

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 associated with a clinically important UTI.
4. Name the most common gram negative and gram positive bacteria associated with adult UTI.
5. Name the predominant 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 tract and lower tract adult UTIs.
8. Describe and perform chemical and microscopic urinalysis, and its limits in the diagnosis of adult UTI.
9. Name dominant 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 indications and use of imaging modalities in the diagnosis of adult UTI.
12. Outline treatment principles of both complicated and uncomplicated adult UTIs.

EPIDEMIOLOGY/SOCIOECONOMICS/EDUCATION

Urinary tract infection (UTI) is a significant health problem in both community and hospital - based settings. It is estimated that 150 million UTIs occur yearly world-wide, 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 originate as UTIs.

Urinary infections are treated with antibiotics and removal of predisposing factors when possible, including indwelling catheters. Antibiotic use should be reserved for symptomatic infections and the decision to proceed with treatment requires thoughtful consideration of collateral impact and antimicrobial resistance patterns.

ETIOLOGY/PATHOGENESIS

Definitions:

Urine is generally considered sterile. The urinary system consists of the kidneys, the collecting system (including the renal calyces, pelvis and the ureter), and the bladder (responsible for storage and elimination 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 penile urethra. The foreskin when present may contribute to infection in select instances. 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 often does not require treatment.

Infection (UTI): the combination of a pathogen(s) within the urinary system and symptoms and/or inflammatory response to the pathogen(s) requiring treatment.

Uncomplicated UTI: infection in a healthy patient with anatomically and functionally normal urinary tract

Complicated UTI: infection associated with factors increasing colonization and decreasing efficacy of therapy. Requires one or all of following:

- o Anatomic or functional abnormality of urinary tract (enlarged prostate, stone disease, diverticulum, neurogenic bladder, etc.)
- o Immunocompromised host
- o Multi-drug resistant bacteria

Recurrent UTI: occurs after documented infection that had resolved

Reinfection UTI: a new event with reintroduction of bacteria into urinary tract

Persistent UTI: UTI caused by same bacteria from focus of infection

Factors Important for the Genesis of UTIs

Bacterial entry. Most UTIs are caused by ascending entry of bacteria from the periurethral area, emphasizing the importance of host factors contributing to entry. 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 develops most often in immunocompromised patients or neonates. Relapsing hematogenous infections can be secondary to incompletely treated prostatic or kidney parenchymal infections (eg emphysematous pyelonephritis).

Risk factors for UTIs

- Reduced urine flow
 - outflow obstruction, prostatic hyperplasia, prostatic carcinoma, urethral stricture, foreign body (calculus)
 - neurogenic bladder
 - inadequate fluid uptake
- Promote colonization
 - sexual activity - increased inoculation
 - spermicide - increased binding
 - estrogen depletion - increased binding
 - antimicrobial agents - decreased indigenous flora
- Facilitate Ascent
 - catheterization
 - urinary incontinence
 - fecal incontinence
 - residual urine with ischemia of bladder wall

Bacterial uropathogenic factors: A limited number of *E. coli* serotypes are responsible for the majority of UTIs. Bacteria that cause infection have increased adhesion, colonization and tissue invasion properties relative to nonpathogenic bacteria. The mediators of these pathogenic features include pili, cell surface structures responsible for adhesion to host tissues which promote colonization and increase resistance to bacteriocidal host activity. Specifically, Type 1 pili adhere to mannose receptors on in the urinary epithelial mucopolysaccharide lining as well as to polymorphonuclear leukocytes (PMNs); Uropathogenic *E. coli* with Type I pili are often associated with cystitis (bladder infection). P pili are mannose resistant and adhere to renal glycolipid receptors. P pili do not bind PMNs and are therefore relatively resistant to phagocytosis and clearing by the host immune system thus 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. Intermittent pili expression decreases opportunity for PMN binding making phagocytosis is less effective. One of the significant factors in resistance to bactericidal activity involves the expression of K antigen (capsular polysaccharide) on bacteria. Another mediator, hemolysin, produced by select bacteria, can augment tissue invasiveness and predispose to infection.

