Urinary Tract Infections: From Simple to Complex

Adriane N Irwin, MS, PharmD, BCACP
Clinical Assistant Professor – Ambulatory Care
October 25, 2014

Learning Objectives

• Develop empiric antimicrobial treatment regimens for acute uncomplicated and complicated urinary tract infections (UTIs)
• Develop antimicrobial treatment regimens for UTIs in response to specific culture and susceptibility testing
• Assess treatment options for complex patient cases

Urinary Tract Infections

Introduction

• Presence of microorganisms in the urinary tract that cannot be accounted for by contamination
• Two types of urinary tract infection
  • Cystitis: Involves the lower urinary tract (bladder)
  • Pyelonephritis: Involves the upper urinary tract (kidney)
## Uncomplicated vs Complicated

<table>
<thead>
<tr>
<th>Uncomplicated</th>
<th>Complicated</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Cystitis</td>
<td>- Pyelonephritis</td>
</tr>
<tr>
<td>- Patient characteristics</td>
<td>- Patient characteristics</td>
</tr>
<tr>
<td>- Women of child bearing age</td>
<td>- Men</td>
</tr>
<tr>
<td>- No structural and/or functional abnormalities</td>
<td>- Structural and/or functional abnormalities (catheters, obstructions, neurologic deficits, transplant)</td>
</tr>
<tr>
<td>- Pathogens</td>
<td>- Pathogens</td>
</tr>
<tr>
<td>Primary: <em>Escherichia coli</em> (80%)</td>
<td>Primary: <em>Escherichia coli</em> (50%)</td>
</tr>
<tr>
<td>Other: Enterobacteriaceae (Klebsiella &amp; Proteus species)</td>
<td>Other: Enterococcus species, miscellaneous gram negatives (<em>Pseudomonas aeruginosa</em>)</td>
</tr>
</tbody>
</table>

## Diagnosis

### Introduction

- **Symptoms suggestive of cystitis:**
  - Dysuria
  - Possibly with any of the following: frequency, urgency, suprapubic pain or heaviness, hematuria
- **Symptoms suggestive of pyelonephritis:**
  - Any indication of upper tract or systemic disease: nausea/vomiting, fever, flank pain, costovertebral angle tenderness, fatigue
  - Dysuria or other classic symptoms of cystitis may not be present

## Diagnosis

### Introduction

- **Patient populations that can present with asymptomatic bacteriuria:**
  - Elderly
  - Children
  - Pregnant women
  - Patients with indwelling catheters
Goals of Treatment

Introduction

1. Eradicate the invading organism
2. Prevent (and treat) systemic consequences of infection
3. Prevent recurrence

Antibiotic Selection

Treatment

• Choice of agent should be individualized based on:
  • Allergies
  • Patient compliance history
  • Most likely organism(s)
  • Local susceptibility
  • Cost
  • Availability
  • Provider threshold for failure

Terminology

Treatment

• Empiric therapy:
  • Treatment prior to a firm diagnosis
  • Antibiotic treatment given before specific microorganism and susceptibilities are known

• Culture driven therapy:
  • Antibiotic treatment tailored to the microorganism
Uncomplicated Cystitis

Treatment

- Woman with...
  - Absence of symptoms suggestive of pyelonephritis
  - Able to take oral medication

<table>
<thead>
<tr>
<th>Empiric Treatment Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitrofurantoin 100 mg BID x 5 days</td>
</tr>
<tr>
<td>Trimethoprim/sulfamethoxazole (TMP/SMX) 160/800 mg BID x 3 days</td>
</tr>
<tr>
<td>Fosfomycin 3 g as a single dose</td>
</tr>
</tbody>
</table>

Empiric Agents:
- Nitrofurantoin
- TMP/SMX
- Fosfomycin

Alternate Agents:
- Fluoroquinolone
- β-lactam

Nitrofurantoin:
- Avoid if pyelonephritis is suspected
- CrCl < 60 mL/min

TMP/SMX:
- Avoid if E. coli resistance ≥20% or unknown
- Use in previous 3 months

