UTI Treatment Guidelines

Eric Myers, Pharm.D.

PGY-2 Infectious Diseases Pharmacy Resident
Objectives

- Evaluate the rationale for new guidelines for the treatment of UTI in long term care

- Design a treatment regimen for empiric and targeted therapy of UTIs using the new guidelines
Rationale for UTI Guideline

1. Improve treatment of UTIs
   - Increase likelihood that empiric therapy covers most common causative organisms

2. Reduce incidence of antimicrobial-related adverse events (C. diff)
   - Prevent unnecessary prescription of antibiotics
   - Reduce prescription of high risk antibiotics (quinolones, 3rd generation cephalosporins)
Adverse Effects of Fluoroquinolones

- GI toxicity
- CNS toxicity (weakness, confusion, delirium, seizures)
- QTc prolongation
- Tendon rupture
- *Clostridium difficile*-associated diarrhea
- Hypo-/hyperglycemia

**Increased risk and/or severity in elderly patients**
C. Diff and the Elderly

2013 CDI Incidence by Age Group

Incidence (per 100,000 population)

Age Groups

1-17, 18-39, 40-49, 50-59, 60-69, 70-84, 85+

Rochester Emerging Infection Program surveillance data
Risk of C. diff Infection (CDI) by Antibiotic Class

Retrospective study
- 7,792 patients and 241 cases of CDI
- Risk of CDI compared between antimicrobial classes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>CDI positive n (%)</th>
<th>CDI negative n (%)</th>
<th>Crude hazard ratio&lt;sup&gt;a,b&lt;/sup&gt; (95% CI)</th>
<th>Adjusted hazard ratio&lt;sup&gt;a,c,d&lt;/sup&gt; (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminoglycosides</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>22 (9)</td>
<td>837 (8)</td>
<td>0.8 (.2, 2.6)</td>
<td>0.9 (.3, 3.0)</td>
</tr>
<tr>
<td>Cephalosporins</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First- and second-generation</td>
<td>94 (39)</td>
<td>3883 (39)</td>
<td>2.4 (1.4, 4.0)</td>
<td>2.4 (1.4, 4.1)</td>
</tr>
<tr>
<td>Third- and fourth-generation</td>
<td>74 (31)</td>
<td>1527 (15)</td>
<td>3.1 (1.9, 5.2)</td>
<td>3.1 (1.9, 5.2)</td>
</tr>
<tr>
<td>Clindamycin</td>
<td>34 (14)</td>
<td>876 (9)</td>
<td>1.7 (.8, 3.9)</td>
<td>1.9 (.8, 4.4)</td>
</tr>
<tr>
<td>Macrolides</td>
<td>48 (20)</td>
<td>1266 (13)</td>
<td>1.7 (.8, 3.4)</td>
<td>1.5 (.7, 3.1)</td>
</tr>
<tr>
<td>Metronidazole</td>
<td>37 (15)</td>
<td>981 (10)</td>
<td>0.3 (.1, .9)</td>
<td>0.3 (.1, 0.9)</td>
</tr>
<tr>
<td>Penicillins</td>
<td>30 (12)</td>
<td>993 (10)</td>
<td>1.7 (.8, 3.6)</td>
<td>1.9 (.9, 4.0)</td>
</tr>
<tr>
<td>β-Lactamase inhibitor combinations</td>
<td>120 (50)</td>
<td>3013 (30)</td>
<td>2.4 (1.6, 3.7)</td>
<td>2.3 (1.5, 3.5)</td>
</tr>
<tr>
<td>Quinolones</td>
<td>132 (55)</td>
<td>3471 (35)</td>
<td>4.5 (3.1, 6.5)</td>
<td>4.0 (2.7, 5.9)</td>
</tr>
<tr>
<td>Sulfas</td>
<td>33 (14)</td>
<td>1158 (12)</td>
<td>1.8 (1.0, 3.0)</td>
<td>1.9 (1.1, 3.4)</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>120 (50)</td>
<td>2741 (28)</td>
<td>2.6 (1.7, 3.9)</td>
<td>2.6 (1.7, 4.0)</td>
</tr>
<tr>
<td>Miscellaneous&lt;sup&gt;h&lt;/sup&gt;</td>
<td>31 (13)</td>
<td>772 (8)</td>
<td>1.4 (.7, 2.7)</td>
<td>1.3 (.7, 2.6)</td>
</tr>
</tbody>
</table>
When to Give Antibiotics: Uncatheterized Patients

