

Urinary Tract Infections

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INTRODUCTION

Urinary Tract Infections (**UTIs**) are the second most common bacterial infections worldwide, affecting about 150 million people each year. They are frequent disease in both ambulatory and acute care settings and results in high morbidity, mortality and increased costs. In the United States, during 2007, there were 10.5 million outpatient visits with UTI symptoms accompanied with great annual financial impact (US \$3.5 billion). UTIs represent the majority of health care-associated infections with 40% and are usually associated with use of urinary catheters. Each episode of catheter-associated UTI is estimated to cost about 600 USD. Anyway, assessment of the burden of UTIs is difficult because they are not reportable disease in surveillance systems of many countries.

UTI occur in patients of all ages, but is more frequent among women, where about 60 % of them have experienced UTI during their lifetime. The term urinary tract infection compresses a large group of conditions that include cystitis, pyelonephritis, ureteritis, urethritis and prostatitis (Table 1).

Table 1: Terminology commonly used for urinary tract diseases.

Bacteriuria	The Presence of Bacteria in Urine
Cervicitis	Infection affecting cervix manifested with dysuria, urgency, vaginal discharge and low back pain; it is usually caused by sexually transmitted agents (<i>Neisseria gonorrhoeae</i> and <i>Chlamydia trachomatis</i>).
Cystitis	Infection involving bladder and presenting with dysuria, urinary frequency and urgency
Complicated UTI	infection associated with structural or functional abnormality of the genitourinary tract, or the presence of an underlying disease that interferes with host defence mechanisms, increasing the risks of acquiring an infection or failing a treatment
Lower UTI	Cystitis, urethritis, prostatitis
Prostatitis	Infection of the prostate; fever is often present
Pyelonephritis	Infection in the kidney presenting with fever, chills, nausea, vomiting and lower back pain as well as dysuria
Relapse	Recurrence of infection with the same infecting microorganism that was present before therapy was started
Reinfection	Infection with a microorganism different from the original infecting bacterium. It is a new infection
Urethritis	Infection of the urethra, presenting with dysuria and discharge. Caused by <i>N. gonorrhoeae</i> , <i>U. urealyticum</i> , <i>C. trachomatis</i>
Urinary tract infection	Infection that affects any part of the genitourinary tract
Urosepsis	Sepsis syndrome which is caused by urinary tract infection
Uncomplicated UTI	Episodes of acute cystitis and acute pyelonephritis in otherwise healthy individuals
Upper UTI:	Pyelonephritis, intra-renal abscess, perinephric abscess

Classification of UTI is based on several criteria such are anatomical level of infection, grade of severity of infection, underlying risk factors and microbiological findings. This classification was prepared by European Association of Urology (**EAU**)/International Consultation on Urologic Diseases (**ICDU**) Urogenital Infections initiative, but is poorly implemented in practice.

The classification of UTIs is very important in their effective management in order to select the most appropriate therapy. In clinical practice, UTIs have been divided based on clinical picture and urinary tract location. From the clinical point, UTIs can be uncomplicated and complicated. Uncomplicated UTIs affect individuals who are healthy and have no abnormalities in the urinary tract and usually are caused by antibiotic-susceptible bacteria. Two main infections in this category are cystitis and pyelonephritis. Risk factors for cystitis are female gender, previous infections, diabetes, sexual activity, obesity and heredity.

Complicated UTI occurs mainly in persons with structural or functional abnormalities. They are associated with risk factors such are urinary obstruction, retention, spinal cord injuries, immunosuppression, renal failure, transplantation and the presence of foreign bodies (indwelling catheters and calculi).

Another classification of UTIs in clinical practice is by its location; they can be distinguished into upper UTI (involving renal parenchyma and ureters, with corresponding pyelonephritis and ureteritis) and lower UTI which involve the bladder (cystitis), the urethra (urethritis) and in males, the prostate (prostatitis).

There is also clinical schedule for classification of UTIs based on frequency of occurrence. Single-episode occurs only once, whereas in recurrent UTIs, patients have repeated episodes of infection. Recurrences of UTI may be relapses or reinfections.

