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Urinary Tract Infections

AIMS:
1. **Understand epidemiology and microbiology of urinary tract infections**
2. **Understand pathogenesis of lower and upper urinary tract infections**
3. **Recognize the clinical signs and symptoms of UTIs**

INTRODUCTION

Urinary tract infection (UTI) is defined as significant bacteriuria in the presence of a constellation of symptoms such as dysuria (painful urination), increased urinary frequency and urgency, suprapubic discomfort and costovertebral angle tenderness. It is a common cause of infections, particularly among young, sexually active women; an estimated 1 in 3 women will develop a urinary tract infection before the age of 24 years.

Infection may involve either only the lower urinary tract or both the upper and lower tracts. The term cystitis is used to describe the syndrome involving dysuria, suprapubic tenderness with urinary frequency and urgency. These symptoms may also be related to lower tract inflammation without bacterial infection and can be caused by urethritis (ex. gonorrheal or chlamydial urethritis). Acute pyelonephritis refers to the syndrome of cystitis accompanied by significant bacteriuria and acute infection in the kidney; it is characterized by clinical symptoms such as flank pain, fever, dysuria, urinary urgency and frequency.

Definitions

Lower UTI: cystitis, urethritis, prostatitis

Upper UTI: pyelonephritis, intra-renal abscess, perinephric abscess (usually late complications of pyelonephritis)

Uncomplicated UTI – Infection in a structurally and neurologically normal urinary tract. Simple cystitis of short (1-5 day) duration

Complicated UTI – Infection in a urinary tract with functional or structural abnormalities (ex. indwelling catheters and renal calculi). Cystitis of long duration or hemorrhagic cystitis.

EPIDEMIOLOGY

The prevalence of urinary tract infections varies with age and sex. Groups at increased risk for infection include neonates, prepubertal girls, young women, older men, individuals with structural abnormalities of the urinary tract or immunosuppression (e.g. diabetes). In neonates, a urinary tract infection occurs more often in males; thereafter they occur more frequently in girls and women. When

infections occur in preschool boys, they are frequently associated with serious congenital abnormalities; it has also been shown that lack of circumcision predisposes young boys and infants to UTIs.

Bacteriuria is rare in men below the age of 50 years, and symptoms of dysuria are more commonly due to a sexually transmitted infection of the urethra or prostate. The incidence of UTIs in men increases after the age of 50 years, probably due to prostatic disease and the resultant instrumentation.

As mentioned above, among young adults, the prevalence of UTIs increases in the female population. Up to 40% of women will experience a symptomatic urinary tract infection at some time during their life and many will have recurrent episodes. Pregnant women have a 4-10% prevalence of bacteriuria which has been shown to increase the risk of premature delivery, fetal mortality and pyelonephritis in the mother. In the hospitalized patient, urinary tract infection may account for close to 50% of hospital-acquired infections and are a major cause of Gram negative bacteremia and mortality. Table 1 lists risk factors for urinary tract infections and prevalence for certain age groups.

Table 1: Risk Factors for Urinary-tract Infections by Age Group

Age in years	Females (% prevalence)	Males (% prevalence)
<1	Anatomic or functional urologic abnormalities (1%)	Anatomic or functional urologic abnormalities (1%)
1-5	Congenital abnormalities; vesicoureteral reflux (4.5%)	Congenital abnormalities, uncircumcised penis (0.5%)
6-15	Vesicoureteral reflux (4.4%)	Vesicoureteral reflux (0.5%)
16-35	Sexual intercourse, diaphragm use, spermicidal jelly, previous urinary tract infection[1] (20%)	Anatomic urologic abnormality. Insertive rectal intercourse. (0.5%)
36-65	Gynecologic surgery, bladder prolapse. Previous urinary tract infection (35%)	Prostate hypertrophy, obstruction, catherization, surgery. (20%)
>65	Estrogen deficiency and loss of vaginal lactobacilli (40%)	All of the above, incontinence, long –term catherization, condom catheters (35%)

1. The risk for a second urinary tract infection in young women is greater than that for the first, with at least 20% developing a recurrent infection by the 6-month follow-up.

