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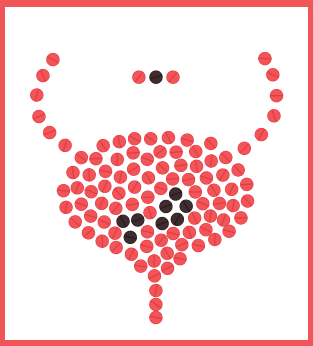
CLASSIFICATION OF URINARY TRACT INFECTION: FROM THE ORENUC SYSTEM TO THE CLINICAL PRACTICE



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Urinary tract infections (UTIs) are one of the most common infectious diseases worldwide, with a substantial impact on society and quality of life. UTIs affect more than 30% of people around the world, with about 150 million medical visits annually.[1, 2] They are one of the most common causes of outpatient visits to general practitioners.[3] Incidence and prevalence rates vary substantially according to the UTI location, patient sex and comorbidities.[4] Infections include several groups of clinical syndromes, ranging from asymptomatic bacteriuria to perinephric abscess and sepsis. The term UTIs describes any infection involving the urinary tract, including the urethra, prostate, bladder, ureters, collecting system and kidneys.[3] The urinary tract can be divided into the upper (kidneys, collecting system and ureters) and lower tract (bladder, prostate, and urethra). The diseases differ in epidemiology, etiology, location, and severity.[5] UTIs are more frequent in women than in men; the higher prevalence in women, according to the current literature, is due to their anatomy and reproductive physiology (women have shorter urethras than men and are therefore far more susceptible to UTIs).[6] Incidence increases with age, and in fact in older women are seen for UTIs at approximately double the rate of the female population overall. Incidence decreases in middle age, but rises in older adults, and it is more frequent in young sexually active women (0.5 to 0.7 per person-year).[7] The most common symptoms depending on infection site include: frequent urination, burning or pain during urination, pain in the lower abdomen, pain above the pubic bone (in women), feeling full in the rectum (in men), bloody or foul-smelling urine, mild fever, and a general feeling of shakiness and fatigue. When infection involves the kidneys, the symptoms include high fever, chills, nausea and vomiting, abdominal pain, cloudy or bloody urine, and pain in the back, just above the waist. A wide range of pathogens are involved in UTIs including Gram-negative, Gram-positive bacteria, and fungi and viruses.[4, 5] Bacterial infection is the most frequent type of UTI, while infections by viral and fungi agents are rare. *Escherichia coli* is the most common bacteria involved in UTIs, and occurs in 80 to 85% of cases.[2] Other pathogens involved are *Staphylococcus species* (*cocci* group), which are involved in 10% to 15%, *Klebsiella pneumoniae*, *Enterococcus*

faecalis, *Group B Streptococcus*, *Proteus mirabilis*, *Pseudomonas aeruginosa*, and *Candida* spp.[2] Generally, bacteria enters the urinary tract from the bowel or the skin.[8] Bacteria most commonly enters the urinary tract via the urethra due to its shorter distance to the bladder and its proximity to the vaginal cavity and rectum in women.

Bacteria can reach the urinary tract in three different ways: the most common, which occurs in 95% of cases, is the ascending or descending from the urethra, and the second and third most common ways are hematic and lymphatic spread.

Bacteria that cause infection have increased adhesion, colonization, and tissue invasion properties relative to nonpathogenic bacteria. There are several risk factors that may promote or encourage bacterial invasion: reduced urine flow, outflow obstruction with incomplete bladder emptying (prostatic hyperplasia, prostatic carcinoma, urethral stricture, pelvic organ prolapse or foreign body), neurogenic bladder, inadequate fluid uptake, urinary tract malformations, voiding dysfunction, catheterization, urinary incontinence, gastrointestinal disorders, fecal incontinence, sexual activity, estrogen depletion, metabolic disease, urethral length (female shorter than male), genetic predisposition (certain HLA and Lewis blood group factors may put patients at higher risk due to increased colonization ability or increased adherence by bacteria to the urinary tract epithelium), and alterations in host defense mechanisms (changes in normal vaginal flora, urinary composition, etc.).[4,5] The most common pathogens involved in ascending mechanism are organisms of enteric origin such as *Escherichia coli* and other *Enterobacteriaceae*.