PATHOGENESIS

The urinary tract is a body system for removing waste and excess water from organism. It is comprised by kidneys, ureters, bladder, urethra and prostate in males. The role of kidneys is to clean the blood and remove waste. This process creates urine, which then exit the kidney via the ureters to arrive in the bladder and finally voided through the urethra in the process of urination.

Innate immunity is cornerstone of antibacterial protection of the urinary tract. Urine represents a good culture medium for growth of many bacteria. Nevertheless, it also has antibacterial activity. Normal urinary tract efficiently eliminates microorganisms that gain access to the bladder through some antimicrobial defense factors in the lower urinary tract: bactericidal activity of urine (osmolality, pH, and organic acids), flushing mechanism of the bladder, inflammatory response and adaptive immune system. Urine has antibacterial activity, which results from a high concentration of urea and osmolality. This activity is related to pH of urine and is higher when a pH is low. In terms of antibacterial activity, urine from men is more inhibitory for microbes than from woman because of the bactericidal effect of fluids present in prostate and differences in pH and osmolality.

The pathogenesis of UTI is determined by the anatomy of urinary tract and is a result of interaction between virulence factors of microorganisms and host defense.

Microorganisms find their way into the urinary tract by three routes:

- ascending,
- hematogenous and
- lymphatic.

Ascending route is the most common way to develop UTI. Urethra is entrance point for bacteria into the urinary tract. Urinary tract infection starts when potential urinary pathogens from the bowel and vagina colonize the urethra and then ascend retrogradely to the bladder and/or kidney; starting process in the pathogenesis of UTI is adherence of microbes enabled through flagella and pili. In the bladder, after interactions between the host and pathogen the outcome will be either infection or elimination of microorganism.

Women are predisposed more to UTIs because of their anatomy of urogenital tract. The short urethra in women, which is closer to the anus, offers easier access for fecal bacteria to enter the urethra. This is main reason for predominance of UTIs among women.

Bacteria may also reach the urinary tract from the bloodstream. Hematogenous route occurs in patients who have bacteremia or endocarditis caused by gram positive organisms (mainly *S. aureus*) and *Candida* spp. Infections of the kidney with Gram negative bacilli is rarely caused by this route.

The impact of the lymphatic way in the pathogenesis of UTI (mainly pyelonephritis) is still not explained in details and is mainly based on animal models.

Catheterization is the most important factor in the pathogenesis of UTIs within the health care facilities. About 15-25% of patients in general hospitals have a catheter inserted during their stay. Urinary catheters increase the risk of bacteriuria in exponential order with duration of catheterization (from around 5% per day during the first week, to almost 100% at 4 weeks).

Under normal condition, urethral flora is constantly flushed away during the process of urination. But, when a catheter is inserted, this mechanism is avoided and bacteria can bypass and move into the bladder. Colonization of bladder is inevitable if catheters are used for long periods. Another factor in pathogenesis of UTIs is contact through the hands of health care workers, who can contaminate the urinary catheter system during their management.

Several virulence factors are attributed in the pathogenesis of UTIs. The most important are adhesines, fimbriae, flagella, toxin production, siderophores, capsular polysaccharides, lipopolysaccharides, biofilm formation and aerobactins.

Common risk factors for UTIs in all ages are neurologic instrumentation or surgical intervention, catheterization, urinary tract obstruction, renal calculi, neurogenic bladder and renal transplantation. In adult females the following factors pose a risk for infection: sexual intercourse, lack of urination after intercourse, spermicidal contraceptives, diaphragm use, pregnancy, menopause and diabetes. Enlarged prostate is important risk factor for infection among males.

MICROBIOLOGY

Various microorganisms may be found in the urine in different clinical settings. Normal bacterial flora of urethral area consists mainly of *Staphylococcus epidermidis*, but in about 10% of cases it may also cause infection, primarily catheter-associated. The microbial agents of urinary tract infections are presented in table 2.

Table 2: Microbial agents of urinary tract infection.

