

MODULE 2: ADULT URINARY TRACT INFECTIONS

KEYWORDS: Urinary tract infection (UTI); cystitis; pyelonephritis; uropathogens; antibiotics

LEARNING OBJECTIVES

At the end of this clerkship, the learner will be able to:

1. Outline the prevalence and socioeconomic impact of adult UTI.
2. List the distinctions between urinary infection, contamination and colonization in diagnosing a UTI.
3. List the important host and bacterial characteristics involved in the genesis of a clinically important UTI.
4. Name the most common gram negative and gram-positive bacteria associated with adult UTI.
5. Name the five organisms constituting normal perineal flora.
6. List methods of urine collection and the advantages of each
7. Describe the different signs and symptoms associated with upper and lower adult UTIs and the organs involved with each.
8. Describe and perform chemical and microscopic urinalysis, and its usefulness in the diagnosis of adult UTI.
9. Name six pathogens or disease entities that need to be considered in the differential diagnosis of UTI.
10. Describe the differences between complicated and uncomplicated adult UTI.
11. List imaging modalities used in the diagnosis of adult UTI, and the indications to order them.
12. Outline treatment principles of both complicated and uncomplicated adult UTIs.

EPIDEMIOLOGY/SOCIOECONOMICS/EDUCATION

Urinary tract infection is a significant health problem, both in community and hospital - based settings. It is estimated that 150 million UTIs occur yearly worldwide, accounting for \$6 billion in health care expenditures. In premenopausal women in the U.S., an annual estimated incidence of UTI is 0.5 - 0.7/person/year. In Medicare beneficiaries 65 years or older, UTIs account for 1.8 million office visits per year.

The majority of community- acquired UTIs manifest as uncomplicated bacterial cystitis, and occur mainly in females. In the health-care setting, approximately 40% of all nosocomial infections are UTIs, and most are associated with the use of urinary

catheters. There are more than 1 million catheter-associated UTIs/year in the U.S., and up to 40% of hospital gram-negative bacteremias/year originates as UTIs.

Urinary infections are treated with antibiotics and removal of predisposing factors if possible –catheters can be removed or changed, and urine collections drained. The use of antibiotics for treatment requires thoughtful consideration of direct medical costs and antimicrobial resistance patterns, both of which increase with greater use of antibiotics. Health care providers need to learn how to diagnose and manage UTIs because of their prevalence and associated health and economic costs to society.

ETIOLOGY/PATHOGENESIS

Definitions:

Urine is normally sterile. The urinary system consists of kidneys, the drainage system (including the renal calyces, pelvis and the ureter), and the bladder (storage of urine). In the female, the urethra exits the bladder near the contiguous vaginal area. In the male, the urethra exits the bladder, passes through the prostate, and then through the penis. The foreskin may or may not be present. When discussing UTI's it is important to distinguish among the following terms:

Contamination - organisms are introduced during collection or processing of urine. No health care concerns.

Colonization - organisms are present in the urine, but are causing no illness or symptoms (asymptomatic bacteriuria). Depending on the circumstances, significance is variable, and the patient may not need treatment.

Infection (UTI) - the combination of a pathogen(s) within the urinary system and human host symptoms and/or inflammatory response to the pathogen(s). Treatment and management needed.

Factors Important for the Genesis of UTIs

Bacterial entry: Most UTIs are caused by ascending entry of bacteria from the periurethral area, making bacterial populations and entry mechanisms in these areas important. Hematogenous spread is an uncommon cause of UTIs. The organisms most commonly involved with hematogenous spread are *Staphylococcus aureus*, *Candida* species and *Mycobacterium tuberculosis*. Hematogenous infection is seen most often in immunocompromised patients or in neonates. Relapsing hematogenous infections can be secondary to incompletely treated prostatic or kidney parenchymal infections.

