Adult Genito-Urinary Infections
Epidemiology, Etiology, and Diagnosis

Geoffrey N. Box, M.D.
Assistant Professor
Director, Laparoscopic Urologic Surgery
The Ohio State University

Outline

- Definitions
- Epidemiology
- Diagnosis
- Pathogenesis/Pathogens
- Bacterial Resistance
- Principles of Antimicrobial Therapy
- Asymptomatic Bacteriuria
- Preventative Strategies

Classification - UTI

- 1) Status of the urinary tract
  - Uncomplicated UTI → Normal urinary tract
  - Complicated UTI → Structurally or functionally abnormal urinary tract

- 2) Pattern of infections
  - Isolated/sporadic → separated by long intervals
  - Unresolved → fail antibiotic therapy (usually bacterial resistance)
  - Recurrent → reinfection (outside) or persistence (within)

- 3) Site of infection
  - Cystitis: clinical syndrome → Dysuria, Frequency, Urgency
  - Pyelonephritis: same as cystitis plus fever and flank pain

Definitions:
- An inflammatory response of the urothelium to bacterial invasion that is usually associated with bacteriuria and pyuria.
- Bacteriuria: presence of bacteria in the urine
- Pyuria: WBCs in the urine

Urinary Tract Infection

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Definitions:
Incidence & Epidemiology

- UTI is considered the most common bacterial infection
- >7 million office visits/yr
  - 1.2% of all ♀ visits and 0.6% of all ♂ visits
- Result in 100,000 hospitalizations/yr
- Community acquired UTI → $1.6 billion in US

Populations at ↑ Risk

- Pregnant women
- The elderly
- Spinal cord injury patients
- Patients with indwelling catheters
- Diabetes
- HIV

Incidence & Epidemiology

- 30% of women have had a UTI by age 24 and 50% will have one in their lifetime.
- Up to 15% of women develop UTIs each year (vs. 3% of men)
  - 25% have at least one recurrence

Differential Diagnosis

- Vaginitis
- Urethritis/Urethral pathology
- STDs
- Bladder cancer
- Interstitial cystitis
### Diagnosis - History

- New onset frequency, dysuria, and urgency in the absence of vaginal discharge or pain → PPV 90%

### Diagnosis

<table>
<thead>
<tr>
<th>Microscopic urinalysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>✓ Pyuria</td>
</tr>
<tr>
<td>• sen 95%, spec 70%</td>
</tr>
<tr>
<td>✓ Bacteria</td>
</tr>
<tr>
<td>• sen 70%, spec 90%</td>
</tr>
<tr>
<td>Indirect Dipstick</td>
</tr>
<tr>
<td>✓ Leukocyte esterase → pyuria</td>
</tr>
<tr>
<td>✓ Nitrite → bacteria</td>
</tr>
<tr>
<td>• Both positive: sen/spec ~95%</td>
</tr>
</tbody>
</table>

### Urine Collection

- Clean catch, mid-stream specimen
- May need to catheterize some women to avoid contamination

### Urine Culture

- Definitive test
- >10^2 cfu/ml (>10^5 cfu/ml)
- Not always necessary
- Indications to perform culture:
  - 1) Symptoms without bacteriuria/pyuria
  - 2) Recent antibiotic exposure
  - 3) Prior empiric therapy (unresolved UTI)
### Evaluation

- None for uncomplicated UTIs
- Factors suggesting complicated UTI
  - Male gender
  - Hematuria
  - Elderly
  - Functional/structural abnormality
  - Immunosuppression
  - Diabetes Mellitus
  - Recent antimicrobial use

### Pathogenesis – UTI

- Ascending event: outside → inside
- Colonization of vagina by *uropathogenic* bacteria.
- Replaces lactobacilli which are normally present and maintain acidic vaginal environment
- Primary bladder defense → complete emptying

### Evaluation

- Recurrent infections and complicated UTIs
  - Post void residual urine
  - Urine culture
  - Consider imaging and cystourethroscopy
  - In patients with recurrent UTIs, important to distinguish between *persistence* and *reinfection*

