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# A REVIEW ON URINARY TRACT INFECTIONS (UTI)

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## ABSTRACT

Urinary tract infections (UTIs) are common bacterial infections, affect men and women of all ages, and vary dramatically in their presentation and sequelae. Although the urinary tract is normally free of bacterial growth, bacteria that generally ascend from the rectal reservoir may cause UTIs. When bacterial virulence increases or host defense mechanisms decrease, bacterial inoculation, colonization, and infection of the urinary tract occur. Careful diagnosis and treatment result in successful resolution of infections in most instances. A better understanding of the pathogenesis of UTI fund the role of host and bacterial factors has improved the ability to identify patients at risk and prevent the infection. Clinical manifestations can vary from asymptomatic bacterial colonization of the bladder to irritative symptoms such as frequency and urgency associated with bacterial infection upper tract infections associated with fever, chills, and flank pain and bacteremia associated with severe morbidity, including sepsis and death. New antimicrobial agents that achieve high urinary and tissue levels, can be administered orally, and are not nephrotoxic have significantly reduced the need for hospitalization for severe infection. Shorter-course therapy and prophylactic antimicrobial agents have reduced the morbidity and host associated with recurrent cystitis in women. Although the vast majority of patients respond promptly and are cured by therapy early identification and treatment of patients with complicated infections that place them at significant risk remains a clinical challenge to urologist.

**KEYWORDS:** Urinary tract infection, flank pain, bacteremia, nephrotoxic, recurrent cystitis, hospitalization.

## INTRODUCTION

Urinary tract infection is a common contagion among men and women but the incidence is quite high among women due to their physiology, in about half of all women experiencing at least once in their lifetime. A 2010 report indicated that 3.1% of urgent care visits were for UTIs. An estimated eight million episodes of UTI occur in the US each year with one out of three women requiring treatment for UTI before age 24.[1]

Of the women affected, 25-30% develop recurrent infections unrelated to any functional or anatomical abnormality of the urinary tract. Most UTIs in women are episodes of acute uncomplicated cystitis which occur in women of childbearing age. Although acute uncomplicated cystitis may not be thought of as a serious condition, it affects the patient's quality of life by causing an estimated six days of discomfort. Acute cystitis refers to symptomatic infection of the bladder in the lower urinary tract. It can occur alone or in conjunction with pyelonephritis, i.e. infection of the kidney in the upper urinary tract. Most episodes of cystitis and pyelonephritis are considered to be uncomplicated infections when occurring in otherwise healthy non-pregnant women. A complicated UTI can occur in either the upper or lower urinary tract, but is accompanied by an underlying condition which increases the risk of therapy failing, such as obstruction, an anatomical abnormality, urological dysfunction, pregnancy or resistant pathogen.[2]

UTI is an inflammatory response of the urothelium to bacterial invasion that is usually associated with bacteriuria and pyuria.

***Bacteriuria** is the presence of bacteria in the urine, which is normally free of bacteria. It has been assumed to be a valid indicator of either bacterial colonization or infection of the urinary tract. Bacteriuria can be symptomatic or asymptomatic.

***Pyuria**, the presence of white blood cells (WBCs) in the urine, is generally indicative of infection and an inflammatory response of the urothelium to the bacterium, stones, or other indwelling foreign body. Bacteriuria without pyuria is generally indicative of bacterial colonization without infection of the urinary tract. Pyuria without bacteriuria warrants evaluation.

It is understood that the infection targets the different parts of the urinary tract and as a consequence results in the contagion of the lower and the upper urinary tracts. The infection

is named based on the site of infection. The infection of urethra and ureter are referred to as urethritis respectively whereas cystitis and pyelonephritis corresponds to bladder and kidney infections. Cystitis is a common type of infection whereas the infection associated with the renal damage is an issue of serious concern. Therefore the infection of bladder and urethra are referred as the infection of the lower urinary tract whereas the kidney and ureter infection is an indication of upper tract infection for tuberculosis, stones, or cancer.[3]

UTIs are classified based on their location in the urinary tract, the presence of relevant complicating factors, and the presence or absence of symptoms. Definitions of some of the major categories of UTIs, based on the most recent German guidelines, are summarized in Table 1.1.[4]

**Table 1: Key classification of UTIS.**

| Classification | Definition |
|---|---|
| Uncomplicated UTI | A UTI where there are no relevant functional or anatomical abnormalities in the urinary tract, no relevant kidney function impairment, and no relevant concomitant diseases promoting the UTI or risk of developing serious complications |
| Acute uncomplicated cystitis | A lower UTI in which the acute symptoms involve only the lower urinary tract, for example, urgency, painful voiding (dysuria), pollakiuria, and pain above the symphysis |
| Acute uncomplicated pyelonephritis | An upper UTI with persistent symptoms including flank pain, flank tenderness, or fever (>38°C) |
| Asymptomatic bacteriuria | A positive urine culture (>105 colony-forming units/ml) in the absence of urinary symptoms |
| Recurrent uncomplicated UTIs | A recurrent UTI refers to the occurrence of ⩾2 symptomatic episodes within 6 months or ⩾3 symptomatic episodes within 12 months |

-The symptoms associated with the bladder and kidney infections are contrasting which includes painful and frequent urination in case of cystitis as a result of bladder infection whereas conditions like high fever and flank pain are commonly experienced in case of kidney contagion which is referred to as pyelonephritis.[3]

-This prevalence of the infection among children and elderly people is not clearly understood and is currently under study.

-Bacteria are the prime perpetrator responsible for conferring the infection among humans but the role of certain fungi and viruses cannot be over looked. However, the incidence of UTI as a result of viral or fungal infection is considered to be rare phenomena. Though the infection

seems to be harmless in the initial stages, the patient shows a variety of symptoms as the stage progresses and can lead to death in severe circumstances. Research studies have defined urinary tract infection as the most common form of bacterial infection.[5,6]

-Urinary tract infection can be a consequence of poor diagnosis and is regarded as the common hospital acquired infection.[7,8]

-The infection encompasses a diverse group of clinical syndromes and diseases that differ in epidemiology, etiology, location severity of the condition.[9]

-In addition to the above factors, it also vary in expressed local symptoms, frequency of recurrence, extent of damage caused, presence of complicating factors and the risk from their reiterate incidence.[10]

-The occurrence of bladder infection is usually followed by kidney infection and results in blood borne infection and in severe circumstances can lead to dire consequences including death. Therefore, UTI is capable of claiming lives under severe circumstances and proper treatment results in quick recovery from the contagion. The invasion of lower urinary tract by the bacteria which usually comprises the bladder causes cystitis which is trailed by the upper urinary tract infection referred to as pyelonephritis. This could be a consequence of blood borne infection. Despite the fact, that 80% of the infection is caused by *Escherichia coli*, the involvement of other pathogens cannot be denied and one of the perpetrators responsible for conferring UTI are Gram positive *cocci*.

