

Urinary Tract Infection: General Considerations

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INTRODUCTION

Urinary Tract Infection (UTI) is common illness of human beings and fortunately responsive to antimicrobial treatment, affecting both men and women of all ages and vary dramatically in clinical presentation. Although urinary tract is normally free of bacterial growth, but can ascend from rectal reservoir and causes UTI.

It is described as inflammatory response of the urothelium to bacterial invasion associated with bacteruria and pyuria. Bacteriuria is the presence of bacteria in urine and is a valid indicator of either bacterial colonization or infection of urinary tract. Pyuria is the presence of degenerating white blood cells in the urine and is indicative of infection and the inflammatory response of urothelium to the bacterium [1].

Infections of the urinary tract are the second most common type of infection in the body, after the flu and common cold. It is particularly common in females, (10 – 20%) of women have UTI at some time in their life and significant number have recurrent infection [2].

Urinary tract infection can be categorized on the anatomical and functional status of urinary tract [1]:

Uncomplicated UTI is an infection in structurally and functionally normal urinary tract for example acute cystitis and acute pyelonephritis.

A complicated infection is associated with structurally or functionally abnormal tract, which increases the chances of acquiring bacteria for example prostate enlargement, renal calculi, diverticula.

Isolated infection is one that occurs in individual, who never had UTI or had remote infection.

An unresolved infection is one that has not responded to antimicrobial treatment.

A recurrent infection is one after the successful treatment of previous infection.

Reinfection is a newer one associated with reintroduction of bacteria in tract from outside.

Bacterial persistence is the recurrent UTI caused by same bacteria emerging from a focus in urinary tract.

Relapse, is when the same microorganism causes a UTI within two weeks of therapy; however, it is usually difficult to distinguish a reinfection from a relapse [3].

EPIDEMIOLOGY

UTIs are one of the most frequent clinical bacterial infections in women, accounting for nearly 25% of all infections affecting female and male, at a ratio of 8:1 [4-6] It account for more than 8 million visits to physician's offices, 1.5 million emergency room visits and 300,000 hospitals admission in the United States annually. These infections cost of more than \$3.5 billion [7].

In the female population, these infections occur in 1-3 % of school girls and then increases markedly in incidence with the onset of sexual activity in adolescence. Incidence in women, in the age group of 20- 40 years, ranges from 25 to 30% whereas in older women, above 60 years of age it ranges from 4 to 43% [7].

Risk Factors [8-10]

Physiological factors:	
1. Sex	More common in female, men because bacteria can reach the bladder more easily in women, the urethra is shorter in women than in men, which is 1.5 inches compared to 8 inches in men and also located near the rectum in women.
2. Age	Young sexual active females are more prone to develop UTI because bacteria can be pushed into the urethra, using a diaphragm make it harder to completely empty the bladder.
3. Rituals	Uncircumcised boys younger than one year old also have a slightly higher risk of developing a UTI.
4. Other Illness	Presence of some metabolic or immunologic disorder can also predispose infection (i.e. diabetes mellitus)

Surgical Causes [10,11]

1. An abnormal backward flow (reflux) of urine from the bladder up the ureters and toward the kidneys, this condition, known as Vesicoureteral Reflux (**VUR**), is present at birth, and about 30% to 50% of children with a UTI are found to have it.
2. Mechanical factors are important. Anything that disrupts normal urine flow or complete emptying of the bladder, or facilitates access of organisms to the bladder, will predispose an individual to infection for example obstruction due to lithiasis, tumours, prostatic hypertrophy, pregnancy, strictures of any sorts including congenital malformations.
3. Functional neuromuscular disorders e.g. spina bifida, paraplegia or multiple sclerosis and also iatrogenic reasons – catheterization.

ETIOLOGY

Bacteria are most common cause of urinary tract infection, organism invading the urinary tract range from Gram positive cocci to Gram negative bacilli (Table 1) in this respect, Gram negative bacilli are considered the most common bacteria incriminated in UTI [12].

