Urinary Tract Infections: Are Our Drugs Going Down the Drain?

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Disclosure Statement

I have no financial interest, arrangement, or affiliation that would constitute a conflict of interest.
Learning Objectives

- Identify common mechanisms of resistance in organisms associated with urinary tract infections
- Discuss factors that can decrease urinary excretion of antimicrobial agents
- Evaluate potential use of new antimicrobial agents in patients with urinary tract infections

Urinary Tract Infections

- New national guideline statements in the past year
  - Infectious Diseases Society of America (IDSA)
    - Complicated UTI (Clinical Infectious Diseases 2010;50:625-63)
    - Uncomplicated UTI to be updated later in 2010?
  - Healthcare Infection Control Practices Advisory Committee (HICPAC)
    - Prevention of catheter-associated urinary tract infections 2009
*E. coli* Antimicrobial Resistance Rates

- The Surveillance Network (TSN) Database – USA
  - 286,187 urine *E. coli* isolates from outpatient women between 1995 and 2001

  - Ampicillin resistant: 36 – 37% per year
  - SMX/TMP resistant: 15 – 17% per year
  - Ciprofloxacin resistant: 0.7 – 2.5% per year (stepwise ↑)
  - Nitrofurantoin resistant: 0.4 – 0.8% per year

**E. coli Antimicrobial Resistance Rates**

![Graph showing antimicrobial resistance rates for E. coli isolates.](image)


**NAUTICA-1**

- **North American Urinary Tract Infection Collaborative Alliance - 1**

  - 1990 outpatient midstream urine isolates collected between April 2003 – June 2004 from
    - 30 United States Medical Centers
    - 11 Canadian Medical Centers

NAUTICA-2

- North American Urinary Tract Infection Collaborative Alliance - 2
  - 1142 outpatient midstream urine *E. coli* isolates collected between April 2003 – June 2004 from
    - 30 United States Medical Centers
    - 10 Canadian Medical Centers


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NAUTICA-1 (US data only)

- *Escherichia coli* 57.6%
- *Proteus mirabilis* 5.5%
- *Enterococcus* species 6.2%
- *Klebsiella* species 14.1%
- Other 16.6%

NAUTICA-1 (US data only)

Percent Sensitive

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>All Organisms</th>
<th>Escherichia coli</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>40%</td>
<td>60%</td>
</tr>
<tr>
<td>SMX/TMP</td>
<td>80%</td>
<td>100%</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>60%</td>
<td>80%</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>80%</td>
<td>100%</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>80%</td>
<td>100%</td>
</tr>
</tbody>
</table>


NAUTICA-2 (US data only)

18% of *E. coli* isolates resistant to ≥ 2 of the 4 antibiotic classes

NAUTICA-1 and NAUTICA-2

- Mountain Region (including Arizona)

<table>
<thead>
<tr>
<th>Therapy</th>
<th>All Organisms (% resistant)</th>
<th>E. coli (% resistant)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>55.3%</td>
<td>37.1%</td>
</tr>
<tr>
<td>SMX/TMP</td>
<td>25.3%</td>
<td>15.4%</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>6.0%</td>
<td>1.4%</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>4.7%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>4.0%</td>
<td>4.2%</td>
</tr>
</tbody>
</table>


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E. coli Antimicrobial Resistance Rates

- 10,289 urine E. coli isolates evaluated between 2005 and 2007 at a US health system clinical microbiology laboratory
  - 176 urine E. coli isolates from college women
    - 67.6% patients had a history of previous UTI

E. coli Antimicrobial Resistance Rates

<table>
<thead>
<tr>
<th></th>
<th>History of UTI (n = 119)</th>
<th>No Previous History of UTI (n = 57)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin</td>
<td>34.5%</td>
<td>45.6%</td>
</tr>
<tr>
<td>SMX/TMP</td>
<td>26.9%</td>
<td>38.6%</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>11.8%</td>
<td>1.8%</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>


