

Urinary Tract Infections in women: Treatment options and Antibiotic resistance

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Abstract:

Urinary tract infections (UTIs) are the infections caused by several bacteria or some fungi in the urinary tract. Women are more prone to acquire UTIs due to several factors like shortness of urethra and proximity to the anus, menstruation, lower Estrogen levels, frequent sexual intercourse etc. Treatment approaches for UTI include initiation with Nitrofurantoin 100 mg BD for 7 days. Special consideration for the treatment in pregnant women is required to ensure safety of maternal and fetal outcomes. The NICE guidelines recommend the first choice of drug to be Nitrofurantoin-50 mg QD or 100 mg BD for 7 days. In developing countries like India, challenges arise due to the low socio-economic problems leading to the increased burden of infectious diseases. Factors like over-the-counter availability of antibiotics, poor awareness, and inadequate public health systems, along with unhygienic sanitation lead to the emergence and transmission of antibiotic-resistant bacteria. Regular surveillance of trends on bacterial resistance and standardizing of drug treatments are the best measures to control the emergence of multi-drug resistant bacteria.

INTRODUCTION

Urinary Tract Infection (UTIs) refers to infection or inflammation caused by multiple bacteria or, in some cases fungi, in any portion of the urinary tract.¹ About 150 million individuals globally are infected annually. It is commonly seen in clinical practice and account for 10-40 percent of all infections in primary care units and hospitals. The female population is 4 times more susceptible than the male.

Lower and upper UTIs are chronic problems for people of all ages, especially elderly and pregnant women in the community.² Community-acquired uncomplicated UTIs account for a significant proportion of infectious diseases in women. A large amount of antibiotics are routinely used in community-based clinical facilities to manage UTIs.^{3,4} People 16-64 years of age are at increased risk of contracting infections due to the physiological nature of the female genitourinary system, sex, pregnancy and personal hygiene. Pregnancy, catheter use, spinal cord injury and diabetes increase the risk.⁵

Urinary tract infections are caused by Gram-negative bacteria, most of which are aerobic bacilli located in the gastrointestinal tract. Several specific bacteria are *Escherichia coli*, *Klebsiella pneumonia*, *Enterobacter*, *Citrobacter*, *Proteus mirabilis* and *Pseudomonas aeruginosa*. Gram-positive bacteria like, *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, *Enterococcus spp.*, and *Serratia spp.* are normally isolated and result in the invasion of the genitourinary tract contributing to UTI. The most common Gram-negative bacteria that cause UTI are *E. coli*, *Klebsiella*, *Proteus* and *Pseudomonas*.⁷

Initially, various broad-spectrum antibiotics are used to manage UTIs, while narrow-spectrum antibiotics might be preferred to prevent the resistance of pathogens. Fluoroquinolones are usually used for empiric therapy with UTIs.⁹ This empiric therapy is implemented without the benefit of culture and sensitivity which can be deemed unacceptable because it can contribute to the creation of worldwide resistance of bacteria to antibiotics, which

could ultimately lead to the production to multidrug resistant strains of bacteria.⁸

Diagnosis may be done by the process of colony count from which the amount of active bacterial colonies can be measured in a milliliter of the sample. It helps to distinguish bacteriuria from bacterial contamination by offering quantitative measurements. Contamination can occur during the incorrect processing of the sample. The occurrence of $\geq 10^5$ colony forming units (CFUs)/ml is known to be significant.⁸

Women can self-diagnose UTI in most situations when they have chronic cystitis. Acute pyelonephritis includes costovertebral angle pain with or without fever, frequently followed by lower urinary tract symptoms. While hematuria, catheter congestion, or costovertebral angle discomfort and tenderness may occur, patients with indwelling urethral catheter may report fever without localizing genitourinary outcomes.¹¹

Anatomy of the urinary tract system in women

The renal papilla is the first gross structure of the upper collecting system into which each renal pyramid drains and is cupped by a minor calyx, narrowing down into an infundibulum which varies in number, length, diameter and combines to form the major calyces. These calyces branch out into the upper, middle, and lower-pole calyces, eventually congregating at the renal pelvis.

