ([Salvatore *et al.*, 2011](#)).

2.5. Acute pyelonephritis: is an infection of the pelvic lining and renal parenchyma that is frequently accompanied by flank discomfort and fever ([Salvatore *et al.*, 2011](#)). While the bacteria that cause infection typically enter the kidney through the ascending path, only 50 % of the cases have symptoms of cystitis.

Systemic symptoms such as rigors, vomiting, septic shock, and fever are frequent, and local symptoms like haematuria and loin pain may be common symptoms of cystitis ([Sheerin, 2011](#)).

2.6. Prostatitis: is the most frequent recurrent UTI in men and can be either acute or chronic, depending on how long the symptoms last ([Grabe *et al.*, 2015](#)). Scrotal or perineal pain, dysuria, frequency, and urgency are typical symptoms. Although more chronic presentations may happen in the absence of infection, this symptoms combination typically suggests an infection ([Sheerin, 2011](#)).

2.7. Idiopathic interstitial cystitis: develops when there is no identified cause. It appears as debilitating and severe lower urinary tract symptoms ([Sheerin, 2011](#)).

2.8. Sterile pyuria: is white blood cells found in urine (without or with symptoms) in the absence of an identified uropathogen. Infections such as urethritis or infections caused by a fastidious bacterium must be examined. Patients must be transferred for urological evaluations if their pyuria doesn't go away to rule out other potential causes, including urinary tract stones or cancer ([Sheerin, 2011](#)).

2.9. A recurrent UTI: is a severe UTI that returns after a prior one has resolved. Reinfections or relapses can both cause recurrent UTIs. Additionally, a recurrence can be defined if the same bacteria from the initial infection are isolated following sufficient antibiotic treatment. This bacterium is typically drug-resistant. On the other hand, reinfection is identified when a second infection has been discovered after efficient antibiotic treatment and an additional negative urine culture is obtained. This is typically drug-susceptible and can be brought on by either the same bacterium that caused it during the first two weeks following therapy or a different one ([Franco, 2005](#)). The majority of cystourethritis relapses are brought on by reinfection.

2.10. Common symptoms of UTIs: include burning pain, dysuria, urgency, frequency, nocturia,

bacteriuria, pyuria, frequent urination, decreased urine production, urinary incontinence, low back pain, lower abdominal pain, and change in the urine smell among the symptoms (Fig.1) ([Malterud and Baerheim, 1999](#)). UTI incidence rises with sexual and age activity ([Stapleton, 1999](#)).

- **Dysuria:** Experiencing pain during urination, burning sensation, or discomfort.
- **Urgency:** An uncontrollable need to urinate caused by an involuntary constriction of the bladder muscles.
- **Frequency:** Having frequent and excessive amounts of urination.

- **Nocturia:** A person is frequently needs to urinate during the night due to a bladder infection or UTI.
- **Bacteriuria:** The existence of bacteria in the urine is referred to as bacteriuria, and substantial bacteriuria is defined as having $>10^5$ bacterial colonies/ ml of urine.
- **Pyuria:** Pus cells (WBCs) are seen in the urine.
- **Urinary incontinence:** Lack of bladder control, where a small amount of urine leaks out that is caused by sneezing, coughing, and/ or laughing ([Kaur and Kaur, 2021](#)).