Positive urine culture

• $\geq 10^5$ cfu/mL

Symptom criteria

• Acute dysuria --OR--
• Fever $+$ $\geq 1$ of following (new or worsening from baseline):
  • Urinary urgency
  • Frequency
  • Suprapubic pain
  • Gross hematuria
  • Costovertebral angle tenderness
  • Urinary incontinence

**New onset delirium is NOT a symptomatic criterion**

When to Give Antibiotics: Indwelling Catheter

Positive urine culture

- $\geq 10^5$ cfu/mL

Symptom criteria

- At least 1 of following (new or worsening from baseline):
  - Fever
  - New costovertebral tenderness
  - Rigors
  - New onset delirium not attributable to another cause

Definitions

- **Uncomplicated UTI**: infection in structurally/functionally normal urinary tract

- **Complicated UTI**: infection + structural/functional abnormality of urinary tract
  - Indwelling catheter, stent, or nephrostomy tube
  - Neurogenic bladder
  - Urinary tract obstruction
  - Recent urinary tract instrumentation
  - Kidney transplant
  - Immunosuppression
  - Hospital-acquired infection
  - Renal failure
  - Diabetes
Definitions

- **Lower UTI**: UTI without involvement of the kidneys
  - Can be complicated or uncomplicated

- **Upper UTI (Pyelonephritis)**: Infection of the kidney(s)
  - Signs/symptoms:
    - Flank pain
    - Fever
EMPIRIC THERAPY
**Severely Ill Patients**

- High fever, shaking chills, hypotension, etc.
- Requires IV antibiotics

<table>
<thead>
<tr>
<th>Agent</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1st line</strong> Ceftriaxone</td>
<td>• Can be used safely in patients with mild penicillin allergy, cross-reactivity very low</td>
</tr>
</tbody>
</table>
| **2nd line** Gentamicin | • ONLY in patients who need parenteral therapy and have severe IgE mediated penicillin allergy  
  • Significant nephrotoxicity/ototoxicity concerns |
## Lower UTI – Females

<table>
<thead>
<tr>
<th>1st line</th>
<th>Agent</th>
<th>Notes</th>
</tr>
</thead>
</table>
|          | Nitrofurantoin | • Most active agent against E. coli (preferred empiric agent if CrCl > 30 mL/min)  
|          |              | • Avoid if CrCl < 30 mL/min or if systemic signs of infection/suspicion of pyelonephritis  
|          |              | • Does not cover Proteus                                               |
|          | TMP-SMX      | • Drug-drug interactions with warfarin                                
|          |              | • Renal dose adjustments, avoid if CrCl < 15 mL/min                   |
| 2nd line | Cephalexin   | • Active against E. coli, Proteus, and Klebsiella                     |

**Fluoroquinolones should be avoided for empiric treatment of UTIs**
## Lower UTI – Men

<table>
<thead>
<tr>
<th>Agent</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1st line</strong></td>
<td>TMP-SMX</td>
</tr>
<tr>
<td></td>
<td>• Drug-drug interactions with warfarin</td>
</tr>
<tr>
<td></td>
<td>• Renal dose adjustments, avoid if CrCl &lt; 15 mL/min</td>
</tr>
<tr>
<td><strong>2nd line</strong></td>
<td>Cephalexin</td>
</tr>
<tr>
<td></td>
<td>• Active against <em>E. coli, Proteus, and Klebsiella</em></td>
</tr>
</tbody>
</table>

- UTIs in males are always considered complicated
- NOTE: Nitrofurantoin not included
  - Men have higher risk of prostatitis/pyelonephritis, nitrofurantoin does not achieve adequate tissue concentrations

**Fluoroquinolones should be avoided for empiric treatment of UTIs**
# Upper UTI/Pyelonephritis

<table>
<thead>
<tr>
<th>Agent</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1st line</strong></td>
<td>• Patient should receive 1 dose of IV ceftriaxone prior to starting oral therapy</td>
</tr>
<tr>
<td>TMP-SMX</td>
<td></td>
</tr>
<tr>
<td><strong>2nd line</strong></td>
<td>• If patient unable to tolerate Bactrim</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td></td>
</tr>
<tr>
<td><strong>3rd line</strong></td>
<td>• Data suggests that oral beta-lactams are inferior to Bactrim or fluoroquinolones for pyelonephritis</td>
</tr>
<tr>
<td>Beta-lactams</td>
<td>• Initial dose of IV ceftriaxone and longer treatment duration of 10-14 days are recommended</td>
</tr>
</tbody>
</table>