The ureters are fibromuscular bilateral tubes, originating at the ureteropelvic junction and drain urine from the renal pelvis to the bladder. These are 22-30 cm in length and are present through the retroperitoneum, piercing the bladder wall obliquely at the ureterovesical junction and terminate in the bladder lumen as ureteral orifices. The intramural ureter is passively compressed by the bladder wall during storage and dynamically during emptying. This prevents the vesicoureteric reflux during steady-state and micturition. Three segments of the ureter which are physiologically narrow are the ureteropelvic junction, the ureterovesical, and where the ureters cross the common

iliac vessels. These areas are susceptible to the ureteral calculi being trapped leading to an obstruction.¹³

The urinary bladder is a neurologically controlled reservoir for the storage of urine and provides a method for conscious voiding when appropriate. Detrusor (smooth muscle in the wall of the bladder from the insertion of the ureters to the dome of the bladder) controls the voiding of the bladder. The bladder neck and the urethral contact with the connective tissue of the anterior wall of the vagina allow the bladder neck to be mobile but can be subjected to stress eventually causing urinary incontinence. Neuromuscular injury to the urethral sphincter during childbirth may have consequences to urinary incontinence. The urethra is about 3-4 cm in length, extending from the bladder neck to the external urethral orifice, embedded behind the symphysis pubis. The functional internal sphincter is formed by the bladder neck and the proximal urethra.¹⁴

Urinary tract infections in women

Urinary tract infections occur more often in women than in men in an 8:1 ratio and about 50-60% of women report at least one UTI in their lifetime. One out of three women experience symptomatic UTI which necessitate antibiotic treatment by the age of 24.¹² This is due to the presence of a short urethra with proximity to the vagina and the anus. More cases are observed in the sexually active, lower economic groups. Certain contraceptive methods are also known to increase this risk.⁶

UTIs in premenopausal women

Menstrual hygiene is an important aspect affecting the premenopausal population and adolescent girls. Women have developed their strategies around the world to deal with menstruation according to an individual's economic status, personal preferences, local traditions, cultural beliefs, and educational status. In India, around 43% to 88% of women use reusable cotton cloths rather than a disposable sanitary napkin. The former may not be well sanitized due to the lack of clean water and soap. UTI is studied to be the most common form of infections in menstruation women which is linked to the unhygienic practices.¹⁵

The penile-vaginal penetration in premenopausal women is a significant risk factor for community-acquired UTI, in particular, its frequency. Vaginal sexual activity is observed to raise the risk of UTI by contaminating the vaginal introitus and periurethral region with bacteria and introducing uropathogens into the urethra and bladder by massaging the urethra, likely causing damage to the urethral meatus. The introduction of uropathogens from the infected partner is also rarely reported to cause uncomplicated UTI.

Contraceptives like diaphragm and condoms with or without spermicides and also spermicides themselves are observed to increase the risk of UTI in women. The diaphragm may cause urinary stasis because of its positioning in the vagina. Spermicides may alter the vaginal microflora by decreasing the lactobacilli levels and increasing vaginal colonization.¹⁶

UTI in pregnant women

UTI is a common occurrence during pregnancy and approximately 90% of pregnant women develop urethral dilation, increased bladder volume, decreased bladder tone, and decreased urethral tone leading to increased urinary stasis and ureterovesical reflux. Pregnancy also causes glycosuria which increases the bacterial concentrations in the urine.¹⁷

The risk of UTI increases from the 6th week of pregnancy and peaks around the 22nd to the 24th week. This risk is mainly attributed to the previous history of UTI, low socioeconomic status, personal hygiene, anaemia, an increase in the number of childbirths or intercourses per week, and a lack of prenatal care. UTI abnormalities and diabetes mellitus during pregnancy are also known to increase the risk. The pressure of a gravid uterus on the ureters may cause stasis of urine flow eventually causing an infection.¹⁸

The consequences of UTI may be serious for both the mother and the child and may be caused due to pyelonephritis, low birth weight, premature labor, preterm birth, hypertension, preeclampsia, etc. Hence, early detection and treatment of UTI are necessary for prenatal care.¹⁷