Hematogenous infection is most closely related to *Staphylococcus aureus*, *Candida species* and *Mycobacterium tuberculosis*. Hematogenous spread often develops in elderly, immunocompromised and neonate patients.[9] There are several risk factors related to UTIs: diabetes, vertebral fractures, rheumatic disease, multi-infarct dementia, undernourishment, neuropathy, fecal and urinary incontinence, chronic diseases, functional abnormalities, estrogen deficiency and immune senescence, hospitalizations, long-term medical institutionalization, anticholinergic agents, sexual activity, vaginal infection, obesity and genetic disease, antibiotics and the presence of urinary catheters.

The classifications and definitions of UTIs have evolved over time. The aim of classification is to organize current knowledge, to provide a basis for guidelines, diagnosis, and treatment, and to define research projects. Classification can be based on clinical presentation, location, duration, risk factors, and severity scale, laboratory data and microbiological findings. Although several consensus guidelines have developed UTI definitions for surveillance purposes, there is no universally accepted definition of symptomatic UTI in older adults.

There are currently several classification systems for the description and classification of UTIs.[10] The classifications are still very heterogeneous and not always clear. Based on location we can classify UTIs as: urethritis and ureteritis when there

is infection of urethra and ureter respectively; and cystitis and pyelonephritis when the bladder and kidneys are involved.

Urethritis is the inflammation of the urethra, and the most common symptoms are dysuria pruritus, and urethral discharge; it is associated with sexually transmitted infections (STIs) and can be divided into gonococcal or nongonococcal infections. The most common pathogen is Neisseria gonorrhea for gonococcal (GU) infections and *Chlamydia trachomatous* non gonococcal urethritis (NGU). Other pathogens associated with urethritis are *Mycoplasma genitalium*, *Trichomonas vaginalis*, *Herpes simplex virus*, *Adenovirus*, *Treponema pallidum*, *Hemophilus influenzae*, *Neisseria meningitides*, *Ureaplasma urealyticum* and *Ureaplasma parvum*, *Candida*. The presence of mycoplasma must especially be suspected when the urethritis is recurrent or persistent.

Urethritis is far more common in males, at a young age, after unprotected sexual intercourse, and with multiple sexual partners.

Cystitis is a clinical syndrome characterized by dysuria, frequency, urgency suprapubic pain, hematuria, and fever. Acute uncomplicated cystitis is the most common UTI, occurring mainly in adult women, especially sexually active young women, and postmenopausal women. Generally according to the literature, after a first episode of a UTI, 27% of women will develop a new episode in six months, and 2.7% will have a second recurrence within six months. The most important risk factors for acute cystitis are diabetes, sexual intercourse, spermicide gel, multiple sexual partners, pregnancy, family history and genetic predisposition, previous UTI and post-menopause. Post-menopause is a risk factor because the estrogen reduction lead to a modification in glycogen production and vulvovaginal flora, especially lactobacilli colonization. Lactobacilli reduces other pathogen colonization, producing lactic acid, which decreases the vaginal pH. In men, its incidence is very low, and it is often associated with prostatitis. The bacteria most frequently involved in cystitis is Escherichia coli, with infection rates that range from 75% to 95% of cases. Other organisms involved in cystitis pathogenesis are *Klebsiella pneumonia, Proteus Mirabilis.* The diagnosis is clinical, with laboratory tests that identify bacteria and other factors such as pyuria, nitrite and leukocytes esterase that are indicative of bacteria presence.

Pyelonephritis is a clinical syndrome characterized by chills, fever, and flank pain, together with bacteriuria and pyuria. It usually comes from an ascending UTI that spreads from the bladder to the kidneys and the upper urinary tract. It should be suspected if, together with genito-urinary symptoms, the patient experiences systemic symptoms such as fever, and tachycardia. The classic triad of pyelonephritis involves fever, flank pain, and nausea or vomiting. Pyelonephritis is usually caused by Gram-negative bacteria, in particular *Escherichia coli*, followed by *Proteus*, *Klebsiella*, and *Enterobacter*. Although pyelonephritis resolves in most cases, it is also related to significant morbidity and mortality. The most common complications are renal or

perinephric abscess formation, sepsis, renal vein thrombosis, papillary necrosis, or acute renal failure, and emphysematous pyelonephritis.