New E. coli Mechanism of Resistance

- E. coli sequence type ST131 (O25:H4)
  - CTX-M-15 extended-spectrum beta-lactamase
    - Significant international source of MDR E. coli
      - Rates increased in Europe significantly between 2002 and 2008
      - Frequently isolated in Canada

New *E. coli* Mechanism of Resistance

- *E. coli* sequence type ST131 (O25:H4)
  - Usually fluoroquinolone resistant
    - Predominant cause of fluoroquinolone-resistant *E. coli* in Canada and Europe

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*E. coli* (2007) - SENTRY/MYSTIC

- From 2007 SENTRY and MYSTIC surveillance programs
  - 1596 *E. coli* isolates from hospitalized patients from 33 US medical centers
    - 127 of 1596 systematically selected isolates evaluated for *bla* \(_{CTX-M-15}\)
    - 34 of 127 isolated determined to be *bla* \(_{CTX-M-15}\)

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**E. coli (2007) - SENTRY/MYSTIC**

- $\text{bla}_{\text{CXT-M-15}}$ genotype \textit{E. coli}
  
  - ~ 17% of 1596 isolates
  
  - ~ 44% of multi-drug resistant isolates

- 52% of the 33 US medical centers evaluated had $\text{bla}_{\text{CXT-M-15}}$ \textit{E. coli}

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**E. coli (2007) – SENTRY/MYSTIC**

<table>
<thead>
<tr>
<th></th>
<th>\textit{E. coli} (n = 1596)</th>
<th>\textit{E. coli}, CXT-M-15 (n = 34)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMX/TMP Resistant</td>
<td>25.4%</td>
<td>65%</td>
</tr>
<tr>
<td>Ciprofloxacin Resistant</td>
<td>25.4%</td>
<td>100%</td>
</tr>
<tr>
<td>SMX/TMP + Ciprofloxacin Resistant</td>
<td>14.5%</td>
<td>65%</td>
</tr>
<tr>
<td>Aminoglycoside Resistant</td>
<td>12%</td>
<td>79%</td>
</tr>
<tr>
<td>(gentamycin and/or tobramycin)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extended-spectrum cephalosporin Resistant</td>
<td>5.4%</td>
<td>100%</td>
</tr>
<tr>
<td>(cefepime, ceftriaxone, and/or ceftazidime)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Table 1 and Table 3 in Johnson JR, et al. *Clinical Infectious Disease*. 2010;51:286-94.
**E. coli (2007) - SENTRY/MYSTIC**

- \( \text{bla}_{\text{CXT-M-15}} \) genotype *E. coli*
  - Likely main cause of recent increases in *E. coli* antimicrobial resistance especially increased fluoroquinolone resistance
  - Virulence Profile \( \rightarrow \) more virulent

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**New Mechanism of Resistance**

- Carbapenem-Resistant or Carbapenemase-producing *Enterobacteriaceae* species
  - Example mechanism of resistance
    - Carbapenemase enzyme: \( \text{bla}_{\text{kpc}} \)
  - Carbapenem-resistant *Klebsiella pneumonia* (CRKP) health-care associated infections in US
    - 1% of isolates in 2001
    - 8% of isolates in 2008

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New *E. coli* Mechanism of Resistance

- Transfer of carbapenem-resistant plasmid from *K. pneumonia* to *E. coli*
  - First isolate identified in 2008 in Israel

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*E. coli* Antimicrobial Resistance Rates

- Institutional specific surveillance studies have found:
  - Urinary isolate resistance rates that exceed the national averages by 2 to 4-fold
  - Antibiogram resistance rates that over-estimate urine isolate resistance rates

- Due to significant differences in regional resistance patterns, it is often difficult to apply national data to a specific medical center
Minimum Inhibitory Concentrations

- Updated in January 2010

- Changes include decreases in *Enterobacteriaceae* species’ MIC cephalosporin and carbapenem breakpoint values


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Minimum Inhibitory Concentrations

- Microbiology laboratories can use:
  - 2009 version (FDA approved)
  - 2010 version (CLSI recommendations)

