Urinary Tract Infections
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Therapeutics III

Required Reading

Suggested Readings

Ability Outcome
Thinking and Decision-making. The student will identify, interpret, analyze, evaluate and synthesize information to make rational and responsible decisions to solve patient-related problems. Students will use the SOAP framework to:
Assess a patient presenting with either symptoms or chemistry suggestive of an urinary tract infection
Evaluate the appropriateness of patient-specific drug therapies, and modify therapy as needed.
Recommend appropriate therapy for urinary tract infections
Monitor therapy for resolution of infection or need for change in therapy
Educate patients and health care professionals regarding therapy and prevention of urinary tract infections

Content Questions
1. Name the most common pathogens/microorganisms responsible for complicated, uncomplicated and special population UTIs
2. Explain why certain patients are at higher risk for developing an UTI
3. Identify urinalysis results suggestive of an UTI
4. Determine whether an infection is present based on symptoms and quantitative culture results
5. Differentiate between the clinical presentation of an upper vs. a lower UTI
6. Explain the advantages and disadvantages of 3-day therapy for acute cystitis
7. Justify therapy for the treatment of a UTI, based on patient-specific and drug-specific data
8. Name and justify 3 empiric treatment regimens for acute pyelonephritis requiring hospitalization
9. Provide rationale for the selection and duration of therapy for bacterial prostatitis

10. List the risk factors and treatment options for fungal UTIs

11. Defend antimicrobial selection based on resistance data

12. Be able to defend a decision to treat bacteriuria or funguria vs. not treating
Epidemiology
- UTIs affect 1 in 3 women before the age of 24 years
- Approximately 50% of women have at least one symptomatic UTI during their lifetime
- UTIs accounted for nearly 7 million office visits and 1 million emergency department visits, resulting in 100,000 hospitalizations in 1997.
- The incidence of symptomatic urinary tract infection in adult men is very low prior to age 50.
- Catheter-associated UTI is the most common nosocomial infection, >1 million cases in hospitals and nursing homes.
- In non-institutionalized elderly, UTIs are the 2nd most common form of infection, nearly 25% of all infections

Financial and Medical Implications
- Estimated annual cost of community-acquired UTI is $1.6 billion
- Estimated annual cost for nosocomia UTI is $424-$451 million
- Source for bacteremia
- Acute Uncomplicated UTI: Fairly benign besides approximately 6 symptomatic days, recurrence, risk for upper UTI
- During Pregnancy: Increased risk of pyelonephritis, premature delivery, fetal complications and mortality, and pregnancy-induced HTN/preeclampsia, infants with low birth weights.
- Pediatrics: impaired renal function, renal scarring and end-stage renal disease

Classification
Lower Tract Infections
Cystitis (bladder)
Urethritis
Prostatitis
Epididymitis

Upper tract infections
Pyelonephritis (kidneys)

Uncomplicated
Rarely occur in men

Complicated
Infections in individuals with functional, structural or metabolic abnormalities of the urinary tract that interfere with normal flow of urine or voiding
- Male sex
- Elderly
- Indwelling catheter/recent instrumentation
- Obstruction/stone
- Prostatic hypertrophy
- Pregnancy
- Diabetes
- Immunosuppression
- Neurologic deficit
- Childhood UTI
- Recent antimicrobial use
- Symptoms for >7 days at presentation
- Hospital-acquired infection
- Presentation in an urban emergency department
**Etiology**

**Uncomplicated Infections**

*Escherichia coli*  
80% of community acquired infections

*Staphylococcus saprophyticus*  
10-15%

*Klebsiella pneumoniae*  
less common

*Proteus sp.*  
*Enterobacter*

*Enterococcus sp.*

**Complicated Infections**

*E. coli*  
< 50%

*Enterococcus faecalis*  
2\(^{\text{nd}}\) most common organism in nosocomial UTIs

*Proteus mirabilis*

*Klebsiella sp.*

*Enterobacter cloacae*

*Serratia marcescens*

*Pseudomonas aeruginosa*

*Staphylococcus aureus*

Group B streptococci

*Candida albicans*  
10% of positive cultures in tertiary care facilities

*Candida sp.* /instrumentation

Pediatrics: *E. coli*, *Proteus sp.*, *Klebsiella sp.*, *Serratia marcescens*

Elderly: *E. coli*, polymicrobial

Diabetes: *Klebsiella sp.*, group B streptococci, *Enterococcus, E. coli, Candida* (non-albicans)

Spinal Cord Injuries or Catheters: *E. coli, Pseudomonas aeruginosa, Proteus mirabilis, Candida* sp., enterococci, *S. aureus.*

HIV/AIDS: *Enterococcus* sp. are the most common

Usually organisms are more resistant or multi-organism infections are present with the presence of stones, indwelling urinary catheters or chronic renal abscesses.