- IDSA guidelines recommend fluoroquinolones over TMP-SMX for pyelonephritis
  - This is based on susceptibility, **not** penetration into kidneys
  - Per St. Ann’s antibiogram, TMP-SMX is preferred for this indication
Streamlined Therapy

- Refers to antimicrobial selection *after* organism identification but *before* susceptibility results

- Select antimicrobial with best susceptibility results per antibiogram

<table>
<thead>
<tr>
<th>Organism</th>
<th>Recommended antimicrobials</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Candida</em></td>
<td>Usually responds to replacement of urinary catheter without antifungal therapy</td>
</tr>
<tr>
<td><em>Citrobacter</em></td>
<td>Nitrofurantoin, TMP-SMX</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>Nitrofurantoin, TMP-SMX</td>
</tr>
<tr>
<td><em>Enterobacter</em></td>
<td>TMP-SMX, ciprofloxacin</td>
</tr>
<tr>
<td><em>Enterococcus</em></td>
<td>Nitrofurantoin, amoxicillin</td>
</tr>
<tr>
<td><em>Klebsiella</em></td>
<td>TMP-SMX, cephalexin</td>
</tr>
<tr>
<td><em>Proteus</em></td>
<td>TMP-SMX, cephalexin</td>
</tr>
<tr>
<td><em>Pseudomonas</em></td>
<td>Ciprofloxacin</td>
</tr>
</tbody>
</table>
Targeted Therapy

- Refers to antimicrobial therapy after susceptibility results are completed

- Select most narrow agent to which organism is susceptible

- Previous preferred agents are still preferred if organism is susceptible

- Fluoroquinolones should be avoided for uncomplicated cystitis unless there are no other options
Duration of Therapy

- **Uncomplicated cystitis:**
  - Bactrim or fluoroquinolones: 3 days
  - Other agents: 5 days
  - Candida: 14 days

- **Complicated UTI or pyelonephritis:**
  - 7 days if patient improves rapidly
  - 10-14 days if patient has delayed response

Gupta K et al. *Clin Infect Dis* 2011;52:e103-20
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Renal adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amoxicillin</td>
<td>500mg TID</td>
<td>CrCl 10-50 mL/min: 500mg BID</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CrCl &lt; 10 mL/min: 500mg once daily</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>1g q24h</td>
<td>None</td>
</tr>
<tr>
<td>Cefpodoxime</td>
<td>100mg BID (uncomplicated cystitis)</td>
<td>CrCl &lt; 30 mL/min: Administer once daily</td>
</tr>
<tr>
<td></td>
<td>200mg BID (pyelonephritis)</td>
<td></td>
</tr>
<tr>
<td>Cephalexin</td>
<td>500mg BID (uncomplicated)</td>
<td>CrCl 10-50 mL/min: max dose 500mg TID</td>
</tr>
<tr>
<td></td>
<td>500mg QID (complicated)</td>
<td>CrCl &lt; 10 mL/min: 500mg once daily</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>250mg BID (uncomplicated cystitis)</td>
<td>CrCl &lt; 30 mL/min: Administer once daily</td>
</tr>
<tr>
<td></td>
<td>500mg BID (pyelonephritis)</td>
<td></td>
</tr>
<tr>
<td>Doxycycline</td>
<td>100mg BID</td>
<td>None</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>200mg once daily</td>
<td>CrCl &lt; 50 mL/min: 100mg once daily</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>≤ 60kg: 60mg IM q24h</td>
<td>CrCl &lt; 30 mL/min: use caution, may need prolonged dosing intervals</td>
</tr>
<tr>
<td></td>
<td>61-80kg: 80mg IM q24h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥81kg: 100-120mg IM q24h</td>
<td></td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>250mg once daily</td>
<td>None</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>100mg BID</td>
<td>CrCl &lt; 30 mL/min: avoid</td>
</tr>
<tr>
<td>TMP-SMX</td>
<td>1 DS tab (800-160mg) BID</td>
<td>CrCl 15-30 mL/min: 1 DS tab once daily</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CrCl &lt; 15 mL/min: avoid</td>
</tr>
</tbody>
</table>
Safety of nitrofurantoin and trimethoprim-sulfamethoxazole for UTIs

