

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 including cystitis, pyelonephritis, epididymitis, and prostatitis.

Introduction

Urinary tract infections are a troubling and increasingly dangerous condition treated by physicians from a number of specialties, including Urology. The landscape of diagnosis and management is changing as new resistance patterns emerge. In this section of the Medical Student Curriculum, we discuss epidemiology, diagnosis, and management of both complex and non-complex urinary tract infections.

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 can be divided into the upper tract, which consists of the kidneys (renal parenchyma and collecting system) and the ureters, and the lower urinary tract, which includes the bladder (responsible for storage and elimination of urine), the urethra (tube through which urine exits the bladder to the outside world), and prostate in men. In the female, the urethra exits the bladder near the vaginal area, the vagina could contribute to contamination of urine specimens. 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.
- **Asymptomatic bacteriuria (Colonization)** - organisms are present in the urine but are causing no illness or symptoms. 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, non-pregnant, pre-menopausal female patient with anatomically and functionally normal urinary tract.
- **Complicated UTI** - infection associated with factors increasing colonization and decreasing efficacy of therapy.
- **Recurrent UTI** - occurs after documented infection that had resolved. Defined as 2 or more infections in 6 months, or ≥ 3 infections in 12 months (JAMA article).
- **Reinfection UTI** - a new event with reintroduction of bacteria into urinary tract or by different bacteria.
- **Persistent UTI** - UTI caused by same bacteria from focus of infection.

Factors Important for the Genesis of UTIs

Bacterial entry:

Bacteria ascending into the bladder through the urethra is the most common cause of UTIs. There are several risk factors that may promote or encourage bacterial ascent.

Risk factors for UTIs

- 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
 - voiding dysfunction
- Promote colonization
 - sexual activity - increased inoculation
 - spermicide - increased binding
 - estrogen depletion - increased binding
 - antimicrobial agents - decreased indigenous flora
- Facilitate Ascent
 - catheterization (chronic or intermittent)
 - urinary incontinence
 - fecal incontinence
 - residual urine with ischemia of bladder wall

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, elderly, or neonates. Relapsing hematogenous infections can be secondary to incompletely treated prostatic or kidney parenchymal infections (e.g. emphysematous pyelonephritis).

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 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, 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 predominates (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, IgA).

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** - High morbidity and mortality from bacteriuria

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 generic form of UTI is cystitis (bladder infection) characterized by irritative symptoms (urinary urgency, frequency, dysuria) hematuria, foul- smelling urine, and suprapubic pain. These symptoms are also common for urethritis and prostatitis. Epididymitis can be associated with cystitis and diagnosed reliably by physical examination in men. 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. In a female patient with recurrent urinary tract infection, a thorough abdominal and pelvic exam should be performed.

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 single bacteria correlate well with urine obtained by other more invasive methods.

Contamination should be suspected when the following factors are noted: growth of normal vaginal flora such as lactobacillus, mixed cultures with more than one organism, or low quantities of pathogenic organisms in an asymptomatic patient. The clinician should also review the urinalysis and may be suspicious of contamination in the presence of epithelial cells or mucus. If a contaminated specimen is suspected, a straight catheterization can be more reliable in obtaining an accurate specimen. Suprapubic aspirate can also be performed but is more invasive and less frequently utilized in clinical practice.

Techniques to improve the accuracy of urine culture include preparation of the urethral meatus and periurethral vaginal epithelium, though this is not been definitively proven as beneficial from an evidence-based standpoint. Avoiding contact of the collection cup with the perineum, labial spreading, and discarding the initial urinary stream in favor of the midstream sample can help prevent contamination of the specimen.

Urinalysis: A chemical analysis (dipstick) is suggestive for UTI if leukocyte esterase and/or nitrite are positive. Detection of leukocyte esterase means that there are white blood cells present in the urine. Leukocyte esterase has a 73-84% specificity and has a 80-92% sensitivity for UTI. The finding of nitrite positivity on urine dipstick, indicates the conversion of nitrate to nitrite by certain gram negative bacteria (not gram positive), is very specific (96-99%) but due to conversion only by Gram negative bacteria, not very sensitive.