Fosfomycin:
- Avoid if pyelonephritis is suspected
- Lower efficacy
- Availability (?)
Uncomplicated Cystitis

**Culture Driven Recommendations**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage/Regimen</th>
</tr>
</thead>
<tbody>
<tr>
<td>TMP/SMX</td>
<td>160/800 mg BID x 3 days</td>
</tr>
<tr>
<td>nitrofurantoin</td>
<td>100 mg BID x 5 days</td>
</tr>
<tr>
<td>fosfomycin</td>
<td>3g single dose</td>
</tr>
<tr>
<td>ciprofloxacin</td>
<td>250 mg BID x 3 days</td>
</tr>
<tr>
<td>levofloxacin</td>
<td>250 mg daily x 3 days</td>
</tr>
<tr>
<td>amoxicillin/clavulanate</td>
<td>500/125mg BID x 5-7 days</td>
</tr>
<tr>
<td>cefuroxime</td>
<td>500 mg BID x 3-7 days</td>
</tr>
<tr>
<td>trimethoprim</td>
<td>100 mg BID x 3-5 days</td>
</tr>
</tbody>
</table>

Complicated Cystitis

**Treatment**

- **E. coli resistance to TMP/SMX < 20%**
  - Preferred: TMP/SMX x 3 days
  - Alternatives:
    - nitrofurantoin x 5 days
    - fluoroquinolones x 3 days (reserved for patients with multiple intolerances)

- **E. coli resistance to TMP/SMX ≥ 20%**
  - nitrofurantoin x 7 days
  - fluoroquinolones x 5-7 days

Pyelonephritis

**Treatment**

- Both complicated and uncomplicated infections
- Important to obtain urine culture with sensitivities

**Empiric Treatment Recommendations**

- Preferred: fluoroquinolones x 7 days*
- Alternatives: TMP/SMX or broad spectrum cephalosporin x 14 days
- Not suitable: nitrofurantoin and fosfomycin

* Consider initial dose of parenteral antibiotic if local E. coli resistance to fluoroquinolones is >10%; patients who require treatment emergent hospital admission, or patients with fluoroquinolone use in past 3 months.
Patient Case 1:

PT is a 23 year old female with a past medical history of allergic rhinitis. Her only medication is an estrogen containing oral contraceptive and only known drug allergy is a history of rash when she takes "sulfa drugs." She calls her primary care provider (PCP) today describing recent onset of dysuria and urinary urgency. She denies any fever, chills, or flank pain.

Which of the following is the best therapeutic choice for PT?
1. Nitrofurantoin monohydrate 100 mg BID x 5 days
2. Ciprofloxacin 500 mg BID x 3 days
3. Fosfomycin 3 g packet as a single dose
4. TMP/SMX 1 DS tablet BID x 3 days

Patient Case 1:

PT's PCP collects a urine sample for UA and culture and starts her on nitrofurantoin as empiric therapy. Two days later, the culture results are finalized (next slide).

Does PT need to be changed to culture-driven therapy?
1. Yes
2. No

<table>
<thead>
<tr>
<th>ESCHERICHIA COLI</th>
<th>Antibiotic</th>
<th>Sensitivity</th>
<th>BioType</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>Resistant</td>
<td>&gt;= 32</td>
<td>Final</td>
<td></td>
</tr>
<tr>
<td>Cefazolin</td>
<td>Resistant</td>
<td>&gt;= 64</td>
<td>Final</td>
<td></td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>Resistant</td>
<td>&gt;= 64</td>
<td>Final</td>
<td></td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Resistant</td>
<td>&gt;= 4</td>
<td>Final</td>
<td></td>
</tr>
<tr>
<td>Ertapenem</td>
<td>Susceptible</td>
<td>&lt;= 0.5</td>
<td>Final</td>
<td></td>
</tr>
<tr>
<td>Gentamicin</td>
<td>Resistant</td>
<td>&gt;= 16</td>
<td>Final</td>
<td></td>
</tr>
<tr>
<td>Imipenem</td>
<td>Susceptible</td>
<td>&lt;= 1</td>
<td>Final</td>
<td></td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>Susceptible</td>
<td>32</td>
<td>Final</td>
<td></td>
</tr>
<tr>
<td>Tobramycin</td>
<td>Intermediate</td>
<td>8</td>
<td>Final</td>
<td></td>
</tr>
<tr>
<td>Trimethoprim +</td>
<td>Susceptible</td>
<td>&gt;= 320</td>
<td>Final</td>
<td></td>
</tr>
<tr>
<td>Sulfamethoxazole</td>
<td>Resistant</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Patient Case 2:

PT is a 78 year old female with a past medical history of allergic hypertension and hyperlipidemia. Her only medications are lisinopril 10 mg and pravastatin 20 mg. She has NKA. Her annual labs were completed about 1 month ago. At the time, her SCr was 1.2 mg/dL (CrCl 48 mL/min). She calls her PCP today describing recent onset of dysuria and urinary urgency. She denies any fever, chills, or flank pain.

Which of the following is the best therapeutic choice for PT?

1. Nitrofurantoin monohydrate 100 mg BID x 5 days
2. Ciprofloxacin 500 mg BID x 3 days
3. Fosfomycin 3 g packet as a single dose
4. TMP/SMX 1 DS tablet BID x 3 days

Patient Case 2:

PT's PCP collects a urine sample for UA and culture and starts her on TMP/SMX as empiric therapy. Two days later, the culture results are finalized (next slide).

Does PT need to be changed to culture-driven therapy?

1. Yes
2. No

<table>
<thead>
<tr>
<th>ESCHERICHIA COLI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotic</td>
</tr>
<tr>
<td>Ampicillin</td>
</tr>
<tr>
<td>Cefazolin</td>
</tr>
<tr>
<td>Ceftriaxone</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
</tr>
<tr>
<td>Ceftriaxone</td>
</tr>
<tr>
<td>Gentamicin</td>
</tr>
<tr>
<td>Imipenem</td>
</tr>
<tr>
<td>Nitrofurantin</td>
</tr>
<tr>
<td>Tobramycin</td>
</tr>
<tr>
<td>Trimethoprim + Sulfamethoxazole</td>
</tr>
</tbody>
</table>
Nitrofurantoin & Reduced Renal Function

Introduction
Nitrofurantoin & Reduced Renal Function

• Current package labeling states that the use of nitrofurantoin is contraindicated in patients with a CrCl < 60 mL/min
• Historical perspective:
  • 1988: Macrodantin product information had a CrCl < 40 mL/min
  • 2003: Macrobid product information had a CrCl < 60 mL/min
• Why?
  • Concentrations may be insufficient to treat infection
  • Increased risk of side effects

Urinary Excretion Data
Nitrofurantoin & Reduced Renal Function

<table>
<thead>
<tr>
<th>CrCl (mL/min)</th>
<th>Patients &amp; Dose</th>
<th>Outcome</th>
<th>Studies</th>
<th>Patients &amp; Dose</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 20</td>
<td>100 mg x 1</td>
<td>Max concentration (mg/L) 10-hr urine collection</td>
<td>Sachs (1968)</td>
<td>100 mg repeated</td>
<td>Max concentration (mg/L) 24-hr urine collection</td>
</tr>
<tr>
<td>20 – 40</td>
<td></td>
<td>&lt; 5 – 10</td>
<td>Schlegel (1967)</td>
<td></td>
<td>&lt; 5 – 15</td>
</tr>
<tr>
<td>41 – 60</td>
<td></td>
<td>&gt; 10</td>
<td>Lippman (1958)</td>
<td></td>
<td>100 – 250</td>
</tr>
<tr>
<td>&gt; 60</td>
<td></td>
<td>&lt; 10</td>
<td>Felts (1971)</td>
<td></td>
<td>“Normal” renal function: 114 – 220</td>
</tr>
</tbody>
</table>

