Learning Objectives

After studying this monograph students will be able to:

- Given a clinical description, diagnose the following: “upper urinary tract infection”, “lower urinary tract infection”, “complicated urinary tract infection”.
- Describe host factors which predispose patients to developing urinary tract infections.
- Describe factors which give certain microbes an advantage in causing urinary tract infections.
- Explain the pathogenesis of ascending vs hematogenous routes of developing urinary tract infection.
- List the most common bacteria which cause urinary tract infections. (Know that \textit{E. coli} is responsible for 80 – 90% of uncomplicated urinary tract infections)
- Explain why pyuria develops in urinary tract infections.
- List the laboratory studies utilized in the diagnosis of urinary tract infections.
- Cite which group of patients do not require urinalyses or cultures to diagnose acute cystitis.
- Select the appropriate first line antibiotic class and duration of therapy for acute uncomplicated cystitis and acute pyelonephritis.
- Summarize why indwelling bladder catheters predispose to the development of UTIs.

Studies will apply their knowledge during a case-based discussion in the lecture hall facilitated by Dr. Albarillo.

As we begin discussing urinary tract infections, it is important to remember that normally bladder urine is usually sterile or contains only small numbers of bacteria. This is because of the anti-microbial properties of intact bladder mucosa and the flushing mechanisms associated with periodic voiding of urine. Urine IgA and IgG serve as protective mechanisms against infections. Tamm-Horsfall proteins are produced by renal tubular cells and serve as a protective mechanisms decreasing attachment of bacteria to urothelium.

Obstruction of urinary flow or reflux can compromise normal host defenses and increased susceptibility to the development of urinary tract infections.

I. Definitions of UTI

Urinary Tract Infections (UTIs) can be categorized as:

- Lower vs Upper
- Uncomplicated vs Complicated
1. **LOWER Urinary Tract Infection**
   Lower UTIs involve the bladder, urethra and/or prostate and are referred to as Cystitis, Urethritis, and Prostatitis respectively.

   Symptoms of lower UTIs include dysuria, increased frequency of urination, urinary urgency, suprapubic pain or tenderness. These are signs and symptoms of bladder and/or urethral irritation.

   Some patients will develop gross hematuria with lower UTIs.

2. **UPPER Urinary Tract Infection**
   Upper UTIs involve the kidney – referred to as acute pyelonephritis.

   Patients with upper UTIs have signs and symptoms of systemic infection such as fever, tachycardia, chills, rigors.

   Patients with acute pyelonephritis often have flank pain and on exam tenderness to palpation at the costovertebral angle.

   Patients may or may not have signs/symptoms of lower UTI.

3. **UNCOMPLICATED Urinary Tract Infection**
   “Uncomplicated UTI” implies a simple cystitis in a structurally and neurologically normal urinary tract.

   Absence of:
   - Pyelonephritis
   - Pregnancy
   - Urologic abnormalities including stones
   - Indwelling foley catheter, stent, nephrostomy tube or urinary diversion
   - Immunosuppression
   - Bacteremia

   Fortunately, most patients develop uncomplicated UTIs localized to the lower urinary tract.

4. **COMPLICATED Urinary Tract Infection**
   UTI is considered to be complicated if there is infection in the presence of factors that predispose to persistent or relapsing infection.

   Patients with complicated UTIs have structural or functional abnormalities of the genitourinary tract that compromise voiding or lead to obstruction of urinary flow.

   - Urinary retention from neurologic disease
   - Calculi or other causes of obstruction
   - Indwelling catheters or other drainage devices
   - Renal failure
   - Immunosuppression: renal transplantation, chemotherapy, steroids, AIDS
   - Pregnancy (why? Urinary stasis from hormonal effects on autonomic muscles of the bladder and growing uterus and ureteric obstruction from pressure of the fetal head at the pelvic brim)
Note that UTI in men and children is considered to be complicated since there is usually an underlying anomaly leading to infection. In older men, for example, this is benign prostatic hyperplasia leading to urinary obstruction and stasis of urine in the bladder.