Urine Microscopy: Urine microscopy is an important adjunct to the urinalysis. 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 like the LE on chemical analysis, less specific for a UTI. Pyuria in the absence of urinary symptoms does not mean UTI is present. Urine microscopy is important for identification of the presence of squamous epithelial cells. More than 15-20 squamous epithelial cells/hpf on microscopy is suggestive of a contaminated specimen and sterile straight catheterized specimen may be desired. In addition, bacteria or yeast species may be seen. UTI can often have associated gross or microscopic hematuria, the number of RBC/hpf should be quantified and documented; if a patient has a negative culture a hematuria evaluation would need to be performed.

Table 1: Sensitivity and Specificity of Indicators of Possible Infections Found on Urinalysis and Microscopy

Test	Sensitivity (%)	Specificity (%)
LE	79 (73-84)	87 (80-92)
N	49 (41-57)	98 (96-99)

LE or N	88 (82-91)	79 (69-87)
LE+N	43 (30-61)	98 (96-99)
WBC	74 (67-80)	86 (82-90)
Bacteria	88 (75-94)	92 (83-96)

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.

Potentially Infective Pathogens in the Urinary Tract

Common Causative Pathogens in Adult UTIs

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

Normal Perineal Flora

- Lactobacillus
- Corynebacterium
- Staphylococcus
- Streptococcus

Anaerobes

Methods to localize infection: For patients who have recurrent UTI, localization may be desired to identify a possible source if not clear with imaging and cystoscopy. Upper urinary tract infections may be isolated using the Stamey test in which a patient is catheterized and urine cultures 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.

Used historically to diagnose chronic bacterial prostatitis, several localization methods have been described, but are otherwise uncommonly used. 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
- 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. If acute bacterial prostatitis is suspected a prostatic massage should NOT be performed for concern of bacteremia.

INDICATIONS FOR RADIOLOGIC IMAGING WITH UTI

Patients with uncomplicated cystitis or uncomplicated pyelonephritis generally do not benefit from imaging studies or endoscopic evaluation. In patients who do not respond to treatment, or in patients with complicated UTIs or recurrent UTIs, imaging with either a kidney and bladder ultrasound or a non-contrast CT scan of the abdomen and pelvis may be useful for identification of potential causes. Cystoscopy or ureteroscopy of the urinary tract may be performed for cases of recurrent UTI to exclude bladder or upper tract pathology.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for recurrent UTI is expansive and includes consideration of other types of non-bacterial infection as well as causes of recurrent UTIs. In addition, it is important to consider the differential diagnosis for non-infectious causes of the same symptoms, specifically urgency, frequency, and dysuria.

DDx of infectious causes:

- STI (Herpes genitalis (HSV), N. Gonorrhoea, Chlamydia, Trichomonas)
- Urethritis
- Prostatitis
- Vaginal Infection/PID
- Candida Infection
- Urinary Tuberculosis
- Intra-abdominal Abscess
- Sepsis - source other than GU

DDx for Recurrent UTIs/Persistent UTI:

- Lower Urinary Tract Neoplasm (bladder cancer or CIS of the bladder)
- Bladder Outlet Obstruction
- Diverticulum (Bladder or Urethral)
- Skene's Gland Abscess
- Urinary Fistula (Vesicovaginal, Enterovaginal, Urethrovaginal)
- VUR or Ureteral anomalies
- Infected stones (Renal, Ureteral, Bladder)
- Foreign Body
- Voiding Dysfunction
- Infected Urachal Cyst
- Chronic Bacterial Prostatitis
- Abnormality of Renal Unit (Medullary Sponge Kidney, Infected Cysts, Atrophic Kidney)

DDx for symptoms:

- Lower Urinary Tract Neoplasm (bladder cancer or CIS of the bladder)
- Bladder Outlet Obstruction
- Interstitial cystitis
- Overactive bladder
- Vaginal Atrophy
- Vaginal Contact Dermatitis
- Distal Ureteral or Bladder stones
- Foreign Body (i.e. mesh)
- Voiding Dysfunction
- Pelvic Floor Muscle Dysfunction

MANAGEMENT OF UTI

Each symptomatic episode of acute cystitis should be evaluated first with a urinalysis and urine culture with sensitivity prior to treating with antibiotics. 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 if present, 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 (pyelonephritis, cystitis, prostatitis, epididymitis, orchitis), 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, epididymitis, or orchitis, selection of antibiotic with proper tissue penetration is 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 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, but in general should be considered in pregnant or post-menopausal females and men. Patients with complicated UTIs are more likely to have medical co-morbidities or conditions with require special consideration. In addition, they may have a greater variety of pathogenic bacteria, more drug resistance, and require a longer duration of antibiotic therapy.