Group	Organisms
Gram negative bacteria	<i>Escherchia coli</i> (Figure 1) <i>Proteus mirabilis</i> <i>Klebsiella spp.</i> (Figure 1) <i>Enterobacter spp.</i> <i>Serratia marsecens</i> <i>Citrobacter spp.</i> <i>Pseudomonas areuginosa</i> <i>Providencia spp.</i> <i>Gardnerella vaginalis</i> <i>Mycoplasma spp.</i> <i>Ureaplasma spp.</i>
Gram positive bacteria	<i>Staphylococcus saprophyticus</i> <i>Staphylococcus epidermidis</i> <i>Staphylococcus aureus</i> <i>Enterococci</i> <i>E.faecalis</i>
Others	<i>Candida spp.</i>



Figure 1: *Escherichia coli* and *Klebsiella* spp. on Mac conkey agar.

PATHOGENESIS

UTI s is result of interaction between uropathogens and the host. Successful infection of urinary tract tract is determined by the virulence factors of the bacteria, the inoculums size and the inadequacy of host defense mechanism [1].

Route of Infection

A) Ascending route

It includes ascend of infectious agents from the external (genital and perineal) to the urinary tract and cause infection [14]. Ascending infection is most common cause of UTI in women than in men [15] as the antibacterial properties of prostatic fluid also account for increase resistance of UTI observed in men [16].

B) Descending route

It includes the transfer of bacteria from circulating blood which contains bacteria to urine through the kidney [17].

C) Lymphatic route

This is rare one, in this pathway bacterial pathogens may travel through the rectal and colonic lymphatic to the prostate bladder, and through the preuterine lmphatics to the female urogenital tract [18].

Despite the presence of several antibacterial factors such as the pH, urea concentration, osmolarity, various organic acids, salt content of the urine, urinary inhibitors to bacterial adherence e.g. Tamm-Horsfall protein (THP), bladder mucopolysaccharide, low-molecular-weight oligosaccharides, secretory IgA and lactoferrin, the uropathogenic bacteria are able to adhere, grow and resist against host defenses that finally resulting in colonization and infection of the urinary tract [19-22].

Following are interacting factors for development of UTI [1,23-29]:

Host factors	Pathogen/ virulence factors	Environmental factors
Age – menopause increases risk of UTI	Source of infection	Vaginal etiology
Sex	Bacterial adherence: P Fimbriae, pili, adhesins	Density of receptors for bacteria
Genetic make over	Biofilm production	Anatomical factors
Blood group P1	Hemolysin	Functional abnormality – spinal cord injury, multiple sclerosis
Immunodeficiency: effecting host immune system against invading bacteria	Serum resistance	Surgical causes
Poor nutritional status, smoking	Haemagglutination	Prolonged hospitalization
Contraception use		

Four groups are at increased risk of UTI: school-age girls, men with lower urinary tract obstruction, the elderly and young women in their sexually active years [30].

Post–menopausal women have higher rate of UTIs because of pelvic prolapsed, lack of estrogen, loss of lactobacilli in the vaginal flora, increased periurethral colonization by *Escherichia coli* [31].

Escherichia coli is the most common cause of uncomplicated UTI and accounts for approximately 75 to 95 percent of all infections, because of presence of this microbe in faecal matter and its readily availability to urethra from perineum [32].

In diabetic patients, *Klebsiella* and group B *streptococcus* infections are more common. *Pseudomonas* infections are more common in chronically-catheterised patients [33-34]. Urinary tract infections due to *Staphylococcus aureus* typically occur secondary to blood-borne infections [35].

Chlamydia trachomatis and *Mycoplasma genitalium* can infect the urethra but not the bladder [36] known as *urethritis* rather than urinary tract infection.

CLINICAL SYNDROMIC APPROACH TO UTI [37]

Asymptomatic Bacteriuria

A diagnosis of ASB can be considered only when the patient does not have local or systemic symptoms referable to the urinary tract. The clinical presentation is usually that of a patient who undergoes ascreening urine culture for a reason unrelated to the genitourinary tract and is incidentally found to have bacteriuria.

Cystitis

The typical symptoms of cystitis are dysuria, urinary frequency, and urgency. Nocturia, hesitancy, suprapubic discomfort, and gross hematuria are often noted as well. Unilateral back or flank pain is generally an indication that the upper urinary tract is involved. Fever also is an indication of invasive infection of either the kidney or the prostate.