-The symptoms of UTIs are generally mild, and inappropriate use of antibiotics can lead to antibiotic resistance; therefore, it is important to establish the appropriate criteria for treatment using narrow-spectrum antibiotics for the optimal duration. (11A variety of antibiotics is available for treating UTIs, but changing antibiotic sensitivities make appropriate empiric treatment a moving target over time. A recently published guideline4 by the Infectious Diseases Society of America and European Society for Microbiology and Infectious Diseases provides evidence-based recommendations for treating pre-menopausal, non-pregnant females with uncomplicated UTI. UTIs which occur in men, pregnant women, and patients with immunosuppression or urinary tract abnormalities, such as congenital malformations, urinary calculi, recent urologic instrumentation, indwelling catheters, neurogenic bladder, and kidney transplant, are considered complicated).[12]

-However, not everyone diagnosed with a UTI and treated with an antibiotic will necessarily have a bacterial infection. At least one-half of women who suspect that they have UTI actually do. Studies have shown that one in 7 patients given an antibiotic for UTI symptoms will return within 28 days for a further prescription of antibiotic. Also, many UTIs are self-limiting, improving without treatment even when culture is positive. Symptomatic treatment of uncomplicated UTI may be an option which merits further research. Phenazopyridine is a time-tested urinary tract antiseptic and analgesic that provide symptomatic relief of the pain, burning, frequency and urgency associated with UTI.[13]

**Epidemology**

-Urinary tract infections (UTIs) are some of the most common bacterial infections, affecting 150 million people each year worldwide.[14]

-In 2007, in the United States alone, there were an estimated 10.5 million office visits for UTI symptoms (constituting 0.9% of all ambulatory visits) and 2–3 million emergency department visits. Currently, the societal costs of these infections, including health care costs and time missed from work, are approximately US $3.5 billion per year in the United States alone. UTIs are a significant cause of morbidity in infant boys, older men and females of all ages.[15,16,17]

-It has been estimated globally that UTIs result in as many as 8.3 million visits to outpatient clinics, 1 million visits to emergency departments, and 100,000 hospitalizations annually.[18]

-They are particularly common among the female population with an incidence of about 1% of school-aged girls and 4% of women through child-bearing years. Incidence of infection in females increases directly with sexual activity and child-bearing. In the women, 25-30% of women between 20-40 years of age will get UTIs.2 In 2007, approximately 3.9% of office visits in USA were related to symptoms involving the genitourinary tract.4 Sixty-one percent of all UTIs are managed in the primary care setting.[13]

-About 25% of these women have spontaneous resolution of symptoms, and an equal number become infected (Sobel 2014).

**Etiology of Infection**

-Many different microorganisms can infect the urinary tract and cause infection, UTIs are mainly caused by both Gram-negative and Gram-positive bacteria, as well as by certain fungi. The most common causative agent for both uncomplicated and complicated UTIs is uropathogenic *Escherichia coli* (UPEC). For the agents involved in uncomplicated UTIs, UPEC is followed in prevalence by *Klebsiella pneumoniae, Staphylococcus saprophyticus, Enterococcus faecalis,* group B *Streptococcus (GBS), Proteus mirabilis, Pseudomonas aeruginosa, Staphylococcus aureus and Candida spp*. For complicated UTIs, the order of prevalence for causative agents, following UPEC as most common, is *Enterococcus spp., K. pneumoniae, Candida spp., S. aureus, P. mirabilis, P. aeruginosa and GBS.*[19]

-Organisms such as *Serratia* and *Pseudomonas* assume increasing importance in recurrent infections and infections associated with urologic obstructions. They also play major role in nosocomial and catheter associated infections. Proteus specie by virtue of urease production and *Klebsiella spp* through the production of extracellular slimy polysaccharides are predispose to stone formation in the kidneys and are isolated more frequently from patient with calculi.[20]

-Gram positive *cocci* play a lesser role in urinary tract infections. However, *Staphylococcuss aprophyticus novobiocin* resistant, coagulase-negative specie accounts for 10 to 15% of acute symptomatic urinary tract infections in young females while *Enterococci* occasionally cause acute uncomplicated cystitis in women.[21]

-Other cause of urinary tract infections includes sex, urinary catheters, diabetes, and lack of circumcision and prostate problems.[22]

-Complicating factors include predisposing anatomic, functional, or metabolic abnormalities. Persons with spinal cord injury are at increased risk for urinary tract infection because of chronic use of catheter, and voiding dysfunction. Virus and parasite are not usually considered as urinary pathogens but however, Virus plays a major role in the pathogenesis of hemorrhagic cystitis.[23]

***Prevalence of Urinary tract infection**

The prevalence of urinary tract infection is high in females compared to the males. Estimate shows that one third of adult women are diagnosed with UTI before 24 years.[24]

-Women are especially more prone to developing UTI due to anatomical factors that allows bacterial quick access to the bladder, poor hygiene; sexual intercourse and use of contraceptive are also contributory factors. Also hormonal changes such as menopause and estrogen loss are responsible for the high prevalence of UTI in older women. With estrogen loss, the system ability to resist bacterial colonization is reduced making it liable to infection.[25]

-UTI in men are rare but when they occur it usually comes with severity and are most times refers to as complicated. Men who are not circumcised tend to be more prone to UTI because the bacterial build at the extra fold of their skin thus making them vulnerable.[26]

-Also elderly men are at increased risk of developing UTI due to factors such as kidney stones or prostate problems. Any abnormality of the urinary tract that interferes with the flow of urine set the stage for increased risk of complicated UTI.