Complicated UTIs requires one or more of following:

- Anatomic or functional abnormality of urinary tract (outlet obstruction, stone disease, diverticulum, neurogenic bladder, VUR etc.)
- Urinary instrumentation or foreign bodies in the urinary tract (i.e. catheters, stents, nephrostomy tubes)
- Systemic disease (renal insufficiency, diabetes, immunodeficiency, organ transplantation)
- Pregnancy
- Multi-drug resistant bacteria

The mainstay of treatment of acute UTI, either non-complicated or complicated infections, is antibiotics. Local antibiograms are useful for determining the prevalence of local resistance patterns and determining optimal antibiotic strategies for patients with complicated UTIs and 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>.

If asymptomatic bacteriuria is suspected, it does not necessarily need to be treated. Clinical signs and symptoms of acute cystitis should prompt treatment rather than the presence of bacteria on urine culture. There are some groups of patients, notably patients undergoing urologic surgery and pregnant women, who should be treated for asymptomatic bacteriuria. Routine surveillance urine cultures for asymptomatic bacteriuria in healthy, uncomplicated patients should not be performed.

Uncomplicated Cystitis

▫ Preferred:

- o Fosfomycin, 3 gram single po dose
- o Nitrofurantoin, 100 mg po bid x 5 days
- o Trimethoprim-sulfamethoxazole DS, 1 pill po bid x 3 days

- Alternative when bacteria are resistant to the preferred antibiotics
 - Ciprofloxacin, 250 mg bid x 3 days - fluoroquinolone antibiotics should not be the first line treatment of uncomplicated cystitis.

Complicated Cystitis in Women

- Urine culture and susceptibility should be performed
- Prior cultures should be reviewed and empiric selection of those results
- Patients who are candidates for outpatient therapy
 - 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)
 - Treat for 14 days
- Failure to respond after 24-72 hours of appropriate antibiotics need further investigation

Cystitis in Men

- Urine culture and susceptibility should be performed
- Preferred:
 - Trimethoprim/sulfamethoxazole 160/800 mg po BID
 - Levofloxacin 500 mg po daily
 - Ciprofloxacin 500 mg po BID
 - Ciprofloxacin ER 1000 mg po daily
- Treatment is generally for 7-14 days, optimal duration is not know

Uncomplicated Pyelonephritis in a Healthy Patient

- Urine culture and susceptibility should be performed
- Preferred:
 - Ciprofloxacin 500 mg po BID x 7 days ± initial Ciprofloxacin 400 mg IV x 1
 - Ciprofloxacin 1000 mg po daily x 7days
 - Levofloxacin 750 mg po daily x 5 days **if fluoroquinolone resistance > 10% initial dose of ceftriaxone 1gm or aminoglycoside 24-hour dose recommended
 - Trimethoprim-Sulfamethoxazole DS (160/800mg) po BID x 14 days **if susceptibility to TMP-SMX is not known, initial dose of ceftriaxone 1gm or aminoglycoside 24-hour dose recommended

Complicated Pyelonephritis (requiring hospital admission)

- Urine culture and susceptibility should be performed
- Adjust antibiotics according to culture results
- For inpatient management of Pyelonephritis
 - IV fluoroquinolone
 - Aminoglycoside +/- ampicillin
 - 3rd generation cephalosporin

- o Extended spectrum penicillin+/- aminoglycoside
- o Carbapenem
- 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 appropriate drainage.

Bacterial Prostatitis

- Acute (*E coli*, *Enterobacteria*, *Pseudomonas*, *Enterococci*)
 - o Treat for 2 weeks duration
 - o 1st Line: Trimethoprim/Sulfamethoxazole or Fluoroquinolone
 - o 2nd Line: 2nd generation cephalosporin
 - o 3rd Line: 3rd generation cephalosporin

New Antimicrobials

- Cefiderocol
 - o Approved by FDA in 2019 for specific urinary infections
 - o Similar to other antibiotics, action is related to inhibition of gram negative bacterial cell wall

Exhibits enhanced stability against β -lactamase

- o Role in treatment of carbapenem resistant and ESBL producing organisms

Special Considerations:

Recurrent UTI

Recurrent UTI is defined as 2 or more infection in a 6-month period or ≥ 3 culture proven infections in 12 months. Both re-infection and relapsing infection contribute to the development of recurrent UTIs. Re-infection is the recurrence of a UTI with the same or different organisms rapidly after cure has been documented. In patients that have re-infection a test of cure after treatment should be performed to establish clearance of the pathogen. If there is concern for a relapsing infection, or failure to eradicate the pathogen despite reasonable treatment course a urologic referral should be made.