Pyelonephritis

Mild pyelonephritis can present as low-grade fever with or without lower-back or costovertebral-angle pain, whereas severe pyelonephritis can manifest as high fever, rigors, nausea, vomiting, and flank and/or loin pain. Symptoms are generally acute in onset, and symptoms of cystitis may not be present. Fever is the main feature distinguishing cystitis and pyelonephritis. The fever of pyelonephritis typically exhibits a high spiking “picket-fence” pattern and resolves over 72 h of therapy. Bacteremia develops in 20–30% of cases of pyelonephritis.

Prostatitis

Prostatitis includes both infectious and noninfectious abnormalities of the prostate gland. Infections can be acute or chronic, are almost always bacterial in nature, and are far less common than the noninfectious entity chronic pelvic pain syndrome. Acute bacterial prostatitis presents as dysuria, frequency, and pain in the prostatic pelvic or perineal area. Fever and chills are usually present, and symptoms of bladder outlet obstruction are common. Chronic bacterial prostatitis presents more insidiously as recurrent episodes of cystitis, sometimes with associated pelvic and perineal pain. Men who present with recurrent cystitis should be evaluated for a prostatic focus.

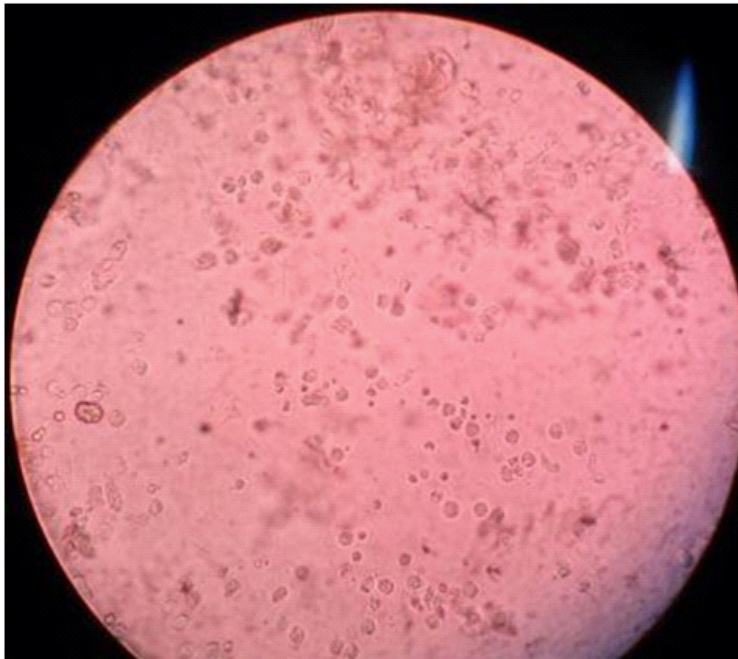
Complicated UTI

It presents as a symptomatic episode of cystitis or pyelonephritis in a man or woman with an anatomic predisposition to infection, with a foreign body in the urinary tract, or with factors predisposing to a delayed response to therapy.

DIAGNOSIS

Urinalysis

Microscopy is a valuable adjunctive diagnostic tool for patients with urinary symptoms, there are limitations in detecting microscopic bacteriuria and pyuria because of lack of standardization for the microscope itself (including magnification) and the volume of urine that can be observed, as well as if the urine is spun or unspun, stained or unstained. However, if microscopy is performed, the absence of pyuria should cause a physician to reconsider UTI as a diagnosis. Indirect dipstick test for bacteriuria (nitrite) or pyuria (leukocyte esterase) can be helpful. Although they are less sensitive than microscopic examination of the urine [38].



Urine Culture

Urine culture and sensitivity testing are the standard diagnostic investigations to detect the causative organism and to determine the type of antimicrobial therapy needed [39,40]. A 'clean-catch' or midstream technique needs to be used when collecting the urine sample, which reduces the risk of vaginal and skin contamination to approximately 30% [41].