II. Pathogenesis of UTI

1. **What are the routes of infection?**
   The two primary routes of infection are a) ascending and b) hematogenous.

   **A. Ascending infection:**
   Ascending infection is the most common route to developing UTIs.

   Ascending infection begins as colonization of the periurethral region with bacteria present in feces. Bacteria causing UTIs usually originate from the normal gut flora (coliform bacteria). Remember that anatomically the anus is in region of perineum. Women are more prone to UTI than men due to short length of urethra compared to men and in turn proximity of the anus to the urethra.

   These bacteria which include uropathogens invade the urethra and ascend into bladder.

   **Note:** Frequent sexual intercourse provides a massaging effect on bacteria promoting ascent into the bladder.
B. Hematogenous Infection:
Bacteria can spread hematogenously into the bladder. This is particularly seen with Staphylococcus aureus infection and in the setting of infectious endocarditis. Hematogenous development of UTIs is far less common than ascending infection.

2. What are Microbial Factors which influence the development of UTIs?
Bacteria, like E. coli, have virulence factors which give them advantages for causing infections.

Pili or fimbriae facilitate adherence of the bacteria to the bladder uroepithelial cells.

Certain bacterial proteins can provide an advantage to causing infection

- Hemolysin- induces pores in cell membrane
- Cytotoxin- Cytotoxic necrotizing factor-1 leads to urothelial cell injury
- Aerobactin- siderophore that scavenges iron that bacteria need to grow

Urease - Proteus species in particular produce an enzyme called urease which breaks down urea into carbon dioxide and ammonia. This causes an elevated urinary pH. This alkalinization of urine facilitates precipitation of organic and inorganic compounds leading to formation of calculi. (remember stones can lead to obstruction predisposing to UTIs).
Proteus is associated with the development of “staghorn” calculi. “Staghorn” describes the configuration of the stone - large branched stones that fill all or part of the renal pelvis and extend the majority of the renal calices.

Serum resistance- some bacteria have mechanisms that allow strains to resist the bactericidal activity of human serum
Biofilms – Biofilms consist of microorganisms, extracellular substances produced by the organisms and urinary components such as proteins, calcium and magnesium which form on foreign body surfaces, such as catheters. The biofilms prohibit antibiotics from permeating to the bacteria, making it difficult to eradicate the bacteria. Biofilms are one of the reasons why patients with indwelling urinary catheters are at increased risk for UTIs

Summary of the Pathogenesis of UTI at Cellular Level

1. Colonization of perineal region.
2. Adherence of bacteria to bladder urothelium via adherence factors: pili or fimbria.
3. Once attached bacteria can invade and multiply in cells leading to apoptosis and exfoliation of urothelial cells which triggers migration of neutrophils into bladder. This is why one sees WBCs (pyuria) in the urinalysis of patients with UTI.
4. In upper urinary tract infections - the bacteria ascend from the bladder to ureters to kidney.
5. In kidney there can be injury to epithelial cells and glomerular cells
6. Bacteria can cross tubular epithelial cell barrier and cause blood stream infection – bacteremia.
3. **What are Host Factors which influence the development of UTIs?**

**A. Behavior**
- Frequency of sexual intercourse – intercourse has a massaging effect facilitating the ascension of bacteria from the periurethral area into the bladder. An increased frequency of intercourse is associated with an increased frequency of symptomatic UTIs.
- Use of diaphragm/vaginal spermicide for contraception – Spermicides can interrupt growth of lactobacillus and other normal flora allowing uropathogens, such as E coli, to colonize the vagina and cause infection.
- Hygiene - direction of wiping in females plays a role. The best way to wipe is from front to back, not back to front which pushes gut flora from anus to periurethral area.