***Types of Urinary Tract Infections**

Generally UTIs are classified based on the factors that trigger the infection and the nature of occurrence. Taking these aspects in to consideration, UTIs can be classified as follows:

i. Uncomplicated or complicated (based on the factor that triggers the infection).
ii. Primary or Recurrent (depending on the nature of occurrence).

**Uncomplicated or Complicated Urinary Tract Infection**

-Uncomplicated describes an infection in a healthy patient with a structurally and functionally normal urinary tract. The majority of these patients are women with isolated or recurrent bacterial cystitis or acute pyelonephritis, and the infecting pathogens are usually susceptible to and eradicated by a short course of inexpensive oral antimicrobial therapy.

-A complicated infection is associated with factors that increase the chance of acquiring bacteria and decrease the efficacy of therapy. The urinary tract is structurally or functionally abnormal, the host is compromised, and/or the bacteria have increased virulence or antimicrobial resistance. The majority of these patients are men. This is a consequence of bacterial infection and the prevalence is higher in women than men. This includes the common form of the infection like the cystitis and pyelonephritis which affects the lower and the upper tracts leading to bladder and kidney infections. In contrast, complicated urinary tract infection occurs in men and women at any point of their life and has the tendency to

produce severe outcomes resulting in death under serious circumstances. These infections are highly intricate and are difficult to treat and they are persistent. These complicated urinary tract infections can lead to outcomes like structural anomalies that blights that capability of the urinary tract to flush out the urine and this in turn provides better scope for the growth of bacteria as urine is considered to be a suitable growth medium and leads to dire consequences. Patients with urinary tract infection are often subjected to medical devices and one such device commonly employed among the patients are the urinary catheters which serve as a common means of infection. In addition, bladder and kidney malfunction and kidney transplants are the other factors for complicated urinary tract infection. The first three months after kidney transplant is very crucial and the patient is vulnerable to develop such complications.

***Primary or Recurrent Urinary Tract Infections**

UTIs may also be defined by their relationship to other UTIS:

-A first or isolated infection is not one that occurs in an individual who has never had a UTI nor has one remote infection from a previous UTI. An unresolved infection is one that has not responded to antimicrobial therapy and is documented to be the same organism with similar resistance profile. A recurrent infection is one that occurs after documented, success resolution of an antecedent infection. Consider these two different types of recurrent infections.

1. Reinfection describes a new event associated with reintroduction of bacteria into the urinary tract from outside

2. Bacterial persistence refers to a recurrent UTI caused by the same bacteria reemerging from a focus within the urinary tract, such as an infectious stone or the prostate. Relapse is frequently used interchangeably. These definitions require careful clinical and bacteriologic assessment and are important because they influence the type and extent of the patients evaluation and treatment.[3]

## CLINICAL MANIFESTATIONS

### Symptoms and Signs

-The characteristic symptoms of UTI in the adult are primarily dysuria with irritating voiding symptoms like urinary urgency, frequency, nocturia, painful voiding, bladder discomfort or stranguria which greatly distress the patient. A sensation of bladder fullness or lower abdominal discomfort is usually present. Pain occurring at the beginning of or during

urination suggests a urethral site of disease, whereas pain after voiding implies pathology within the bladder or prostate area. Sometimes a patient will relate a history of pain in the suprapubic area.[27]

-Although suprapubic pain and tenderness may occur, they are only found in approximately 20% of women with an uncomplicated UTI. The urine is often turbid.[2]

-Because of the referred pain pathways, even simple lower UTI may be accompanied by flank pain and costovertebral angle tenderness. In the emergency department, however, it is assumed that the presence of these symptoms represents upper UTI. Bloody urine is reported in as many as 10% of cases of UTI in otherwise healthy women; this condition is called hemorrhagic cystitis.[13]

-.The most diagnostic symptoms of UTI Include change in frequency, dysuria, Urgency and presence or absence of vaginal discharge in women.[28]

-Cystitis is usually associated with dysuria, frequency, or urgency of urine. Suprapubic pain and hematuria are less common. The latter refer to a group of symptoms, including weight loss, fever, fatigue, chills, night sweats and a decreased appetite.[2]

-Pyelonenephritis is classically associated with (cystitis symptoms) along with fever, chills, and flank pain. costovertebral angle tenderness (back pain). Nausea and vomiting may be present Renal or perirenal abscess may cause indolent fever and flank mass and tenderness In the elderly, the symptoms may be much more subtle (eg, epigastric or abdominal discomfort) or the patient may be asymptomatic. Patients with indwelling catheters often have asymptomatic bacteriuria but fever associated with bacteremia may occur rapidly and become life threatening

**Pathogenesis of Urinary Tract Infections**:

-Bacteria that cause urinary tract infections usually enter the bladder through the urethra. However, infection may also occur via the blood or lymph. It is believed that the bacteria are usually transmitted to the urethra after a bowel movement. After gaining entrance, organism such as E. coli attaches to the bladder wall and form a biofilm that resists the body's immune response.[29]

-Other bacterial characteristics such as motility are also important in the organism pathogenesis of UTIs because it enable the organism to ascend to the upper urinary tract and obstruct urine flow which might result in pyelonephritis.[21]

-Virulence factors of bacteria play an important role in urinary tract infections. Some organism particularly uropathogenic E. coli (UPEC) which is present within bowel flora can infect the urinary tract by expressing some specific virulence factors that permit adherence and colonization of the lower urinary tract causing urinary tract infections.[30]

-Adherence of this microorganism depends on three major features; bacteria's own adhesive mechanism, the receptive features of the urothelium organism and finally the fluid that is present between both surfaces. Adhesins found on the surface of the bacterial membrane are responsible for initial attachment onto urinary tract tissues forming a biofilm. With biofilm formation, bacterial cooperate with one another to remain viable.[21]

-This biofilm form an irreversible association with the host cell and prevent the host's neutrophils from penetrating its surface.[21]

-Bacteria that have irreversibly attached to a surface usually serve as a means for continued replication and recruitment of other bacteria.

