Urinary Tract Infections

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Clinical Scenario #1

• 23 y.o woman presents to her doctor complaining of 1 day of increased urinary frequency, dysuria and sensation of incomplete voiding
• She is otherwise healthy, takes no medications, and is sexually active, using spermicide-coated condoms for contraception. She says she does not have fever, chills, vaginal discharge, or flank pain
• Sexually active with one partner, no hx/o sexually transmitted diseases
Clinical Scenario #1

- She looks a little uncomfortable but is afebrile, with a normal blood pressure
- Her abdominal exam is notable for mild suprapubic tenderness, no RUQ tenderness, no costovertebral tenderness
- Pelvic exam is deferred

Clinical Scenario #1 : Labs

- Urinalysis: pyuria (WBC too numerous to count), RBC and bacteria present
- Urine dipstick: positive leukocyte esterase and nitrite
- Urine culture: not done
- Patient receives 3 days of TMP/SMX for UTI
Gram stain of urine shows numerous Gram-negative rods. 

*E. coli* grew from this urine specimen

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**Urinary Tract Infections**

- Definitions
- Clinical Symptoms and Diagnosis
- Microbiology and Epidemiology
- Pathogenesis
  - Host Factors
  - Bacterial Factors
- Clinical Scenario
- Treatment and Prevention
UTI: Definitions

- **Lower UTI**: cystitis, urethritis, prostatitis
- **Upper UTI**: pyelonephritis, intra-renal abscess, perinephric abscess (usually late complications of pyelonephritis)
- **Uncomplicated UTI** – Infection in a structurally and neurologically normal urinary tract. Simple cystitis of short (1-5 day) duration
- **Complicated UTI** – Infection in a urinary tract with functional or structural abnormalities (ex. indwelling catheters and renal calculi). Cystitis of long duration or hemorrhagic cystitis.

UTI: Clinical Symptoms and Presentation

- **Cystitis in the adult**:  
  - Dysuria, urinary urgency and frequency, bladder fullness/discomfort  
  - Hemorrhagic cystitis (bloody urine) reported in as many as 10% of cases of UTI in otherwise healthy women
- **Pyelonephritis (upper UTI) in the adult**:  
  - Fever, sweating  
  - Nausea, vomiting, flank pain, dysuria  
  - Signs and symptoms of dehydration, hypotension
- **A history of vaginal discharge suggests that vaginitis, cervicitis, or pelvic inflammatory disease is responsible for symptoms of dysuria (pelvic examination)**  
  - Important additional information includes a history of prior sexually transmitted disease (STD) and multiple current sexual partners.
- **UTI in children**:  
  - < 2 years - enuresis, fever, poor weight gain  
  - > 3 years - dysuria, lower abdominal pain
Diagnosis of UTI

• U/A microscopic examination
  – WBC, RBC
  – Presence of bacteria
• Urine dipstick test: rapid screening test
  – leukocyte esterase test
  – Nitrate → nitrite test
• Indications for urine culture
  – Pyelonephritis
  – Children, pregnant women
  – Patients with structural abnormalities of the urinary tract

Indications for Evaluating the Urinary Tract

• Children
  – ultrasound, IVP, CT scan
• Bacteremic pyelonephritis not responding to therapy
  – ultrasound, IVP, CT scan
• Nephrolithiasis or Neurogenic Bladder
  – Ultrasound, CT, or IVP with post-voiding films
• Men with 1st or 2nd infection
  – Careful prostate examination
  – Ultrasound or IVP with post-voiding films
Etiology of Uncomplicated UTI in Sexually Active Women

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

Microbial Species Most Often Associated with Specific Types of UTI’s

<table>
<thead>
<tr>
<th>Organism</th>
<th>Acute uncomplicated cystitis</th>
<th>Acute uncomplicated pyelonephritis</th>
<th>Complicated UTI</th>
<th>Catheter-associated UTI</th>
</tr>
</thead>
<tbody>
<tr>
<td>E.coli</td>
<td>79%</td>
<td>89%</td>
<td>32%</td>
<td>24%</td>
</tr>
<tr>
<td>S. saprophyticus</td>
<td>11%</td>
<td>0%</td>
<td>1%</td>
<td>0%</td>
</tr>
<tr>
<td>P. mirabilis</td>
<td>2%</td>
<td>4%</td>
<td>4%</td>
<td>6%</td>
</tr>
<tr>
<td>Klebsiella spp.</td>
<td>3%</td>
<td>4%</td>
<td>5%</td>
<td>8%</td>
</tr>
<tr>
<td>Enterococcus spp.</td>
<td>2%</td>
<td>0%</td>
<td>22%</td>
<td>7%</td>
</tr>
<tr>
<td>Ps. aeruginosa</td>
<td>0%</td>
<td>0%</td>
<td>20%</td>
<td>9%</td>
</tr>
<tr>
<td>Mixed</td>
<td>3%</td>
<td>5%</td>
<td>10%</td>
<td>11%</td>
</tr>
<tr>
<td>Other*</td>
<td>0%</td>
<td>2%</td>
<td>5%</td>
<td>10%</td>
</tr>
<tr>
<td>Candida spp.</td>
<td>0%</td>
<td>0%</td>
<td>1%</td>
<td>28%</td>
</tr>
<tr>
<td>S. epidermidis</td>
<td>0%</td>
<td>0%</td>
<td>15%</td>
<td>8%</td>
</tr>
</tbody>
</table>