Clinical Presentation	Etiological Agents
Cystitis & Pyelonephritis	Gram negative bacilli: <i>Escherichia coli</i> , <i>Klebsiella spp.</i> , <i>Enterobacter spp.</i> , <i>Proteus mirabilis</i> , <i>Pseudomonas aeruginosa</i> , <i>Acinetobacter species</i> Gram positive cocci: <i>Staphylococcus aureus</i> , <i>Staphylococcus saprophyticus</i> , Coagulase negative Staphylococci, <i>Streptococcus β-haemolyticus gr.B</i> , <i>Enterococcus spp.</i> , <i>Aerococcus urinae</i> <i>Mycobacterium tuberculosis</i> (hematogenous source) <i>Corynebacterium urealyticum</i> , <i>Leptospira interrogans</i> . <i>Salmonella typhi</i> (with gastroenteritis) Fungi: <i>Candida albicans</i> , <i>Candida glabrata</i> , <i>Cryptococcus neoformans</i> <i>Trychosporon beigeli</i> Parasites: <i>Schistosoma haematobium</i> Viruses: Adenoviruses, <i>Herpes simplex virus</i>
Urethritis	<i>Chlamydia trachomatis</i> , <i>Neisseria gonorrhoeae</i> , <i>Mycoplasma hominis</i> , <i>Ureaplasma urealyticum</i> , <i>Gardnerella vaginalis</i> <i>Mobiluncus spp.</i> , <i>Candida spp.</i> , <i>Trichomonas vaginalis</i>
Prostatitis	<i>Escherichia coli</i> , <i>Klebsiella spp.</i> , <i>Proteus mirabilis</i> , <i>Enterococcus spp.</i> , <i>Enterobacter spp.</i> , <i>Neisseria gonorrhoeae</i> , <i>Mycobacterium tuberculosis</i> <i>Candida spp.</i> , <i>Cryptococcus neoformans</i> , <i>Blastomyces dermatidis</i> , <i>Coccidioides immitis</i> , <i>Histoplasma capsulatum</i>

In primary care settings, more than 95% of uncomplicated UTIs are monomicrobial; the predominant pathogen is *Escherichia coli*, causing 70-95% of urinary tract infections. Among *E. coli* the most prevalent serogroups are 01, 02, 04, 06, 07, 08, 075, 0150, 018ab. Other group of microorganisms causing UTIs includes Gram-positive cocci, such as *Staphylococcus saprophyticus* and *Enterococcus faecalis*. *S. saprophyticus* is usually causal factor of infection in young females who are sexually active, whereas infections with Enterococci are seen among older patients in association with urinary tract instrumentation and prostate hypertrophy.

Complicated UTIs are usually seen among hospitalized patients and patients in long term care facilities. Common microorganisms isolated in these infections include antibiotic-resistant *E.coli*, *Klebsiella spp.*, *Pseudomonas aeruginosa*, *Proteus species*, *Enterobacter species*, and *Acinetobacter species* as well as *Staphylococcus aureus*, Enterococci and fungi.

Sometimes, *S. aureus* can invade the kidneys through the hematogenous route causing sepsis. This invasion results in intrarenal or perinephric abscesses. Most cases of urosepsis occur among elder patients and among those undergoing urological instrumentation and with renal stones.

Anaerobic organisms are rarely pathogens in the urinary tract but their role have to be considered if they are isolated from suprapubic aspirates.

Among viruses, Adenoviruses have been identified as etiologic agents in children with hemorrhagic cystitis and those undergoing transplantation. Infections with fungi (particularly *Candida spp.*) occur in patients with urinary catheters. Several factors contribute for presence of fungi in urinary tract: critical illness, instrumentation of urinary tract, increased use of broad-spectrum antibiotics.

Less common agents retrieved from clinical samples of patients with UTI are *Gardnerella vaginalis*, *Mobiluncus spp*, *Ureaplasma urealyticum* and *Mycoplasma hominis*. Nevertheless, their causal role in pathogenesis of UTIs is controversial.