MICROBIOLOGY

Organisms causing UTI are derived primarily from the aerobic members of the fecal flora. An overwhelming majority of uncomplicated urinary tract infections (95%) are caused by a single organism. In contrast, infections among hospitalized patients, patients with urinary catheters, or individuals with structural abnormalities of the urinary tract may be polymicrobial.

The most common pathogens are Gram negative rods. See **Figure 1** for classification of Gram negative organisms implicated in pathogenesis of UTIs. *Escherichia coli* causes about 80% of acute infections in patients without urinary tract abnormalities. Other Gram negative organisms include

Proteus mirabilis and *Klebsiella pneumoniae*, organisms which colonize the enteric tract. *Enterobacter*, *Serratia*, and *Pseudomonas* are infrequent in the outpatient population, but they are more frequent in patients with complicated UTI. They are important pathogens in individuals with structural abnormalities of the urinary tract and in individuals with urinary tracts that have been instrumented.

Staphylococcus saprophyticus, a Gram positive coagulase negative staphylococcus, causes about 10% of infections among young, sexually active women.

In contrast, in catheterized patients and individuals with structural abnormalities of the urinary tract, *E. coli* accounts for only 35% of infections and the other Gram negative species are more important, as are Gram positive organisms like *Enterococcus* spp. and the coagulase-negative staphylococci.

Figure 2 Etiology of Uncomplicated Urinary Tract Infections in Sexually Active Women

Legend:
- E. coli 79%
- S. saprophyticus 11%
- Klebsiella 3%
- Mixed 3%
- Proteus 2%
- Enterococcus 2%
- Other 2%
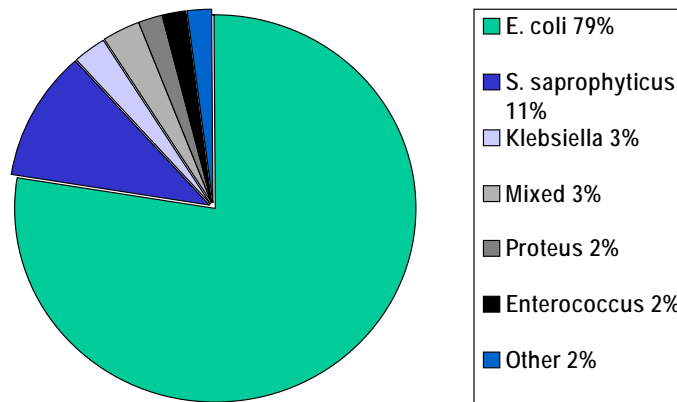
PATHOGENESIS

There are two important routes by which bacteria can invade and spread within the urinary tract: the ascending and hematogenous pathways. There is little evidence to support a lymphatic spread of infection to the urinary tract with any regularity.
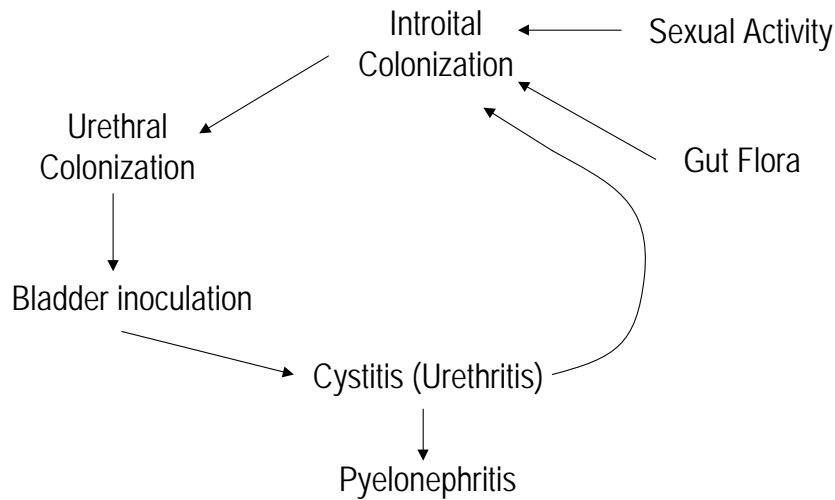
Hematogenous Route.:
Infection of the renal parenchyma by blood-borne organisms occurs in humans, albeit less commonly than by the ascending route. The kidney is frequently the site of abscesses in patient with bacteremia or endocarditis caused by a Gram positive organism, *Staphylococcus aureus*; infections of the kidney with Gram negative bacilli rarely occur by the hematogenous route.