### Pathogenesis – UTI

- Host susceptibility factors
  - Genetic
    - ABO blood group antigens
  - Biologic
    - Anatomic abnormalities
    - Diabetes
    - Estrogen depletion
  - Behavioral
    - Sexual activity
    - Spermicide use
  - Bacterial virulence
### Pathogens

- **Uncomplicated UTI**
  - *Escherichia coli* (80%)
  - *Staphylococcus saprophyticus* (15%)
  - *Klebsiella pneumoniae*
  - *Enterococcus faecalis*

- **Complicated UTI**
  - *Escherichia coli*
  - *Klebsiella pneumoniae*
  - *Enterobacter cloacaes*
  - *Serratia marcescens*
  - *Proteus mirabilis*
  - *Pseudomonas aeruginosa*
  - *Enterococcus faecalis*
  - *Group B strep*

### Bacterial Resistance

- **Natural**
  - I.E. all proteus species are resistant to nitrofurantoin

- **Selection of resistant mutants (5-10%)**
  - Chromosomal resistance
  - Antimicrobial drug concentration is not high enough to kill all of the bacteria

- **Transferable, plasmid-mediated (5-45%)**
  - Plasmids contain genetic material for resistance
  - Transferable within species and across genera

### Antibiograms

<table>
<thead>
<tr>
<th>Gram Negative Rods</th>
<th>Enterococcus</th>
<th><em>Streptococcus</em></th>
<th><em>Staphylococcus</em></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfonamides</td>
<td>+</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Beta-lactams</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Quinolones</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

### Basis of Bacterial Resistance

<table>
<thead>
<tr>
<th>CLASS</th>
<th>Chromosomal</th>
<th>Plasmid</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-lactams</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Aminoglycosides</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Sulfonamides</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Tetracycline</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Trimethoprim</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Quinolones</td>
<td>+</td>
<td>-</td>
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</table>
Principles of Antimicrobial Therapy

- Eliminate bacterial growth in the urinary tract.
  - Kill bacteria → bactericidal
  - Prevent growth of bacteria → bacteriostatic
- Urinary levels of antimicrobial agents is often several hundred times greater than serum levels.
- Efficacy dependent on the urinary levels and the duration this remains above the minimal inhibitory concentration (MIC)

Asymptomatic Bacteriuria Prevalence

- Healthy adult woman: 2-5%
- Pregnant woman: 2-11%
- Diabetic women: 7-9%
- Elderly nursing home residents: 5-50%
- Spinal cord injury: 50%
- Chronic indwelling catheter: 100%
Prevention

<table>
<thead>
<tr>
<th>Cranberry Juice/Tablets</th>
</tr>
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<tbody>
<tr>
<td>Contains proanthocyanidins → inhibits bacterial adherence to uroepithelial cells</td>
</tr>
<tr>
<td>↓ Recurrent UTI by 30%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Topical Estrogen (postmenopausal women)</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ Episodes of symptomatic bacteriuria</td>
</tr>
<tr>
<td>Discontinuation of spermicide use</td>
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Pyelonephritis

<table>
<thead>
<tr>
<th>Cystitis very rarely progresses to pyelonephritis</th>
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<tbody>
<tr>
<td>~20 to 1 ratio in patients with recurrent UTI</td>
</tr>
<tr>
<td>Not as well defined as UTI</td>
</tr>
<tr>
<td>Typical presentation:</td>
</tr>
<tr>
<td>Cystitis + flank pain and fevers</td>
</tr>
<tr>
<td>Septic shock is uncommon → important to consider an obstructive etiology</td>
</tr>
<tr>
<td>E. coli in 90%</td>
</tr>
<tr>
<td>Unique virulence characteristics</td>
</tr>
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Preventative Strategies