Other agents, such as *Cryptococcus neoformans*, *Trychosporon beigeli*, *Schistosoma haematobium*, *L. monocytogenes*, diphtheroids and Salmonella are rarely identified in UTI and they are usually associated with multisystem diseases.

Isolation of *Bacillus spp.* from urine samples is considered contamination. Several cases of UTI caused by *M. tuberculosis* has been reported in patients with HIV or other cases of immunosuppression.

During the last decade, in the spectrum of complicated UTIs in acute care hospitals have been reported multiresistant bacteria such as Enterobacteriaceae producing Extended-Spectrum *B*-Lactamases (**ESBLs**), AmpC β -lactamase and carbapenemases.

Recently was discovered a plasmid-borne colistin resistance gene, *mcr-1*. The gene has been identified in *Escherichia coli* and other members of the Enterobacteriaceae from human, animal, food and environmental samples worldwide.

CLINICAL MANIFESTATIONS

The clinical picture of UTIs can be variable. About 50% of infections do not produce recognizable illness and are discovered incidentally during a medical examination. The typical symptoms of acute uncomplicated cystitis are urinary urgency, dysuria (painful urination), frequency (frequent voiding), hematuria and suprapubic pain. In cases of lower UTIs, fever is usually absent but if it's accompanying clinical manifestations than it suggest the upper UTI. In a male, presence of fever with only symptoms of cystitis may indicate acute prostatitis. UTI in women is usually associated with the presence of symptoms, which lasts for one week.

Acute pyelonephritis is characterized with abdominal pain, fever, nausea, vomiting, and tenderness in costovertebral angle. Symptoms of cystitis may or may not be present in patients with pyelonephritis. If present, these signs can occur 24-48 hours prior to appearance of symptoms of pyelonephritis. Some patients with acute pyelonephritis can also have signs of sepsis.

Severe pain with radiation into the groin is rare in acute pyelonephritis and if present, indicates the presence of a renal calculus. Sometimes the pain from kidney is felt in the epigastrium and lower abdominal quadrants mimicking appendicitis and gallbladder disease.

UTIs occur in 1-2% of infants, about 5% of girls, and 0.5% or less of boys during their preschool years. UTIs in children can present with various symptoms, which in children under 2 years of age are nonspecific, and can include fever, vomiting and failure to thrive. After the age of 2 years, they may develop frequency, dysuria, and abdominal pain.

During adulthood, UTIs are predominant in women. Many of these patients previously had UTIs as children and continue to have infections as adults. The majority of infections occur in young, sexually active women aged 18-24 years. During this age the recurrent episodes are frequent disease.

The majority of older patients with urinary infection is asymptomatic or often has atypical symptomatology for UTI. At least 10% of men and 20% of women older than 65 years have asymptomatic bacteriuria. If they have symptoms, they can include abdominal pain or deterioration of mental status.

UTI is the most frequent source of bacteremia produced by gram-negative bacilli, which may result in the sepsis syndrome. Bacteremia may occur with no urinary symptoms, especially in hospitalized patients with the presence of an indwelling catheter.

DIAGNOSIS

Urine is the most commonly processed specimen in the microbiology laboratory. Urine in the bladder is usually sterile. Urethra contains many bacteria which comprise the normal flora and they frequently contaminate the clinical samples (e.g., *Lactobacillus*, *Streptococci*, and *Staphylococci*). But, these organisms are also implicated in UTI and sometimes are difficult to decide if the growth in urine culture is representing infection or contamination.

Quantification of bacteria in midstream voided urine sample is used to differentiate contamination from infection in urinary tract. Majority of patients with infection have at least 10^5 bacteria/mL in urine in the bladder. Patients without infection have sterile bladder urine, whereas sometimes even smaller amount of 10^2 - 10^4 may be significant in symptomatic patients. Calibrated loops in diameter 0.01 and 0.001 mL are used for bacteriological quantification of urine specimens.

