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

KATHRYN R. MATTHIAS, PHARM.D., BCPS
2010 ARIZONA PHARMACY ALLIANCE 6TH ANNUAL MEETING
JULY 18, 2010

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

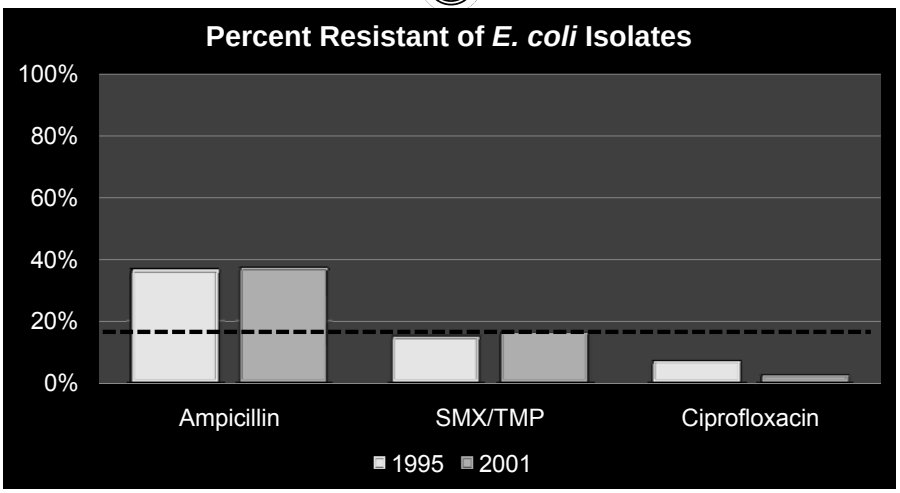
Antimicrobial Resistance

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

Karlowsky JA, et al. *Antimicrobial Agents and Chemotherapy*. 2002;46(8):2540-5.

E. coli Antimicrobial Resistance Rates



Karlowsky JA, et al. *Antimicrobial Agents and Chemotherapy*. 2002; 46: 2540-5.

NAUTICA-1

- **N**orth **A**merican **U**rinary **T**ract **I**nfection **C**ollaborative **A**lliance - 1
  - 1990 outpatient midstream urine isolates collected between April 2003 – June 2004 from
    - **30 United States Medical Centers**
    - **11 Canadian Medical Centers**

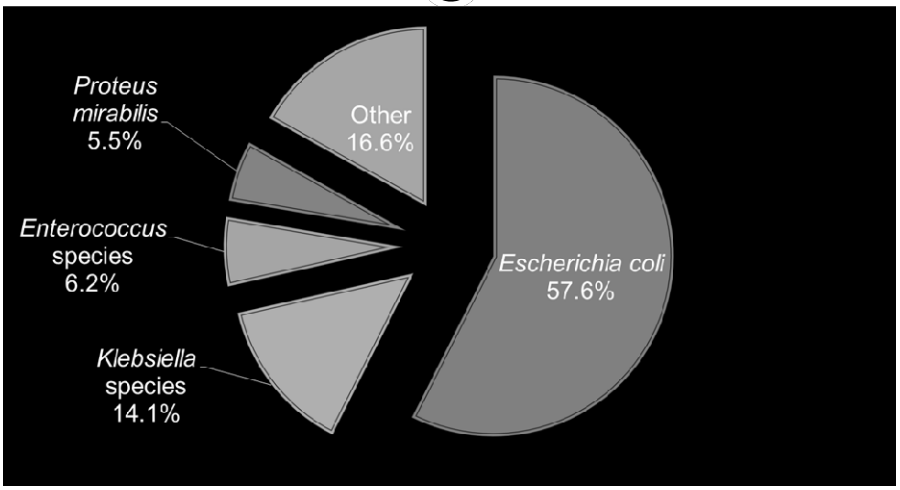
Zhanel GG, et al. *International Journal of Antimicrobial Agents*. 2005; 26: 380-8.

NAUTICA-2

- **N**orth **A**merican **U**rinary **T**ract **I**nfection **C**ollaborative **A**lliance - 2
  - 1142 outpatient midstream urine *E. coli* isolates collected between April 2003 – June 2004 from
    - **30 United States Medical Centers**
    - **10 Canadian Medical Centers**