**B. Susceptibility to local colonization**
- Receptors: women who are of P1 blood group (have P antigen on their red blood cells) have epithelial receptors that mediate attachment of bacteria. In turn they have an elevated risk of recurrent UTI.
- pH of urine (as in discussion on urease)

**C. Anatomic/physiologic changes**
- Urinary stasis, such as with prostatic enlargement in men
- Vesicoureteral Reflux from urinary anomalies particularly in children
- Pregnancy hormonal and structural changes
- Neurological disorders, such as spinal cord injury
- Diabetes mellitus may lead to the development of autonomic neuropathy resulting in stasis of urine in the bladder

**D. Instrumentation/Foreign bodies**
- Presence of indwelling bladder catheters, stents, nephrostomy tubes place patients at high risk for developing UTIs. Biofilms as previously discussed play a role.

### III. Epidemiology of UTIs

**Etiologies of acute uncomplicated UTIs**
- *E.coli* - 80%
- *S. saprophyticus* in women who are sexually active
- *Klebsiella*
- *Proteus*
- Others (ie Enterococcus)

**Etiologies of Complicated or Recurrent UTIs**
- *E.coli*
- *Proteus*
- *Providentia*
- *Klebsiella*
Prevalence of UTIs Age and Sex Distribution

- 8.6 million ambulatory visits for UTI (84% women) in 2007
- Self-reported annual incidence in women is 12%
- By age 32, one half of all women report at least one UTI
  - 2-5% have recurrent UTIs with genetic predisposition (ie P1 blood group)
- Among healthy women with cystitis, 25% recur within six months
- Acute uncomplicated pyelonephritis less common
  - Estimated one episode per 28 episodes of cystitis

Table summarizing epidemiology of UTIs based on age:

<table>
<thead>
<tr>
<th>Age</th>
<th>Prevalence (%)</th>
<th>Sex</th>
<th>Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates</td>
<td>1</td>
<td>M &gt; F</td>
<td>GU Abnormalities</td>
</tr>
<tr>
<td>Children</td>
<td>4 – 5</td>
<td>F &gt;&gt; M</td>
<td></td>
</tr>
<tr>
<td>Sexually active adults</td>
<td>10</td>
<td>F</td>
<td>Sexual Activity contraception</td>
</tr>
<tr>
<td>Elderly</td>
<td>30-40</td>
<td>M = F</td>
<td>Prostate hypertrophy, bladder prolapse, incontinence</td>
</tr>
</tbody>
</table>

**What to notice:**
- UTIs more common in infant males than females due to genitourinary malformations
- In adolescents and sexually active adults – UTIs much more common in women
- In elderly – gender distribution about equal due to comorbidities

IV. Clinical Features of UTI: Cystitis and Acute Pyelonephritis

1. **Cystitis:**
   Typically in young sexually active women acute cystitis is characterized by symptoms and signs of bladder irritation:
Acute onset of dysuria (pain on voiding)
Frequency (frequent urination)
Urgency (need to void immediately once the urge is felt)
Suprapubic pain and tenderness
About half of patients may experience gross hematuria

Important to note that dysuria can be caused by other process which must be distinguished from cystitis. It is important to ask about the patient’s sexual history:

**Major causes of acute dysuria in women**

- Cystitis – *E. coli, S. saprophyticus, Proteus species, Klebsiella species*

- Urethritis – Sexually transmitted disease *N. gonorrhoeae, C. trachomatis*, Human Simplex Virus (HSV)

- Vaginitis – Candida, *Trichomonas vaginalis*, vaginal flora (Bacterial vaginosis)

2. **Acute Pyelonephritis:**

   Pyelonephritis has associated systemic findings of infection

   - Acute onset of flank pain, tachycardia, often nausea or vomiting and frequently lower tract symptoms (dysuria, frequency, urgency)
   - Costovertebral angle tenderness

   Complications: Bacteremia and septic shock may occur with overwhelming infection. Other complications are the development of perinephric abscess and papillary necrosis (particularly in patients with diabetes mellitus and sickle cell disease)

   The risk of pyelonephritis is greater in pregnant women than in non-pregnant women.

