

Urinary Tract Infections

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

Objectives

Identify how male and female anatomy contributes to the development of UTI.

Identify clinical differences between uncomplicated and complicated UTI.

Identify how age, medical history, patient complaints, & diagnostic studies can be used in the diagnosis of UTI.

Identify appropriate treatment strategies for uncomplicated, complicated, and recurrent UTI.

Identify non-pharmaceutical (behavioral) strategies for uncomplicated recurrent, and complicated UTI.

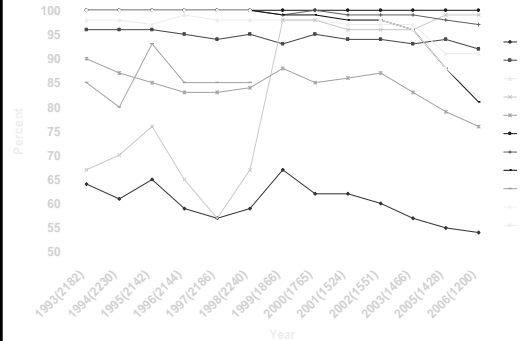
Case

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.

E. Coli



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?

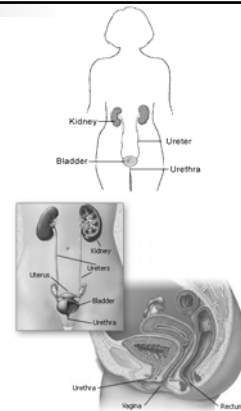
Epidemiology of UTIs in the United States

- ◆ 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

Warren JW, et al. *Clin Infect Dis*. 1999;29:745-758.
 Hooton TM, et al. *N Engl J Med*. 1996;335:488-474.
 Foxman B. *Am J Med*. 2002;113(Suppl):5S-13S.

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

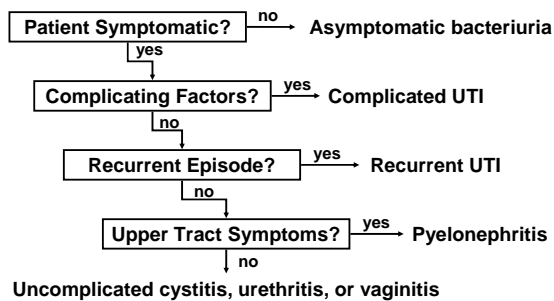
- ◆ Cystitis (approx. 30% occult pyelonephritis)
- ◆ Asymptomatic bacteriuria (ASB)
- ◆ Urethral syndrome

Clinical Characteristics

	Uncomplicated UTI	Complicated UTI	Uncomplicated Pyelonephritis
Age/Gender	Sexually active young women	Middle-age men, elderly women	All ages, more women
Etiology	Community-acquired	Nosocomial	Community-acquired
Comorbid Conditions	Healthy	Functional, metabolic, or structural abnormality	Healthy
Symptoms	Localized	Localized	Systemic
Consequences	Self-limited	Bacteremia	Bacteremia

Hooton TM, Stamm WE. *Infect Dis Clin North Amer*. 1997;11:551-581.
 Stamm WE, Hooton TM. *N Engl J Med*. 1993;329:1328-1334.

Differential Diagnosis of Bacteriuria



Orenstein R, Wong ES. *Am Fam Phys*. 1999;59:1225-1234.

Signs and Symptoms of UTI

Subjective symptoms

- ◆ Dysuria
- ◆ Urgency
- ◆ Increased frequency
- ◆ Subpubic or low back pain

Objective signs (not required for uncomplicated UTI)

- ◆ Bacteriuria (10² to ≥10⁵ colony-forming units/mL)
- ◆ Pyuria (WBC >10/mm³)

Hooton TM, Stamm WE. *Infect Dis Clin North Amer*. 1997;11:551-581.

Laboratory Diagnosis of UTI

Urinalysis

- ◆ \pm 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

Hooton TM, Stamm WE. *Infect Dis Clin North Amer.* 1997;11:551-581.
Falagas ME, Gorbach SL. *Infect Dis Clin Pract.* 1995;4:241-257.

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.

Hooton TM, et al. *N Engl J Med.* 1996;335:468-474.
Hooton TM, Stamm WE. *Infect Dis Clin North Amer.* 1997;11:551-581.

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

Hooton TM, Stamm WE. *Infect Dis Clin North Amer.* 1997;11:551-581.
Gupta, K, et al. *Ann Intern Med.* 2001;135:41-50.

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

Hooton TM, Stamm WE. *Infect Dis Clin North Amer.* 1997;11:551-581.
Stamm WE, Norrby SR. *J Infect Dis.* 2001;183(Suppl 1):S1-S4.

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%)

Gupta K, et al. *Clin Infect Dis.* 2001;33:89-94.

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

Falagas ME, Gorbach SL. *Infect Dis Clin Pract*. 1995;4:241-257.
Hooton TM. *Int J Antimicrob Agents*. 2001;17:259-268.

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

Nicolle LE. *Am J Med*. 2002;113:355-445.

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

Gupta, K, et al. *Ann Intern Med*. 2001;135:9-16.
Hooton TM. *Int J Antimicrob Agents*. 2001;17:259-268.

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.

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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)

Stamm WE, Hooton TM. *N Engl J Med.* 1993;329:1328-1334.
Falagas ME, Gorbach SL. *Infect Dis Clin Pract.* 1995;4:241-257.

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**

Stamm WE, Hooton TM. *N Engl J Med.* 1993;329:1328-1334.
McCue JD. *Infect Med.* 1999;16:533-540.
Richards MJ, et al. *Crit Care Med.* 1999;27:887-892.

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

McCue JD. *Infect Med.* 1999;16(8):533-540.

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

McCue JD. *Infect Med.* 1999;16:533-540.

Complicated UTI Etiology

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

Nicolle LE. *J Infect Dis.* 2001;183:S5-S8.

Antibiotic Options for Complicated UTIs

Parenteral (2–3 days)	Oral (7 days)
Levofloxacin	Levofloxacin
Ciprofloxacin	Ciprofloxacin
Gentamicin	TMP/SMX
Amikacin	Cephalosporin
Imipenem	Amoxicillin ± clav
Cephalosporin	
Ampicillin	
Piperacillin ± tazo	

Nicolle LE. *Drugs Aging.* 2001;18:243-254.

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*

Falagas ME, Gorbach SL. *Infect Dis Clin Pract*. 1995;4:241-257.
Hooton TM, Stamm WE. *Infect Dis Clin North Amer*. 1997;11:551-581.

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)

Hooton TM, Stamm WE. *Infect Dis Clin North Amer*. 1997;11:551-581.

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

Warren JW, et al. *Clin Infect Dis*. 1999;29:745-758.

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

Warren JW, et al. *Clin Infect Dis*. 1999;29:745-758.

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

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

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

n: 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**