Diagnosis of UTI is made through combination of clinical findings and laboratory criteria. Acute dysuria is the main symptom in cystitis and pyelonephritis. Anyway, this symptom is present also in other diseases, such are urethritis, vaginitis and in infections caused by *C. trachomatis*, *N. gonorrhoeae* and *Herpes simplex virus*, which are not isolated by routine urine culture. In women with symptoms of cystitis accompanied by vaginal discharge or irritation, it is recommended to conduct vaginal examination and urine culture and then initiate treatment.

Anamnesis and physical examination provides important clues for correct diagnosis. The diagnosis of infection in the asymptomatic patient is made on at least two cultures of urine samples in which the same microorganism is present in titers $\geq 10^5$ /mL. If the patient is symptomatic, than one specimen can be enough. Although for long period colony count was considered as gold standard in diagnosis of UTI, nowadays the diagnosis of UTI also takes into consideration laboratory and clinical data.

Presumptive diagnosis of UTI is made through rapid screening tests, which include direct Gram stains and commercially available products - dipstick methods, bioluminescence, and filtration devices. The majority of patients with symptomatic or asymptomatic bacteriuria have pyuria. Pyuria is presence of at least 10 leukocytes/mm³ of midstream urine. Assessment for pyuria and bacteriuria is often performed with rapid dipstick tests, which test for the presence of

leukocyte esterase and nitrites. A positive test indicates UTI, whereas in patients with a negative test and presence of UTI symptoms, a urine microscopic examination and urine-culture should be conducted for further diagnostic evaluation. A urine culture is performed to confirm the presence of bacteriuria and the antimicrobial susceptibility of the infecting uropathogen.

There are 3 methods for urine sampling: midstream clean catch, catheterization and suprapubic aspiration. The voided midstream method is most common method for the routine collection of urine-culture. Prior to urine collection, the patient must be instructed in the proper technique of obtaining the urine sample in order to minimize contamination with bacteria. The urine should be processed immediately and transported to the laboratory within 2 hours, or, if refrigerated at 4° C, it can be cultured within 24 hours.

In patients unable to cooperate and collect midstream urine sample, the alternative method is catheterization.

The suprapubic aspiration method is preferred method for collection of urine in premature infants, neonates, children, adults, and even pregnant patients, but is rarely used. This method is indicated in sampling from children when urine is difficult to obtain by classical methods. Another indication is in cases when interpretation of previous results from voided specimens was antagonistic. This method is suitable also for diagnosis of UTI caused by anaerobes.

Patients with UTI sometimes have hematuria, which can indicate presence of calculi, tumor, glomerulonephritis, vasculitis and renal tuberculosis. Proteinuria is also a common laboratory finding in patients with UTI.

MANAGEMENT

Management of UTIs should take into consideration several factors, including age, gender, microorganism involved, comorbidities, and location of infection, prior UTIs and potential risk factors.

Nonantimicrobial Prevention of UTI

There are several strategies for nonantimicrobial prevention of recurrent acute uncomplicated cystitis. One of the most common method is consumption of large amounts of fluids. This activity reduces the concentration of bacteria and removes infected urine. But, there is no evidence that taking fluids improves the outcome of appropriate antimicrobial therapy.

In prevention of UTI it is recommended abstinence or reduction in frequency of sexual intercourse and avoiding spermicides as a method for contraception or prevention of infection; another nonantimicrobial approach in prevention of UTIs is urination soon after intercourse, not routinely delaying urination, and good hygiene after defecation, avoiding tight-fitting underwear and douching.

Second group of strategies for prevention is the use of biologic mediators: cranberry juice, topical estrogen in some postmenopausal women and adhesion blockers. Use of probiotics as another strategy for prevention of UTIs is controversial.

Asymptomatic Bacteriuria

Bacteriuria is the presence of bacteria in urine. Asymptomatic bacteriuria is defined as the presence of significant bacteriuria ($\geq 10^5$ CFU/mL) in the absence of the signs and symptoms of UTI. Treatment of asymptomatic bacteriuria has no benefit for the patient, except in three conditions: in pregnant women, in patients who undergo surgical interventions in the urogenital tract and in patients after renal transplantation.