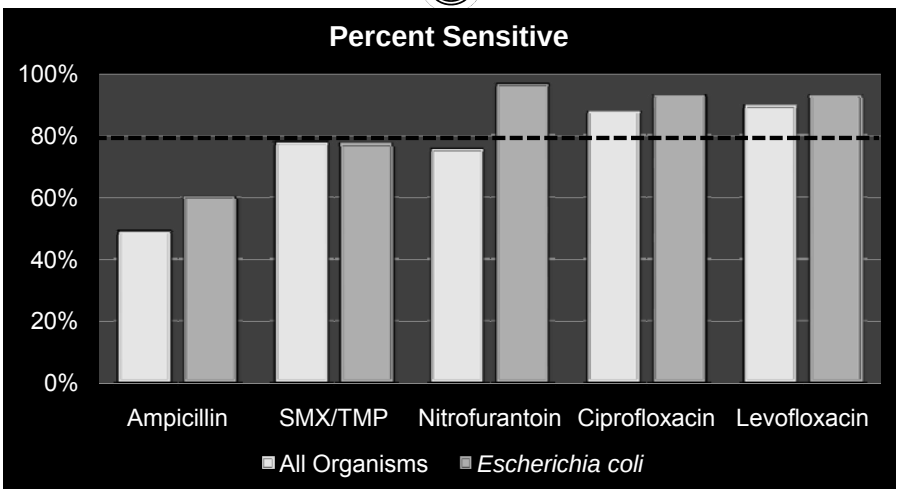
Zhanel GG, et al. *International Journal of Antimicrobial Agents*. 2006; 27: 468-75.

NAUTICA-1 (US data only)



Zhanel GG, et al. *International Journal of Antimicrobial Agents*. 2005; 26: 380-8.

NAUTICA-1 (US data only)



Zhanel GG, et al. *International Journal of Antimicrobial Agents*. 2005; 26: 380-8.

NAUTICA-2 (US data only)

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

Zhanel GG, et al. *International Journal of Antimicrobial Agents*. 2006; 27: 468-75.

NAUTICA-1 and NAUTICA-2

- Mountain Region (including Arizona)

Therapy	All Organisms (% resistant)	*E. coli* (% resistant)
Ampicillin	**55.3%**	**37.1%**
SMX/TMP	**25.3%**	**15.4%**
Nitrofurantoin	6.0%	1.4%
Ciprofloxacin	4.7%	4.2%
Levofloxacin	4.0%	4.2%

Zhanel GG, et al. *International Journal of Antimicrobial Agents*. 2005; 26: 380-8.
Zhanel GG, et al. *International Journal of Antimicrobial Agents*. 2006; 27: 468-75.

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

Olson RP, et al. *Antimicrobial Agents and Chemotherapy*. 2009;53(3):1285-6.

E. coli Antimicrobial Resistance Rates

	History of UTI (n = 119)	No Previous History of UTI (n = 57)
Ampicillin	34.5%	**45.6%**
SMX/TMP	26.9%	**38.6%**
Ciprofloxacin	**11.8%**	1.8%
Nitrofurantoin	0%	0%

Olson RP, et al. *Antimicrobial Agents and Chemotherapy*. 2009;53(3):1285-6.

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

Oteo J, et al. *Current Opinion in Infectious Disease.* 2010;23:320-6.

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

Johnson JR, et al. *Clinical Infectious Disease.* 2010;51:286-94.

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 $bla_{\text{CTX-M-15}}$
    - 34 of 127 isolated determined to be $bla_{\text{CTX-M-15}}$

Johnson JR, et al. *Clinical Infectious Disease.* 2010;51:286-94.

E. coli (2007) - SENTRY/MYSTIC

- *bla*$_{\text{CXT-M-15}}$ genotype *E. coli*
  - ~ 17% of 1596 isolates
  - ~ 44% of multi-drug resistant isolates
- 52% of the 33 US medical centers evaluated had *bla*$_{\text{CXT-M-15}}$ *E. coli*

Johnson JR, et al. *Clinical Infectious Disease.* 2010;51:286-94.

E. coli (2007) – SENTRY/MYSTIC

	E. coli **(n = 1596)**	***E. coli*,** **CXT-M-15** **(n = 34)**
SMX/TMP Resistant	25.4%	65%
Ciprofloxacin Resistant	25.4%	100%
SMX/TMP + Ciprofloxacin Resistant	14.5%	65%
Aminoglycoside Resistant (gentamycin and/or tobramycin)	12%	79%
Extended-spectrum cephalosporin Resistant (cefepime, ceftriaxone, and/or ceftazidime)	5.4%	100%

Adapted from Table 1 and Table 3 in Johnson JR, et al. *Clinical Infectious Disease.* 2010;51:286-94.

E. coli (2007) - SENTRY/MYSTIC

- $bla_{CXT\text{-}M\text{-}15}$ genotype *E. coli*
  - Likely main cause of recent increases in *E. coli* antimicrobial resistance especially increased fluoroquinolone resistance
  - Virulence Profile → more virulent

Johnson JR, et al. *Clinical Infectious Disease.* 2010;51:286-94.

New Mechanism of Resistance

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

MMWR. 2009;58(10):256-260.
Coque TM, et al. *Emerging Infectious Diseases.* 2008;14(2):195-200.

New *E. coli* Mechanism of Resistance

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

Goren GM, et al. *Emerging Infectious Diseases*. 2010;16(6):1014-7.

