Urinary Tract Infections

John C. Rotschafer, Pharm. D. FCCP
Professor
College of Pharmacy
University of Minnesota

Case

You are contacted by a FP resident regarding the use of a FQ in a 24 year old semi-professional soccer player with an apparent UTI.

She has complained of dysuria and frequency for the last 24 hours. Her UA is positive for bacteria using a nitrate dipstick and WBC’s using a dipstick esterase test.

Her past medical history is significant for DM. She has no allergies and other than her diabetes there has been no other significant medical problems.
Case

You have been consulting in a Nursing Home for the past several years. An asymptomatic 84 year old male with an indwelling foley catheter has a positive urine culture for *P. aeruginosa*. You have been contacted regarding the appropriate dose and interval for ciprofloxacin to begin therapy.
Case

You have been consulted on a 72 year old female nursing home patient. She recently was treated for 10 days with ceftriaxone and azithromycin for presumed CAP. During her hospitalization a foley catheter was placed. She is currently afebrile and asymptomatic of any UTI symptoms but a culture of her urine at the end of her antibiotic therapy had a significant growth of yeast. How should she be managed?

Epidemiology of UTIs in the United States

- 8 million physician visits/year
- 10.8% annual prevalence
- 40%–50% lifetime prevalence in women
- 1 in 3 women will require antimicrobial therapy before 24 years of age
- 0.5–0.7 episodes/person-year in sexually active women
- $1 billion/year for evaluation and treatment

Foxman B. Am J Med. 2002;113(Suppl):S5-S13S.
Pathogenesis

• Rectal and/or vaginal reservoirs
• Colonization of perianal area
• Bacterial migration to perivaginal area
• Bacteria ascend through urethra to bladder
• Intercourse may contribute urethral colonization and ascending infection
• ASB in 1st trimester of pregnancy may cause pyelonephritis in 3rd trimester

Urinary Tract Infection

Upper
◆ Pyelonephritis (± bacteremia)

Lower
◆ Cystitis
  (approx. 30% occult pyelonephritis)
◆ Asymptomatic bacteriuria (ASB)
◆ Urethral syndrome
Clinical Characteristics

<table>
<thead>
<tr>
<th>Age/Gender</th>
<th>Uncomplicated UTI</th>
<th>Complicated UTI</th>
<th>Uncomplicated Pyelonephritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sexually active young women</td>
<td>Middle-age men, elderly women</td>
<td>All ages, more women</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Community-acquired</th>
<th>Nosocomial</th>
<th>Community-acquired</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comorbid Conditions</td>
<td>Healthy</td>
<td>Functional, metabolic, or structural abnormality</td>
<td>Healthy</td>
</tr>
<tr>
<td>Symptoms</td>
<td>Localized</td>
<td>Localized</td>
<td>Systemic</td>
</tr>
<tr>
<td>Consequences</td>
<td>Self-limited</td>
<td>Bacteremia</td>
<td>Bacteremia</td>
</tr>
</tbody>
</table>

Differential Diagnosis of Bacteriuria

- **Patient Symptomatic?**
  - **no** → Asymptomatic bacteriuria
  - **yes**
    - **Complicating Factors?**
      - **no**
      - **yes** → Complicated UTI
    - **yes** → Complicated UTI
    - **yes** → Complicated UTI
      - **no**
      - **yes** → Recurrent UTI
      - **no**
      - **yes** → Pyelonephritis
      - **no**
      - **yes** → Pyelonephritis

- **Uncomplicated cystitis, urethritis, or vaginitis**

References:
Signs and Symptoms of UTI

Subjective symptoms
- Dysuria
- Urgency
- Increased frequency
- Subrapubic or low back pain

Objective signs (not required for uncomplicated UTI)
- Bacteriuria
  \(10^2\) to \(\geq 10^5\) colony-forming units/mL
- Pyuria (WBC >10/mm³)