**Pathophysiology**

3 Routes

a. ascending

b. hematogenous/descending

c. lymphatic
Defense Mechanisms
- Low pH
- Extremes in osmolality
- High urea concentration
- High organic acid concentration
- Prostatic secretions
- Stimulation of bladder emptying/diuresis
- Antiadherence
  - Glycosaminoglycan layer
  - Tamm-Horsfall protein
- Immunoglobulins
  - IgM, IgG and IgA

Virulence
- Ability to adhere to epithelial cells
  - Bacterial fimbriae
- Hemolysin
- Bacterial Glycocalyx
- Urease production

Risk factors for UTI development
- Female sex
- Extremes of age
  - Infants and elderly
- Obstruction (stone, BPH)
- Diabetes
- Immunosuppression
- Pregnancy
- Neurologic dysfunction
  - MS, spinal cord injury, stroke
- Renal disease
- Sexual intercourse
- Use of diaphragm or spermicide
- Antimicrobial use
- History of UTI

Why women > men?
- Short length of female urethra
- Proximity of urethra to perirectal area
- Use of spermicides and diaphragms
- Lack of prostatic fluid which has antibacterial activity

Clinical Presentation
Lower tract
- Dysuria
- Urgency
- Frequency
- Nocturia
- Suprapubic tenderness
- +/- gross hematuria
Upper tract
- Lower tract symptoms are common if ascending mechanism of upper tract infection
- Flank pain/costovertebral angle tenderness
- Abdominal pain
- Fever
- Nausea/Vomiting
- Malaise
- Increased WBC

Elderly
- fever and urinary symptoms may be absent
- May present with altered mental status, change in eating habits, or gi symptoms.

**Recurrent UTI**
Symptomatic UTI that follows clinical resolution of an earlier UTI generally after treatment

Re-infection
UTI that occurs more than 2 weeks after treatment of the original UTI.

Risk Factors:
- Sexual intercourse
- Diaphragm-spermicide use
- History of recurrent UTIs
- Having first UTI at <15 years old
- Mother with a history of UTIs
- Reduced levels of estrogenic hormones

No proven association with:
- pre- and post-coital voiding patterns
- Frequency of urination
- Delayed voiding habits
- Wiping patterns
- Douching
- Use of hot tubs
- Frequent use of pantyhose or tights
- BMI

Relapse
UTI caused by the same species as the original and occurring within 2 weeks after treatment

Relapse may be due to:
- Resistance
- Nonadherence
- Inappropriate choice of antibiotic
- Complicating factors

25-35% of initial UTI episodes are followed by recurrent episodes within 3-6 months. In up to 60% of cases of recurrent UTI, the 2\(^{nd}\) infection is caused by a strain identical to that which caused the prior infection.
**Symptomatic Abacteriuria**

Urethritis
- *C. trachomatis, N. gonorrhoeae*, herpes simplex virus
- Gradual onset, mild symptoms, vaginal discharge or bleeding, lower abdominal pain, new sexual partner, cervicitis or vulvovaginal herpetic lesions on exam
- Usually pyuria, rarely hematuria

Vaginitis
- *Candida, Trichomonas vaginalis*
- Vaginal discharge or odor, pruritus, external dysuria, no increased frequency or urgency, vulvovaginitis on exam
- Rarely pyuria or hematuria

**Diagnosis**

Clinical Presentation and . . .

For Uncomplicated UTI or patients without risk factors:
- History alone is sufficient
- May need dipstick urinalysis

For Complicated UTI or patients with risk factors:
- Need urinalysis, urine culture and susceptibility

**Urinalysis**

- **pH**
  - normal = 4.5-8.0
  - UTIs caused by urea-splitting bacteria such as *Proteus mirabilis* can cause a more alkaline urine (via ammonia production)

- **Leukocyte Esterase**
  - Normal = 0-trace
  - ≥ 2 is significant pyuria on dipstick
  - Phenazopyridine can cause false negative or unreadable results

- **Nitrite**
  - Normal = 0
  - Positive result indicates gram negative bacterial metabolism of dietary nitrates