**V. Diagnosis of uncomplicated urinary tract infection**

In women with typical symptoms of lower urinary tract infection, no vaginal discharge, no associated comorbidities, and no history of recurrent cystitis the probability of having acute cystitis is >90%:

A urinalysis is NOT required. A urine culture is NOT required. Patient can be empirically treated with antibiotics [Bent et al- JAMA. 2002;287(20):2701-2710].

In all other patients, a diagnostic evaluation is warranted to confirm the diagnosis and identify the pathogens
1. Urine Specimen collection
   Urine specimen must be collected in a manner that avoids contamination with normal flora.
   This can be accomplished by
   - Clean-voided, midstream urine
   - Catheterization if it is not possible for the patient to obtain a clean-voided midstream urine
   - Suprapubic aspiration – extreme case in patient with severe obstruction

2. Microscopic examination of Urine
   3 important features:
   --Pyuria = more than 10 WBC's/microliter (10,000/ml) of urine OR more than 2 - 5 WBC's/high power field on slide prepared from sediment of centrifuged urine

   Sensitivity 95%; specificity 71%
   Note: When one sees pyuria there may be other etiologies (ie cancer, autoimmune disease) therefore not very specific

   --Presence of white blood cell casts - indicates pyelonephritis

   --Gram stain of uncentrifuged urine
     One or more bacteria per oil-immersion field correlates with >10^5 bacteria/ml of urine

Pyuria

White blood cell cast
- Microscopic cylindrical structures
- Associated with the presence of WBCs and bacteria in the urine sediment
- Formed in the distal convoluted tubule and collecting ducts of nephrons
- Indicative of tubulointerstitial disease: pyelonephritis, acute interstitial nephritis (AIN), lupus nephritis, acute papillary necrosis
3. Chemical screening tests
   Leukocyte esterase - detects pyuria
   Nitrite - detects action of the bacterial enzyme nitrate reductase on urinary nitrates. Present in Gram negative rods: *E.coli, Klebsiella, Proteus*. However, not all uropathogens have the enzyme (so may be false “negative” for UTI on screening).

4. Microbiological tests
   **Quantitative urine culture** - $>10^5$ bacteria/ml usually (80% correlation) indicates infection
   
   Caveats:
   
   Less than 1000 ($10^3$) bacteria/ml usually indicates contamination
   
   Lower numbers, i.e., $10^2$ - $10^4$ /ml, may be significant in young women with cystitis, males, and patients with indwelling catheters

Blood culture - may be positive in acute pyelonephritis or acute prostatitis

*LUMC protocol: Urinalysis with Reflex to Urine Culture*

- *Although pyuria alone without other signs or symptoms of UTI should not be used to confirm a UTI diagnosis, the absence of pyuria strongly suggests the patient does not have a UTI. Therefore, urine cultures will only be processed if the urinalysis shows >6 WBCs/hpf.*
- *Exemptions to this protocol include:*
  - Neutropenic patients (WBC < 1K/UL) (why – not enough WBC to respond to infection in urine)
  - Pregnancy
  - Neonatal status
  - Pediatric patients with known congenital anomalies of the urinary tract
  - Patients scheduled for transurethral resection of the prostate
  - Patients scheduled for urologic procedure for which mucosal bleeding is anticipated*
VI. Management of UTI

1. Uncomplicated Cystitis (Infectious Disease Society America [IDSA] guidelines)
   A. First line regimens:
      • Nitrofurantoin 100 mg PO BID x 5 days
         Nitrofurantoin only concentrates in the bladder
      • Trimethoprim-sulfamethoxazole (T-S)160/800 mg BID x 3 days (avoid if resistance prevalence is >20% or if used in previous 3 months)
         Some concerns:
            Side effects: allergies, acute kidney injury, hyperkalemia
MHD I
Urinary Tract Infections

Resistance: look at hospital’s prevalence of resistance to this antibiotic

* Fosfomycin 3 gm x single dose
  Concentrates very well in bladder, increasing in favor due to bacterial resistance to other antimicrobial agents
  Expensive

B. Alternative regimens
   Fluoroquinolones x 3 days
   Cautions: increased resistance
   Black box warning: QT prolongation, spontaneous Achilles Tendon rupture.