**Urinary Pathogens**

Most UTIs are caused by facultative anaerobes usually originating from the bowel flora Uropathogens such as *Staphylococcus epidermidis* and *Candida albicans* originate from the flora of the vagina or perineal skin *E. coli* is by far the most common cause of UTIs, accounting for 85% of community-acquired and 50% of hospital acquired infections. Other gram-negative *Enterobacteriaceae* including *Proteus* and *Klebsiella*, and gram-positive *E. faecalis* and S*taphylococcus saprophyticus* are responsible for the remainder of most community-acquired infections. Nosocomial infections are caused by *E. coli, Klebsiella, Enterobacter, Citrobacter, Serratia, Pseudomonas aeruginosa, Providencia. E. faecalis, and S. epidermidis*(Kennedy et al, 1965). Less common organisms such as *Gardnerella vaginalis,* Mycoplasma species, and Ureaplasma urealyticum may infect patients with intermittent or indwelling catheters (Josephson et al, 1988; Fairley and Birch, 1989) E. coli strains mediating extraintestinal infections are typically grouped into broad phylogenetic classes by multiplex

polymerase chain reaction (Clermont et al, 2000), where 70% of uropathogenic *E. coli* (UPEC) isolates fall into the B2 group (Johnson et al, 2001).

Pathogenesis can also be through ascending or hematogenous route. Ascending route is the most common route of infection in females and is aided by conditions such as pregnancy, urethra obstruction and instrumentation. Blood borne route (hematogenous route) occurs as a result of bacteremia although it is mostly not common.[19]

**Ascending Route**

Most bacteria enter the urinary tract from the bowel reservoir via ascent through the urethra into the bladder. Adherence of pathogens to the introital and urothelial mucosa plays a significant use in ascending infections. This route is further enhanced inviduals with significant soilage of the perineum with feces who use spermicidal agents (Hooton et al. 1996; Foxman Handley et al, 2002), and patients with intermittent or indwelling catheters. The cystitis is often restricted to the bladder approximately of infections can extend into the upper urinary tract (Busch and Huland, 1984). The weight of clinical and experimental evidence strongly suggests that most episodes of pyelonephritis are caused by retrograde ascent of bacteria from the bladder through the ureter to the renal pelvis and parenchyma. Although reflux of urine is probably not required for ascending infections, edema associated with cystitis may cause sufficient changes in the ureterovesical junction to permit reflux. Once the bacteria are introduced into ureter, they may ascend to kidney unaided. However, this ascent would be greatly increased by any process that interferes with the normal ureteral peristaltic function. Gram-negative bacteria and their endotoxins, as well as pregnancy and ureteral obstruction, have a significant antiperistaltic effect. Bacteria that reach the renal pelvis can enter the renal parenchyma by means of the collecting ducts at the papillary tips and then ascend upward within the collecting tubules. This process is hastened and exacerbated by increased intrapelvic pressure from ureteral obstruction or vesicoureteral reflux, particularly when it is associated with intrarenal reflux.[3]

**Hematogenous Route**

Infection of the kidney by the hematogenous route is uncommon in normal individuals. However, the kidney is occasionally secondarily infection in patients with *Staphylococcus aureus* bacteremia originating from oral sites or with *Candida fungemia*. Experimental data indicate that infection is enhanced when the kidney is obstructed (Smellie et al, 1975).[3]

**Lymphatic Route**

Direct extension of bacteria from the adjacent organs via lymphatic may occur in unusual circumstances, such as a severe bowel infection or retroperitoneal abscesses. There is little evidence that lymphatic routes play a significant role in the vast majority of UTIs.[3]

**Predisposing Risk Factors of UTI**

The urinary system is biologically structured to help ward off infections. The ureters and bladder are supposed to prevent urine from backing up towards the kidneys. The flow of urine from the bladder is designed to wash bacterial out of the body. Women are particularly at risk of developing UTIs because of their short urethra, and certain behavioral factors which include delay in micturition, sexual activity and the use of diaphragms and spermicides which promote colonization of the periurethral area with coliform bacteria. Patients undergoing long term treatment are also vulnerable to the infection due to moist hospitalized conditions. In addition, diabetes enhances the incidence due to elevated blood sugar levels and other factors like parity, gravidity, hormonal imbalance, immunosuppressant and geographical location also has a significant role in the incidence of the infection. Infection in women most often results from perineal or periurethral bacteria that enter the urethra and ascend into the bladder, often in association with sexual activity, or due to mechanical instrumentation such as catheterization.so the infections occurs due to some predisposing factors such as alterations to the host's natural defense mechanisms, anatomical and physiological factors, premenopausal / menopausal factors, age and sex, obstruction, instrumentation etc.[18]

**Common presisposing factors for UTIs are listed in table1.2**

**Table 1-2: Predisposing Risk Factors for UTI.**

| Patient Population | Risk Factors |
|---|---|
| Premenopausal women of any age | • Diabetes<br>• Diaphragm use, especially those with spermicide<br>• History of UTI or UTI during childhood<br>• Mother or female relatives with history of UTIs<br>• Sexual intercourse |
| Postmenopausal and older adult women | • Estrogen deficiency<br>• Functional or mental impairment<br>• History of UTI before menopause<br>• Urinary catheterization<br>• Urinary incontinence |
| Men and women with structural abnormalities | • Extrarenal obstruction associated with congenital anomalies of the ureter or urethra, calculi, extrinsic ureteral compression, or benign prostate hypertrophy<br>• Internal obstruction associated with nephrocalcinosis, uric acid nephropathy, polycystic kidney disease, hypokalemic or analgesic nephropathy, renal lesions from sickle cell disease |

UTI = urinary tract infection. Information from: Grabe M, Bartoletti R, Bjerklund Johansen TE, et al, for the European Association of Urology. Guidelines on Urological Infections. 2015; and Sobel JD, Kaye D. Urinary tract infections. In: Mandell GL, Bennett JE, eds. Principles and Practice of Infectious Diseases, 8th ed. Philadelphia: Elsevier Saunders, 2014:886-913.

**Diagnosis**

A clinical diagnosis of uncomplicated cystitis or pyelonephritis is made in a patient who has the signs and symptoms of a UTI and laboratory evidence of pyuria, i.e. the presence of white blood cells in the urine; and/or bacteriuria, i.e. the presence of bacteria in the urine. Laboratory diagnostic tools include urinalysis, either by microscopy or dipstick, and urine culture.