Laboratory Diagnosis of UTI

Urinalysis
- ± Macro or microscopic hematuria
- Alkaline ph with urea splitting bacteria
  - Urea converted to ammonia via enzyme
- 10 WBC/hpf is the usual upper limit of normal
- Positive result on leukocyte esterase dipstick test correlates well for detecting >10 WBC/hpf
- Positive nitrate dipstick test result for bacteriuria
  - False-negative results are common
- Urine cultures not necessary in women with uncomplicated UTI

Risk Factors and Pathogenesis

Risk Factors
- Sexual activity with different partners
- Diaphragm or spermicide use
- History of prior UTI

Pathogenesis
- Uncomplicated UTI: mostly ascending uropathogens
  - *E. coli*, *S. saprophyticus*, *Proteus* spp., *Klebsiella* spp.

Antibiotic Selection Considerations
- Local antibiotic resistance patterns
- Pharmacokinetics
  - Drug concentration in urinary tract (renal excretion of active drug)
  - Once-daily vs multiple daily doses
- Effects on normal enteric and vaginal flora
- Safety (adverse events, allergies)
- Patient age
- Prior antibiotic courses

Treatment of Uncomplicated UTI

Antibiotic Therapy

◆ 3-day course recommended
  – TMP/SMX
  – Fluoroquinolone
◆ Single-dose therapy is less effective
  – Especially with β-lactams
◆ 7-day regimens are no more effective than 3 days
  – Increased cost and side effects


Etiology of Uncomplicated UTIs in the US (Women 15–50 years old)

Gram-Negatives

◆ *Escherichia coli* (72%)
◆ *Klebsiella* species (6%)
◆ *Proteus* species (4%)
◆ Other (5%)

Gram-Positives

◆ *Enterococcus* species (5%)
◆ Other Gram-positive organisms (7%)

Miscellaneous Antibiotics

• Nitrofurantoin
  • Therapeutic concentrations only in urine
  • Must have normal renal function
  • Can be used in pregnancy
  • Has been associated with a number of ADR’s
    • Nitrofurantoin lung
    • Drug fever
    • Peripheral neuropathy

• Mandelamine
  • Must be converted to formaldehyde to be active
  • Primarily time dependent process
  • Possibly aided by acidic urine

Recurrent
Uncomplicated UTIs
Recurrent Uncomplicated UTI: Pathogenesis and Epidemiology

Pathogenesis
- Most cases of recurrent UTI due to reinfection, usually *E. coli* (not always from the same strain as the original infection)

Epidemiology
- 20%–30% of young women with uncomplicated cystitis have recurrent UTI
- Risk factors: sexual intercourse, spermicide, first UTI at early age, maternal history of UTI

Management of Recurrent UTI

Three treatment options:
- Long-term, low-dose prophylaxis (usually 6–12 months)
  - TMP/SMX, TMP, nitrofurantoin, norfloxacin
- Postintercourse, low-dose prophylaxis
  - Single dose of TMP/SMX, TMP, nitrofurantoin, cephalexin, fluoroquinolone
- Self-treatment and diagnosis (3 days)
  - TMP/SMX, TMP, fluoroquinolone
Self-Diagnosis and Treatment of Recurrent UTIs

- Study to determine accuracy and efficacy of patient-initiated treatment of recurrent UTI
  - Treated with ofloxacin 200 mg BID for 3 days or levofloxacin 250 mg QD for 3 days
- Urine samples from 84% of self-diagnosed cases were culture positive, 11% were sterile pyuria
- Self-treated cases result in:
  - 92% clinical cure
  - 96% microbiological cure


Preventing UTIs Patient Education Brochure

There are a number of things you can do to prevent urinary tract infections:

- Empty your bladder every three hours while you are awake, whether or not you feel an urge to do so. Avoid long intervals between urination.
- Drink at least six to eight glasses of water daily.
- Shower instead of taking a bath. Avoid using bubble bath or other cosmetic bath products.
- Avoid using any feminine hygiene sprays and scented douches.
- Avoid using a vaginal diaphragm if you are prone to UTIs.
- Empty your bladder after sexual intercourse. Sexual relations may cause UTIs.
- After a bowel movement, clean the area around the anus gently, wiping from front to back and never repeating with the same tissue. Soft, white, no scented tissue is recommended.
- After urination, wipe from front to back.