C. Oral beta-lactams
   Amoxicillin- clavulanate
   Cephalaxin
   Cefuroxime
   Cefdinir
   Duration: 3-7 days
   Decreased rates of cure therefore close follow-up required

2. **Pyelonephritis - uncomplicated**
   A. Fluoroquinolone
      * Ciprofloxacin x 7 days
      * Levofloxacin x 5 days
   B. Parenteral cephalosporin (ceftaxalone) if hospitalized
   C. Trimethoprim/sulfamethoxazole – 14 days
      * If organism sensitive
      * Complete 7 days of therapy if patient responded promptly, otherwise, 10-14 days is recommended when there is delay in response or with severe infection

**What about “Cranberry Juice”?**
Randomized – Placebo controlled trial: Among otherwise healthy college women with an acute UTI, those drinking 8 oz of 27% cranberry juice daily did not experience a 6-month incidence of a second UTI, compared with those drinking placebo

**Asymptomatic Bacteriuria**
* Positive urine culture without any signs and symptoms of UTI

* Screening only recommended for:
  * Pregnant women (routine UA and culture recommended in trimesters 1 and 3, even if the woman not having symptoms. Why? Pregnant women very prone to developing UTI. Colonized urine can develop into UTI and/or pyelonephritis with serous maternal illness and even fetal loss)
  * Patients undergoing transurethral resection of the prostate (high rate of bacteremia with this procedure if there are bacteria in the bladder)
Patients undergoing urologic procedures for which mucosal bleeding is anticipated (high rate of bacteremia with this procedure if there are bacteria on the bladder mucosal surface)

Cather-Associated UTI (CAUTI)
- As mentioned, patients with indwelling urethral, suprapubic, or intermittent catheterization are at increased risk for developing urinary tract infections referred to as “catheter-associated urinary tract infection (CAUTIs).
- UTI is diagnosed in this patient population when they have signs and symptoms compatible with UTI along with ≥ 10^3 CFU/mL of bacterial species from a urine sample.
- Same diagnostic criteria in patients whose catheters have been removed within 48 hours.

Because there is significant morbidity and mortality with CAUTI – important to PREVENT CAUTI
- Limit unnecessary catheterization
- Discontinuation of catheterization
- *Methods with no data for recommendations:*
  - Antimicrobial coated catheters
  - Prophylaxis with systemic abx
  - Prophylaxis with methenamine salts
  - Prophylaxis with cranberry products
  - Enhanced meatal care
  - Catheter irrigation
  - Antimicrobials in the drainage bag

Hospital acquired UTI
Hospital acquired UTI refers to a UTI developed while a patient is hospitalized and is also referred to as a nosocomial infection. This is important because sometimes patients may have infection with multi-drug resistant organisms.
### First Aid Review: UTI BUGS

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>BUG</th>
<th>Gram stain</th>
<th>Culture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leading cause of UTI</td>
<td><em>Escherichia coli</em></td>
<td>Gram negative rods</td>
<td>Colonies show green metallic sheen on EMB agar</td>
</tr>
<tr>
<td>Usually nosocomial and drug resistant</td>
<td><em>Pseudomonas aeruginosa</em></td>
<td>Gram negative rods</td>
<td>Blue-green pigment and fruity odor</td>
</tr>
<tr>
<td>Produces urease; associated with struvite stones</td>
<td><em>Proteus mirabilis</em></td>
<td>Gram negative rods</td>
<td>Motility causing “swarming” on agar</td>
</tr>
<tr>
<td>2nd leading cause of UTI in sexually active women</td>
<td><em>Staphylococcus saprophyticus</em></td>
<td>Gram positive cocci is clusters, pairs</td>
<td>White, round, smooth colonies</td>
</tr>
</tbody>
</table>
Another common cause of UTI. Usually nosocomial as well. Has large mucoid capsule.

*Klebsiella pneumoniae*  
Gram negative rods  
Large mucoid colonies

**Suggested Reading.**