Urinalysis (UA) is a relatively simple, office-based test that can be used to evaluate patients with urinary complaints. In urgent care settings where UA is available, dipstick results rather than microscopic analysis may be more likely to be utilized. The different components of dipstick testing vary in their accuracy for predicting infection, with nitrite having the highest specificity (adjusted odds ratio of 6.36 in one study) but poor sensitivity (i.e., it will be negative in many patients who have a UTI). The combination of dipstick-positive leukocyte esterase and blood may have the highest sensitivity (77%) and specificity (70%).Urinalysis results may also suggest diagnoses other than UTI or the need for additional history or examination, as when clue cells or trichomonads are found in a specimen.[31]

Urine culture is traditionally the gold standard for diagnosing UTI, and, though a culture showing no growth essentially rules out UTI caused by the most common organisms, sensitivity and specificity will vary depending on the threshold colony count used and whether a specimen is obtained by catheterization or other methods. As well, the time required for culture results often exceeds the time to clinical cure with empiric treatment, and cultures can add significantly to the cost while not improving the quality of care in the majority of cases.

As with any clinical situation, diagnostic tests should be used when their results may improve management compared with not using them. The finding that, in patients with at least one UTI symptom, even a completely normal further history, physical exam, and dipstick UA cannot rule out UTI is often used as a rationale to not perform UA in patients with typical

symptoms. Still, UA may have some use when there is diagnostic uncertainty, and, though it requires microscopy, findings of pyuria without bacteriuria increase the chance that a sexually transmitted infection rather than a UTI is present. An interesting study showed no significant difference in clinical outcomes whether patients were treated with antibiotics, in an immediate or delayed fashion, based on symptoms alone or based on UA results, though antibiotics were used less often if testing or delayed prescribing was employed. A cost effectiveness analysis8 showed that basing antibiotic treatment on dipstick testing was cost-effective, compared with treating immediately without testing, if avoiding a day of moderately severe symptoms was valued at $15 (10 British pounds) or more. Though the monetary cost may not be directly paid by them, this is probably the case for most patients.

Urine culture ideally obtained before and without delaying antibiotics is recommended in patients with acute pyelonephritis and in the management of pediatric UTIs. Culture is also recommended in patients with complicated UTIs (men, pregnant women, and patients with immunosuppression or urinary tract malformations, urinary tract stones, recent urologic instrumentation, indwelling catheters, neurogenic bladder, and kidney transplant) and may also be helpful, while starting empiric therapy, in patients with a previous history of known resistant infections, failure of empiric antibiotics, or multiple recurrent UTIs. The yield of culture is lower in patients who are taking antibiotics at the time of testing.

Basic blood work (CBC, chemistry panel, blood culture) rarely helps decision-making for patients with uncomplicated UTI, and no useful role has been shown for erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP). Patients with suspected concomitant urinary tract obstruction or who show signs of severe systemic infection usually require prompt imaging with ultrasound or CT, and typically blood work is obtained for these patients and anyone else requiring hospitalization. CT without contrast is preferred for diagnosing urinary calculi and obstruction. Intravenous (IV) contrast may be used for a “CT urogram” and both IV and oral contrast is typically used is inflammatory disorders such as appendicitis or diverticulitis need to be excluded, though more recent evidence shows that unenhanced CT may be adequate.[32]

**Management**

Uncomplicated UTIs are usually treated empirically with antibiotics as recommended by primary care guidelines. Antibiotics for empiric treatment of uncomplicated UTI include.

**First-line antibiotic**: Trimethoprim/sulfamethoxazole in communities with resistance rates for E. coli <20%. Avoid in women who have been treated within six months, as they are more likely to have resistant organisms.

**Second-line antibiotics or first-line in resistant communities**: Fluoroquinolones, such as ciprofloxacin, levofloxacin, norfloxacin and ofloxacin. Although, antibiotic treatment supports clinical cure in individual patients but also leads to emerging resistance rates in the population. Resistance has increased to various antimicrobials and more than one-quarter of E. coli strains causing acute cystitis are resistant to amoxicillin, sulfa drugs and cephalexin and resistance to co-trimoxazole is now approaching these levels. Resistance to fluoroquinolones is also rising.

Akram et al reported ciprofloxacin resistance rates ranging from 47 to 69% among the gram-negative organisms in their study in India.12 High levels of extended-spectrum beta-lactamase (ESBL) producers among gram-negative community-acquired uropathogens is seen in our country. This, along with the alarming rate of resistance to ciprofloxacin, sulfamethoxazole-trimethoprim and amoxicillin, precludes the use of these commonly used antibiotics for empiric treatment of community acquired UTI in India.[13]

To prevent resistance, antibiotics should be used judiciously; they should be prescribed for as short a period as possible. Milo and colleagues reviewed 32 randomized controlled trials (with a total of 9,605 patients) comparing three days of oral antibiotic therapy with longer courses for women 18-65 years of age. Pregnant women and women with symptoms that suggest upper UTI (e.g., fever, flank pain, vomiting, positive blood cultures) were excluded. For short- and long-term resolution of symptoms, the reviewers found no difference between a 3-day antibiotic course and a course lasting 5-10 days. Longer courses were more effective at clearing the bacteria on follow-up culture but also caused more adverse effects, and it was not clear that bacterial clearance resulted in improved patient-oriented outcomes.

However, not everyone diagnosed by a general practitioner with a UTI and treated with an antibiotic will necessarily have a bacterial infection. At least one-half of women who suspect that they have UTI actually do.[15] Fifty percent of patients consulting with urinary tract symptoms may not have a clinically important infection on culture. In a study by Eshwarappa et al in a South Indian population, only 510 of the 5,564 suspected cases (9.17%) were proved by culture.[16] Studies have shown that one in 7 patients given an antibiotic for UTI

symptoms will return within 28 days for a further prescription of antibiotic. In many patients without additional risk factors, UTI seems to be a self-limiting condition. Studies have shown that many UTIs are self-limiting, improving without treatment even when culture is positive. One trial in Belgium has shown that half of the patients were free of symptoms after three days of placebo. If the volume of antibiotic prescribing is to be reduced and the increasing problem of resistant organisms addressed, alternative diagnostic and treatment strategies in primary care are needed.[20] Symptomatic treatment of uncomplicated UTI may be an option which merits further research.