The first classification, according to the symptoms, divided UTIs into symptomatic and asymptomatic. Symptomatic UTIs can be divided into complicated and uncomplicated UTIs, and urosepsis.[11]

Symptomatic UTI is common among sexually active women. At least one in three women will have one UTI by the age of 24 years, and 40% to 50% of women will have at least one UTI during their lifetime. The definition of symptomatic UTI is based on the presence of specific genitourinary symptoms, urinary tract inflammation (pyuria) and the presence of $>10^5$ cfu/mL of pathogenic bacteria identified as the urinary pathogen.

Based on their relationship to other UTIs, they can be defined as:

- first or isolated infection occurs in a patient who has never had an UTI or has one remote infection;
- unresolved infection, when the infection does not respond to antimicrobial therapy and is caused by the same organism with similar resistance features;
- recurrent UTIs refer to the occurrence of more than two symptomatic episodes within six months, or more than three symptomatic episodes within 12 months. It can also be divided into reinfection, a new event associated with the reintroduction of the pathogen into the urinary tract; and bacterial persistence, when the same pathogen infects again from a focus within the urinary tract, such as an infectious stone.

According to the EAU guidelines, asymptomatic bacteriuria is defined as a condition with the presence of $>10^5$ cfu/mL of pathogenic bacteria, without exhibiting any clinical symptoms:[12, 13]

- in women, two consecutive specimens with the same bacteria species isolated, with at least 10^5 colony-forming units (cfus) per mL of urine;
- in men, a single specimen with one bacteria species isolated with at least 100,000 cfus per mL of urine;
- in catheterized women or men, a single specimen with one bacteria species isolated with at least 100 cfus per mL of urine.

It is a very common and usually benign, phenomenon, especially in women, and in both men and women with abnormalities of the genitourinary tract. Asymptomatic bacteriuria (ASB) is not considered an infection but a risk factor for UTI in certain circumstances. Few patients with ASB need to be treated, in particular pregnant women and patients undergoing invasive urologic interventions accompanied by mucosal trauma. ASB incidence is 5% in healthy premenopausal women and 15%

in women and men aged 65-80 years. Escherichia coli is the most common bacteria identified in patient with ABS.

In 1992 the Infectious Diseases Society of America (IDSA) and the European Society of Clinical Microbiology and Infectious Diseases (ESCMID) introduced the concepts of uncomplicated UTI and complicated UTI (cUTI) to obtain more homogeneous study groups when evaluating new anti-infective drugs in clinical trials.[10, 14, 15] According to these classifications, patients with uncomplicated UTIs have no known risk factors, while patients with cUTI have several risk factors related to the urinary tract (obstruction, urinary stones, diversion, catheterization, diabetes mellitus, malignancies, or immune deficiency). This classification also considers the different bacterial composition of the two entities: in uncomplicated UTI, *E. coli* is the major pathogen, whereas pathogens other than *E. coli* are common in cUTIs.

Uncomplicated UTIs generally occur in healthy, non-pregnant women, with a normal genitourinary tract and no recent history of instrumentation which may include bladder catheterization. Uncomplicated UTIs include acute uncomplicated cystitis (AUC) and acute uncomplicated pyelonephritis (AUP), and are mostly common in women. Most uncomplicated UTIs are experienced during the years of maximum sexual activity, usually between the ages of 18 and 39.[10]

Complicated urinary tract infections occur in the setting of a urinary tract that has metabolic, functional, or structural abnormalities. Their primary significance is related to a significantly increasing rate of therapy failures.[10]

Structural abnormalities associated with complicated UTI are infected cysts, renal/bladder abscesses, certain forms of pyelonephritis, spinal cord injury (SCI), obstruction, hydronephrosis, renal tract calculi, or colovesical fistula, immune compromised state (steroid use, post chemotherapy, diabetes, elderly population, HIV), atypical organisms causing UTI, multi-drug resistant organisms, infections during pregnancy, infections following the use of nephrostomy tubes, ureteric stents, suprapubic tubes or Foley catheters, infections in renal transplant patients, infections in patients with impaired renal function and infections following prostatectomies or radiotherapy.