UTI in postmenopausal women

Elderly women experience atrophy of the vulva, vagina, and the urinary tract, which has a big impact on the quality of life. Symptoms of urogenital atrophy include irritation, itching, vaginal dryness, pain during sexual intercourse, etc. Incidence of UTI is higher in postmenopausal women due to bladder or uterine prolapse, which causes incomplete emptying of the bladder, loss of Estrogen, and changes in the vaginal flora which typically includes the loss of lactobacilli, allowing peri-urethral colonization with bacteria. The likelihood of medical illnesses like diabetes is more in elderly women and is known to increase the risk of UTI.¹⁹ Post-menopausal women frequently present with genitourinary symptoms, with 29% of the women exhibiting urinary incontinence. Estrogen deficiency also plays a major role in the development of bacteriuria in elder women. Estrogen hormone stimulates the proliferation of lactobacillus in the vaginal epithelium, reduces the pH, and reduces the chances of colonization of the vagina.²⁰

UTI in post-partum women

UTIs are common post-partum infections observed in 2% to 4% of all deliveries. Post-partum UTI usually presents as a mild infection and is associated with discomfort, prolonged hospital stay, and readmission. It has also been associated with an increased risk with the discontinuation of breastfeeding.²¹

Patients infected with postpartum urinary tract infections were most likely to have been catheterized intermittently. Some risk factors such as prior urinary tract infection during pregnancy, obesity, long duration of labor and ruptured membranes, and epidural anesthesia are associated with an increased risk of postpartum urinary tract infections.²²

Treatment of Urinary Tract Infections:

Multiple considerations should be weighed when choosing an antibiotic treatment for UTIs. Originally, a distinction must be created between asymptomatic and symptomatic bacteria. ASB is normal with growing age and does not necessarily need care, except for conditions such as pregnancy. ASB is linked with an elevated risk of pyelonephritis and adverse pregnancy outcomes.

Trimethoprim-sulfamethoxazole, while popular earlier, has restricted usage due to increased resistance. Quinolones are common with UTIs and are recommended at higher doses for the treatment of complicated UTIs. Aminoglycosides and carbapenem are medicines of choice for susceptibility to Quinolones. Persistence or recurrence of infection suggests the need for another antibiotic depending on the susceptibility profile and culture.²³ Beta-lactam and fluoroquinolones are suggested for use in complicated cystitis. The treatment regimen of UTIs according to ICMR (Indian Council for Medical Research) has been illustrated in Table.1.

Treatment during pregnancy

UTIs require special therapy and diagnostic workup during pregnancy. Proper use of antibiotics is important so that both maternal and fetal outcomes are favoured and safety is ensured. According to the NICE (National Institute for Health and Clinical Excellence) guidelines, the first choice of drug is Nitrofurantoin- 50 mg four times a day or 100 mg (modified release) twice a day for 7 days. The second choice is Beta-lactam antibiotics like Cephalexin or Amoxicillin. Commonly, Penicillin and Cephalosporins are accepted in pregnancy. Due to low protein binding, Cephalexin is preferred. Nitrofurantoin and Fosfomycin are rarely preferred.²⁴

Treatment in elderly women

Treatment of uncomplicated UTI in elderly women is similar to the treatment given to younger women. International Clinical Practice Guidelines recommend Nitrofurantoin monohydrate/macro crystals 100 mg twice

daily for 5 days or Trimethoprim–Sulfamethoxazole 160/800 mg twice daily for 3 days, if there are no patterns of resistance recorded. Sulfamethoxazole can be preferred as an empirical treatment in older women. Treatment of ASB is only necessary before any urologic procedures for which mucosal bleeding might occur.¹⁰

Treatment of recurrent infections in women:

Continuous low-dose antibiotic prophylaxis can be effective in the prevention of infections. Allergies, local resistance patterns, cost and side effects of antibiotics are assessed to determine the choice of the drug. Nitrofurantoin, followed by Cephalexin exhibits the highest rate of discontinuation of treatments. Patients are to be made to understand the potential side effects of all the antibiotics, as the treatment last for a long-term.²⁵

The Public Health England recommends low dose of Trimethoprim 100 mg or Nitrofurantoin 50-100 mg every night for women who frequently experience symptoms. Other suggested antibiotics include Cephalexin and Norfloxacin. Trimethoprim/ Sulfamethoxazole (TMP-SMX) and Fluoroquinolones prevent recurrent UTIs by inhibiting the recovery rate of uropathogens from the faecal reservoir. Prior to the treatment, a confirmation on the elimination of the previous infection is to be determined by a negative culture, 1-2 weeks post treatment.²⁶