Jonathan Seah

PGY-2 Infectious Diseases Pharmacy Resident
Objectives

1. Describe evidence for the use of lower CrCl cut-off for nitrofurantoin

2. Describe the risks for nitrofurantoin-related pulmonary toxicity

3. Summarize the evidence for hyperkalemia and sudden death with trimethoprim-sulfamethoxazole (co-trimoxazole)
Nitrofurantoin
(1 - [(5-nitrofurfurylidene) amino] hydantoin)
Formulation of Macrobid

- 25% macrocrystalline $\rightarrow$ slower dissolution and absorption
- Remaining nitrofurantoin monohydrate $\rightarrow$ forms a gel in GI tract that releases drug over time

**Pharmacokinetics**

- Good bioavailability
- Peak serum levels are low; highly soluble in the urine
- High levels not reached in renal parenchyma i.e. not for pyelonephritis

**Pharmacodynamics**

- Bactericidal in urine at therapeutic doses
- Does not drive cross-resistance with sulfonamides and other antibiotics
CONCERNS

1. Lack of efficacy when renally impaired
   - Contraindicated when CrCl < 60mL/min

2. Risk for pulmonary toxicity
   - Acute, sub-acute or chronic pulmonary reactions reported
   - Chronic reactions occur rarely and generally on long term therapy

3. Other severe adverse drug effects
   - Peripheral neuropathy, hepatotoxicity, hematologic disorders
Revised Beers criteria 2012

Rationale

Potential for **pulmonary toxicity**; safer alternatives available

**Lack of efficacy** in patients with CrCl < 60 mL/min due to inadequate drug concentration in the urine

**Recommendation** (strong)

Avoid for long-term suppression; avoid in patients with CrCl < 60 mL/min
Is nitrofurantoin contraindicated when CrCl <60mL/min?

CrCl cutoff changed for Macrobid & Macrovantin in 2003

Oplinger et al reviewed evidence for nitrofurantoin use in renal impairment

- Reported 4 studies that related nitrofurantoin urine levels and CrCl
- Studies were from 1958-1971
1. Small sample sizes
2. CrCl not well defined
3. Some single dose studies
4. Older formulations with poorer bioavailability
5. Most lack clinical outcomes

Review of nitrofurantoin in renal impairment

- Retrospective chart review
- Treated for suspected UTI between 2004 to 2008

Aim

Compare efficacy and safety of nitrofurantoin for GFR $\leq$ 50mL/min (impaired) vs. $>50$mL/min (control)

Primary outcome

Cure – clinical or microbiological

Follow up for 14 days
Results

Included 356 patients

Mean age: 73 years in control; 86 years in impaired renal function group

About 1/3 with renal impairment, mean CrCl 40 mL/min (range 15-50)

- Similar cure rates between the 2 GFR groups (impaired 71% vs. 78% control)

- Similar adverse events – 7-8% with GI upset or headache

→ Suggests that nitrofurantoin is effective and safe in renal impairment

- Not many with severe renal impairment in this study
Pulmonary toxicity

Swedish analysis of 921 adverse reactions to nitrofurantoin (from 1966-1976)

- Acute pulmonary reactions (43%) and allergic reactions (42%)
- These were mainly described as hypersensitivity reactions
- **Chronic pulmonary reactions** (interstitial pneumonitis) affected older patients (median age 68 years), *often after prolonged treatment with relatively small doses*, n=49 (~5%)
- Acute reactions do not predispose to chronic ones

Requires early recognition of the reactions and prompt withdrawal
Severe adverse events

Overall incidences of severe adverse events are very low: <0.001%

Table IV. Worldwide adverse drug reaction data for nitrofurantoin (reproduced from D’Arcy, [47] with permission)

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Treatment courses 121.4 million</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>total no.</td>
</tr>
<tr>
<td>Pulmonary</td>
<td></td>
</tr>
<tr>
<td>acute</td>
<td>1138</td>
</tr>
<tr>
<td>subacute</td>
<td>22</td>
</tr>
<tr>
<td>chronic</td>
<td>281</td>
</tr>
<tr>
<td>miscellaneous</td>
<td>283</td>
</tr>
<tr>
<td>Hepatic</td>
<td>312</td>
</tr>
<tr>
<td>Neurological</td>
<td>847</td>
</tr>
<tr>
<td>Haematological</td>
<td>500</td>
</tr>
</tbody>
</table>
Summary

Nitrofurantoin remains effective for treatment of cystitis
- Can be used even in moderate renal impairment
- Avoid in severe renal impairment