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

Boyd LB, et al. *BMC Infectious Diseases.* 2008;8. doi:10.1186/1471-2334/8/4
Miller LG, et al. *Mayo Clin Proc.* 2004;79(8):1048-54.

Minimum Inhibitory Concentrations

- Updated in January 2010
  - Changes include decreases in *Enterobacteriaceae* species' MIC cephalosporin and carbapenem breakpoint values

Reference: M100-S20 Performance Standards for Antimicrobial Susceptibility Testing; Twentieth Informational Supplement. Clinical and Laboratory Standards Institute. January 2010.

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

	Enterobacteriaceae Group*
	MIC Sensitive Breakpoint (mcg/ml)
Cefazolin	≤ 8
Ceftriaxone	≤ 8
Cefepime	≤ 8
Aztreonam	≤ 8
Ertapenem	≤ 2
Meropenem & Imipenem	≤ 4
Gentamicin & Tobramycin	≤ 4
Amikacin	≤ 16
Ciprofloxacin	≤ 1
TMP/ SMX	≤ 2/38
Nitrofurantoin	≤ 32
Minocycline	≤ 4

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

M100-S19 Performance Standards for Antimicrobial Susceptibility Testing; Nineteenth Informational Supplement. Clinical and Laboratory Standards Institute. January 2009.

2010 - Minimum Inhibitory Concentrations

	Enterobacteriaceae Group*
	MIC Sensitive Breakpoint (mcg/ml)
Cefazolin	**≤ 1**
Ceftriaxone	**≤ 1**
Cefepime	**≤ 8**
Aztreonam	**≤ 4**
Ertapenem	**≤ 0.25**
Meropenem & Imipenem	**≤ 1**
Gentamicin & Tobramycin	≤ 4
Amikacin	≤ 16
Ciprofloxacin	≤ 1
TMP/ SMX	≤ 2/ 38
Nitrofurantoin	≤ 32
Minocycline	≤ 4

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

Reference: M100-S20 Performance Standards for Antimicrobial Susceptibility Testing; Twentieth Informational Supplement. Clinical and Laboratory Standards Institute. January 2010.

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

Drug	% Excreted (normal renal function)
Ciprofloxacin (oral)	30 – 50%
Levofloxacin (oral)	61 – 86%
Moxifloxacin (oral)	10 – 20%

Micromedex® 1.0. Accessed June 22, 2010.
Gilbert DN. *Clin J Am Soc Nephrol.* 2006;1: 327-31.

% Renal Excretion of Unchanged Drug

Drug	% Excreted (normal renal function)
Amikacin	> 90%
Gentamicin	> 90%
Tobramycin	> 90%

Micromedex® 1.0. Accessed June 22, 2010.
Gilbert DN. *Clin J Am Soc Nephrol.* 2006;1: 327-31.

% Renal Excretion of Unchanged Drug

Drug	% Excreted (normal renal function)
SMX (oral) TMP (oral)	10 – 30% 50 – 75%
Nitrofurantoin	27 – 56%

Micromedex® 1.0. Accessed June 22, 2010.
Gilbert DN. *Clin J Am Soc Nephrol.* 2006;1: 327-31.

% Renal Excretion of Unchanged Drug

Drug	% Excreted (normal renal function)
Ampicillin (oral)	75 – 92%
Cephalexin (oral)	91 – 100%

Micromedix. Accessed June 22, 2010.
Gilbert DN. *Clin J Am Soc Nephrol.* 2006;1: 327-31.

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?

Urinary Excretion

- Approximately 20% of 100 mg of drug is excreted in the urine during a 24 hour period
  - 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

Micromedex® 1.0. Accessed June 22, 2010.

Daptomycin

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

Benvenuto M, et al. Antimicrob Agents Chemother 50 (10): 3245-9, 2006.

Telavancin

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

Micromedex® 1.0. Accessed June 22, 2010.
Wong SL, et al. *J Antimicrob Chemo* 2008;62(4):780-3.

Tigecycline

- Potential use include: MDR *E. coli*
- Urinary excretion
  - 14 - 33% unchanged within 24 hours

Micromedex® 1.0. Accessed June 22, 2010.

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

Talbet GH, et al. *Clinical Infectious Diseases*. 2006;42:657-68.

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

Stone PW, et al. *Am J Infect Control*. 2005;33:501-9.

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)

Russo TA, et al. *Microbes and Infection*. 2003;5:449-56.

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

Russo TA, et al. *Microbes and Infection*. 2003;5:449-56.

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

Russo TA, et al. *Microbes and Infection*. 2003;5:449-56.

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)

http://www.cdc.gov/hai/recoveryAct/PDF/Oct09/5-0130_Srinivasan_HAI_Prevention_Day1.pdf (Umschied C. Presentation at HICPAC, March 2009) accessed on June 22, 2010.

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

http://www.azdhs.gov/plan/report/ahs/ahs2008/pdf/text4c.pdf accessed June 22, 2010.

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 ?