- How can you tell which version is being used?
### 2009 - Minimum Inhibitory Concentrations

<table>
<thead>
<tr>
<th>Enterobacteriaceae Group*</th>
<th>MIC Sensitive Breakpoint (mcg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefazolin</td>
<td>$\leq 8$</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>$\leq 8$</td>
</tr>
<tr>
<td>Cefepime</td>
<td>$\leq 8$</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>$\leq 8$</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>$\leq 2$</td>
</tr>
<tr>
<td>Meropenem &amp; Imipenem</td>
<td>$\leq 4$</td>
</tr>
<tr>
<td>Gentamicin &amp; Tobramycin</td>
<td>$\leq 4$</td>
</tr>
<tr>
<td>Amikacin</td>
<td>$\leq 16$</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>$\leq 1$</td>
</tr>
<tr>
<td>TMP/ SMX</td>
<td>$\leq 2/38$</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>$\leq 32$</td>
</tr>
<tr>
<td>Minocycline</td>
<td>$\leq 4$</td>
</tr>
</tbody>
</table>

*Enterobacteriaceae group include Citrobacter spp., Enterobacter spp., Escherichia coli, Klebsiella spp., Salmonella spp., Serratia spp., and Shigella spp.


### 2010 - Minimum Inhibitory Concentrations

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<th>MIC Sensitive Breakpoint (mcg/ml)</th>
</tr>
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<tr>
<td>Cefazolin</td>
<td>$\leq 1$</td>
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<tr>
<td>Ceftriaxone</td>
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</tr>
<tr>
<td>Cefepime</td>
<td>$\leq 8$</td>
</tr>
<tr>
<td>Aztreonam</td>
<td>$\leq 4$</td>
</tr>
<tr>
<td>Ertapenem</td>
<td>$\leq 0.25$</td>
</tr>
<tr>
<td>Meropenem &amp; Imipenem</td>
<td>$\leq 1$</td>
</tr>
<tr>
<td>Gentamicin &amp; Tobramycin</td>
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*Enterobacteriaceae group include Citrobacter spp., Enterobacter spp., Escherichia coli, Klebsiella spp., Salmonella spp., Serratia spp., and Shigella spp.

Resistance Issues

- Does *in vitro* testing predict outcome in UTI?
  - Urine drug concentration levels
    - MIC versus urine concentration
    - May depend on renal function

Pharmacokinetic Parameters

ANTIMICROBIAL URINE EXCRETION
% Renal Excretion of Unchanged Drug

- Percent excreted in urine depends on glomerular filtration and net tubular secretion of drug
  
  - Urine concentration (mcg/ml) depends on volume of urine produced and amount of drug excreted over time
  
  - Most reported urine excreted % from a 24 or 48 hour urine collection period

Urinary Excretion

- Drug urine concentrations
  
  - Unchanged drug
  
  - Metabolites
    - Active
    - Non-active
% Renal Excretion of Unchanged Drug

<table>
<thead>
<tr>
<th>Drug</th>
<th>% Excreted (normal renal function)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ciprofloxacin (oral)</td>
<td>30 – 50%</td>
</tr>
<tr>
<td>Levofloxacine (oral)</td>
<td>61 – 86%</td>
</tr>
<tr>
<td>Moxifloxacine (oral)</td>
<td>10 – 20%</td>
</tr>
</tbody>
</table>


% Renal Excretion of Unchanged Drug

<table>
<thead>
<tr>
<th>Drug</th>
<th>% Excreted (normal renal function)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amikacin</td>
<td>&gt; 90%</td>
</tr>
<tr>
<td>Gentamicin</td>
<td>&gt; 90%</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>&gt; 90%</td>
</tr>
</tbody>
</table>

% Renal Excretion of Unchanged Drug

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<thead>
<tr>
<th>Drug</th>
<th>% Excreted (normal renal function)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMX (oral)</td>
<td>10 – 30%</td>
</tr>
<tr>
<td>TMP (oral)</td>
<td>50 – 75%</td>
</tr>
<tr>
<td>Nitrofurantoin</td>
<td>27 – 56%</td>
</tr>
</tbody>
</table>