Max concentration (mg/L) 24-hr urine collection

“Normal” renal function: 114 – 220

“Azotemia”: < 10

Mean range max urine concentration (mg/L)

“Normal” renal function: 114 – 220

CrCl: < 30 ml/min: 2.5

CrCl: 30 – 60 ml/min: 1.8

Study Limitations

Nitrofurantoin & Reduced Renal Function

- The number of patients included within each CrCl group is unclear
- Information on key parts of the methodology is scarce
- Endpoints not consistent between studies and may not be consistent with treatment dosing and/or clinical practice
- No evaluation of clinical endpoints

Clinical Data

Nitrofurantoin & Reduced Renal Function

- Retrospective chart review of 356 patients treated with nitrofurantoin for suspected UTI between 2004 – 2008 in long-term and acute care hospitals
- Impaired renal function was defined as CrCl < 50 mL/min
- Primary endpoint:
  - Clinical cure: Absence of clinical symptoms and no additional antimicrobials within 14 days of nitrofurantoin treatment completion
  - Microbiologic cure: Repeat negative cultures

Clinical Data

Nitrofurantoin & Reduced Renal Function

- Primary endpoint:
  - Cure rates were comparable in both groups – 71% (95% CI 63 – 79) in the renally impaired groups vs 78% (95% CI 73 – 84)
- Limitations:
  - Retrospective nature
  - Suspected UTI (not microbiologically confirmed)
  - Relatively moderate renal impairment (average CrCl 40 mL/min, range 15 – 50 mL/min)
  - Under powered
  - Selection bias as patients needed to be hospitalized at 14 days
Conclusions
Nitrofurantoin & Reduced Renal Function

• There is a need for additional research that incorporates clinical outcomes to better assess the use of nitrofurantoin in patients with reduced renal function
• Conflict exists between package labeling and the realities of clinic practice including implementation of the IDSA guidelines
• Use of nitrofurantoin in patients with in patients with reduced renal function should be evaluated on a case by case basis

Patient Case 2:
PT’s PCP had started her on TMP/SMX. However, after seeing the results of her urine culture decides to change her antibiotic therapy.

Which of the following is now the best option for PT?
1. Start nitrofurantoin monohydrate 100 mg BID x 5 days
2. Start ertapenem 1 g IM qday
3. Call the laboratory to see if they have susceptibilities to fosfomycin.
4. All of the above

<table>
<thead>
<tr>
<th>ESCHERICHIA COLI</th>
<th>Sensitivity</th>
<th>SusceptType</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>Resistant</td>
<td>&gt;= 32</td>
<td>Final</td>
</tr>
<tr>
<td>Cefazolin</td>
<td>Resistant</td>
<td>&gt;= 64</td>
<td>Final</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>Resistant</td>
<td>&gt;= 64</td>
<td>Final</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>Resistant</td>
<td>&gt;= 4</td>
<td>Final</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>Susceptible</td>
<td>&lt;=0.5</td>
<td>Final</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>Resistant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Imipenem</td>
<td>Susceptible</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>Susceptible</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tobramycin</td>
<td>Intermediate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trimethoprim + Sulfamethoxazole</td>
<td>Resistant</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Introduction
ESBL Producing Organisms

What is an ESBL?
• Extended spectrum β-lactamase (ESBL)
• Beta lactamase capable of hydrolyzing...
• Pencillins
• Cephalosporins
• Monobactams (e.g., aztreonam)
• Plasmid mediated form of resistance → Multiple resistance genes transferred between bacteria

“...alarmed by the prospect that effective antibiotics may not be available to treat seriously ill patients in the near future.”
— Joseph R Dalovisio, MD, IDSA President
Antibiotic Resistance Pattern
ESBL Producing Organisms

