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

Definitions

- Urinary Tract Infection (UTI)
  - M/o present in the urine not accounted for by contamination
- Cystitis
  - Lower tract infections
- Pyelonephritis
  - 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>Vesicouretral reflex</td>
<td>Tumors</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Anti-ACH agents</td>
</tr>
</tbody>
</table>
  - Catheterization
  - Pregnancy
  - Diabetes

<table>
<thead>
<tr>
<th>Miscellaneous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calciuli</td>
</tr>
<tr>
<td>Neurologic disease</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 → microcolonies
    - Small microcolonies coalesce → form bacterial biofilms
    - Glycocalyx

### Pathogenesis (cont.)
- **Facilitating issues (cont.)**
  - Catheters
    - Can be traumatic
    - Biofilm adherence
    - Bacterial aggregates can block catheter
    - Catheter can shed bacteria
    - Antibiotics 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

Clinical presentation (cont.)

- 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

- Abdominal radiograph
- Ultrasound
- Stamey-Meares 4-glass test
- Urethral catheterization
- IVP, retrograde cystography

- Procedure
- Condition
  - Nephrolithiasis
  - Hydronephrosis
  - Prostatic Localization
  - Upper vs. Lower or Bladder Washout
  - Anatomical defect functional disorder

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.

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

Etiology

Uncomplicated UTI

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>Ofloxacin (Floxin)</td>
<td>200 mg q12h</td>
</tr>
<tr>
<td>Enoxacin (Penetrex)</td>
<td>400 mg q12h</td>
</tr>
<tr>
<td>Lomefloxacin HCl (Maxaquin)</td>
<td>400 mg q24h</td>
</tr>
<tr>
<td>Norfloxacin (Noroxin)</td>
<td>400 mg q12h</td>
</tr>
<tr>
<td>Eflornoxacin (Flloxin)</td>
<td>200 mg q12h</td>
</tr>
<tr>
<td>Trimethoprim (Proloprim, Trimex)</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>
</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

- 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
  - Flu
  - Increased resistance patterns

- NOT to be use in
  - Pregnant women
  - Males
  - Upper UTI infections
  - Renal failure
  - Indwelling catheter

Uncomplicated UTI Treatment (cont.)
**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

**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>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>E. coli</td>
<td>40%</td>
</tr>
<tr>
<td>P. mirabilis</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

**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/Subbactam
    - Piperacillin
    - 3rd generation cephalosporins (cefotaxime, ceftriaxone)
  - Nursing home resident or indwelling cath (suspect Pseudomonas)
    - Cefaz or piperillin + gent.
  - Suspect Enterococcus
    - Amp/piperillin/vanco + AG
    - D/C AG in 3 days if pt. responds

**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 abx
- 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 ½ 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
  - Nitrofurantoin
- Avoid
  - Tetracycline (teratogenic)
  - Sulfas (3rd trimester hyperbilirubinemia)
  - Quinolones (teratogenic)

ASB

Dx

- 2 consecutive UCx >10⁵ 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. coli</em></td>
<td><em>E. coli</em></td>
<td><em>Chlamydia</em></td>
</tr>
<tr>
<td><em>K. pneumoniae</em></td>
<td><em>K. pneumoniae</em></td>
<td><em>Trichomonas</em></td>
</tr>
<tr>
<td><em>P. mirabilis</em></td>
<td><em>P. mirabilis</em></td>
<td><em>Ureaplasma</em></td>
</tr>
<tr>
<td><em>Serratia</em></td>
<td><em>E. faecalis</em></td>
<td></td>
</tr>
<tr>
<td><em>Enterobacter</em></td>
<td><em>S. aureus</em></td>
<td></td>
</tr>
<tr>
<td><em>Staphylococcus</em></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**
    - Severe illness:
      - 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