Bacterial uropathogenic factors: A limited number of *E. coli* serotypes cause most UTIs. Bacteria that cause infection have increased adhesion, colonization and tissue invasiveness relative to nonpathogenic bacteria. The mediators of these pathogenic

features include pili, substances that increase resistance to bacteriocidal activity and mediators of invasiveness. Pili control bacterial adherence. Specifically, Type 1 pili adhere to mannose in the urinary epithelial mucopolysaccharide lining, and to polymorphonuclear leukocytes (PMNs); they are often associated with cystitis (bladder infection). P pili are mannose resistant and adhere to renal glycolipid receptors. They do not bind PMNs and are therefore relatively resistant to phagocytosis and clearing by PMNs. They are most often associated with kidney infections (pyelonephritis). One characteristic of *E. coli* that allows it to ascend to the kidney is the phasic variation of Type 1 pili; because of this, PMN binding is minimized and phagocytosis is less effective. One of the significant factors in resistance to bacteriocidal activity involves the expression of K antigen (capsular polysaccharide) on bacteria. Another mediator, hemolysin, produced by certain bacteria, can augment tissue invasiveness and predispose to infection.

Host defenses: There are several factors relating to host defenses that determine susceptibility to UTIs. Mechanical issues such as urethral length (female shorter than male), completeness of bladder emptying (leading to residual urine in the bladder) and the integrity of the natural ureterovesical junction “valve” (leading to vesicoureteral reflux) are important anatomic issues that predispose to UTIs. Biochemical properties are normally important in making bacterial survival difficult in urine: acid pH, high urea content, and high osmolality. In addition, mucosal mucopolysaccharide within the lining of the urinary tract as well as systemic and local antibody production may be protective for UTIs. Normal vaginal flora such as lactobacillus protect the estrogenized vaginal vestibule from Enterobacteriaceae colonization by blocking bacterial adherence. Finally, it is clear that there may be a genetic predisposition to UTIs, as certain HLA and Lewis blood group (non-secretor status) factors may put patients at higher risk due to increased colonization ability or increased adherence by bacteria to the urinary tract epithelium.

Table 1: Potentially Infective Pathogens in the Urinary Tract

Common Causative pathogens in Adult UTIs

- E. Coli* (80% of outpatient UTIs)
- Klebsiella; Enterobacter*
- Proteus*
- Pseudomonas*
- Staphylococcus saprophyticus* (5 - 15%)
- Enterococcus*
- Candida*
- Adenovirus type 11*

Normal perineal flora:

- Lactobacillus*
- Corynebacteria*
- Staphylococcus*
- Streptococcus*
- Anaerobes*

DIAGNOSIS OF UTI

Clinical symptoms: Symptoms are very helpful in the diagnosis of a UTI, but do not help to accurately localize the infection within the urinary tract is difficult. In many cases, however, UTIs can be asymptomatic. The most common form of UTI is cystitis (bladder infection) characterized by irritative symptoms such as urinary urgency, frequency, dysuria, as well as hematuria, foul-smelling urine, and suprapubic pain. These symptoms are also typical for urethritis and prostatitis in addition to cystitis. An associated epididymis, diagnosed reliably by physical examination in men, is an easily localizable variation of UTI. Symptoms associated with "upper urinary tract" infections, exemplified by pyelonephritis, may include those typical of cystitis, as well as fever, rigors or chills, flank or abdominal pain, and nausea and vomiting. Fever in particular, is often an indicator of an upper urinary tract infection. In children, the presence of a febrile UTI increases the likelihood of discovering vesicoureteral reflux.

Collection method: Analysis of the urine is critical in determining the likelihood of infection. The method of urine collection is important to distinguish between contamination and true infection. There are three commonly used methods of collection: a) clean catch midstream voided urine, b) catheterized urine and c) suprapubically aspirated urine. The most variable of these three is the midstream-voided urine, especially in females, where contamination of urine by vaginal or perineal organisms is common during collection. The sterility of a midstream voided urine specimen should be questioned if microscopy reveals squamous epithelial cells. Voided urines that are sterile or contain high colony counts (>100,000) of a single bacteria correlate well with urine obtained by other methods.