Diagnosis of UTI is influenced by which of the clinical UTI syndromes is suspected [37].

Uncomplicated cystitis in women

If the symptoms are not specific or if a reliable history cannot be obtained, then a urine dipstick test should be performed. A positive nitrite or leukocyte esterase result in a woman with one symptom of UTI increases the probability of UTI from 50% to ~80%, and empirical treatment can be considered without further testing. In this setting, a negative dipstick result does not rule out UTI, and a urine culture, close clinical follow-up, and possibly a pelvic examination are recommended.

Cystitis in men

Collection of urine for culture is strongly recommended when a man has symptoms of UTI, as the documentation of bacteriuria can differentiate the less common syndromes of acute and chronic bacterial prostatitis from the very common entity of chronic pelvic pain syndrome, which is not associated with bacteriuria and thus is not usually responsive to antibacterial therapy. If the diagnosis is unclear, localization cultures using urine collection after prostate massage

should be undertaken to differentiate between bacterial and nonbacterial prostatic syndromes. Men with febrile UTI often have an elevated serum level of prostate-specific antigen as well as an enlarged prostate and enlarged seminal vesicles on ultrasound—findings indicative of prostate involvement.

Asymptomatic Bacteriuria (ASB)

The diagnosis of ASB involves both microbiologic and clinical criteria. The microbiologic criterion is usually ≥ 105 bacterial CFU/mL except in catheter-associated disease, in which ≥ 102 CFU/mL is the cutoff. The clinical criterion is that the person has no signs or symptoms referable to UTI.

Urinalysis, either by dipstick or microscopy, for the detection of pyuria, as a method for predicting a UTI has a sensitivity of 80–90% and a specificity of 50%, but it only detects those bacteria which reduce nitrates to nitrites in the urine. Bacteria such as *Staphylococcus saprophyticus* lack that enzyme, which makes the nitrite test considerably less useful. Dipstick analysis for leukocyte esterase (the enzyme produced by neutrophils) is indirect and detects pyuria with a sensitivity of 72–97% and a specificity of 41–86%, as organisms other than uropathogens can also produce leukocyte esterase [42].

Further investigations including radiologic investigations and cystoscopy are important if a patient is believed to have any of the following: hematuria, a complicated UTI suggested by a history of calculi, obstruction (upper or lower urinary tract), neuropathic bladder, recent genitourinary surgery or catheterization, unusual organisms (such as tuberculosis, fungus, or urea-splitting organisms), compromised immune system, diabetes, or renal failure. Similarly, investigations are required in patients who do not respond to appropriate antimicrobial therapy after 5 to 6 days of treatment.

Currently, renal ultra sonography is the preferred urinary tract imaging technique because it is noninvasive, easy to perform, and relatively inexpensive. Computed tomography and Magnetic resonance imaging offer the best anatomical detail [38].

More advanced investigations, such as cystoscopy, are advised in women over the age of 50 [43]. Ultrasound of the kidneys, an Intravenous Pyelogram (IVP) and a CT scan can help in detecting congenital structural urogenital anomalies [39].

MANAGEMENT OF URINARY TRACT INFECTIONS

General Therapies

- Patients should be advised and encouraged to drink plenty of fluids (two to three litres per day) and to urinate frequently to help flush bacteria from the bladder. Holding urine for a long time allows bacteria to multiply within the urinary tract, resulting in cystitis.
- Preventive measures related to sexual intercourse may reduce the recurrence rate. Moreover,

women are encouraged to clean the genital areas before and after sex and to wipe from front to back, which will reduce the spread of *E. coli* from the perigenital area to the urethra [44].

- Skin allergens introduced to the genital area, such as bubble bath liquids, bath oils, vaginal creams and lotions, deodorant sprays or soaps are better avoided as they could alter vaginal *flora* and ultimately result in UTIs [45].
- Use of oestrogen: Oestrogen use stimulates the proliferation of *lactobacillus* in the vaginal *epithelium*, reduces pH and avoids vaginal colonization by uropathogens, specifically after the menopause [46,47].
- Cranberry juice and tablets have been shown to reduce Recurrent UTIs as they contain a compound called tannin, or proanthocyanidin, which reduces *E. coli* vaginal colonization [48].
- Probiotics are beneficial microorganisms that could protect against UTIs. *Lactobacilli* strains are the best-known probiotics and are found in fermented milk products, mainly yogurt [49,50].
- Methenamine is hydrolysed to ammonia and formaldehyde when in acidic urine, which act as a bactericide to some strains of bacteria [51]. Patients should be informed regarding adequate hydration, adverse effects and the need to avoid milk products and antacids to help keep the urine acidic.