Ascending Route:
Urinary tract infections in women develop when uropathogens from the fecal flora colonize the vaginal introitus and displace the normal flora (diphtheroids, lactobacilli, coagulase-negative staphylococci, and streptococcal species). Colonization of the vaginal introitus with E.coli seems to be one of the critical initial steps in the pathogenesis of both acute and recurrent UTI. Most uropathogens originate in the rectal flora and enter the bladder via the urethra. The female urethra is short and proximal to the vulvar and perineal areas, making contamination likely. In women in whom UTIs develop, the urethra is colonized and the uropathogen gains entry to the bladder, presumably by means of the urethral massage that accompanies sexual intercourse. (Figure 3) Whether infection develops depends upon the particular

organism, the size of the inoculum, and the adequacy of host defenses. Once the bacteria ascend into the bladder, they may multiply and then pass up the ureters, particularly if vesicoureteral reflux is present, to the renal parenchyma.

Figure 3

Introital Colonization ← Sexual Activity

Urethral Colonization

Gut Flora

Bladder inoculation

Cystitis (Urethritis)

Pyelonephritis

Abnormalities of the urinary tract which lead to obstruction of the urinary flow are a major factor in the development of urinary infection. Extra-renal obstruction due to posterior urethral valves in infant boys or urethral strictures in adult men are uncommon but important to consider. More common is incomplete bladder emptying due to prostatic hyperplasia. Dysfunction of the bladder due to mechanical (prostate, pelvic floor relaxation) or neurological causes also contributes to the development of UTI's.

HOST FACTORS IN URINARY TRACT INFECTION

The host employs several defense mechanisms to eliminate pathogenic and nonpathogenic microorganisms that gain access to the bladder. Factors favoring bacterial elimination include high urine flow rate, high voiding frequency, bactericidal effects of bladder mucosa, secreted proteins that bind to fimbrial adhesins on the bacterial wall, and the inflammatory response mediated by PMNs and cytokines.

Table 2. Antibacterial Host Defenses in the Urinary tract

Urine osmolality, pH, organic acids
Urine flow and micturition
Urinary inhibitors of bacterial adherence:

Bladder mucopolysaccharides
Secretory immunoglobulin A (SIgA)
Inflammatory response (PMNs, and cytokines)
Prostatic secretions
Humoral and cell-mediated immunity

In young women, on the other hand, several factors predispose to infection, and these include: 1) short urethra; 2) sexual intercourse and lack of post-coital voiding; 3) diaphragm use (manipulation involved in placing it on the cervix may promote bacterial colonization); and 4) spermicide use (raises vaginal pH and is toxic to the normal flora, especially the lactobacilli; it also increases adherence of E.coli to vaginal epithelial cells).

Estrogen deficiency has been recognized as a risk factor for recurrent UTIs in postmenopausal women because of ensuing vaginal flora changes: protective lactobacilli are replaced by E.coli and other uropathogens. There may also be genetic factors predisposing young women to UTIs. Women who are of P_1 blood group have epithelial cell receptors that mediate attachment of bacteria. 97% of young women with recurrent pyelonephritis are P_1 positive, significantly higher than in uninfected controls. Interestingly, patients who had upper tract disease secondary to ureteral reflux had P_1 phenotype frequency similar to that in the general population. This highlights the major importance of structural changes in urinary-tract infection. Urinary obstruction, reflux, or other anatomic changes make it possible for less virulent bacteria to produce a urinary tract infection.

BACTERIAL FACTORS IN URINARY TRACT INFECTION

Symptomatic bacteriuria is highly correlated with the presence of bacteria that mediate attachment to uroepithelial cells. And thus certain strains of E.coli are selected from the fecal flora by the presence of virulence factors that enhance both colonization and invasion of the urinary tract and the ability to produce infection. Bacteria with enhanced adherence to vaginal and periurethral cells would be selected to colonize the anatomic regions adjacent to the urethral orifice. Binding to the uroepithelial surface, in turn, prevents bacterial washout during micturition and is the first step to bacterial invasion.

