Urinary Tract Infections

Khalid Ibrahim, Pharm.D
University of Minnesota
Overview

- Urinary Tract Infections (UTI)
  - Uncomplicated
  - Complicated
- Prostatitis
Epidemiology

- Approximately 7 million physician visits annually (community)
  - 25 - 35% women ages 20-40
  - <1% men ages 21 – 50
- Most commonly occurring nosocomial infection
- UTI in children
  - Belief that trend was underestimated in the past
  - Prevalence ranging from 4.1-7.5% febrile children

*Crit Care Med* 1999 May;27(5):853-4
Definitions

- Urinary Tract Infection (UTI)
  - M/o present in the urine not accounted for by contamination

- Cystitis
  - Lower tract infections

- Pylonephritis
  - Upper tract infections (kidneys, systemic)
Definitions (cont.)

- **Uncomplicated**
  - Typically in females of childbearing age
  - No structural/neurologic abnormalities interfering with urine flow

- **Complicated**
  - Flow impedance secondary to
    - Lesion
    - Congenital abnormality
    - Stone
    - Indwelling catheter
    - Prostatic hypertrophy
    - Physical obstruction
    - Neurologic deficit
Definitions (cont.)

- **Recurrent**
  - Re-infection or relapse with same organism

- **Reinfection**
  - New organism culprit.

- **Asymptomatic bacteriuria (ASB)**
  - Significant bacteriuria ($>10^5$) without symptoms

- **Symptomatic abacteriuria**
  - Symptoms without $10^5$ CFU/ml
Pathogen reservoirs

- Females (urethra proximal)
  - Rectal
  - Vaginal
- Males (urethra distal)
  - Rectal
# Predisposing factors

<table>
<thead>
<tr>
<th>Structural abnormalities</th>
<th>Residual urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstruction</td>
<td>Prostatic hypertrophy</td>
</tr>
<tr>
<td>Vesicourethral reflex</td>
<td>Tumors</td>
</tr>
<tr>
<td></td>
<td>Anti-ACH agents</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Calculi</td>
</tr>
<tr>
<td>Catheterization</td>
<td>Neurologic disease</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Diabetes</td>
</tr>
</tbody>
</table>
Pathogenesis

- Ascending
  - Rectal and/or vaginal reservoirs
  - Colonization of perianal area/ migration to perivaginal
- Hematogenous
- Lymphatic
Pathogenesis (cont.)

- Facilitating issues
  - Females
    - Reservoir(s) and urethra proximity
    - Urethra length
    - Sexual intercourse
      - Spermicide and diaphragm
      - Condoms
    - Pregnancy
  - Biofilm (slime) theory:
    - Bacteria interact $\rightarrow$ microcolonies
    - Small microcolonies coalesce $\rightarrow$ form bacterial biofilms
    - Glycocalyx
Pathogenesis (cont.)

- Facilitating issues (cont.)
  - Catheters
    - Can be traumatic
    - Biofilm adherence
    - Bacterial aggregates can block catheter
    - Catheter can shed bacteria
    - Abx drained immediately
  - Aging
    - Bladder wall collagen content
    - Detrusor muscle thickens
    - Neurologic diseases
Host defense mechanisms

- pH (normal range 5-8)
- Urea concentrations
- Osmolality
- Organic acid concentrations
- Prostatic secretions (males)
- Urine flow
Clinical presentation

- Common symptoms of lower UTIs
  - Dysuria
  - Frequency
  - Urgency
  - Hesitancy
  - Nocturia
  - Superpubic pain/heaviness
Common symptoms of upper UTIs
- Flank pain
- Costovertebral tenderness
- Abdominal pain
- Fever
- HA
- N+V
- Malaise
Clinical presentation (cont.)