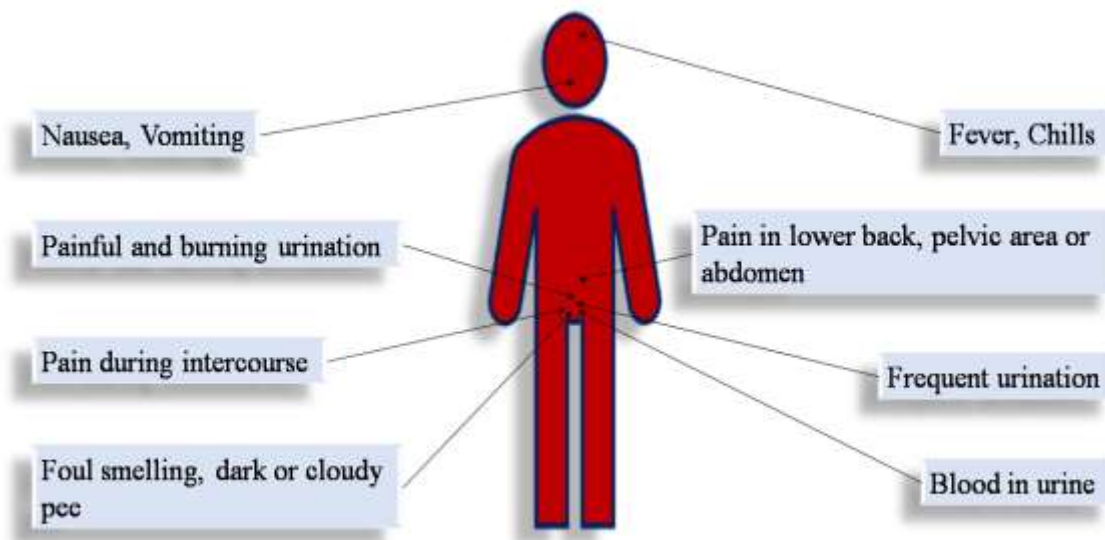


Fig. 1: Common symptoms of a urinary tract infection

3. Bacterial pathogens and causes of UTIs

Urine is often sterile. It does contain waste materials, fluids, and salts but is generally free of

viruses, fungi, and bacteria. When microscopic organisms mainly bacteria from the digestive system stick to the urethral opening and start to grow, an infection arises. The majority of infections are caused

by the same bacterial genera, including *E. coli*, which usually occurs in the intestines ([Komala and Kumar, 2013](#)). *Aerococcus urinae* and *Aerococcus sanguincola* are the two species of Aerococci that are most frequently responsible for UTIs. UTIs have rarely been linked to *Aerococcus viridans* ([Mohan *et al.*, 2017](#)). Gram-negative bacteria from the gut flora are the causes of UTIs. Microorganisms that have been shown to independently cause UTI are known as primary uropathogens. Primary uropathogens include the Gram-negative pathogens such as *E. coli* (the model bacterium used in UTI studies that accounts for 70-95 % of the uncomplicated UTIs), *K. pneumoniae*, *Proteus mirabilis* (2-5 % of uncomplicated UTIs; however, the percentage rises in individuals with complicated conditions and it could be associated with the development of struvite stones). The Gram-positive pathogens include *E. faecalis* (it can simply produce un-complicate sporadic UTIs; however, it is also linked to catheter-associated infections and transplants), and *Staphylococcus saprophyticus* (uncomplicated UTIs account for 5-10 % of cases; particularly in young, sexually active women) ([Koves and Wullt, 2016](#)).

Secondary uropathogens are more common as colonizers of the urethral flora and have a decreased ability for causing diseases. These secondary uropathogens include Gram-positive pathogens such as *Staphylococcus aureus* (mainly in immunocompromised persons, and may cause hematogenous UTIs), Gram-negative pathogens such as *Providencia stuartii*, *Serratia marcescens*, *Citrobacter* sp. and *Enterobacter cloacae* (low-virulence, uncommon pathogens that are typically detected in those persons with poor health or compromised conditions), *Pseudomonas aeruginosa* (typically found in the hospital-acquired or complicated UTIs), and other pathogens such as *Candida* sp. (that is typically related with immunosuppression or following antibiotic therapy, thus producing ecological disruptions) ([Koves and Wullt, 2016](#)).

Urethritis is primarily a disease caused by *Trichomonas vaginalis*, *Chlamydia trachomatis*, *Mycoplasma genitalium*, and *Neisseria gonorrhoeae* that can be transmitted sexually ([Sheerin, 2011](#)). *E. coli*, which is present in 70-95 % of the cases, is the most common uropathogen that is responsible for both spontaneous and recurrent UTI. Other causal microorganisms include *K. pneumoniae*, *P. mirabilis* ([Kodner and Gupton, 2010](#)), and *Staphylococcus saprophyticus* (10-15 % of cases) ([Nosseir *et al.*, 2012](#)). A significant proportion of *E. coli* infections of the urinary tract and bloodstream are caused by the four *E. coli* sequence types (STs) 69, 73, 95, and 131, and each of these STs has a distinct antibiotic susceptibility ([Doumith *et al.*, 2015](#)). Small quantity of the original uropathogenic strain may continue to live in the host after a UTI resolves and causes infection stones (like *P. mirabilis*) ([Gillenwater *et al.*, 2002](#)). In a previous study conducted on 1745 patients, a negative bacterial growth was detected in 1204 (69 %), and a positive bacterial growth was detected in 541 (31 %). Among the 541 patients who tested positive, 216 (39.9 %) were men and 325 (60 %) were women. The group with the highest percentage of positive patients was the older people (>61 years). There were 425 (78.5 %) Gram-negative pathogenic strains, 107 (19.7 %) Gram-positive pathogenic strains, and 9 (1.7 %) *Candida* spp. *E. coli* is the Gram-negative strain that is mostly isolated (53.5 %), while *E. faecalis* is the most prevalent Gram-positive strain with a frequency of 12.9 % ([Folliero *et al.*, 2020](#)).