% Renal Excretion of Unchanged Drug

<table>
<thead>
<tr>
<th>Drug</th>
<th>% Excreted (normal renal function)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampicillin (oral)</td>
<td>75 – 92%</td>
</tr>
<tr>
<td>Cephalexin (oral)</td>
<td>91 – 100%</td>
</tr>
</tbody>
</table>

Urinary Excretion

• 100 mg of drug U is administered to a patient with an estimated creatinine clearance of 120 ml/min
  ○ Approximately 20% is excreted unchanged in the urine
  ○ What is the patient’s urine concentration?

20 mg excreted in the urine in a 24 hour period
Assume patient produced 2000 ml of urine in a 24 hour period
Therefore, average urine concentration is 10 mcg/ml
Urinary Excretion

- 100 mg of drug U is administered to a patient with an estimated creatinine clearance of 0 ml/min (no urine output)
  - Approximately 20% is excreted in the urine
  - What is the patient’s urine concentration?

New Antimicrobial Therapy

... FOR URINARY TRACT INFECTIONS?
Linezolid

- Potential use include: VRE, MRSA
- Urinary excretion
  - ~30% unchanged within 24 hours


Daptomycin

- Potential use include: VRE, MRSA
- Urinary excretion
  - <68% unchanged within 24 hours

Telavancin

- Potential use include: VRE, MRSA

- Randomized, double-blind, parallel-group, gender stratified study (2008)
  - Urinary excretion:
    - 64 - 76% unchanged within 24 hours


Tigecycline

- Potential use include: MDR E. coli

- Urinary excretion
  - 14 - 33% unchanged within 24 hours

ESBL-producing *E. coli*

- A recent IDSA report stated that:
  - ESBL-producing *E. coli* and *Klebsiella* spp. are among the six drug resistant microbes for which new therapies urgently needed


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Cost of UTI
**UTI Health-Care Costs**

- Systematic review of 70 research published from January 2001 to June 2004
  
  - Mean attributed cost of UTI: $1,006 (S.D. $503)
    - Minimum: $650 per episode
    - Maximum: $1361 per episode


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**E. coli Uncomplicated Cystitis**

- 6 - 8 million episodes of uncomplicated cystitis due to *E. coli* in premenopausal women in the US per year (130-175 million worldwide per year)

- $1 billion dollars direct US health-care costs per year
  
  - Average of 2 restricted-activity days plus average of 6 symptom days (? indirect cost)

**E. coli Pyelonephritis**

- 250,000 episodes of pyelonephritis due to *E. coli* in the US per year (estimated 5.4 million worldwide per year)

- 100,000 episodes require hospitalization

- $175 million dollars direct US health care costs per year


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**Catheter-Associated UTI**

- 1 - 1.5 million episodes of catheter-associated UTI in the US per year

- $0.6 – 1.1 billion dollars direct US health care costs per year

  - $170 – 350 million dollars due to *E. coli* associated infections

UTI Health-Care Preventable Costs

- Preventable UTI
  - 17 – 69% UTI episodes are considered preventable
  - If these UTIs prevented, it is estimated that
    - 2000-9000 deaths per year in US will be avoided
    - $ 0.1 – 2 billion health-care costs avoided (in 2009 dollars)

UTI Emergency Department Visits

- 32,987 emergency room visits for UTIs in Arizona in 2008
  - 17% age < 15 years old
  - 9% age 15-19 years old
  - 38% age 20-44 years old
  - 16% age 45-64 years old
  - 19% age >65 years old
Learning Assessment

• True / False

The majority of UTIs are caused by an organism that is usually susceptible to SMX/TMP, nitrofurantoin, or ciprofloxacin

Learning Assessment

• True / False

A patient’s estimated renal function should be considered when recommending UTI therapy
Learning Assessment

- True / False

Only antimicrobial agents with > 60% active drug urinary excretion should be considered for UTI therapy

Questions ?