The adhesive properties of E.coli, for example, are facilitated by fimbriae, filamentous surface organelle. The most common ones are **Type 1 and P-fimbriae**. The attachment of Type 1 is blocked by mannose (mannose-sensitive, MS-adhesins), while the latter is mannose resistant (MR-adhesins). The P-fimbriae augment the virulence of uropathogenic E.coli by allowing more efficient spread from the intestinal tract to the urinary tract and thereby causing ascending infection. Once in the urinary tract, P-fimbriated strains adhere, persist and invade the kidney, inducing bacteremia and resulting in pyelonephritis.

Type 1 fimbriae increase susceptibility to polymorphonuclear phagocytosis, while P-fimbriae block phagocytosis. It is hypothesized that there are dual-phase kinetics of bacterial adherence in the pathogenesis of urinary tract infection. After entry into the bladder, MS-adhesins which are present on the majority of the Enterobacteriaceae, facilitate attachment to the bladder epithelium. However, when the bacteria ascend to the renal parenchyma, they undergo phase variation and do not express type 1 fimbriae which, as noted above, enhance phagocytosis. Rather, in the upper tract, P-fimbriae are expressed, allowing attachment to renal parenchymal cells.

Other Gram negative bacterial uropathogens, such as *Proteus mirabilis* and *Klebsiella* species, have demonstrated similar ability to adhere to the vaginal and periurethral cells, thereby enhancing their

pathogenicity. Among Gram positive organisms, in contrast, *Staphylococcus aureus* uncommonly causes cystitis and ascending pyelonephritis, whereas *Staphylococcus saprophyticus*, which adheres significantly better to uroepithelium than do *Staphylococcus aureus* or *Staphylococcus epidermidis*, is a frequent cause of lower urinary tract infections.

In an individual with structural abnormalities of the urinary tract or with a catheter, even organisms of low pathogenicity can cause infection of bladder, kidney, or both, and the above-described properties of the bacteria are not essential.

CLINICAL PRESENTATION

Symptoms of urinary-tract infection vary with the age of the patient and the location of infection. Neonates and children less than 2 years old do not complain of dysuria: fever, emesis, and failure to gain weight are the usual symptoms. Children over 3 years will complain of burning on urination and lower abdominal pain; previously toilet-trained children may develop enuresis.

Adult patients with cystitis have dysuria, suprapubic pain, urinary frequency and urgency. The urine often is cloudy and malodorous and may be bloody. Fever and systemic symptoms usually are absent in infection limited to the lower tract. Acute dysuria in adult women can also be due to acute urethritis (chlamydial, gonococcal, or herpetic) or to vaginitis/vaginosis.

While it may be difficult to distinguish upper tract infection from lower tract infection based on clinical signs alone, systemic symptoms of fever (usually greater than 101° F.), nausea, vomiting, and pain in the costovertebral areas, are highly suggestive of upper urinary tract infection (pyelonephritis). This is frequently accompanied by urinary frequency, urgency and dysuria. Rigors (shaking chills) may indicate bacteremia. It is important to note that these symptoms may vary greatly: flank tenderness is frequent and more intense when there is obstructive disease (renal calculi), and severe pain with radiation to the groin suggests the presence of renal calculus. The pain from an inflamed kidney may be felt in or near the epigastrium and may radiate to one of the lower quadrants. Patients with urinary-catheter-associated infection often are asymptomatic, but may have fever, chills, leukocytosis, etc.

DIAGNOSIS

The diagnosis of UTI can only be proven by culture of an adequately collected urine sample. This is essential in all suspected cases in males, infants and children. In sexually active young women, in whom sexually transmitted infections are unlikely, typical clinical features of cystitis in the presence of pyuria, hematuria or bacteriuria are highly suggestive of UTI.

Microscopic examination of the urine for the presence of bacteria and leukocytes (pyuria) is the first step in the laboratory diagnosis of urinary tract infection. Proper collection methods are essential. Collection of a clean, mid-stream specimen is the method of choice, since it entails no morbidity, but a straight "in-and-out" catheter specimen should be used if a clean-voided specimen cannot readily be obtained. Urine must be processed immediately; if it remains at room (or warmer) temperature, the small numbers of bacteria present as contaminants will grow into "significant" numbers. A specimen taken from a woman is easily contaminated, but quantitative estimation of the number of bacteria in a voided specimen makes it possible to distinguish contamination from bacteriuria. A count of $>10^{5}$ bacteria per milliliter indicates infection. However, about one third of young women with symptomatic lower tract infection may have lower bacterial counts of common urinary pathogens such as *E. coli*, *Proteus*, or *Staphylococcus saprophyticus*. The presence of pyuria (more than 10 leukocytes/μl) in a symptomatic individual is also indicative of infection. Hematuria and proteinuria, if present, suggest that the patient

has crossed the line from an uncomplicated cystitis to a complicated cystitis or an upper tract infection.