With the push towards antibiotic stewardship increased consideration is be given to non-antibiotic options for UTI prevention. Vaginal estrogen may be useful for post-menopausal women who have recurrent UTIs. It is established that after menopause there is thinning of the vaginal epithelium and alkalization; use of vaginal estrogen preparations may reverse these changes. There is low systemic absorption of vaginal estrogen preparation, but consideration should be given to individual patients, risks, and patient preference. There are numerous supplements that may be used for the prevention of UTIs in some patients, though for many of these there is little supporting evidence and recommendation is based more anecdotally. The 2012 Cochrane review concluded that cranberry juice can no longer be recommended, and other cranberry preparations need to be quantified prior to use in clinical studies. The

active ingredient of cranberries is proanthocyanidins (PAC) specifically type A. It has been determined that 36mg of PAC are needed to prevent the binding of E coli to urothelial cells. Methenamine hippurate is metabolized to formaldehyde in acidic urine and bacteriostatic. The 2012 Cochrane review concluded that there is evidence that methenamine may be useful for short-term prophylaxis. Vitamin C can be added to acidify urine alone or in combination with methenamine; it may have a bacteriostatic effect. Finally, both D-Mannose and Probiotics may be useful in the prevention of infections, but evidence is limited.

However, at times, despite attempts at preventative measures prophylactic antibiotics are required for management of recurrent UTIs. Any prior cultures should be reviewed to determine if antibiotic resistance exists. Options for prophylaxis include a post coital or continuous form. If daily prophylaxis is considered the best option for the patient, it should be continued for a minimum of 6 months.

Table 4: Antibiotic Prophylaxis Regimens for Recurrent Cystitis

Long Term Daily Prophylaxis	Post-coital Prophylaxis
Fosfomycin 3 gm every 10 days	Nitrofurantoin 50-100 mg single dose
Nitrofurantoin 50-100 mg daily	Trimethoprim/sulfamethoxazole 80/400mg single dose
Cephalexin 125-250 mg daily	Cefixime 400 mg single dose

**FDA warnings are posted for use of Nitrofurantoin long term due to severe pulmonary and hepatic long term effects

Asymptomatic Bacteriuria

Asymptomatic bacteriuria is defined as a specific number of bacteria isolated from urine in individuals without symptoms or signs of a UTI. In women the Infectious Diseases Society of American has defined this as > 10(5) cfu/ml of the same organism on 2 consecutive clean catch urine samples, and in men is a > 10(5) cfu/ml in a single clean-catch urine. The presence or absence of pyuria does not differentiate symptomatic from asymptomatic bacteriuria. Screening and treatment is recommended for patients who are pregnant and patients with planned urology procedures where mucosal bleeding is anticipated (ISDA ref) or ureteroscopy (my opinion). For patient preparing for joint arthroplasty there is no consensus on screening and treatment.

Catheter associated UTI (CAUTI)

Patients with indwelling urethral catheter will universally develop bacteriuria over time; 10-25% of these will develop symptoms. Risk factors included female gender, elderly, DM, error in catheter care and bacterial colonization of the drainage bag. Pyuria, cloudy appearance, and foul odor has not been demonstrated to be associated with bacteriuria or UTI (uptodate.com/contents/catheter-associated-urinary-tract-infection-in-adults)

CAUTI has multiple definitions.