Park Nicollet Institute © 2005
Complicated UTIs

Definition

- Complicated UTI is a urinary tract infection in a patient with a functionally, metabolically, or anatomically abnormal urinary tract, including:
  - Foreign body (catheter, stent)
  - Obstruction (calculi, congenital anomaly, prostatic disease, stricture, tumor)

Epidemiology/Pathogenesis

- Most common UTI in men aged 16–35 years
- Most common nosocomial infection
  - Catheter-related UTI accounts for up to 31% of hospital-acquired infections
  - Prolongs hospital stay
  - Increases hospitalization costs
- *E. coli* less common compared to uncomplicated UTI


Risk Factors for Complicated Urinary Tract Infection

- Advanced age, debility
- Male gender
- Hospitalization
- Long-term care
- Diabetes mellitus
- Functional/anatomic abnormalities
- Immunosuppression or suppressive drugs
- Pregnancy or menopause
- Catheter or stent
- Stones in bladder or urinary tract
- Recent antibiotic use
- Recent urinary tract instrumentation
- Renal transplant
- Symptoms >7 days

Clinical Implications of Complicated UTI

- Pathogens: wide range of Gram-negative and Gram-positive organisms
- Resistance to TMP/SMX common
- Therapy: 7–14 days of antimicrobial therapy
- Follow up: repeat urinalysis and culture
  - 1–2 weeks after completion of antibiotic therapy


Complicated UTI Etiology

<table>
<thead>
<tr>
<th>Bacterial Uropathogen</th>
<th>Prevalence in Complicated UTI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Escherichia coli</em></td>
<td>21 – 54</td>
</tr>
<tr>
<td><em>Klebsiella pneumoniae</em></td>
<td>1.9 – 17</td>
</tr>
<tr>
<td>Enterobacter species</td>
<td>1.9 – 9.6</td>
</tr>
<tr>
<td>Citrobacter species</td>
<td>4.7 – 6.1</td>
</tr>
<tr>
<td><em>Proteus mirabilis</em></td>
<td>0.9 – 9.6</td>
</tr>
<tr>
<td>Providencia species</td>
<td>18</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em></td>
<td>2 – 19</td>
</tr>
<tr>
<td>Enterococci species</td>
<td>6.1 – 23</td>
</tr>
</tbody>
</table>

Antibiotic Options for Complicated UTIs

<table>
<thead>
<tr>
<th>Parenteral (2–3 days)</th>
<th>Oral (7 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levofloxacin</td>
<td>Levofloxacin</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Ciprofloxacin</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>TMP/SMX</td>
</tr>
<tr>
<td>Amikacin</td>
<td>Cephalosporin</td>
</tr>
<tr>
<td>Imipenem</td>
<td>Amoxicillin ± clav</td>
</tr>
<tr>
<td>Cephalosporin</td>
<td></td>
</tr>
<tr>
<td>Ampicillin</td>
<td></td>
</tr>
<tr>
<td>Piperacillin ± tazo</td>
<td></td>
</tr>
</tbody>
</table>


Acute Pyelonephritis
Acute Pyelonephritis: Epidemiology and Pathogenesis

Epidemiology
- About 250,000 patients per year in the US

Pathogenesis
- Infection of the upper urinary tract
- Implicated pathogens include:
  - *E. coli*
  - *P. mirabilis*
  - *K. pneumoniae*


Symptoms of Pyelonephritis

Symptoms develop rapidly (<24 hours) and may include:
- Fever >38°C
- Chills
- Nausea/vomiting
- Diarrhea
- Symptoms of cystitis
- Generalized muscle tenderness
- Flank pain (+ CVA tenderness)