*Serratia, Providencia, Enterobacter, Acinetobacter, Citrobacter
UTI: Epidemiology and Risk Factors by Age Group

<table>
<thead>
<tr>
<th>Age in years</th>
<th>Females (% Prevalence)</th>
<th>Males (% Prevalence)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 1</td>
<td>Anatomic/functional abnormalities (1%)</td>
<td>Anatomic/functional abnormalities (1%)</td>
</tr>
<tr>
<td>1-5</td>
<td>Congenital abnormalities, Vesicoureteral reflux (4.5%)</td>
<td>Congenital abnormalities, uncircumcised penis (0.5%)</td>
</tr>
<tr>
<td>6-15</td>
<td>Vesicoureteral reflux (4.5%)</td>
<td>Vesicoureteral reflux (0.5%)</td>
</tr>
<tr>
<td>16-35</td>
<td>Sexual intercourse, spermicide use, previous UTI (20%)</td>
<td>Anatomic, insertive anal intercourse (0.5%)</td>
</tr>
<tr>
<td>36-65</td>
<td>Gynecologic surgery, bladder prolapse (35%)</td>
<td>Prostate hypertrophy, obstruction, catherization (20%)</td>
</tr>
<tr>
<td>&gt;65</td>
<td>Estrogen deficiency and loss of lactobacilli (40%)</td>
<td>All of the above; urinary catheters (35%)</td>
</tr>
</tbody>
</table>

Pathogenesis of UTI

- Hematogenous Route
- Ascending Route
  - Colonization of the vaginal introitus
  - Colonization of the urethra
  - Entry into the bladder
  - Infection
UTI in Women: Factors Predisposing to Infection

- Short urethra
- Sexual intercourse & lack of post coital voiding
- Diaphragm, spermicide use
- Estrogen deficiency
- P₁ blood group - upper UTI
Host Factors Predisposing to Infection

• Extra-renal obstruction
  – Posterior urethral valves
  – Urethral strictures
• Renal calculi
• Incomplete bladder emptying
• Neurogenic bladder
• Immunocompromised individuals (e.g. DM, transplant recipients)

Bacterial Virulence Factors-I

• Enhanced adherence to receptors on uroepithelial cells
  – **Type 1 fimbriae**: mediate binding to uroplakins, mannosylated glycoproteins on the surface of bladder uroepithelial cells
  – **P fimbriae**: bind to galactose disaccharide on the surface of uroepithelial cells and to P blood group antigen (D-galactose-D-galactose residue) on RBCs
    • 97% of women with recurrent pyelonephritis are P1 blood group (+)
    • Higher prevalence of P-fimbriated *E.coli* in cystitis-causing strains than in strains from asymptomatic persons (60% vs. 10%)

• Phase variation:
  – Type 1 fimbriae increase susceptibility to phagocytosis, P-fimbriae block phagocytosis
  – Type 1 down-regulated, Type P upregulated in strains that cause upper-tract infections (PAP gene expression triggered by temperature, [glucose], concentration of certain amino acids)
Electron microscopic view of an *E. coli* showing the fimbriae (pili) bristling from the bacterial cell wall.