4. Factors responsible for developing urinary tract infections

Using urinary catheters is a major cause of UTIs. Another risk factor is the urethral manipulation. After kidney transplantation, UTIs are quite prevalent, mainly due to vesicoureteral reflux and immunosuppressive medications. Diabetes mellitus and the usage of antibiotics against the resistant bacterial strains are additional risk factors ([Bono *et al.*, 2023](#)). Several other risk factors raise the possibility of bacterial entry into the bladder including:

4.1. Infrequent urination: Bacteria can multiply and establish a stronger hold in the bladder because they spend more time there.

4.2. Incomplete urination: An excess of urine remains in the bladder, where every void and bacteria are not eliminated from the bladder ([Komala and Kumar, 2013](#)).

4.3. Diabetes: Recurrent UTIs and the occurrence of asymptomatic bacteriuria are also associated with diabetes ([Geerlings *et al.*, 2000a](#)). In a nationwide investigation involving 589 women between the ages of 18 and 75 who suffered from Type 1 or Type 2 diabetes, the same risk factors as those in younger women (*i.e.*, sexual activity and use of oral contraceptives) for Type 1 diabetes and the existence of asymptomatic bacteriuria for Type 2 diabetes, have increased the risk of developing a symptomatic UTI ([Geerlings *et al.*, 2000b](#)).

4.4. Personal hygiene: UTIs can result from fecal contamination of the perineum, which raises the risk of coliform bacteria in the vagina and the area around the urethra.

4.5. Sexual activity: In addition to increasing the risk of infection, trauma to the urethra and its surrounding tissue can push the microorganisms into the urethra mechanically ([Komala and Kumar, 2013](#)).

4.6. Pregnancy: Pregnancy-related UTI development is associated with ureteric stasis, which impairs emptying the bladder and is associated with raised urine pH, raised postvoid residual urine quantity, and vesicoureteral reflux ([Krcmery *et al.*, 2001](#)).

4.7. Genetic factors: According to a previous research conducted by [Raz *et al.*, \(2001\)](#), women who have a first-degree relative with a history of UTI are more likely to experience pyelonephritis and recurrent UTI. This lends credence to the theory that defensive mechanisms in the urogenital tract are influenced by genetics.

4.8. Menopause: In women, the chance of UTIs rises with age. Around 10-15 % of women in their 65-70s and 20-50 % of women in their 80s experience bacteriuria. The two main causes of recurrent UTIs in older hospitalized women are urethral catheterization and functional status deterioration ([Minardi *et al.*, 2011](#)).

4.9. Immunosuppression: This condition, which impairs a person's capacity to fight back against infections, has several etiological factors ([Komala and Kumar, 2013](#)).

5. Risk factors for developing UTIs

5.1. UTIs in women: One of the most common infections that affect women at different stages of life is UTIs, due to the structure of the female lower urinary system and its proximity to the reproductive organs ([Czajkowski *et al.*, 2021](#)). In all age categories, women experience UTIs at a higher rate than men do ([Rowe and Juthani-Mehta, 2013](#)). Because the female urethra is shorter than the male, the bacteria cannot enter the body as far ([Czajkowski *et al.*, 2021](#)). Between 30 % and 50 % of women over age of 50 are thought to be affected by UTIs. Every other woman is expected to have experienced a UTI at least once in her lifetime, with 10-60 % of all women reporting symptoms of a UTI at some point. As people age increases, their risks of infection rises ([Czajkowski *et al.*, 2021](#)). The pregnant women frequently experience both acute and asymptomatic bacteriuria because of several physiological changes that occur during pregnancy. The urinary tract infection is caused by a lack of diagnosis during pregnancy, which increases the possibility of infection and places the pregnant women at risk for severe complications. According to their conclusion, the infection occurs at a rate of 56 % among pregnant women, with the rate increasing to 50 % during the second trimester ([Vasudevan, 2014](#)). Young and sexually active women are more likely to get a UTI; reporting incidence rates that range from 0.5 to 0.7/person/year. More than 10 % of women over 65 have been observed to have a UTI in the previous 12 months. For women around the age of 85, this