- Elderly
  - Typically not specific urinary symptoms
    - Altered mental status
    - Altered dietary habits
Laboratory findings

- **U/A**
  - Pyuria ( > 5 WBC/HPF or WBC esterase)
    - Sensitivity of dipstick WBC esterase method 75-85%
  - Bacteria ( > $10^5$ CFU/ml urine)
    - microscopic or dipstick NO3 --> NO2
  - Hematuria (approximately 1/3 gross hematuria)
  - Elevated pH (6.5-8)
  - Leukocyte esterase and nitrite dipsticks

- **U/C**
  - 100-100,000 CFU/ml
## Adjunctive diagnostic measures

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominal radiograph</td>
<td>Nephrolithiasis</td>
</tr>
<tr>
<td>Ultrasound</td>
<td>Hydronephrosis</td>
</tr>
<tr>
<td>Stamey-Meares 4-glass test</td>
<td>Prostatic Localization</td>
</tr>
<tr>
<td>Urethral catheterization</td>
<td>Upper vs. Lower or Bladder Washout</td>
</tr>
<tr>
<td>IVP, retrograde cystography</td>
<td>Anatomical defect functional disorder</td>
</tr>
</tbody>
</table>
Differential diagnosis

- Uncomplicated UTI
  - Vaginitis
  - Urethritis
  - STD
    - Odor
    - Itching
    - Pain on intercourse

- Complicated UTI
  - Depends on contributing underlying diseases
Non-Rx treatment/prevention

- Behavior modification
  - Personal toilet hygiene
  - Patient’s choice of fabric and clothes
  - Frequent voiding
  - Voiding after intercourse
  - Method of contraception
Non-Rx treatment/prevention (cont.)

- Cranberry juice
  - Believed to have preventative/treatment effects
    - Increases fluid intake and urine output
    - Acidifies urine (study pH = 6 vs. CTN pH = 5.5)
    - May interfere with bacterial attachment (Fructose or polymeric cpd acts as lectin inhibitor)
    - Benzoic acid --> hippuric acid which may have intrinsic antibacterial properties
  
- Database review of literature conclusion
  - Small number/poor quality trials : no reliable evidence re: Px
  - No randomized trials assessing Tx effects

*Cochrane Database of Systematic Reviews. (2):CD001321 and CD001322, 2000.*
Treatment

- **Algorithms**
  - Goal is to deliver optimal patient care
  - Large literature base to draw from
  - Uncomplicated UTI is short term condition
  - Eliminates wide variation in management and antibiotic prescribing
  - Should reflect national trends and local needs
  - Should limit legal liability
Treatment (cont.)

- Algorithms (cont.)
  - Streamlines the use of healthcare professionals
  - Both functional for daily practice and educational for training programs
  - Provides for the cost effective use of laboratory studies and antibiotics
  - Feedback loop provides for continuous refinement and state of the art care
Treatment (cont.)

Complicating factors
- Symptoms > 7 day duration
- Rigors
- Flank pain
- Temperature > 101 F
- Pregnancy
- DM
- Immune-suppressed
- Kidney stones
- Catheterization/instrumentization within 2 weeks
- Hospital D/C within 2 weeks
- >4 UTI’s within last 12 months
Uncomplicated UTI

Etiology

Young women

- *E. coli* 80%
- *S. saprophyticus* 10-15%
- Others 5-10%
  (Klebsiella/Proteus)

Women >65 years

- *E. coli* 70%
- *P. mirabilis* 10%
- Other Gram (-) 20%
  (Pseudomonas)
Uncomplicated UTI Treatment

- Conventional therapy
  - PO abx 7-14 days

- 3-Day therapy
  - Superior to single-dose
  - Optimal regimen for SMX/TMP
  - β-lactams should be admin > 5 days
  - Fluoroquinolones are valid options of 3-day
### Uncomplicated UTI Treatment (cont.)

- **3 day treatment options**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin</td>
<td>100 mg q12h</td>
</tr>
<tr>
<td>Enoxacin (Penetrex)</td>
<td>400 mg q12h</td>
</tr>
<tr>
<td>Lomafloxacin HCl (Maxaquin)</td>
<td>400 mg q24h</td>
</tr>
<tr>
<td>Norfloxacin (Noroxin)</td>
<td>400 mg q12h</td>
</tr>
<tr>
<td>Ofloxacin (Floxin)</td>
<td>200 mg q12h</td>
</tr>
<tr>
<td>Trimethoprim (Proloprim, Trimpex)</td>
<td>100 mg q12h</td>
</tr>
<tr>
<td>Trimethoprim/sulfamethoxazole</td>
<td>160 mg TMP/</td>
</tr>
<tr>
<td>(Bactrim, Cotrim, Septra, etc.)</td>
<td>800 mg SMX</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Uncomplicated UTI
Fluoroquinolones