The urine leukocyte esterase test is a rapid screening test for detecting pyuria. Although its sensitivity and specificity are high for detecting more than 10 leukocytes cells/μl, patients with negative leukocyte esterase test and symptoms of a UTI should have a microscopic examination for pyuria and a urine culture. A number of rapid indirect methods have been devised to detect bacteriuria. Most common are tests that detect the presence of urine nitrite, which is formed when bacteria reduce the nitrate that is normally present in urine.

Urine should be cultured in individuals in whom the diagnosis of cystitis is in question or in patients with pyelonephritis. Urine also should be cultured in children, pregnant women, and individuals with underlying structural abnormalities of the urinary tract. In women who present with acute onset of symptoms of lower urinary tract infection (frequency, urgency, and dysuria), urine culture is not mandatory; it is more cost-effective to do a leukocyte esterase-nitrate test. If positive, empiric treatment is prescribed; if negative, a culture is done and empiric treatment is prescribed.

It is difficult to determine whether bacteria detected in a specimen come only from the bladder or also from the kidney. Administration of a single, large dose of antibiotic and culture of urine at 48 hours have been used to differentiate upper-tract from lower-tract disease in women. The assumption is that bladder bacteria would be eliminated whereas renal parenchymal bacteria would persist. Unfortunately, this test is not completely reliable. Furthermore, fluoroquinolone antibiotics may remain in the urine at inhibitory levels for up to 5 days.

In males, a technique to localize the site of infection to the urethra, bladder, or prostate has been used. (Figure 4) Four specimens are collected. The first few milliliters of voided urine (first voided bladder, VB1) represent urethral colonization, a mid-stream specimen (midstream voided bladder, VB2) represents the bladder, kidney, or both. After the bladder has been emptied, a prostatic massage is performed and prostate fluid is collected (expressed prostatic secretion, EPS.); a fourth specimen, the first 10 ml of urine after prostate massage (VB3) is also collected. These last two specimens represent prostatic infection.

Figure 4

VB1   **VB2**   **EPS**   **VB3**
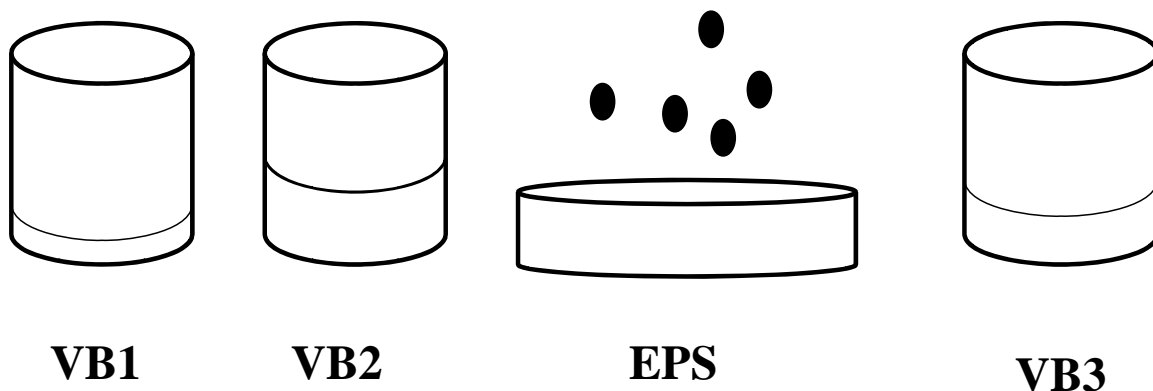
Radiographic studies (e.g. ultrasound, intravenous pyelography, or a CT scan) are indicated in a patient in whom an abnormality of the urinary system is highly likely, or if an abscess is suspected, or in a patient with pyelonephritis who does not respond to appropriate therapy within 72 hours. In men with

urinary tract infections, a careful prostate examination is necessary to rule out prostatitis.