In developing countries like India, challenges arise due to the low socio-economic problems leading to the increased burden of infectious diseases. Factors like over-the-counter availability of antibiotics, poor awareness, and inadequate public health systems, along with unhygienic sanitation lead to the emergence and transmission of antibiotic-resistant bacteria. Regular surveillance of trends on bacterial resistance and standardizing of drug treatments are the best measures to control the emergence of multi-drug resistant bacteria. Information on individual antibiotic resistance is required as susceptibility patterns vary geographically, for optimal treatment.²⁷

Table.1. The treatment regimen for Urinary tract infections according to ICMR

Clinical conditions	Common pathogens	Empiric AMA	Alternate AMA	Comments
Acute Cystitis	<i>E.coli, Proteus sp, Klebsiella sp.</i>	<ol style="list-style-type: none"> 1 Nitrofurantoin 100 mg BD for 7 days 2 Cotrimoxazole 500/125 mg BD for 3-5 days 3 Ciprofloxacin 500 mg BD for 3-5 days 	<ol style="list-style-type: none"> 1 Cefuroxime 250 mg BD for 3-5 days 2 Cefixime 400 mg BD for 5 days 	The duration of treatment is longer in pregnant women.
Acute pyelonephritis	<i>E.coli, Klebsiella sp, Proteus sp, S.aureus</i>	<ul style="list-style-type: none"> • Piperacillin tazobactam 4.5 gm IV 6 hourly for 10 days • Ertapenem 1 g IV OD for 7 days 	<ul style="list-style-type: none"> • Imipenem 500 mg IV 8 hourly for 10 days or • Inj Amikacin 5 mg/ kg IV once daily for 10 days 	Urine and blood culture are to be performed before starting the treatment. Amikacin 1gm OD IV or Gentamicin 7 mg/kg as prescribed doses. A close monitor on renal parameters is needed.

Antibiotic resistance:

Globally, the uropathogens treated empirically with antibiotics are regarded as the potential cause for the emergence of antibiotic resistance among various groups of bacteria. Though clinical acceptance for empirical bacteria exists, bacteria are developing resistance to various antibiotics faster than the development of newer antibiotics. Broad-spectrum antibiotics are commonly prescribed to treat infections in empirical therapy, instead of specific or narrow-spectrum antibiotics. Antibiotic misuse, patient non-compliance, incompleteness of antibiotic therapy can increase the rate of antibiotic resistance by bacteria.²⁸

Resistance is commonly observed towards drugs like Trimethoprim/sulfamethoxazole (TMP-SMX), Cephalosporins in recent times. Fluoroquinolone resistance is also being observed to increase by 10%. Information on antibiotic resistance is mainly based on the data from hospitals or laboratories in selective patients, even though the majority of the prescription of antibiotics takes place in a primary care setting. Therefore, the resistance profiles of uropathogens cannot be generalized to all the patients. Urine samples of patients are generally not tested for resistance and usually, these resistance patterns vary greatly between different regions and countries.²⁹

This problem may be overcome by continuous surveillance of the usage of antibiotic drugs regularly. These measures may also guide the decision-makers, Antibiotic drug stewardship programs, guidelines for the empirical treatment of UTIs that also allow the monitoring of trends in antibiotic resistance and the impact of the intervention in reducing its development. This can be limited in developing countries due to limited financial and human resources with poor quality of microbiological laboratories.³⁰

The multiple antibiotic resistance index (MAR index) is calculated as the ratio of the number of antibiotics to which the organism exhibits resistance, to the total number of antibiotics to which the organism is exposed to. Multiple antibiotic resistance index with values greater than 0.2 indicates a high risk for contamination, abuse, or misuse of these antibiotics.³¹ It gives an analysis of health risks and checks the extent of antibiotic resistance. Differentiation of isolates from different sources using antibiotics can be done using the MAR index. It is a cost-effective method, which is easy to perform, rapid, and does not require special training or expensive equipment.³²

Worldwide data indicates the increasing resistance of uropathogens to conventional drugs. Resistance to the drug amoxicillin among uropathogens has become common and should be monitored. The emergence of resistance to even the latest and more potent antibiotic drugs is also concerning.³³

CONCLUSION:

As UTIs are more common in women, they are at a greater risk of developing antibiotic resistance. Regular surveillance programs, prescription of antibiotics based on the culture of the affecting organisms are helpful in

reducing the rate of the developing resistance and initiating a targeted therapy. Determination of the resistance patterns of the organism may help in improving the prescription patterns to administer the most efficacious and cost effective agent against the organism causing the infection.

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