Host defenses: Several factors relating to host defenses 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; VUR) 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. 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.

Natural Defenses of Urinary Tract

1. Periurethral and urethral region - Normal flora in these areas contain: lactobacilli, coagulase negative staph, corynebacterium and streptococci that form barriers against colonization. Changes in estrogen, low vaginal pH and cervical IgA affect colonization by normal flora
2. Urine: high osmolality, high urea concentration, low pH, high organic acid are protective. Glucose in urine may facilitate infections. Tamm Horsfall proteins may be protective.
3. Bladder: Epithelium expresses Toll-like receptors (TLRs) that recognize bacteria and initiate immune/inflammatory response (PMNs, neutrophils, macrophages, eosinophils, NK cells, mast cells and dendritic cells). Adaptive immune response then predominant (T and B lymphocytes). Induced exfoliation of cells also occurs to allow excretion of bacterial colonization.
4. Kidney: local immunoglobulin/ antibody synthesis in the kidney occurs in response to infections (IgG, SIgA).

Alterations in Host Defense Mechanisms

- **Obstruction:** key factor in increasing susceptibility to UTI but does not necessarily predispose to infection.
- **VUR:** Hodson and Edwards (1960) described association of VUR, UTI, and eventual renal scarring.
- **Underlying Disease:** Diabetes mellitus (DM), sickle cell disease (SCD), nephrocalcinosis, gout, analgesic abuse, aging, hyperphosphatemia, hypokalemia.
 - DM: Glycosuria may contribute to severity of infections due to immune compromise. Majority of infections (80%) are in the upper tracts.
 - Papillary necrosis: due to DM, pyelonephritis, obstruction, analgesics, SCD, transplant rejections, cirrhosis, dehydration, contrast media, renal vein thrombosis.
 - HIV: UTIs 5x more prevalent in this population and they recur more frequently.

- **Pregnancy:** Bacteriuria in pregnancy = 4-7% and incidence of acute clinical pyelonephritis = 25-35% in untreated patients.
- **Spinal Cord injury with high pressure bladder:** provokes reflux with high morbidity and mortality from bacteriuria

Table 1: Potentially Infective Pathogens in the Urinary Tract

Common Causative pathogens in Adult UTIs

E. Coli (80% of outpatient UTIs)
F. Klebsiella
G. 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 may not accurately localize the infection within the urinary tract.. In many cases, however, colonization of the urinary tract can be asymptomatic. The most common form of UTI is cystitis (bladder infection) characterized by irritative symptoms such as urinary urgency, frequency, dysuria, hematuria, foul- smelling urine, and suprapubic pain. These symptoms are also typical for urethritis and prostatitis in addition to cystitis. An associated epididymitis, 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, flank or abdominal pain, and frequently associated with nausea and vomiting.

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 colonization. There are 3 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. Voided urines that are sterile or

contain high colony counts (>100,000) of a single bacteria correlate well with urine obtained by other more invasive 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 certain gram negative bacteria (not gram positive), is very specific but only about 50% sensitive for a urinary tract infection. 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 considered diagnostic for UTI. However, as mentioned above, the probability of a UTI also depends 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 historically 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) collection of expressed prostatic secretions, captured from the penile urethra while massaging the prostate with a rectal exam, and 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.