*Increased adhesion with uropathogenic E. coli* Adherence of uropathogenic *Escherichia coli* onto uroepithelial cells. Courtesy of Agnès Labigne, MD, Institut Pasteur, Paris.
Bacterial Virulence Factors-II

• Flagella- enhanced motility
• Production of hemolysin—induces pore formation in cell membrane
• Production of aerobactin (a siderophore) → iron acquisition in the iron-poor environment of the urinary tract

Antibacterial Host Defenses

• Urine flow and micturition
• Urine osmolality and pH
• Inflammatory response (PMNs, cytokines)
• Inhibitors of bacterial adherence
  – Bladder mucopolysaccharides
  – Secretory immunoglobulin A
The pathophysiology of infection by uropathogenic Escherichia coli in bladder epithelial cells

From Cohen & Powderly: Infectious Diseases, 2nd ed., 2004
Clinical Scenario #2

• 43 y.o woman with DM presents to the ER complaining of chills, nausea and low back pain for the past 2 days. Earlier in the week she developed increased urinary frequency and dysuria.
• Recognizing the symptoms of UTI she took two days of TMP/SMX but was unable to finish treatment because of nausea and vomiting
• Past medical history is notable for frequent UTIs treated with TMP/SMX and a history of Diabetes Mellitus
• No hx/o STDs, no vaginal discharge

Clinical Scenario #2

• She looks unwell and appears uncomfortable
• She is febrile to 101.2, tachycardic to 100 with a BP 100/60
• On exam her mucous membranes are dry; there is suprapubic tenderness, and severe right flank and right costovertebral tenderness
• Urinalysis, Urine microspic examination and urine culture are performed: pyuria, hematuria, bacteriuria
• Blood cultures are drawn
• Patient is admitted to the hospital for IV antibiotics and pain management
Clinical Scenario #2

• The next day, urine and blood cultures show Gram-negative rods
• After 72 hours of hydration and intravenous antibiotics your patient is still febrile and repeat urine examination is still notable for pyuria and bacteriuria
• You are concerned about
  – urinary obstruction
  – intrarenal/perinephric abscess
  – infection with resistant organism
• Microbiology lab informs you that the pathogen is an \textit{E.coli} sensitive to fluoroquinolones, resistant to TMP/SMX
• Renal CT is notable for a large renal abscess
• Diagnosis: pyelonephritis complicated by a renal abscess in a diabetic patient
UTI: Upper Tract Disease

- Symptoms suggestive of upper tract disease (pyelonephritis):
  - Fever (usually greater than 101° F.),
  - Nausea, vomiting, and
  - Pain in the costovertebral areas
  - Urinary frequency, urgency and dysuria
  - Renal abscess: patients with urinary tract abnormalities, diabetic patients
- Evaluation: urine culture, +/- blood cultures,
  - Imaging if no improvement
- Microbiology: *E.coli*, and *Citrobacter, Pseudomonas aeruginosa, Enterococci, Staphylococcus* spp.
- Initial therapy: intravenous antibiotics for 10-14 days (perinephric abscess treat longer, +/- drainage)
Pyelonephritis: glomerular hemorrhage

Pyelonephritis - papillary necrosis
Treatment: General Principles

- Quantitative cultures may be unnecessary before treatment of typical cases of acute uncomplicated cystitis.
- Culture urine in patients with upper UTI, complicated UTI, or with treatment failure.
- Susceptibility testing is necessary in all recurrent or complicated infections, perhaps not for uncomplicated cases.
- Identify or correct factors predisposing to infection
  - Obstruction, calculi
  - Diabetic patients who are at risk for recurrent infections, pyelonephritis and perinephric abscesses
- Recurrent infections common in young women (20% by 6 months).
  - Majority are exogenous infections rather than failure to cure initial infection
- Duration of therapy depends on the site and duration of the infection.

Empiric Antimicrobials

- Choice of antimicrobial agents
  - Primary excretion routes through the urinary tract
  - Achieve high concentration in urine and vaginal secretions
  - Inhibit *E. coli*, the primary pathogen
- Short course (3-day) therapy for uncomplicated infections
- Longer duration (10-14 days) for complicated infection (e.g. pyelonephritis)
- Oral vs. intravenous agents (TMP/SMX, Fluoroquinolones)
Treatment of Asymptomatic Bacteriuria

- Pregnant women
- Patients with neurological or structural abnormality of the urinary tract
- Patients undergoing urologic surgery

Cohen & Powderly: Infectious Diseases, 2nd ed., 2004
Prevention of Recurrent UTI

- Risk factors for recurrent uncomplicated UTI
  - P1 blood group positive; postmenopausal status; diabetes
  - Recent antimicrobial use
  - Behavioral risk factors (spermicide use, new partner, first UTI <15 y.o.)

- Prevention Strategies
  - Contraception
  - Postcoital voiding and increased fluid intake
  - Cranberry juice (sexually active women with previous UTI)
  - Antibiotic prophylaxis
    - >2 symptomatic UTIs within six months or >3 over 12 months
    - Postcoital prophylaxis vs. continuous prophylaxis vs. self-treatment

Antimicrobial Resistance

- Reports of increased resistance to TMP/SMX
- Regional variation
- Rates between 18-40%