Uncomplicated Cystitis and Pyelonephritis

In the past, 7 to 10 days of antimicrobial therapy was recommended for women with uncomplicated cystitis. But, recent studies proved that cystitis can be cured with much shorter courses of therapy and, sometimes with only a single dose of antibiotic. This approach have several advantages including a better compliance of patients, reduced cost, less side effects and decrease of possible emergence of antimicrobial resistance among microorganisms.

In clinical practice the most common applied recommendation are guidelines prepared by Infectious Disease Society of America (**IDSA**) and the European Society for Microbiology and Infectious Diseases (**ESCMID**). These guidelines recommend treatment of uncomplicated cystitis with nitrofurantoin (100 mg every 12 hours for 5 days), fosfomycin (a single dose of 3 g) and if local resistance rate is under 20% of isolates, TMP-SMX (160 mg and 800 mg, twice a day for 3 days).

Second line of treatment consists of fluoroquinolones (ciprofloxacin, 250 mg twice daily for 3 days; levofloxacin, 250 mg or 500 mg once daily for 3 days). The guidelines also list β -lactam agents (amoxicillin-clavulanate, cefdinir, cefaclor, and cefpodoxime-proxetil) in 3-7-day regimens as choices for therapy in cases when other recommended agents can't be used.

Most episodes of acute uncomplicated pyelonephritis are now treated in the outpatient settings. In treatment of these episodes a urine culture and susceptibility test should always be performed. For treatment with oral therapy, guidelines recommend use of ciprofloxacin 500 mg twice daily or 1 g once daily or a 5-day course of levofloxacin 750 mg once daily if local fluoroquinolone resistance is under 10%.

Pyelonephritis in hospitalized patients is treated initially with parenteral antibiotics. Recommended antibiotics are fluoroquinolones, an extended-spectrum cephalosporins (ceftriaxone or piperacillin-tazobactam with or without an aminoglycoside), or a carbapenem agent. Fluoroquinolone should be given for 7 days, and other agents should be given for 14 days.

UTIs are becoming increasingly difficult to treat due to increased resistance worldwide. Of particular concern are members of the family Enterobacteriaceae. Amoxicillin and ampicillin

are no more recommended as reliable agents because at least 35% of isolates from community-acquired UTI are now resistant to these agents. In many parts of the world, *E. coli* resistance to TMP-SMX has already exceeded 20%. Therefore, this antibacterial agent is no longer taken in consideration for empiric treatment. Due to large consumption of fluoroquinolones, resistance to these agents is also growing rapidly.

Infection in Children

UTI in children younger than 3 months of age is usually caused by *E. coli* or *Enterococcus faecalis*. After obtaining urine cultures, recommended empiric therapy is usually a β -lactam antibiotic and aminoglycoside intravenously followed by treatment based on susceptibility profile in duration of a total period of 7 to 14 days.

After 3 months of age, IV therapy is used in seriously ill children as for those younger than 3 months with inclusion of third-generation cephalosporins in treatment protocol. There is evidence indicating that circumcision may have protective effect against UTI in male infants.

Management of Bacteriuria of Pregnancy

During the pregnancy, hormonal changes are accompanied by changes in urether and urethra, making them more susceptible to microbial adherence and infection. Also, the enlarging uterus puts pressure on the bladder impacting the urinary flow.

All pregnant women with significant bacteriuria should be treated with antibiotics. This approach has been proved to prevent pyelonephritis. The screening is recommended in every trimester of pregnancy.

The diagnosis and management of UTI in the geriatric population is difficult because they have more comorbidities. In this age group incidence of UTI increases in both genders but with decrease in female-to-male ratio. This is due to increase of obstructive conditions in males caused by the prostate.

Fungal Infections

Most UTIs caused by *Candida spp.* are seen in patients with indwelling catheters. Removal of the catheter support successful cure in 30-40% of these patients. Treatment is preferred with amphotericin B bladder irrigation or oral fluconazole, 200 to 400 mg/day for 7 days.

The future investigation in the complex field of UTIs should be tailored with emphasis to enlight the process of ecologic damage caused by specific antimicrobial agents and the potential role of probiotics and vaccines in prevention of urinary tract infections.

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