TREATMENT

Treatment of urinary-tract infection is based on its location (in the upper or the lower tract), and on patient characteristics. Lower-urinary-tract infection in the healthy, young female with symptoms of recent onset (< 48 hours) can be treated with a brief course (3 days) of oral antibiotics. All other women with lower tract infections should receive a 5-7 day course. It is important to identify diabetic patients who are at risk for recurrent infections, pyelonephritis and perinephric abscesses.

In the case of acute pyelonephritis, initial therapy is often given intravenously with completion of therapy orally after the patient is afebrile. Total duration of therapy is 10-14 days. All patients with pyelonephritis should have a repeat urine culture 5-9 days after completing therapy, since a percentage of patients will have symptomatic or asymptomatic relapse; the repeat urine culture will detect this. Such patients should have 2-4 more weeks of therapy.

The antimicrobial agents selected should inhibit *E. coli*, since it accounts for 80% of uncomplicated lower urinary-tract infections. Trimethoprim, co-trimoxazole, and fluoroquinolones are ideal agents, since they are effective orally, they achieve good urine concentrations, and tend not to disturb the anaerobic flora of the gut and the vagina.

Treatment of patients who are found to have asymptomatic bacteriuria is still controversial. Cultures should first be repeated to establish the diagnosis. A pregnant woman, who has a high risk of pyelonephritis and premature delivery should be cultured and treated if positive during the first trimester. Cultures should be repeated in the third trimester. An individual with known neurological or structural abnormality of the urinary system in whom $\geq 10^5$ CFU/ml of a single species are present should also be treated.   Finally, prophylactic pre-operative treatment of asymptomatic bacteriuria is beneficial to those undergoing urologic surgery, as it will reduce the chance of post-operative infections.

Asymptomatic bacteriuria in a patient with an indwelling urethral catheter should not be treated, since the only result will be selection of resistant bacteria. In many situations, removal of the catheter will eliminate the bacteria. If organisms are present 48 hours after removal of a catheter, a short course of antibiotic therapy is indicated.

Acute cystitis in adult men (which can be caused by the same organisms that possess virulence factors for pyelonephritis) will respond to 7-10 days of treatment, but acute prostatitis from the same organisms will require 6-12 *weeks* to eradicate the offending organism, with a 70% cure rate. Non-bacterial *prostatosis* is probably caused by chlamydiae or ureaplasmata, and will respond to tetracyclines, erythromycins or fluoroquinolones.

SPECIAL CONSIDERATIONS

Candiduria: is seen primarily in catheterized patients who are often asymptomatic. However, diabetics may have true candidal UTI's, as may immunocompromised patients.   The persistence of candiduria 48-72 hours after catheter removal, or fever/leukocytosis suggest that the infection is more than asymptomatic and transient colonization. Thought should be given to ruling out possible candidal pyelonephritis in this setting. It is important to rule out contamination of the urine specimen by vaginal candidosis in the asymptomatic patient. Treatment of infections that do not respond to catheter removal is indicated; oral fluconazole or bladder irrigation with amphotericin B have been used successfully.

Catheters: Urinary catheters are extremely likely to lead to colonization of the bladder and subsequent infection.   Bacteria adhere to the catheter surface and contribute to the production of a biofilm composed of bacteria, bacterial glycocalyces, host proteins, and urinary salts like apatite and struvite (calcium-magnesium-ammonium sulfate). The bacteria travel beneath this biofilm along the catheter into the bladder. Brief use of indwelling urinary catheters after operations or in critically ill patients to measure urine output will not result in infection for up to 7 days if the catheter connections are left undisturbed and a closed drainage system is scrupulously maintained. Long-term use of urinary catheters will always result in colonization and infection, about 8%-10% per day.

Condom catheters in males are also a potential source of infection, since urine accumulates in the condom part and may reflux into the urethra and upward into the bladder. Chronic condom catheterization carries about the same risk of infection as chronic indwelling (Foley) catheterization.   If at all possible, a system of intermittent, straight catheterization should be used, especially in patients who cannot void because of neurologic disease. This relieves stasis of urine in the bladder and prevents damage to bladder mucosa that is in contact with the balloon used to retain the indwelling catheter.