Major adverse events are rare, including pulmonary toxicity
- Chronic pulmonary toxicity associated with prolonged use (prophylaxis)
- Shorter durations (e.g. 5 days for cystitis) are safer
TRIMETHOPRIM-SULFAMETHOXAZOLE (CO-TRIMOXAZOLE)
Co-trimoxazole (Bactrim)

- Annually, about 20 million prescriptions in the US
- Commonly used for UTIs, skin & soft tissue infections (with activity against MRSA) and also as prophylaxis against *Pneumocystis jiroveci* pneumonia (PCP)
- Dose varies according to indication

**Concerns**

- Allergies
- Blood disorders
- Hyperkalemia
- Use in renal impairment

Bactrim & hyperkalemia

Mechanism of action

Trimethoprim (TMP)

- Structural and pharmacologic similarities to amiloride, a potassium-sparing diuretic

- At usual doses (80-160mg BID), TMP blocks sodium channel in distal nephron → impaired renal excretion of potassium by 40%
### Summary of hyperkalemia studies

<table>
<thead>
<tr>
<th>Concomitant medications</th>
<th>Adj OR for hyperkalemia-associated hospitalizations</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE-I or ARB</td>
<td>6.7; 95% CI 4.5-10</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>12.4, 95% CI 7.1 to 21.6</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>5.1 (for Bactrim vs. amoxicillin)</td>
</tr>
</tbody>
</table>

### Study limitations
- Based on administrative data
- No direct access to serum potassium levels, renal function or medication adherence
- No indication if dose adjusted for renal impairment

Bactrim & hyperkalemia and AKI– Dose response

Design

- Retrospective chart review

Results

- Included 6162 patients
- Mean antibiotic duration was 10.4 days

- More hyperkalemia (3% vs. 1%) or AKI (2% vs. 0.7%) with high-dose Bactrim (>5mg/kg/day trimethoprim)
- High-dose Bactrim was also independently associated with hyperkalemia & AKI in multivariate analyses
Bactrim and sudden death

Aim

Determine if Bactrim co-prescribed with an ACE-I or ARB was linked to sudden death

Design

- Population based nested case-control study; Apr 1994-Jan 2012 (18 years)
- Elderly on chronic ACE-I or ARB

Case: Sudden death within 7 days of receiving outpatient antibiotics

Excluded those who received other antibiotics in 14 days preceding

Bactrim and sudden death

Results

- 1027 deaths within 7 days of antibiotics, matched to 3733 controls

Compared to amoxicillin,

**Bactrim linked to ↑ risk of sudden death** (adj OR 1.38, 95% CI 1.09-1.76)

- Equals about 3 sudden deaths within 14 days with Bactrim, compared with one with amoxicillin, per 1000 prescriptions dispensed

- **Ciprofloxacin also linked** (adj OR 1.29, 1.03-1.62)
### Guidelines recommendation

#### Lower UTI – women (complicated or uncomplicated)

<table>
<thead>
<tr>
<th>Agent</th>
<th>Notes</th>
</tr>
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<tbody>
<tr>
<td><strong>1st line</strong></td>
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</table>
| Nitrofurantoin| - Most active agent against E. coli  
               - Avoid if CrCl < 30 mL/min or if systemic signs of infection/suspicion of pyelonephritis  
               - Does not cover Proteus                                                                  |
| TMP-SMX       | - Drug-drug interactions with warfarin  
               - Renal dose adjustments, avoid if CrCl <15mL/min                                        |
| **2nd line**  |                                                                                                 |
| Cephalexin    | - Active against E. coli, Proteus, and Klebsiella                                                |

#### Lower UTI – men (always considered complicated)

<table>
<thead>
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| TMP-SMX       | - Drug-drug interactions with warfarin  
               - Renal dose adjustments, avoid if CrCl <15mL/min                                        |
| **2nd line**  |                                                                                                 |
| Cephalexin    | - Active against E. coli, Proteus, and Klebsiella                                                |
Hence, for Bactrim

- ↑ risk of hyperkalemia, especially with concomitant ACE-I, ARB and spironolactone
- Risk ↑ with higher doses of Bactrim
- Associated with sudden death; but ciprofloxacin was similarly linked

→ Used with caution in certain patient populations, and dose adjust appropriately
To sum up...

Nitrofurantoin and Bactrim are recommended antibiotics for cystitis. They have toxicities that can be reduced by:

1. Avoiding certain patient populations
2. Using appropriate doses and for short durations
3. Appropriate monitoring
Medicine of the Highest Order