percentage rises to about 30 %. The incidence of UTI in a huge prospective cohort study of postmenopausal women who live in the communities is 0.07/person/year and 0.12/person/year among the older women with diabetes ([Rowe and Juthani-Mehta, 2013](#)). Asymptomatic bacteriuria raises the possibility of getting symptoms of UTIs. About 8 % of the females having asymptomatic bacteriuria have developed symptoms UTIs within a week ([Hooton *et al.*, 2000](#)). Recurrent UTIs are most frequently observed in the females and young girls and are linked to ascending colonization through the fecal flora. The growth of bacteria in the distal urethra and vagina leads to infection, which then rises in the bladder ([Epp *et al.*, 2010](#)). For women, recurrent UTIs are those that occur at least twice in 6 months or at least three times in 12 months. An estimated 25-50 % of the infections in women are thought to be recurrent UTIs ([Geerlings, 2016](#)). The susceptible patients may still have bacteria reservoirs in their gastrointestinal system and vagina. According to certain theories, the household contacts may potentially serve as reservoirs for re-colonization of those UTI susceptible persons ([Johnson and Clabots, 2006](#)).

5.2. UTIs in men: The reported incidence of UTI in those young males between the ages of 18 and 24 is 0.01 cases/ per person/ year, which is predicted to rise to 0.05 / person/ year in men of age 65-74 years ([Rowe and Juthani-Mehta, 2013](#)). Different treatment protocols apply to treat the male UTIs. The Strategy for the Control of Antimicrobial Resistance in Ireland (SARI), the National Institute for Health and Care Excellence (NICE), and the Intercollegiate Guideline Network (SIGN) in Scotland, along with the National Institute for Health and Care Excellence (NICE) in the UK, recommend trimethoprim or nitrofurantoin as the initial line of treatment for male UTIs for seven days. For the chronic kidney disease (defined by national cut-off points), the guidelines suggest pivmecillinam or ciprofloxacin. Based on the culture results, the usage of second-line antibiotics has been evaluated, considering any alternative diagnoses. This is comparable to Denmark, Sweden, Norway, and

Germany, where pivmecillinam is likewise the first-line of treatment, along with trimethoprim and nitrofurantoin ([Farrell *et al.*, 2021](#)). The lower urinary tract irritative symptoms such as frequency, urgency, nocturia, and dysuria are typical male UTI symptoms ([Jones *et al.*, 2010](#)). If these symptoms are not promptly and appropriately treated, they may develop pyelonephritis (kidney infection), which is characterized by fever and soreness in the costovertebral angle ([Schaeffer and Nicolle, 2016](#)).

5.3. UTIs in children: One of the most prevalent bacterial diseases in children is UTIs. During the first year of life, they are equally common in boys and girls, and after that, they are more common in girls ([Tullus and Shaikh, 2020](#)). According to a 2008 systematic review, 7 % of children between the ages of 2 and 24 months who have expressed a fever without a known cause and 8 % of children between the ages of 2 and 19 months who displayed potential urinary symptoms had a UTI diagnosis ([Shaikh *et al.*, 2008](#)). Between the ages of one month and 11 years, up to 8 % of children will have at least one UTI, and in the first 6 to 12 months following an initial UTI, up to 30 % of infants and children will get recurrent infections. Every year, over 1.5 million kid ambulatory visits for UTIs occur in the US ([Millner and Becknell, 2019](#)). Beyond sexual orientation, several additional important risk factors for UTIs have been reported including congenital abnormalities of the kidneys and urinary tract (CAKUT), bladder-bowel dysfunction (BBD) that involves vesicoureteral reflux (VUR), and the status of circumcision in young boys ([Mattoo *et al.*, 2021](#)). In 2013, 630 million Dollars were spent on UTI control and treatment across the US healthcare system ([Millner and Becknell, 2019](#)). UTIs may cause in long-term renal damage, such as irreversible kidney scarring, in addition to short-term morbidities, including dysuria, flank discomfort, and fever ([Oliveira and Mak, 2020](#)).