Treatment of Pyelonephritis

Eradicate pathogens in kidney and urothelium, and treat/prevent bacteremia

- Hospitalized patients: IV antibiotic first
  48–72 hours, followed by 7 days of oral antibiotic therapy
    - Fluoroquinolone IV, then PO
    - Aminoglycoside ± ampicillin IV, then TMP/SMX PO or amox/clav
    - Third-generation cephalosporin IV, then TMP/SMX PO or amox/clav
- Ambulatory patients: 7–14 days of PO therapy with one of the antimicrobials above


IDSA Treatment Guidelines:
Acute Uncomplicated Pyelonephritis

Mild or moderate symptoms:
- Outpatient treatment (total of 7–14 days)

Oral treatment:
- Fluoroquinolone
- TMP/SMX, if uropathogen is known to be susceptible
- If Gram-positive pathogen: amoxicillin or amoxicillin-clavulanate

### Gram-Negative Surveillance
**TRUST 11 (2006-2007) % Susceptible**

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Total n</th>
<th>LVX</th>
<th>CIP</th>
<th>AMP</th>
<th>CRO</th>
<th>CAZ</th>
<th>IPM</th>
<th>PTZ</th>
<th>GEN</th>
<th>SXT</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S marcescens</em></td>
<td>324</td>
<td>96.0</td>
<td>94.4</td>
<td>13.6</td>
<td>96.0</td>
<td>96.6</td>
<td>99.4</td>
<td>98.1</td>
<td>96.9</td>
<td>97.5</td>
</tr>
<tr>
<td><em>Citrobacter spp</em></td>
<td>457</td>
<td>95.3</td>
<td>93.4</td>
<td>28.4</td>
<td>91.9</td>
<td>90.2</td>
<td>100</td>
<td>91.9</td>
<td>94.5</td>
<td>86.7</td>
</tr>
<tr>
<td><em>K pneumoniae</em></td>
<td>1207</td>
<td>93.3</td>
<td>92.2</td>
<td>4.3</td>
<td>95.8</td>
<td>95.7</td>
<td>99.8</td>
<td>94.4</td>
<td>95.5</td>
<td>89.9</td>
</tr>
<tr>
<td><em>E cloacae</em></td>
<td>530</td>
<td>88.3</td>
<td>86.4</td>
<td>12.8</td>
<td>75.5</td>
<td>73.8</td>
<td>100</td>
<td>80</td>
<td>90.9</td>
<td>83</td>
</tr>
<tr>
<td><em>E coli</em></td>
<td>1724</td>
<td>80.5</td>
<td>79.9</td>
<td>51.1</td>
<td>96.1</td>
<td>96.7</td>
<td>100</td>
<td>95.5</td>
<td>91.4</td>
<td>73.7</td>
</tr>
<tr>
<td><em>P mirabilis</em></td>
<td>624</td>
<td>78.4</td>
<td>72.6</td>
<td>80.6</td>
<td>99.7</td>
<td>99.7</td>
<td>100</td>
<td>100</td>
<td>90.5</td>
<td>74.8</td>
</tr>
<tr>
<td><em>P aeruginosa</em></td>
<td>866</td>
<td>68.8</td>
<td>70.8</td>
<td>0</td>
<td>22.6</td>
<td>86.7</td>
<td>82.6</td>
<td>89.8</td>
<td>87.8</td>
<td>13.6</td>
</tr>
</tbody>
</table>

LVX = levofloxacin  
CIP = ciprofloxacin  
AMP = ampicillin  
CRO = ceftriaxone  
CAZ = ceftazidime  
IPM = imipenem  
PTZ = piperacillin-tazo  
GEN = gentamicin  
SXT = trimethoprim-sulfa

a: 5732 isolates were tested from 45 geographically distributed sites. Moxifloxacin was not tested against Enterobacteriaceae as there are no CLSI breakpoints for moxifloxacin.

### Summary

- **Treatment Options (Treatment Algorithm)**
  - Once-daily
  - 3 days—uncomplicated urinary tract infection
  - 10 days—complicated urinary tract infection or acute pyelonephritis
- Broad-spectrum activity against uropathogens
- Achieves high concentration in urine
- Rapid bactericidal activity
- Excellent safety profile