Correctable GU abnormalities resulting in bacterial persistence:

- Infected stones
- Chronic bacterial prostatitis
- Unilateral infected atrophic kidneys
- Ureteral duplication and ectopic ureters
- Foreign bodies (i.e. retained ureteral stent)
- Urethral diverticula
- Unilateral medullary sponge kidneys
- Infected ureteral stumps after nephrectomy

- Infected urachal cyst
- Infected communicating cysts of renal calyces
- Papillary necrosis
- Colovesical fistula

INDICATIONS FOR RADIOLOGIC IMAGING WITH UTI

Patients with uncomplicated cystitis or uncomplicated pyelonephritis generally do not benefit from imaging studies to evaluate for potential 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
- Urinary tract tuberculosis
- Urinary tract neoplasm
- Intra-abdominal abscess
- Sepsis - source other than GU system
- Overactive bladder

MANAGEMENT OF UTI

The combination of clinical findings and urine evaluation is essential for diagnosis of UTI. Treatment is based upon pathogen identification and the type and degree of clinical illness, as well as the presence or absence of 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.

**Highest mean urine concentration (from highest to lowest):
Cabrenicillin > Cephalexin > Ampicillin > TMP/SMX > Cipro > Nitrofurantoin**

However, in cases of pyelonephritis, prostatitis or epididymitis, proper tissue antibiotic concentrations are important.

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. Use of diaphragm and spermicidal contraceptives which 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.

Of note, often local antibiograms will be useful for determining the prevalence of local resistance patterns and determining optimal antibiotic strategies, particularly for nosocomial infections.

Additionally, use of antibiotics in pregnancy should be tailored according to the American Board of Obstetrics and Gynecology committee opinion and local consultation with the treating obstetrician is often necessary to determine an optimal and safe strategy for therapy: <http://www.acog.org/-/media/Committee-Opinions/Committee-on-Obstetric-Practice/co494.pdf?dmc=1>.

Uncomplicated UTI (cystitis, some pyelonephritis)

- Nitrofurantoin 100 mg BID x 5 days or a 3 day course of oral trimethoprim/sulfamethoxazole (TMP/SMX) is 95% effective
- If TMP/SMX resistance is > 10 - 20% (U.S. West coast, Europe), consider fluoroquinolones.
- Only use fluoroquinolones or beta-lactams if one of these recommended antibiotics cannot be used due to availability, allergy, or tolerance

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)

- Patients who are candidates for outpatient therapy may utilize:
 - Oral ciprofloxacin 500 mg BID x 7 days
 - Once daily oral fluoroquinolone (ciprofloxacin 1000 mg ER x 7 days or levofloxacin 750 mg x 5 days)
 - Oral TMP-SMX DS BID x 14 days (not for Enterococcus or Pseudomonas)
 - Use of initial one-time IV agent (ceftriaxone 1 g, aminoglycoside, fluoroquinolone)
- Adjust antibiotics according to culture results
- For inpatient management
- IV fluoroquinolone
- Aminoglycoside +/- ampicillin
- 3rd generation cephalosporin
- Extended spectrum penicillin
- Carbapenem
 - 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.

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.

REFERENCES

Pontari, M. AUA Core Curriculum for Residents "Urinary Tract Infections"
<http://www.auanet.org/eforms/elearning/core/index.cfm?topic=41>

Shoskes, D. (2011): Urinary Tract Infections Retrieved From: The American Urological Association Educational Review Manual in Urology: 3rd Edition Chapter: 23 Page: 737-766.

Smith's General Urology 16th edition 2004. Tanagho and McAninch, eds. Chapter 13. "Bacterial Infections of the Urinary Tract" Nguyen, Hiep. pp. 203 - 227.

Stamm, WE, Norrby, SR. Urinary Tract Infections: Disease Panorama and Challenges. J Infect Dis. 2001 Mar 1; 183 Suppl 1:S1-4.

Hooten, TM, Scholes, D, Hughes, JP, et al. A Prospective Study of Risk Factors for Symptomatic Urinary Tract Infection in Young Women. NEJM 1996; 335: 468-74

Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, Moran GJ, Nicolle LE, Raz R, Schaeffer AJ, Soper DE; Infectious Diseases Society of America; European Society for Microbiology and Infectious Diseases. (2011) International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis. Mar 1; 52(5):e103-20.

(Updated July 2016)