<table>
<thead>
<tr>
<th>No Proven Benefit</th>
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<tr>
<td>✔ Frequent voiding</td>
</tr>
<tr>
<td>✔ Increasing fluid intake</td>
</tr>
<tr>
<td>✔ Postcoital voiding</td>
</tr>
<tr>
<td>✔ Personal hygiene (i.e. wiping front to back)</td>
</tr>
<tr>
<td>✔ Avoiding constipation</td>
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Conclusions

| UTIs are the most common bacterial infection and will affect more than 50% of women in their lifetime. |
| If symptoms do not resolve following therapy, it is important to consider other potential etiologies. |
| Complicated UTIs have special treatment considerations as these patients have increased chances of acquiring bacteria and therapy has decreased efficacy. |
| Choice of antimicrobial therapy should be based on likely pathogen, local susceptibilities and patient factors. |
Genito-Urinary Infections in the Adult Management

Jason P. Gilleran, MD
Assistant Professor, Dept of Urology
The Ohio State University Medical Center

Outline
• Cystitis
  ✓ Antibiotic use and treatment courses
• Pyelonephritis
• Epididymitis
• Prostatitis
• Special Situations
• Indications for specialist referral

Principles of Management
• Identify uropathogen by culture/sensitivity
• Achieve adequate antimicrobial concentration
  ✓ Compliance with full regimen
  ✓ Dose appropriately
• Use of antimicrobial with lowest MIC (minimal inhibitory concentration) on sensitivity testing
• Documentation of sterility
• Prevent emergence or worsening of resistance to antimicrobial agent

Trimethoprim / Sulfamethoxazole (TMP-SMX)
• Bactrim, Bactrim DS
• 80-85% bacterial cure rate
• Eliminates pathogens from vaginal flora in addition to urine
• Considered first-line therapy (3 days)
• Allergies to sulfa-based medications common
  ✓ TMP alone as effective as TMP-SMX
**Nitrofurantoin**

- Effective against *E. coli* and most other uropathogens
- Universal resistance with *Proteus*
- Secreted solely in urine
  - Minimal risk of diarrhea, yeast infections
- Seven-day course
- Pulmonary fibrosis – rare but serious complication.
  - Symptoms of new cough while on drug, discontinue and obtain chest radiograph
  - More common in individuals on drug for extended periods of time as suppressive agent

**Penicillins/Cephalosporins**

- Less effective
- Use of a β-lactamase inhibitor (amoxicillin-clavulanic acid) greatly improves susceptibility
- Cephalosporins do NOT cover *Enterococcus*

**Quinolone Therapy**

- Ciprofloxacin (Cipro), Levofloxacin (Levaquin), Moxifloxacin (Avelox)
- Highly effective, more expensive than nitrofurantoin or TMP-SMZ
- Second-line therapy if fails TMP-SMZ or allergic to sulfa meds
- Poor absorption with antacids
- Achilles tendon rupture – rare but serious complication

**Aminoglycosides**

- Preferred drug in combination with penicillin (ampicillin) in treatment of urosepsis
  - Emerging use of piperacillin-tazobactam
- Once-daily dosing vs q 8 hr dosing
  - 7 mg/kg if creatinine clearance > 60 mL/min
- Nephro-, ototoxicity
### Uncomplicated Acute Cystitis

- Structurally normal urinary tract
- Otherwise healthy female
- No signs/symptoms of pyelonephritis, vaginitis, cervicitis
- Episodes can be treated by telephone consultation with follow-up culture

### Low-Dose Prophylaxis

- Use of a daily (or other regimen) low-dose antibiotic to suppress bacterial growth
- Used for 3-12 months at a time
- Concerns for yeast infections and change in bowel flora
- TMP
- Nitrofurantoin

### Treatment Uncomplicated Cystitis

- Trimethoprim (TMP) or Trimethoprim – Sulfamethoxazole (TMP-SMX) for 3 days
  - 93% success rate
- Quinolones (Ciprofloxacin, levofloxacin) for 3 days
  - Second-line therapy
  - Resistance to TMP-SMX > 20%
- Nitrofurantoin (Macrobid 50 mg q.i.d., Macrobid 100 mg b.i.d.) for 7 days
- Fosfomycin single dose
  - Higher chance of recurrence