6. Diagnosis of UTIs

Diagnosis of an UTI depends on the occurrence of upper urinary tract symptoms in complicated or

pyelonephritis UTI (*i.e.*, chills, fever, malaise, allograft pain, or hemodynamic instability), and lower urinary tract symptoms in cystitis (*i.e.*, urinary urgency or suprapubic pain, dysuria), as well as a significant quantitative number of bacteria in a urine specimen that has been collected appropriately ([Goldman and Julian, 2019](#)). UTIs can be more precisely diagnosed by the physicians with the use of a urine sample microscopic analysis and urine dipstick urinalysis results, which can alter the pretest probability of UTIs ([Chu and Lowder, 2018](#)). If a UTI is suspected, urine analysis and a culture should be performed, and blood cultures should be taken if the systemic symptoms are severe. When UTI is present, urine microscopy should reveal a pyuria, which is defined as the existence of more than 10 white blood cells/ ml of urine (WBC/ml); in addition, the urine dipstick analysis must be typically positive for leukocyte esterase, nitrites, and blood protein ([Suarez-Fernandez *et al.*, 2021](#)).

6.1. Urine culture: Urine culture is the most common method for UTI diagnosis and is thought to be the most suitable screening test for asymptomatic bacteriuria in pregnancy. Although catheterized specimens are occasionally obtained, clean midstream urine samples are often taken. Between cleaning and not cleaning before midstream urine collection, probably there won't be any difference in contamination ([LaRocco *et al.*, 2016](#)). Using the right growth thresholds to differentiate between an infection and colonization is essential for an accurate culture-based diagnosis of UTIs. Asymptomatic bacteriuria can produce a growth quantity that mimics infection and defies the culture-based classifications. In order for a threshold to be established, this depends on several criteria, such as the type of specimen, the age of the patient, and possibly even the type of the microorganism. The majority of laboratories that serve adult populations only define significance using a threshold value of $\geq 10^5$ cfu/ ml ([Doern and Richardson, 2016](#)).

6.2. Microscopic urinalysis: Manual or an automated light microscopy is used to perform microscopic urinalysis. The presence of bacteria (bacteriuria,

defined as 15 bacterial cells/ high power field) or leukocytes (pyuria, defined as >5 -10 leukocytes/ hpf) in the urine can be useful in the detection of UTI. A UTI may also be indicated by hematuria along with bacteriuria or pyuria. Squamous epithelial cells can occasionally be a sign of contamination, and WBC castings can be a sign of infection and/ or inflammation of the upper urinary tract. Both bacteriuria and pyuria can be useful in determining the presence of an infection, but the cut-off definitions affect the specificity and sensitivity of the test ([Chu and Lowder, 2018](#)). The absence of pyuria with bacteriuria may indicate contamination or colonization instead of an active infection ([Stamm, 1983](#)). However, bacteriuria regularly has greater specificity and sensitivity than pyuria, and it may be more accurate to diagnose a UTI in the context of clinical symptoms and dipstick urine results. Dipstick analysis and microscopic urinalysis are probably comparable in women exhibiting signs of UTI ([Lammers *et al.*, 2001](#)). Microscopic examination of bacteriurias is useful for screening and diagnosing UTI in terms of the person's clinical presentation, although it will not be based on the test results only ([Kayalp *et al.*, 2013](#)).

6.3. Dipstick urinalysis: Leukocyte esterase and nitrites tests are two quick urine dipstick tests that are helpful for early UTI detection ([Rangaiahagari *et al.*, 2015](#)). Dipstick nitrite test is very specific and sensitive when performed correctly using the first urine in the morning, because it takes at least four hours for the microorganisms to convert nitrate to nitrite in the bladder ([Marahatta *et al.*, 2011](#)). Urine dipsticks are quick and inexpensive to perform and they are effective and widely used tests ([Baral and Nepal, 2017](#)). Therefore, there is no strong link between a substantial bacteriuria and the nitrite test in urine samples collected from patients with draining catheters or random specimens collected at any time. False positive results are frequently the consequence of improper specimen collection or storage, which can lead to contamination and post-collection bacterial growth. On the other hand, false-negative results can be caused by urobilinogen, ascorbic acid, or low pH (<

6) (Sharma *et al.*, 2011). A very accurate indicator of bacterial UTI is the microscopic analysis of urine to detect the presence of pyuria using the nitrite test (Mohamed Ali, 2010). Metagenomics is a powerful tool used to detect the diverse microbial communities and analyzes all DNA in a urine sample to provide complete information about the condition of a patient's urinary tract microenvironment. This allows the healthcare providers to target the disease-causing microorganisms with greater accuracy, known as 'precision medicine' (Dixon *et al.*, 2020).