- The IDSA in patient with an indwelling catheter (urethral or suprapubic) or CIC or culture within 48 hours of catheter removal positive for $>10^3$ cfu/ml of uropathogenic bacteria with the following any of the following symptoms: fevers, suprapubic/CVA tenderness, unexplained systemic symptoms of mental status change, hypotension, systemic inflammatory response syndrome without other identifiable cause or source of those symptoms and signs
- The National Health Safety Network (NHSN) defines it as $>10^5$ cfu/ml of no more than 2 organisms with symptoms of fever, suprapubic tenderness or CVA pain

Prevention of recurrent urinary tract infections

Historically, suppressive antibiotic therapy has been utilized for the prevention of recurrent urinary tract infections. Prophylactic antibiotic use has been shown to decrease the likelihood of experiencing recurrent urinary tract infections compared to no antibiotic prophylaxis. However, appropriate antibiotic stewardship remains a concern when long-term antibiotic prophylaxis is utilized. There is also a risk of side effects associated with antibiotic suppressive therapy. Antibiotics that have been studied for the prevention of recurrent urinary tract infections include nitrofurantoin, fosfomycin, trimethoprim, trimethoprim with sulfamethoxazole, and cephalosporins. Fluoroquinolones have also been utilized for prophylaxis, but the FDA has issued warnings regarding the complications associated with fluoroquinolone use. These can include cardiac effects such as QT interval prolongation, seizures, aneurysm rupture, tendon rupture, tendonitis, and neurological side effects.

The American Urological Association Guidelines for recurrent urinary tract infections in female patients acknowledges these concerns and recommends that clinicians prescribing antibiotic prophylaxis discuss the risks and benefits as well as the alternatives to antibiotic prophylaxis in this patient population.

Cranberry supplementation in the diet may be utilized to help reduce the risk of recurrent urinary tract infections as per the American Urological Association Guidelines. The challenges of applying this recommendation is that cranberry supplementation may come in various forms, including juice, tablets, and cocktails. It is believed that the proanthocyanidins help prevent bacterial adhesion to the urothelium.

Increased fluid intake in healthy patients may help reduce the risk of recurrent UTIs. Research on other non-antibiotic prophylaxis options is not robust enough to make strong recommendations in favor of their routine use. Nonetheless, many of these options are utilized by patients and practitioners, including lactobacillus, methenamine, and D-mannose. Healthy female peri- or post-menopausal women with recurrent UTIs can be prescribed intravaginal (not oral) estrogen to decrease the risk of infection, assuming there are no contraindications to estrogen supplementation.

SUMMARY

- Urinary tract infections are both prevalent and costly.
- Bacterial UTIs (different from urinary colonization or asymptomatic bacteriuria) 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

- Colgan, R, Williams, M. (2011). Diagnosis and treatment of acute uncomplicated cystitis. *American Family Physician*, 84(7), 771-776.
- Concia, E, et al. Clinical evaluation of guidelines and therapeutic approaches in multi drug-resistant urinary tract infections. *J Chemother*. 2017 Dec;29(sup1):19-28.
- Grigoryan, L, et al. Diagnosis and Management of Urinary Tract Infections in the Outpatient Setting. *JAMA* 2014;312(16):1677-1684
- Gupta, K, et al. 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.
- Hooton, T., *Acute complicated urinary tract infection (including pyelonephritis) in adults*. Retrieved from <https://www.uptodate.com/contents/acute-complicated-urinary-tract-infection-including-pyelonephritis-in-adults>
- Hooten, TM, et al. A Prospective Study of Risk Factors for Symptomatic Urinary Tract Infection in Young Women. *NEJM* 1996; 335: 468-74
- Nguyen, H. (2013) *Bacterial Infections of the Urinary Tract*. In Tanagho and McAninch, (eds) *Smith & Tanagho's General Urology* (pp 203-227). McGraw-Hill Companies, Inc.
- Pontari, M. *AUA Core Curriculum: Urinary Tract Infection*. Retrieved from https://university.auanet.org/core_topic.cfm?coreid=92
- Stamey, TA, et al. The Localization and Treatment of Urinary Tract Infections: The Role of Bactericidal Urine Levels as Opposed to Serum Levels. *MEDICINE* 44(1); 1-36. January 1965.

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

Brusch, J, *Urinary Tract Infection (UTI) and Cystitis (Bladder Infection) in Females.* Retrieved from <https://emedicine.medscape.com/article/233101-overview>

Zhanel GG, Golden AR, Zelenitsky S, et al. Cefiderocol: A Siderophore Cephalosporin with Activity Against Carbapenem-Resistant and Multidrug-Resistant Gram-Negative Bacilli. *Drugs* 2019; 79(3): 271-289.

FDA, July 2018, www.fda.gov/news-events/press-announcements/fda-updates-warnings-fluoroquinolone-antibiotics-risks-mental-health-and-low-blood-sugar-adverse

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