### Recurrent UTI in Women

### Differential Diagnosis

- Abnormal vaginal flora
- Infection stone
- Urethral diverticulum
- Colovesical fistula
  - Pneumaturia, fecaluria
- History of Crohn’s, UC, diverticulitis
- Foreign body
- Upper tracts (ureter, nonfunctioning kidney, renal cysts)
Treatment of Recurrent, Uncomplicated UTIs

- Cranberry and push po fluids
  - Tablets vs juice (100% non-concentrate)
  - Mechanism of action - lower urinary pH
- Pre-/Post-coital prophylaxis
  - Macrodantin 50 mg or ½ strength TMP-SMX
- Self-start therapy
  - 3 day course of trimethoprim or quinolone at first signs and symptoms of UTI
  - Reasonable course of tx with consistent bacteria on urine cx
  - Home dipstick tests; mail-in cultures

Management of Pyelonephritis

- Uncomplicated
  - Normal urinary tract; clinical status determines management
  - Outpatient/Inpatient
  - Oral / parenteral
  - Nitrofurantoin of little clinical use due to poor tissue penetration
- Complicated
  - Associated with hospitalization, catheterization, urologic surgery, or GU tract abnormality
  - Inpatient ➔ parenteral – oral
  - Treat obstruction

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Complicated Cystitis

- Men
- Children
- Structural or abnormal function
  - Neurogenic bladder, prior or recent urologic history, use of catheter or foreign body
- Assess for reflux in children (VCUG)
- Consider treatment for 7-21 days with follow-up culture

Talan et al. JAMA 2000; 283: 1583-1590

Complicated Pyelonephritis

- Fluoroquinolone - parenteral to oral
- Duration of Therapy
  - Uncomplicated – 7 days
  - Complicated – 21 days
- Repeat urine cultures
  - 5-7 days after initiation of therapy
  - 4-6 weeks after discontinuation of therapy
Complications of Pyelonephritis

- Renal/perinephric abscess
  - Percutaneous drainage
  - 14-21+ day course of parenteral vs oral antibiotics
- Xanthogranulomatous pyelonephritis
  - Associated with stone
  - May mimic renal cancer
  - Nephrectomy

MRSA and VRE

- Methicillin-resistant Staph aureus
  - May account for 30-50% of hospital isolates
  - Incidence in outpatient setting is rising
  - Resistance rate with quinolones 70-80%
  - If sensitive, can be treated with quinolone or TMP-SMX + rifampin
  - Cautious use of Vancomycin
- Vancomycin-resistant Enterococcus
  - Linezolid (Zyvox) 400-600 mg po q12 hrs
  - Watch for myelosuppression

Uropathogen Resistance

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<th>E.Coli %</th>
<th>S.saprophyticus %</th>
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<tbody>
<tr>
<td>Ampicillin</td>
<td>60.6%</td>
<td>29.3%</td>
</tr>
<tr>
<td>TMP-SMX</td>
<td>81.7%</td>
<td>93.9%</td>
</tr>
<tr>
<td>Cefazidime</td>
<td>99.1%</td>
<td>No data</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>99.7%</td>
<td>74.5%</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>97.4%</td>
<td>99.1%</td>
</tr>
<tr>
<td>Levofoxacin</td>
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<td>98.2%</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>97.0%</td>
<td>100%</td>
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Epididymo-Orchitis

- Acute bacterial infection of epididymitis
- Retrograde mechanism
- Common uropathogens (E.coli, Klebsiella, Staph)
  - Urine culture often indicative of pathogen
- Isolated episodes may not need specialist evaluation
  - Treatment 10-14 days of TMP-SMX or quinolones
  - Poor tissue penetration by nitrofurantoin
- Recurrent episodes
  - Consider evaluation for bladder outlet obstruction

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Prostatitis

- Most common urologic diagnosis in men younger than 50
- Dysuria, perineal and penile pain
- Fever, chills, retention → urosepsis
- Urine culture often not indicative
  ✓ Post-prostatic massage urine culture