The definition of complicated and uncomplicated UTIs is still very heterogeneous and not always clear. In 2011 the EAU Section of Infections in Urology proposed the ORENUC classification system based on the clinical presentation, anatomical level, infection grade of severity, categorization of risk factors and availability of appropriate antimicrobial therapy for UTIs. This classification was introduced to overcome all problems related to different classifications.[10, 16] ORENUC is an acronym of O-NO known factors (events in women of premenopausal age with no known risk factors); R-Risk for recurrent UTI (use of contraceptive devices, hormonal cycle alterations, or the presence of controlled diabetes mellitus); E-Extra urogenital risk factors (pregnancy, uncontrolled diabetes mellitus, immunodeficiency or immunosuppression,

concomitant connective tissue diseases, preterm childbirth, and difficult to-treat UTIs in men); N-Nephropathy; U-Urological risk factors that can be resolved by therapy; and C-catheter and the risk factors that cannot be resolved by therapy.

The last classification of EAU Urological Infections Guidelines defines uncomplicated UTIs in cystitis, pyelonephritis and recurrent UTI.

Complicated UTI involves cystitis, pyelonephritis, catheter-associated UTI, recurrent UTI and UTI in men. This UTI has a high risk of developing into urosepsis, while the risk of urosepsis in very low in uncomplicated UTI[17] (Table 1.I).

Catheter-associated UTI (CAUTI) is the most common nosocomial infection, with >1 million cases each year, and is frequently asymptomatic. The most important risk factors related to CAUTI are the duration of catheterization, female gender, diabetic or immunocompromised patients, fecally incontinent patients, presence of chronic wounds, and poor self-care of the catheter. *E. coli* is the most common bacteria related to CAUTI, and Pseudomonas and Proteus are quite common. When catheterization has been used for a long period, CAUTI etiology is usually polymicrobial. The presence of biofilm on the catheter surface is the first step to permitting the infection. Bacteria adhere to the biofilm, which is also a physical barrier for antibiotics, and penetrate the urinary tract.

Table 1.I. Classification of urinary tract infections.

Syndrome	Sign and symptoms	Laboratory tests
Asymptomatic bacteriuria (ASB)	No urinary symptoms	$\geq 10^5$ cfu/mL in two consecutive cultures
Uncomplicated cystitis	Dysuria, urgency, frequency; less commonly suprapubic pain, malaise, nocturia, hematuria	$\geq 10^3$ cfu/mL
Acute uncomplicated pyelonephritis	Fever, chills, flank pain, frequency, urgency, dysuria, vomiting, anorexia, malaise	$\geq 10^4$ cfu/mL
Complicated UTI	Any combination of urinary symptoms plus one or more factors associated with a complicated UTI	$\geq 10^5$ cfu/mL in women $\geq 10^4$ cfu/mL in men or urine from catheter in women
Recurrent UTI	At least 3 episodes of UTI in the past year documented by uriculture: women only	

UROSEPSIS

Sepsis is a clinical syndrome characterized by physiologic, biologic, and biochemical abnormalities caused by a dysregulated host response to infection.[18-20] Urosepsis is sepsis originating from the urogenital tract, and the most important cause are cystitis, pyelonephritis, acute bacterial prostatitis, prostatic abscess, renal abscess, and urolithiasis. This condition occurs in 25% of sepsis case and it is generally related to specific bacteria, such as *Escherichia coli*, *Proteus*, *Enterobacter*, *Kleibsiella*, *Pseudomonas aeruginosa* and some Gram-positive bacteria. Urosepsis presents with a varying spectrum of signs and symptoms related to the different parts of the urogenital tract affected by infection. Bacteria causes the initial disease, but the host response is the most important factor that drives and defines the sepsis and its severity. It is most important to recognize and treat this process in the shortest time possible, in order to avoid severe consequences such as renal failure, septic shock or death. The prognosis depends on the type of bacteria, antimicrobial resistance and patient comorbidity and mortality ranges from 30% to 40%.

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