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Source</td>
<td>Urine</td>
<td>Urine</td>
<td>Blood</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>-</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Ceftazidime</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Carbapenem</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Aminoglycoside</td>
<td>78%</td>
<td>79%</td>
<td>68.4%</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>22%</td>
<td>43%</td>
<td>8.7%</td>
</tr>
<tr>
<td>TMP/SMX</td>
<td>27%</td>
<td>40%</td>
<td>15.2%</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>94%</td>
<td>92%</td>
<td>-</td>
</tr>
</tbody>
</table>

Clinical Data
ESBL Producing Organisms

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Subjects</th>
<th>Primary Endpoint &amp; Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burgess (2003)</td>
<td>ESBL infections (n = 18)</td>
<td>1st endpoint: Clinical cure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Carbapenem: 100%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Pip/tazo + FQ or AG: 56%</td>
</tr>
<tr>
<td>Endimiani (2004)</td>
<td>ESBL K. pneumoniae bacteremia (n = 17)</td>
<td>1st endpoint: Clinical failure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Imipenem: 20% (2 of 10)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Ciprofloxacin: 71.4% (5 of 7)</td>
</tr>
<tr>
<td>Paterson (2004)</td>
<td>ESBL K. pneumoniae bacteremia (n = 71)</td>
<td>1st endpoint: Mortality</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Carbapenem: 4.8%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Non-carbapenem: 27.6%</td>
</tr>
</tbody>
</table>

Conclusions
ESBL Producing Organisms

- Most clinical literature on the treatment of ESBL bacteria involves parenteral agents in the hospital setting.
- Current literature provides little guidance on managing UTIs in the outpatient setting. Selecting therapy requires assessment of infection severity, patient characteristics, and patient convenience.
- Fluoroquinolones, nitrofurantoin, TMP/SMX, and possibly fosfomycin are usually the only oral antibiotics to consider when reviewing an ESBL susceptibility report.
Common Questions

UTI Recurrences

Common Questions

- Recurrences generally do not require prolonged therapy and can be treated with standard empiric therapy.
- Time to recurrence:
  - Less than 6 months → Choose a different agent
  - Greater than 6 months → May choose same agent
Prophylaxis
Common Questions

1. Self initiated therapy at the onset of symptoms
2. Postcoital therapy
3. Continuous low dose prophylaxis
   - Individuals with > 3 episodes per year
   - Nitrofurantoin 50 mg qday x 6 months
   - TMP/SMX ½ SS tablet qday x 6 months
   - Other agents may be acceptable based on patient characteristics

UTIs & Pregnancy
Common Questions

- Asymptomatic bacteriuria in pregnancy translates to an increased risk of (1) pyelonephritis and (2) preterm delivery and low birth weight
- Optimal agent and duration is unclear. Culture with sensitivities often recommended prior to selection of agent

<table>
<thead>
<tr>
<th>Good</th>
<th>β-lactams*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Okay</td>
<td>TMP/SMX and nitrofurantoin (except in women near term)</td>
</tr>
<tr>
<td>Avoid</td>
<td>Tetracyclines, fluoroquinolones</td>
</tr>
</tbody>
</table>

*Due to resistance, may need to consider broad-spectrum oral cephalosporins such as cefuroxime or cefpodoxime

Cefuroxime Susceptibility
Common Questions

- Most E. coli are susceptible to cefuroxime
- Reasonable empiric choice for symptomatic patients and/or pregnant women with bacteriuria
- Culture results:
  - cefazolin (susceptible) - - > cefuroxime (susceptible)
  - ceftriaxone (susceptible) - - > cefuroxime (likely susceptible)
  - ceftriaxone (resistant) - - > cefuroxime (resistant)
Enterococcus Species
Common Questions
• Preferred --> amoxicillin or nitrofurantoin
• Alternatives -->
  • linezolid: not renally eliminated
  • vancomycin: often the only option due to resistance, intolerances, and renal impairment
• Not acceptable --> cephalosporins

Urinary Tract Infections:
From Simple to Complex

Adriane N Irwin, MS, PharmD, BCACP
Clinical Assistant Professor - Ambulatory Care
October 25, 2014