7. Treatment of UTIs

UTI has a significant negative impact on the quality of life for those who get it, as well as significant financial and public health costs (Kostakioti *et al.*, 2012). Antibiotics, including ampicillin, ciprofloxacin, trimethoprim-sulfamethoxazole, and others, are currently the most often prescribed treatments for UTIs (Foxman, 2010). The Gram-positive bacteria (*E. faecalis*) showed a strong resistance to erythromycin, while Gram-negative bacteria (*E. coli*) have shown a strong resistance to ampicillin (Folliero *et al.*, 2020).

Uncomplicated acute cystitis has traditionally been treated with antibiotics for seven to ten days. However, a previous research reported by Lamb, (2016) indicated that a 3-day antimicrobial treatment course is just as effective as extended treatment courses, with >90 % eradication rates. β -lactam treatments, such as first-generation amoxicillin and cephalosporins, have become less effective than the other drugs due to the development of antibiotic resistance. Recurrent UTIs can be defined as two or more UTIs in 6 months or three or more within a year. Acute self-treatment, postcoital prophylaxis, and continuous prophylaxis are methods used for preventing recurrent UTIs in women. Continuous prophylaxis techniques include using antibiotics once a day, every other night, or three nights per week (Epp *et al.*, 2010). This method has been shown to decrease recurrent UTIs by 95 %; however, it may be related to the uropathogen resistance (Lichtenberger and Hooton, 2011). The most popular antibiotics used for treatment of UTIs

and their potential negative effects are discussed as following:

7.1. Macrochantin (*i.e.*, nitrofurantoin or macrodid): Long-term usage of macrochantin may cause peripheral neuropathy and lung fibrosis and/ or scarring. This drug is generally regarded as safe (GRAS) to be used during pregnancy; except for the uncommon inherited metabolic impairments.

7.2. Bactrim (*i.e.*, Septra or sulfa/TMP): This medication should not be taken in the first trimester of pregnancy since it may reduce the efficacy of oral contraceptives.

7.3. Doxycycline, Quinolones (*i.e.*, Levofloxacin, Levaquin, or Cipro), and Trimethoprim: During pregnancy, it is not safe to use any of them (Komala and Kumar, 2013).

7.4. Levofloxacin, Ciprofloxacin: Their use may cause greater risk of tendon rupture in those patients with immunosuppressive conditions or elderly adults.

7.5. β -lactams (*i.e.*, cefdinir, cefaclor, cefpodoxime, and amoxicillin-clavulanate): Avoid using amoxicillin or ampicillin because of their poor efficiency and high resistance (Chu and Lowder, 2018).

Treatment of UTIs is getting harder and harder since a variety of antibiotic resistance processes are continuously spreading. Members of the *Enterobacteriaceae* family, such as *K. pneumoniae* and *E. coli*, are especially concerning since both have acquired plasmids expressing extended-spectrum β -lactamases (Garau, 2008). These plasmids promote resistance to several antibiotics and the third-generation cephalosporins quite quickly. Enterococci are also prone to multidrug resistance as they naturally resist penicillins, cephalosporins, clindamycin, and trimethoprim (Pendleton *et al.*, 2013). *Enterococcus* spp. is exhibiting higher levels of resistance to glycopeptides; especially vancomycin, which is one of the last lines of protection against the multidrug-resistant microorganisms (Gupta and Bhadelia, 2014).

Recently, the medicinal herbs have been more popular for treating and preventing a wide range of microbial diseases ([Farhadi *et al.*, 2019](#)). It has been demonstrated that herbal remedies may be quite effective in treating a particular kind of UTI ([Shaheen *et al.*, 2019](#)). Some species of herbs that are useful for treating UTIs, include *Juniperus communis* (juniper), *Arctostaphylos uva-ursi* (bearberry), *Vaccinium macrocarpon* (cranberry), *Cinnamomum verum* (cinnamon), *Vaccinium myrtillus* (blueberry), *Agathosma betulina* (buchu), *Equisetum arvense* (horsetail), *Urtica dioica* (nettle), and *Armoracia rusticana* (horseradish) ([Fazly Bazzaz *et al.*, 2021](#)).