Urinalysis: A positive chemical (dipstick) leukocyte esterase is 64 - 90% specific and has a similar level of sensitivity for UTI. The finding of nitrite positivity on urine dipstick, indicating the conversion of nitrate to nitrite by gram-negative bacteria, is very specific but only about 50% sensitive for a urinary tract infection. Gram-positive bacteria such as enterococcus faecalis do not convert nitrate to nitrite on a urinary dipstick. The finding of elevated white blood cells in the urine (pyuria) is the most reliable indicator of infection (>10 WBC/hpf on spun specimen) is 95% sensitive but much less specific for a UTI.

Quantitative urine culture: In general, > 100K colonies/mL on urine culture is diagnostic for UTI. However, the probability of a UTI does depend on the method of collection. In general, lower colony counts obtained by sterile urethral catheterization or by suprapubic aspiration can represent true infection; but clean catch, mid-stream urine that harbors < 100K colonies/mL in a female requires further verification or repeat sampling to confirm a UTI.

Methods to localize infection: Used mainly to diagnose prostatitis, several localization methods have been described, but are otherwise uncommonly used. Upper urinary tract infections may be isolated using the Stamey test in which the bladder urine is

cultured after catheterization, both before and after a thorough saline wash. If the second, post-wash bladder culture is positive, this may indicate upper tract bacteria entering the bladder. Combining bladder washing with selective ureteral catheterization is a more precise way to localize the laterality of the upper tract infection.

To diagnose chronic prostatitis, a “four glass” quantitative culture test can be used. With this method, urine is collected in four separate containers:

1. an initial voided urine that reflects bacterial activity within the urethra (urethral pathogens)
2. a subsequent, mid-stream urine to evaluate bacteria within the bladder
3. the collection of expressed prostatic secretions, captured from the penile urethra while massaging the prostate with a rectal exam
4. a post-massage voided urine collection that may reflect prostatic bacteria

Significantly increased bacterial colony counts in the third (expressed prostatic secretion) and fourth (post-prostatic secretion) cultures are diagnostic of chronic prostatitis.

INDICATIONS FOR RADIOLOGIC IMAGING WITH UTI

Patients with uncomplicated cystitis or uncomplicated pyelonephritis generally do not benefit from imaging studies to look for anatomic abnormalities. In patients who do not respond to treatment, or in patients with predisposing factors, imaging with kidney and bladder ultrasound, or a non-contrast CT scan of the abdomen and pelvis may be useful. Cystoscopic or ureteroscopic evaluation of the urinary tract is not typically performed with uncomplicated UTI or pyelonephritis.

DIFFERENTIAL DIAGNOSIS

Other pathogens, processes and conditions that can cause symptoms that mimic UTI include:

Herpes genitalis (HSV)

Urethritis

N. Gonorrhoeae

Chlamydia

Trichomonas

Vaginitis

Prostatitis

Nephrolithiasis

Trauma

GU tuberculosis
GU neoplasm
Intra-abdominal abscess
Sepsis - source other than GU system

MANAGEMENT OF UTI

The combination of clinical findings and urine evaluation are used to diagnose UTI. Treatment is based upon pathogen identification and the type and degree of clinical illness, and presence or absence of other predisposing host factors. In general, the treatment consists of hydration, relief of urinary tract obstruction, removal of foreign body or catheter if feasible, and judicious use of antibiotics.

The type and duration of antibiotic treatment is dependent on site of infection (if known), host factors and severity of illness. Most antibiotics are highly concentrated in the urine and therefore are very effective at clearing bacteria from the urinary tract. However, in cases of pyelonephritis, prostatitis or epididymitis, proper tissue antibiotic concentrations are important.

Care must be taken when prescribing an antibiotic to avoid an adverse reaction or interaction with other medications. Unlike many antibiotics, Nitrofurantoin is one of the antibiotics least likely to prolong anticoagulation when taken in conjunction with warfarin.