**Symptomatic Treatment of Uncomplicated UTI**

Symptomatic UTIs are among the most common of bacterial infections. Though relatively benign and self-limiting, these irritating voiding symptoms like urinary urgency, frequency, nocturia, painful voiding, bladder discomfort or stranguria greatly distress the patient and have a detrimental influence on patient quality-of-life. Symptomatic treatment allows time for microbiological investigation and helps to reduce unnecessary prescribing of antibiotics. A urinary tract analgesic would have an immense reassuring effect on the patient. Phenazopyridine is a urinary tract antiseptic and analgesic that has for long been used to provide symptomatic relief of the pain, burning, frequency and urgency associated with UTI during the first 24-48 hours of therapy.

**Urinary tract infections and asymptomatic urinary tract infections in pregnancy**

A UTI in a pregnant woman is a significant risk factor for low birth weight infants and prematurity. Asymptomatic bacteriuria, i.e. the presence of bacteria in the urine without UTI symptoms, occurs in 5-9% of women, and does not require treatment, except in pregnant women. Therefore, pregnant women should be screened at 12-16 weeks gestation for bacteriuria. If left untreated during pregnancy, progression to a symptomatic UTI, including acute cystitis and pyelonephritis, occurs in 15-45% of pregnant women. This is largely owing to a less robust immune response in pregnant women.

Bacteriuria should be treated in pregnant women with a three day course of an antimicrobial agent, e.g. cefixime 250mg, once daily, for three days, which reduces the risk of a symptomatic UTI by 80-90%.

Fluoroquinolones are contraindicated in pregnancy. Therefore, the following empirical antimicrobial agents should be used for the treatment of acute cystitis, with de-escalation to a

narrowerspectrum agent once the urine culture and susceptibility results have become available:

- Amoxicillin and clavulanate 875 mg/125 mg orally, 12 hourly, before the third trimester
- Cefuroxime 250 mg orally, eight hourly, is preferred in the third trimester
- Cystitis should be treated for five days.

The management of acute pyelonephritis in pregnant women usually includes hospital admission so that a parenteral antimicrobial agent can be administered.[11] Antimicrobial therapy can be converted to an oral regimen tailored to the suscepti- bility profile of the isolated organism following clinical improvement. Broad-spectrum parenteral beta-lactams, e.g. cefazolin, are preferred as initial empirical therapy for pyelonephritis.

Fluoroquinolones and aminoglycosides, which are often used for pyelonephritis in non-pregnant women, should be avoided in pregnancy, if possible. Once afebrile for 48 hours, pregnant patients can be switched to oral therapy, and discharged to complete 10-14 days of antimicrobial treatment.

**Recurrent urinary tract infections in women** Recurrent uncomplicated UTIs are common in young, healthy women, even though these women have anatomically and physiologically normal urinary tracts. Recurrent UTIs are ≥ 2 infections in six months, or ≥ 3 infections in one year. Most recurrences are thought to represent reinfection, rather than relapse.

Antimicrobial prophylaxis has been shown to be highly effective in reducing the risk of recurrent UTIs in women. Continuous prophylaxis and postcoital prophylaxis (taken within two hours of intercourse) are effective in the management of recurrent uncomplicated cystitis. The choice of treatment depends on the frequency and pattern of recurrence, as well as patient preference. The choice of an antimicrobial agent should be based on the susceptibility patterns of the strains which caused the patient's previous UTIs. Before any prophylaxis regimen is initiated, eradication of a previous UTI must be assured by obtaining a negative urine culture 1-2 weeks after treatment.

Options for continuous and post-coital antimicrobial prophylaxis in women with recurrent UTIs are outlined in Table IV.

Table IV: Options for continuous and post-coital antimicrobial prophylaxis for women with recurrent urinary tract infections.

| Continuous antimicrobial prophylaxis | Post-coital antimicrobial prophylaxis |
|---|---|
| • Cotrimoxazole 40/200 mg, once daily, | • Cotrimoxazole 40mg/200 mg stat, |
| Or | |
| • Nitrofurantoin 50-100 mg, once daily | • Nitrofurantoin 50-100mg, stat |

**Treatment Considerations**

-Antimicrobial prophylaxis is the prevention of infection of the urinary tract by the administration of antimicrobial drugs If the term is used correctly in reference to the urinary tract, it can be assumed that bacteria have been eliminated before prophylaxis is begun. Surgical antimicrobial prophylaxis entails administration of an antimicrobial agent before and for a limited time after a procedure to prevent local or systemic post procedural infections.

-Antimicrobial suppression is the prevention of growth of a focus of bacterial persistence that cannot be eradicated. A low, nightly dosage of an antimicrobial agent usually results in the urine showing no growth, as in the case of a stone colonized with bacterial infection stone) or in bacterial prostatitis caused by *Escherichia coil.*

-Suppressive is also a useful term when recurrent acute symptoms prevented in a poor-risk patient, such as one with a large stag horn calculus in whom the antimicrobial agent reduces but do eliminate the bacteria in the urine. Domiciliary or outpatient UTIS occur in patients who are not hospitalized or institutionalized at the time they becomes infected.

-Nosocomial or health care-associated UTIS occur in patients who are hospitalized or institutionalized, and these are typically caused by Pseudomonas and other more antimicrobial-resistant strains.

-The main element of treatment for UTI in the United States is antibiotics; phenazopyridine may be prescribed as an adjunct to alleviate symptoms. An evidence-based guideline for the antimicrobial treatment of UTI in adults was published in March2011 by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases4 and included interesting considerations, balancing the positives of likely efficacy with negatives, termed “collateral damage,” relating to the “ecological adverse effects of antimicrobial therapy.” The following recommendations come from that guideline.

**Antibiotic Treatment for Uncomplicated Acute Cystitis.**[33]

| |
|---|
| Nitrofurantoin 100 mg BID for 5 days<br>OR<br>Trimethoprim-sulfamethoxazole DS (160/800 mg) BID for 3 days (if prevalence of resistance is < 20%)<br>OR<br>Fosfomycin trometamol 3 gm single dose<br>OR<br>Pivmecillinam 400 mg BID for 5 days (not available in the United States)<br>**If availability or allergy history precludes these choices, then use:**<br>Fluoroquinolones for 3 days<br>OR<br>Beta-lactams (amoxicillin-clavulanate, cefdinir, cefaclor, or cefpodoxime-proxetil) for 3 to 7 days Abbreviations: BID, twice a day; DS, double strength |

Recommended treatment for patients with uncomplicated cystitis includes nitrofurantoin monohydrate macrocrystals (100mg twice daily for five days) and trimethoprim-sulfamethoxazole (160/800mg [1 double-strength tablet] twice-daily for three days) can be used when resistance prevalence to it is less than 20%. Fosfomycin trometamol (3g in a single dose) is an option, though there is some evidence of decreased efficacy compared to the above regimens.