- **Protein**
  - Normal = 0-1+
  - Little (<0.5 g/day) → lower UTI
  - Moderate (0.5-3 g/day) → pyelonephritis

- **Red Blood Cells**
  - Normal = 1-3/high-power field
  - Increases with glomerulonephritis and pyelonephritis
  - If ↑ rbc and epithelial cells → probable blood from vaginal wall

- **White Blood Cells**
  - Normal = 0-2/hpf
  - Significant pyuria is ≥ 3 wbc/hpf
  - Bacterial UTI
  - Inflammation in urinary tract
  - Urethritis
♦ Casts
  White cell casts indicate intrarenal inflammation and/or upper UTI

**Urine Culture**

**Symptomatic women without any complicating factors**
♦ no culture is needed

**Symptomatic Patients**
♦ $>10^5$ organisms/ml indicates infection
♦ up to 1/3 of women with symptomatic infection have less than that

**Asymptomatic Women**
♦ $10^4$-$10^5$ organisms/ml indicates contamination
♦ $>10^5$ indicates infection, but a second culture with similar results increases the chance that a true infection exists.

**Men**
♦ $>10^3$ organisms/ml indicates infection

Organism will be identified and susceptibility data will be available within 48 hours
♦ Most sensitivity data is based on achievable blood concentrations
♦ Most β-lactams, fluoroquinolones and SMX/TMP achieve high urine concentrations despite decreased GFR, whereas nitrofurantoin does not

**Resistance**

**Risk Factors for Resistance**
- Recent or current use of any antibiotic
- Age
- Diabetes
- Recent hospitalization
- History of UTI
- Cancer
- Chronic neurologic or urologic disorder
- Residence of a long term care facility

See graph and table below for resistance rates
- 1 in 3 strains causing cystitis or pyelonephritis are resistant to amoxicillin
- A survey from 1/00 – 9/00 found that 7% of E.coli isolates from the community were resistant to $>3$ drugs tested. The most common combination of drugs was ampicillin, cephalothin and TMP/SMX
E. coli susceptibility to TMP/SMX by region:
- Western U.S. 78%
- Northeastern U.S. 88-89%

Treatment
Goals of Therapy
1. Prevent or treat systemic consequences of infection
2. Eradicate the invading organism
3. Prevent recurrence of infection

Characteristics of appropriate Therapy
- Well tolerated
- Safe for the patient
- Well absorbed
- Achieve high urinary concentrations
- Cover suspected pathogen

Acute Uncomplicated Cystitis
**Single-dose therapy**
65-100% cure rates
- Trimethoprim/Sulfamethoxazole DS #2
- Gatifloxacin 400mg x 1
- Fosfomycin 3g x 1
3-day therapy

- superior to single-dose therapy
- equal efficacy to 7-day therapy
- increase compliance and decrease cost and ADRs compared to 7-day therapy

Preferred: TMP/SMX DS 1 po bid
           TMP 200mg po bid (for patients with a sulfa allergy)

If *E. coli* resistance is >10-20%:
   Fluoroquinolones
       Ciprofloxacin 100-250mg po bid
       Gatifloxacin 200-400mg po qd
       Levofoxacin 250mg po qd

*Ofloxacin, lomefloxicin, norfloxacin and enoxacin are also approved for the treatment of UTI, but have fallen out of favor secondary to their more limited spectrum of activity, lower potency, higher frequency of spontaneous bacterial resistance, shorter half-lives and lower serum drug concentrations.*

Alternatives: Trimethoprim 100mg po bid
               Nitrofurantoin 50-100 mg po Q6H x 7 days
               Amoxicillin/clavulanate 875mg po bid
               Amoxicillin 500mg po Q8-12H
               Cephalexin 500mg po Q6H

Short-course therapy is inappropriate for:
- Complicated UTIs
- History of infections caused by resistant bacteria
- Patients with comorbidities

**Complicated Cystitis**
- Treat for 7-10 days

**Drug Interactions with Fluoroquinolones**
All: interact with Al, Mg, Ca & Fe-containing products
Cipro & Levo: Increase PT with warfarin
Cipro: interact with theophylline, methylxanthines and cyclosporine

**Urinary Analgesia**
Pyridium (phenazopyridine)
- 100-200 mg po tid x 2 days
- Will discolor urine
- Do not use if Cr Cl < 50 ml/min
Monitor
Resolution of symptoms within 24-48 hours
Follow up urine culture for identification and sensitivity of organism
Repeat UA and culture only if symptoms not resolving or worsening
Adverse effects of drug therapy