Special Situations

Prostatitis

- Acute Bacterial vs Chronic Bacterial
- Patients may require 4-6 weeks of therapy with quinolone or TMP-SMX, with additional 6 weeks if prostate cultures remain positive
- Chronic non-bacterial (CPPS)

UTI in the Pregnant Patient

- Screen in first trimester
- Prevalence of bacteriuria 4-7%
- Acute pyelonephritis in 25-35% of untreated bacteriuria
- Women with pyelonephritis in pregnancy at higher risk for:
  ✓ Pre-term labor
  ✓ SGA infants
  ✓ Fetal mortality
  ✓ Low birth-weight infants
Treatment in the Pregnant Patient

- **SAFE**
  - Penicillins, cephalosporins
- **USE WITH CAUTION**
  - TMP-SMX → antifolate (1st trimester) and hyperbilirubinemia (3rd trimester)
  - Nitrofurantoin → hemolytic anemia in G6PD deficiency; avoid at term
- **AVOID**
  - Fluoroquinolones → cartilage abnormalities
  - Tetracyclines → teeth and liver abnormalities
  - Erythromycin → jaundice

UTI in the Geriatric Population

- Asymptomatic bacteriuria in women over 65 approximately 20% in women and 10% in men
- 25-75% rate of bacteriuria in female nursing home residents over 65
- Treat urea-splitting organisms on culture
  - *Proteus, Klebsiella*
  - *E coli* NOT a urea-splitting organism

UTI in the presence of a urinary catheter

- Clean intermittent catheterization (CIC)
- Indwelling Foley catheter
  - Aseptic technique
  - Maintain closed system
  - Change catheter if acutely infected
- Candida albicans or other fungal pathogen → removal of Foley
- Do NOT treat positive culture if patient asymptomatic

Prevalence of Bacteriuria

- Prevalence probably declines at puberty and teen-age years before sexual activity
Topical Vaginal Estrogen

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estriol (n=50)</th>
<th>Placebo (n=43)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Episodes of Bacteriuria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptomatic</td>
<td>12.0</td>
<td>111.0</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>10.0</td>
<td>103.0</td>
</tr>
<tr>
<td></td>
<td>2.0</td>
<td>8.0</td>
</tr>
<tr>
<td>Total person-months observed</td>
<td>310.0</td>
<td>225.0</td>
</tr>
<tr>
<td>Urinary Tract Infections</td>
<td>0.5</td>
<td>5.9*</td>
</tr>
</tbody>
</table>

*p<0.005

Raz and Stamm NEJM 1993; 329 (11): 756

Genitourinary Tuberculosis

- Rare chronic GU infection
  - Kidney, ureter, bladder, prostate
  - Immunosuppressed, immigrants
- Sterile pyuria
  - Leukocytes and negative standard urine culture
- Diagnosis requires 3 morning first void samples
  - Acid-fast bacilli (AFB) → 42 days

UTI in the Immunosuppressed

- Poorly-controlled diabetics
  - Assess bladder function, sensation and emptying (post-void residual, PVR)
  - Tighter diabetic control
- HIV +
  - Viral, fungal and parasitic
- Transplant patients or chronic steroid use for autoimmune disease
  - Retained, non-functional renal units

Indications for Urologic Referral

- Hydronephrosis
- Repeated negative urine cultures with symptoms
  - Interstitial Cystitis (IC)
- Microscopic or gross hematuria
  - > 5 RBC/hpf on urinalysis or > 2-3/hpf on 2 out of 3 specimens
- Persistent irritative symptoms (with/without bacteria) in a smoker
Current Areas of Research

- Vaccine
  - Uro-vaxom® and Strovac®
  - Only available in Europe as of now
- Probiotics
  - Lactobacillus intake to alter vaginal flora
- Biofilm formation
  - Re-emergence vs “eruption” of bacteria within bladder epithelium


Conclusions

- Treatment based on type of infection
- Consider identifiable and correctible causes of infection
- Judicious use of antibiotics in appropriate cases, doses, and lengths