-Though not sold in the Unites States, pivmecillinam 400mg twice a day for five days is an additional alternative, where available.

-Three-day regimens of fluoroquinolones like ofloxacin, ciprofloxacin, and levofloxacin, are very effective but have higher rates of collateral damage, and the guideline authors recommend that these be reserved for more serious infections and only be considered alternates for uncomplicated acute cystitis.

-Beta-lactam agents, including amoxicillin-clavulanate, cefdinir, cefaclor, and cefpodoxime-proxetil, in three- to sevenday regimens are appropriate choices if the other recommended agents cannot be used, though they have lower efficacy and a higher rate of adverse effects.
-There is less evidence to support the use of cephalexin and other beta-lactams than those above, though the guideline authors felt that they might be “appropriate in certain setting while not elaborating on what those settings. Amoxicillin and ampicillin are not recommended for patients with cystits.

**Outpatient Antibiotic Treatment for Uncomplicated Acute Pyelonephritis.**[33]

| |
|---|
| **If fluoroquinolone resistance prevalence is less than 10%:** |
| Ciprofloxacin 500mg BID for 7 days, with or without an initial 400-mg dose of IV ciprofloxacin or 1g of IV ceftriaxone or a consolidated 24-hour IV dose of an aminoglycoside |
| OR |
| Ciprofloxacin XR 1000 mg once daily for 7 days |
| OR |
| Levofloxacin 750mg once daily for 5 ays |
| **If fluoroquinolone resistance prevalence is 10% or more, then use:** |
| Ciprofloxacin 500 mg BID for 7days, plus initial 1 g dose of IV ceftriaxone or a consolidated 24-hour IV dose of an aminoglycoside |
| OR |
| Ciprofloxacin XR 1000mg once daily for 7 days, plus initial 1g dose of IV ceftriaxone or a consolidated 24hour IV dose of an aminoglycoside |
| OR |
| Levofloxacin 750mg once daily for 5 days, plus initial 1g dose of IV ceftriaxone or a consolidated 24-hour IV dose of an aminoglycoside |
| **If infecting organism is known to be susceptible:** |
| Trimethoprim-sulfamethoxazole DS (160/800mg) BID for 14 days, plus an initial 1g dose of IV ceftriaxone or a consolidated 24-hour IV dose of an aminoglycoside |
| **Only if above regimens are contraindicated** |
| Oral beta-lactam (amoxicillin-clavulanate, cefdinir, cefaclor, or cefpodoxime-proxetil) for 10-14 days, plus an initial 1 g dose of IV ceftriaxone or a consolidated 24-hour IV dose of an aminoglycoside. |

To be managed as outpatients, individuals with pyelonephritis should be able to maintain their hydration and take oral antibiotics; fluoroquinolones are the primarily recommended. Oral ciprofloxacin (500mg twice daily for seven days), with or without an initial 400-mg dose of intravenous (IV) ciprofloxacin (or 1g of IV ceftriaxone or a consolidated 24-hour dose of an aminoglycoside) can be used for outpatients if fluoroquinolone resistance prevalence is less than 10%. There is no rate of resistance at which a definite recommendation could be made to use something other than a fluoroquinolone.

If, however, resistance is known or thought to exceed 10%, then a single initial dose of 1g of ceftriaxone or a consolidated 24-hour dose of an aminoglycoside should be given IV prior to starting outpatient oral therapy with ciprofloxacin 500mg twice daily. Other oral fluoroquinolone regimens (ciprofloxacin extended-release 1000mg once a day for seven days or levofloxacin 750mg for five days) are alternatives and may be given without consideration of an initial IV dose unless fluoroquinolone resistance prevalence exceeds 10%.

In this case, as with the above situation, a single initial IV dose of 1g of ceftriaxone or a consolidated 24-hour dose of an aminoglycoside should start treatment. Oral trimethoprim-

sulfamethoxazole (160/800mg [1 doublestrength tablet] twice-daily for 14 days) may be used, but only if the infecting organism is known to be susceptible. Patients receiving this regimen should all receive a starting IV dose of a long-acting antibiotic, e.g., 1 g of ceftriaxone or a consolidated 24-hour dose of an aminoglycoside. The guideline authors give a weaker recommendation to use oral beta-lactams (e.g., amoxicillin-clavulanate, cefdinir, cefaclor, and cefpodoximeproxetil) due to lower effectiveness. These should be taken for 10-14 days and may be considered in situations where there are contraindications to the other treatment options. All patients with pyelonephritis treated with oral beta-lactams should receive a starting IV dose of a long-acting antibiotic as above.

## CONCLUSION

Urinary tract infection is a common contagion among both genders with higher prevalence among women due to their physiology and pregnancy enhances the occurrence of the infection due to a variety of physiological changes during the course of pregnancy, and is frequent indication for the prescription of an antimicrobial agent. Antimicrobial resistance in uropathogens, particularly E. coli, is directly associated with prescribing in primary care. In addition, age is an important factor where elderly people with urinary devices like catheters are prone to the infection. The symptoms of UTI are associated with burning micturition, pain during voiding and increased frequency of urination can be a source of great discomfort and can greatly affect patients' quality-of-life. In addition, diabetes enhances the incidence due to elevated blood sugar levels and other factors like parity, gravidity, hormonal imbalance, immunosuppressant and geographical location also has a significant role in the incidence of the infection. Uncomplicated UTIs are usually treated empirically with antibiotics. However, antibiotics should not be prescribed excessively, particularly in view of the increasing prevalence of antibiotic resistance. Healthcare professionals should discuss the appropriate use of an antimicrobial agent with patients. The potential for antimicrobial resistance developing can also be reduced if patients complete the recommended treatment course, and do not stop treatment as soon as their symptoms improve. Such practices are also linked to an increased risk of antimicrobial resistance. Increasing concern about an association between the use of antimicrobial agents and acquired antimicrobial resistance has highlighted the need for rational pharmacotherapy when treating UTIs Symptomatic treatment is an option which allows time for microbiological investigation and helps to reduce unnecessary prescribing of antibiotics Patients undergoing long term treatment are also vulnerable to the infection due to moist hospitalized conditions.