- Advantages
  - Excellent bioavailability (PO = IV)
  - Uncomplicated dosage regimen (BID or QD for 3 days)
  - Broad spectrum with low incidence of resistance for UTI pathogens
  - Drug concentrates in urinary tract (& prostate for males)
  - Quinolones are concentration dependent killers
    - Rapid rate of kill
    - With AUC / MIC ratios >250 limited selection of resistant subvariant bacterial populations
Uncomplicated UTI
Fluoroquinolones

- Disadvantages
  - Some limited drug interaction problems
  - Expensive in comparison to TMP/SMX
  - Long term effect on rectal and vaginal colonization unknown
  - Routine use could cause selection of resistant strains and premature therapeutic demise for this class of antibiotics
Uncomplicated UTI Treatment (cont.)

- Single-dose therapy (SDT)
  - SMX/TMP 2 DS tablets
  - Amoxicillin 3 gms

Advantages
- Decreased cost
- Increased compliance
- Reduced AE
- Masked Dx and Tx

Disadvantages
- UTI progression
- F/u
- Increased resistance patterns
Uncomplicated UTI Treatment (cont.)

- Single-dose therapy (cont.)
  - NOT to be use in
    - Pregnant women
    - Males
    - Upper UTI infections
    - Renal failure
    - Indwelling catheter
Uncomplicated UTI Treatment (cont.)

- Other therapy options
  - TMP/SMX DS 1 BID X 3 Days
  - TMP 100mg 1 BID X 3 Days
  - Nitrofurantoin 100mg QID X 7 Days
  - Macrobid 100mg BID X 7 Days
  - Quinolone QD or BID X 3 Days
Uncomplicated UTI
Adjunct therapy

- Post coital single dose antibiotic therapy
- Vaginal estriol therapy in post-menopausal women
- Bedtime prophylactic antibiotic therapy
- Self initiated antibiotic therapy
### Complicated UTI

**Etiology**

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>E. coli</em></td>
<td>40%</td>
</tr>
<tr>
<td><em>P. mirabilis</em></td>
<td>10%</td>
</tr>
<tr>
<td>Other Gram (-)</td>
<td>40%</td>
</tr>
<tr>
<td>Gram (+)</td>
<td>10%</td>
</tr>
</tbody>
</table>

Gram stain of Ucx should be performed.
Complicated UTI Management

- Depending on status, may need to admit
  - Severely ill
    - Direct therapy towards bacteremia/sepsis
    - Hospitalize + IV abx.

- Treatment
  - Single dose therapy not effective
  - Patients may be treated 10 to 14 days
  - Patients failing 10 to 14 day antibiotic course should then be treated for 4-6 weeks
Complicated UTI Treatment

- **Empiric**
  - Gent + Ampicillin IV
  - Alternatives to Ampicillin
    - Amp/Sulbactam
    - Piperacillin
    - 3rd generation cephalosporins (cefotaxime, ceftriaxone)
  - Nursing home resident or indwelling cath (suspect Pseudomonas)
    - Ceftaz or piperacillin + gent.
  - Suspect Enterococcus
    - Amp/piperacillin/vanco + AG
    - D/C AG in 3 days if pt. responds
Complicated UTI
Treatment (cont.)

- Duration
  - PO
    - Single dose therapy not effective
    - Patients may be treated 10 to 14 days
    - Patients failing 10 to 14 day antibiotic course should then be treated for 4-6 weeks
  - IV
    - IV treatment maintained until afebrile for 24 hours
    - PO treatment continued for 10-14 days post IV
Catheter-related UTI

Treatment

- Asymptomatic + bacteruric
  - Remove catheter
  - Hold systemic abxs

- Symptomatic
  - REMOVE CATHETER
  - Start abx treating complicated UTI
## Recurrent UTI

### Classification
- <2-3 episodes/year
- >3 episodes/year

### Management strategies

<table>
<thead>
<tr>
<th>Post coital single dose antibiotic (SMX/TMP SS)</th>
<th>Bedtime Px</th>
<th>Self-initiated abx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaginal estradiol therapy in post-menopausal women</td>
<td>Continuous low-dose Px (SMX/TMP $\frac{1}{2}$ SS Norflox 200 mg, Nitrofurantoin 50-100 mg)</td>
<td>Cranberry juice</td>
</tr>
</tbody>
</table>
UTI in pregnancy