When considering treatment, first determine whether the UTI is complicated or uncomplicated in nature. Uncomplicated infections include acute cystitis in a non-pregnant, premenopausal female and acute pyelonephritis in an otherwise healthy patient. Young post-pubertal females are susceptible to uncomplicated UTIs because of sexual intercourse in combination with delayed post-coital bladder emptying and the use of diaphragm and spermicidal contraceptives that alter the normal vaginal flora and may allow colonization by pathogenic *E. coli*. Complicated UTIs are those that occur when certain predisposing factors are present. These factors include: Obstructed urinary flow due to congenital causes, prostatic obstruction or urinary stones; incomplete bladder emptying due to anatomic (prostatic or urethral) or neurogenic (congenital or acquired spinal cord abnormalities) reasons; vesicoureteral reflux, foreign bodies in the urinary tract (instruments, catheters, drainage tubes); systemic illness such as diabetes; pregnancy and males participating in anal intercourse.

Uncomplicated UTI (cystitis, some pyelonephritis)

- 3-day course of oral TMP/SMX is 95% effective; 7 days is no more effective.
- If TMP/SMX resistance is > 10 - 20% (U.S. West coast, Europe), use fluoroquinolones.
- Higher percentages of resistance to TMP/SMX also imply possible resistance to ampicillin, cephalosporins, and tetracycline.

- Nitrofurantoin is also effective in treating uncomplicated cystitis and may lead to less microbial resistance as it has low systemic absorption with high urinary drug concentrations.

Other uncomplicated UTI

- A full 7 - 10 day antibiotic course should be used in patients with: diabetes, symptom duration before treatment of > 7 days, pregnancy, age >65 years, or past history of pyelonephritis or UTI with resistant organisms.

Complicated UTI (acute pyelonephritis)

- Empiric parenteral treatment after culture with:
- Ampicillin plus aminoglycoside or
- Ampicillin/ Vancomycin (for beta-lactam allergy) plus aminoglycoside or third-generation cephalosporin (if no *enterococcus*)
- Adjust antibiotics according to culture results
- Blood cultures positive in 20 - 40% of patients
- Switch from parenteral to oral therapy at 48 hours after clinically well
- Treat for 14 days.

Acute pyelonephritis with intrarenal, perirenal or pararenal abscess

- Treatment for complicated UTI and add appropriate drainage.

Epididymitis

- TMP/SMX or fluoroquinolones for at least 3 weeks to obtain adequate tissue levels.

Acute bacterial prostatitis

- TMP/SMX or fluoroquinolones for at least 4 weeks to obtain adequate tissue levels

Chronic bacterial prostatitis

- TMP/SMX or fluoroquinolones for 6 - 12 weeks.

Re-infection

- A test of cure should be undertaken by repeat culture in pregnancy, pyelonephritis, and complicated or relapsing UTI.
- Re-infection is the relatively rapid recurrence of a UTI with the same or different organism after cure has been documented.
- Each infectious episode should be treated separately.
- Consider 6 - 12 months of antibiotic prophylaxis (once a day oral intake of TMP/SMX or nitrofurantoin at 1/3 to 1/2 of a daily treatment dose)
- For patients with recurrent cystitis related to coitus, consider self-administered single-dose antibiotics post-coital treatment.

Relapsing infection

- Failure to clear or completely eradicate the pathogen despite a reasonable treatment course.
- Should trigger a urologic investigation that includes imaging to define possible anatomical causes and prolonged therapy in the meantime.

Asymptomatic bacteriuria

- Generally, does not need treatment, except in pregnancy.
- Treatment is not indicated in the elderly (20 - 40% incidence) and patients on catheterization (90% incidence).

SUMMARY

- Urinary tract infections are both prevalent and costly.
- Bacterial UTIs (different from urinary colonization) results from the interaction of multiple host and bacterial factors.
- The diagnosis of UTI is made by urine examination and a clinical picture of illness.
- A broad differential diagnosis can exist with urinary tract symptoms that include nonbacterial pathogens and non-infectious conditions.
- Effective treatment of bacterial UTI depends on the pathogen, severity and site of illness, and other complicating patient factors.

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