**REFERENCES**


1. Weinick RM, Burns RM, Mehrotra A. Many emergency department visits could be managed at urgent care centers and retail clinics. Health Affairs. 2010; 29(9): 1630-36.
2. Urinary tract infections in women Jacky van Schoor, South African Family Practice, 2016; 58(1): 6-10
3. Cambell walsh urology 11 edition.
4. An introduction to the epidemiology and burden of urinary tract infections, Martha Medina and Edgardo Castillo-Pino Ther Adv Urol, 2019; 11: 3 –7 DOI: 10.1177/ 1756287219832172
5. Demilie T, Beyene G, Melaku S, et al. Urinary bacterial profile and antibiotic susceptibility pattern among pregnant women in north west ethiopia. Ethiop J Health Sci., 2012; 22(2): 121–128.
6. Parveen K, Momen A, Begum AA, et al. Prevalence of urinary tract infection during pregnancy. J Dhaka National Med Coll Hos., 2011; 17(2): 8–12.
7. Koffuor GA, Boye A, Siakwa PM, et al. Asymptomatic urinary tract infections in pregnant women attending antenatal clinic in Cape Coast, Ghana. E3 Journal of Medical Research, 2012; 1(6): 74–83.
8. Kolawole AS, Kolawole OM, Kandaki-Olukemi YT, et al. Prevalence of urinary tract infections (UTI) among patients attending Dalhatu Araf Specialist Hospital, Lafia, Nasarawa State, Nigeria. International Journal of Medicine and Medical Sciences, 2009; 1(5): 163–167.
9. Lucas MJ, Cunningham FG. Urinary tract infections in pregnancy. Clin Obstet Gynecol, 1993; 36(4): 855–868.
10. Gupta K, Stamm WE. Pathogenesis and management of recurrent urinary tract infections in women. World J Urol, 1990; 17(6): 415–420.
11. Urinary Tract Infections By Helen S. Lee, Pharm. D., BCPS-AQ ID; and Jennifer Le, Pharm. D., M.A.S., FIDSA, FCCP, FCSHP, BCPS-AQ ID.
12. Diagnosis and treatment of urinary tract infections across age groups Christine M. Chu, MD; Jerry L. Lowder, MD.
13. Urinary Tract Infections in Women Ramesh hot ChandanI*, kk aggarwal**.
14. Stamm WE, Norrby SR. Urinary tract infections: disease panorama and challenges. J Infect Dis, 2001; 183(1): S1–S4. [PubMed: 11171002.
15. Schappert SM, Rechtsteiner EA. Ambulatory medical care utilization estimates for 2007. Vital Health Stat, 2011; 13: 1–38.

16. Foxman B. Urinary tract infection syndromes: occurrence, recurrence, bacteriology, risk factors, and disease burden. Infect Dis Clin North Am, 2014; 28: 1–13. This paper presents the most recent information about UTIs and their socioeconomic impact. [PubMed: 24484571].
17. Foxman B. The epidemiology of urinary tract infection. Nature Rev Urol, 2010; 7: 653–660. [PubMed: 21139641.
18. Naber, K. G., Schito, G., Botto, H., Palou, J. andMazzei, T. European Urology, 2008; 54(5): 1164-1175.
19. Urinary tract infections: epidemiology, mechanisms of infection and treatment options. Ana L. Flores-Mireles*, Jennifer N. Walker*, Michael Caparon, and Scott J. Hultgren Department of Molecular Microbiology and Center for Women's Infectious Disease Research, Washington University School of Medicine, Box 8230, 660 South Euclid Avenue, St. Louis, Missouri 63110–1093, US. Published in final edited form as: Nat Rev Microbiol, 2015; 13(5): 269–284. doi:10.1038/nrmicro3432.
20. Nicolle, L. E., Bradley, S. and Colgan, R. Clinic of Infectious Disease, 2005; 40: 643.
21. Nicolle, L. E. Urology Clinics North America, 2008; 35(1): 1–12.
22. Stapleton, A. E., Dziura, J. and Hooton, T. M. A randomized controlled trial. Mayo Clinical Process, 2012; 87(2): 143-156.
23. Tim Taylor, M. Inner Body Journal, 2014; 52: 16-18.
24. Foster, R. T. S. Obstetrics & Gynecology Clinicians North American, 2008; 35: 235–48.
25. Perrotta, C., Aznar, M., Mejia, R., Albert, X. andNg, C. W. Cochrane database of systematic reviews (Online), 2008; (2): 5131.
26. Raynor, M. C. andCarson, C. C. The Medical Clinics of North America, 2011; 95(1): 43–54.
27. Wrenn K. Dysuria, frequency, and urgency. Chapter 18. In: Clinical Methods: The History, Physical, and Laboratory Examinations. 3rd edition, Walker HK, Hall WD, Hurst JW (Eds.), Butterworths: Boston; 1990.
28. Diagnosis and treatment of urinary tract infections across age groups Christine M. Chu, MD; Jerry L, Lower, MD.
29. Salvatore, S., Cattoni, E., Siesto, G., Serati, M., Sorice, P. and Torella, M. European Journal of Obstetrics, Gynecology, and Reproductive Biology, 2011; 156(2): 131–136.
30. Litza, J. A. andBrill, J. R. Prime Care, 2010; 37(3): 491- 507.

31. Little P, Turner S, Rumsby K, et al. Developing clinical rules to predict urinary tract infection in primary care settings: sensitivity and specificity of near patient tests (dipsticks) and clinical scores. Br J Gen Pract, 2006; 56(529): 606–612.
32. Little P, Moore MV, Turner S, et al. Effectiveness of five different approaches in management of urinary tract infection: randomised controlled trial. BMJ, 2010; 340: c199.
33. Gupta K, Hooton TM, Naber KG, et al. Infectious Diseases Society of America, European Society for Microbiology and Infectious Diseases. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis, 2011; 52(5): e103-20.