8. Prevention of UTIs

Modifications of the lifestyle may help to avoid certain UTIs. For example, a woman may apply estrogen cream to her vaginal area after menopause to decrease the risk of developing new microbial infections ([Komala and Kumar, 2013](#)).

8.1. Probiotics: Probiotics can prevent the vagina from urinary pathogen colonization by steric hindrance or blocking possible sites of adherence, producing hydrogen peroxide that is microbicidal to the urinary pathogens, stimulating the anti-inflammatory cytokine response in the epithelium cells, and maintaining a low pH. Few random controlled trials have been conducted on *Lactobacillus* probiotics in women for UTI prevention; however, the majority of these studies didn't establish whether the probiotic treatment led to the development of a probiotic strain colonizing the vagina or not ([Pietrucha-Dilanchian and Hooton, 2017](#)).

8.2. Anti-microbial prophylaxis: Anti-microbial prophylaxis helps to prevent catheter-associated bacteriuria. Meanwhile, the prevalence of drug-resistant microorganisms rises when antibiotic prophylaxis is used ([Maki and Tambyah, 2001](#)).

8.3. Hydration: Increasing the urine volume through hydration causes the bacteria to be washed out of the bladder, which prevents the bacteria from growing

there. Additionally, staying hydrated helps to avoid encrustation-related urethral catheter blockage.

8.4. Catheter exchange: Typically, a normal catheter swap takes place every 4-6 weeks. The ideal frequency of catheter swap varies from patient to patient since catheter encrustation might occasionally occur more quickly. Catheter exchanges ought to be done more regularly in these situations ([Wagenlehner *et al.*, 2012](#)).

8.5. Cranberry juice: Cranberry, also known as *Vaccinium macrocarpon*, *Vaccinium erythrocarpum*, and *Vaccinium oxycoccos* is a plant of the *Ericaceae* family. Cranberries are mostly water (88 %), with a complex mixture of fructose, organic acids, ascorbic acid, anthocyanidins, flavonoids, catechins, triterpenoids, and proanthocyanidins ([Guay, 2009](#)). Conflicting data supports the use of cranberries and their products for prevention of UTIs, and less researches support its use for management of acute UTIs ([Sihra *et al.*, 2018](#)). Proanthocyanidins and anthocyanidins are tannins that act as a natural plant defense mechanism against the microbial infection, and are believed to be mostly therapeutically useful for reducing UTIs in women ([Hisano *et al.*, 2012](#)).

8.6. Ascorbic acid: Supplementation with vitamin C (ascorbic acid) is widely acknowledged as a non-antibiotic prophylactic treatment for UTIs. There are two proposed modes of action of ascorbic acid. First, urine acidification ([Hickling and Nitti, 2013](#)), and second is decreasing the conversion of urinary nitrate to reactive nitrogen oxides, which has a bacteriostatic effect ([Wawrysiuk *et al.*, 2019](#)).

Conclusion

This review provides valuable information regarding the epidemiology, uropathogenic, diagnosis, prevention, and treatment of UTIs. Both genders are susceptible to UTIs; however, women are more likely to be infected because of the changes in their physiology and pregnancy itself, which increase the risk of such infections. It is important to diagnose UTIs as soon as possible, especially in newborns and

babies. The elderly person with urinary devices such as catheters is especially at risk for such infections. While the use of antibiotics has proven helpful in treating UTI, the first-line of therapies for the pregnant is nitrofurantoin and β -lactams. The majority of physicians have been giving too many medications for long periods, which has been a huge mistake in UTI care. Alternative therapies are needed because of the negative effects of antibiotics and drug resistance. Numerous herbal medicines are beneficial in the field of medical research. Being natural goods, herbal treatments are fundamentally better than strong synthetic medicines, which can induce undesirable side effects. Overall, this study highlights the plant-based remedies such as cranberry juice as effective means for treating UTIs. Future research is needed to assess the cost-effectiveness of this herbal technique and improve the diagnostic tests, which will help in early detection of UTI in those people with baseline urine symptoms.

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Conflicts of interests

The authors declare they do not have any conflicts of interest.

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Author's Contributions

Conceptualization: S.S., D.N. and V.G.; Investigation: S.S., M.Y., D.N. and R.K.R.; Methodology: S.S., R.K.R., D.N. and M.Y.; Supervision: D.N.; Roles/Writing-original draft: S.S.; Reviewing, and editing: S.S. and D.N.

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