A) Recommendations for acute cystitis [52]:

Antibiotic	Dosage	General Consideration
Nitrofurantoin	100 mg bid for 5 days	An appropriate choice due to minimal resistance and collateral damage and efficacy comparable to 3 days of trimethoprim-sulfamethoxazole.
Trimethoprim-sulfamethoxazole	160/800 mg bid for 3 days	If local resistance rates of uropathogens causing acute uncomplicated cystitis do not exceed 20% or if the infecting strain is known to be susceptible.
Fosfomycin trometamol	3 g in a single dose	appropriate for therapy where it is available due to minimal resistance and propensity for collateral damage
Pivmecillinam	400 mg bid for 3–7 days	appropriate choice for therapy in regions where it is available
Fluoroquinolones,	dose varies by agent; 3-d regimen	highly efficacious but have a propensity for collateral damage and should be reserved for important uses other than acute cystitis.
β-Lactams,	dose varies by agent; 5- to 7-d regimen	
		Recommended when other recommended agents cannot be used.

B) Recommendations for Acute Pyelonephritis

In patients suspected of having pyelonephritis, a urine culture and susceptibility test should always be performed, and initial empirical therapy should be tailored appropriately on the basis of the infecting uropathogen.

Antibiotic	Dosage	General Consideration
Oral ciprofloxacin	500 mg bid for 7 days	appropriate choice for therapy in patients not requiring hospitalization where the prevalence of resistance of community uropathogens to fluoroquinolones is not known to exceed 10%.
Ceftriaxone i/v	1 gm	If the prevalence of fluoroquinolone resistance is thought to exceed 10%, an initial 1-time intravenous dose of a long-acting parenteral antimicrobial, such as 1 g of ceftriaxone or a consolidated 24-h dose of an aminoglycoside, is recommended
Oral trimethoprim-sulfamethoxazole	160/800 mg twice-daily for 14 days	choice for therapy if the uropathogen is known to be susceptible.
Oral b-lactam agents		less effective
I/V FQ; an aminoglycoside, an extended-spectrum cephalosporin or extended-spectrum penicillin; or a carbapenem		Choice of therapy in women with pyelonephritis requiring hospitalization, choice between these agents should be based on local resistance data.

I/V- Intravenous; FQ- Fluoroquinolones

C) Asymptomatic bacteriuria in pregnant women:

Recommendation: Pregnant women should be screened for bacteriuria by urine culture at least once in early pregnancy, and they should be treated if the results are positive .

- The duration of antimicrobial therapy should be 3–7 days.
- Periodic screening for recurrent bacteriuria should be undertaken after therapy .
- No recommendation can be made for or against routine repeated screening of culture-negative women in the later phase of pregnancy.

D) UTI in Men [37]

Since the prostate is involved in the majority of cases of febrile UTI in men, the goal in these patients is to eradicate the prostatic infection as well as the bladder infection.

- A 7- to 14-day course of a fluoroquinolone or cotrimoxazole is recommended if the uropathogen is susceptible.
- If acute bacterial prostatitis is suspected, antimicrobial therapy should be initiated after urine and blood are obtained for cultures.
- Therapy can be tailored to urine culture results and should be continued for 2–4 weeks.
- For documented chronic bacterial prostatitis, a 4- to 6-week course of antibiotics is often necessary.
- Recurrences, which are not uncommon in chronic prostatitis, often warrant a 12-week course of treatment.

E) Complicated UTI [37]

Therapy for complicated UTI must be individualized and guided by urine culture results. Frequently, a patient with complicated UTI will have prior urine culture data that can be used to guide empirical therapy while current culture results are awaited.

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