- 4-7% pregnant patient
- Pathogenesis
  - Sever dilatation of renal pelvis and ureters
  - Decreased arterial peristalsis
  - Reduced bladder tone
  - Hormonal changes
- Monitor
  - Quantitative urine Cx
- Treatment
  - Any significant bacteriuria
UTI in pregnancy

Treatment

- **Duration**
  - Minimum of 7 days

- **Acceptable agents**
  - β-lactams
  - Nitrofurantion

- **Avoid**
  - Tetracycline (teratogenic)
  - Sulfas (3rd trimester hyperbilirubinemia)
  - Quinolones (teratogenic)
ASB

- Dx
  - 2 consecutive UCx >$10^5$ CFU/ml without symptoms
- Nursing home issues
  - Routine U/A and U/Cx performed q 6-12 hours
  - ? Need to treat
  - Cohort study: UTI no effect on mortality. Unknown effect on morbidity
Asymptomatic bacteriuria

- Organisms to suspect
  - Small number of *E. coli*
  - Staphylococci
  - *Chlamydia trachomatis*
  - *Neisseria gonorrhea*

- Treatment
  - 3-day therapy: DS SMX/TMP
  - Suspect Chlamydia:
    - Doxycycline 100 mg BID x 7 days
    - Azithromycin 1 gm
Prostatitis

Khalid Ibrahim, Pharm.D
University of Minnesota
Definitions and classification

- **Prostatitis:**
  - Inflammation of the prostate & surrounding tissues

- **Bacterial prostatitis:**
  - Inflammation in presence of bacteria and significant inflammatory cells
    - Acute: severe illness, sudden onset, fever
    - Chronic: recurrent infection with same organism

- **Nonbacterial prostatitis:**
  - S+S in presence of inflammatory cells WITHOUT bacteria

- **Prostatodynia:**
  - S+S with bacteria WITHOUT leukocytosis
Pathogenesis

- Ascending
- Reflux
- Hematogenous
- Lymphatic
- Other
  - Catheter, urethral instrumentation, transurethral prostatectomy
Protective host factors

- Prostatic fluid
  - Antibacterial factor (PAF)
  - High concentrations of zinc
    - Note: concentrations of Zn decreased in elderly
  - pH
    - Normal: 6.6-7.6
    - Inflamed: 7-9
## Etiology

<table>
<thead>
<tr>
<th>Acute Bacterial</th>
<th>Chronic bacterial</th>
<th>Chronic non-bacterial</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>E. coil</em></td>
<td><em>E. coli</em></td>
<td>Chlamydia</td>
</tr>
<tr>
<td><em>K. pneumoniae</em></td>
<td><em>K. pneumoniae</em></td>
<td>Trichomonas</td>
</tr>
<tr>
<td><em>P. mirabilis</em></td>
<td><em>P. mirabilis</em></td>
<td>Ureplasma</td>
</tr>
<tr>
<td>Serratia</td>
<td><em>E. faecalis</em></td>
<td></td>
</tr>
<tr>
<td>Enterobacter</td>
<td><em>S. aureus</em></td>
<td></td>
</tr>
<tr>
<td>Staphylococcus</td>
<td><em>S. epidermidis</em></td>
<td></td>
</tr>
</tbody>
</table>
Clinical presentation

**Acute**
- Local
  - Uncomplicated UTI symptoms
- Systemic
  - High fever
  - Malaise
  - Chills
  - Myalgia
- Prostate
  - Swollen
  - Tender
  - Warm

**Chronic**
- Difficult to Dx, commonly asymptomatic
- Vague symptoms
  - Frequency
  - Urgency
  - Dysuria
  - Lower back pain
  - Superpubic discomfort
- Prostate
  - May reveal normal gland
Treatment

- Empiric
  - Acute
    - Severely ill:
      - AG + β-lactam IV
    - Patient able to take PO
      - SMX/TMP
      - Fluoroquinolone
  - Duration
    - IV therapy until patient is afebrile + less symptomatic
    - Continue PO for 4 weeks post IV
Treatment (cont.)

- Chronic
  - SMX/TMP X 4-16 weeks
  - Fluoroquinolone X 4-16 weeks