Acute Pyelonephritis
♦ Hospitalization/need for IV antibiotics determined by presence of N/V, dehydration and pregnancy

Uncomplicated – PO Therapy
FQ x 14 days  OR  Cipro 500mg po bid x 7 days

TMP/SMX DS po bid x 14 days

If gram+ cocci present on gram stain → ampicillin 1-2g po q6h or amoxicillin/clavulanate

Complicated – PO Therapy
FQ x 14 days
Ciprofloxacin 500 mg po q12h
Gatifloxacin 400mg po q24h
Levofloxacin 500mg po q24h

Complicated or Uncomplicated requiring hospitalization – IV Therapy
FQ (as above, only IV)
Can increase doses if UTI caused by less susceptible uropathogens, such as Pseudomonas aeruginosa
Cipro 400mg IV q12h
Levofloxacin 250-500mg IV q12h
Gatifloxacin 400mg IV q24h

Adverse Effects:
Cipro 400mg IV q12h  drug interactions, GI
Levofloxacin 250-500mg IV q12h  QT prolongation, GI
Gatifloxacin 400mg IV q24h  QT prolongation, GI, Hypo & hyperglycemia

Aminoglycoside +/- ampicillin
Ampicillin 1-2g IV q4-6h
Gentamicin 1-2mg/kg IV q8h or 5mg/kg q24h
Tobramycin 1-2mg/kg IV q8h or 5mg/kg q24h

Adverse Effects:
nephro-, ototoxicity

3rd or 4th generation cephalosporins
Ceftriaxone 1-2g IV q24h
Cefotaxime 1-2g IV q8h
Ceftizoxime 1-2g IV q8-12h
Ceftazidime 1-2g IV q8h
Cefepime 1-2g IV q12h

Adverse Effects:
hypersensitivity, hepatic effects
hematologic effects
cholecystitis, ↑BUN
β-lactam/β-lactamase inhibitor combinations +/- aminoglycoside

- Ampicillin/sulbactam 1.5-3g IV q6h
- Ticarcillin/clavulanate 3.1g IV q6h
- Piperacillin/tazobactam 3.375 IV q6h

GI effects
- hypersensitivity
- neurologic effects

Extended-spectrum penicillin, ceftazidime, aztreonam or imipenem + aminoglycoside (x 3 days)

- IF complicating factors are nursing home resident, urinary catheter or hospitalization in past 6 months.

Duration of therapy: 14 days
IV to PO switch: Afebrile x 24 hours

**Monitor**

Symptoms should resolve after 48-72 hours of therapy
F/U urine culture in 2 weeks to ensure eradication
Renal function for antibiotic dosing and renal impairment
Adverse effects of drug therapy

**Prostatitis**

Inflammation of the prostate gland and surrounding tissue as a result of infection
Rare in men < 30 years old

**Acute**
- sudden onset of fever, tenderness and urinary symptoms (frequency, dysuria, nocturia, retention)
- Swollen, tender, warm and indurated prostate

**Chronic**
- relapsing UTI
- symptoms of urinating difficulty, low back pain, and/or perineal and suprapubic tenderness
- Prostate may be boggy, indurated or normal
- usually the result of incomplete eradication of bacteria from the prostate gland

**Risk Factors**

- Sexual intercourse
- Indwelling urethral or condom catheters
- Urethral instrumentation
- Transurethral prostatectomy
- Altered prostate secretory function
- BPH

**Common Pathogens**

- *E. coli* 75%
- *Klebsiella pneumoniae*
- *Proteus mirabilis*
- *Pseudomonas aeruginosa*
- *Serratia marcescens*

**Treatment of Acute Bacterial Prostatitis**
- PO or IV antibiotics depending on severity
- Treat empirically like pyelonephritis
- Treat x 4 WEEKS!!
**Treatment of Chronic Bacterial Prostatitis**
- FQ
- TMP/SMX
- Treat x 4-6 WEEKS

**Asymptomatic Bacteriuria (ASB)**
- Approximately 4-10% of pregnant women will have ASB, and 1-4% will develop acute cystitis for the 1st time during pregnancy
- 2 consecutive urine cultures with > $10^5$ of the same organism
- Risk Factors: pregnancy, elderly, female patients with diabetes, history of UTI, lower education

**Treatment**

**Children**
- Treat like cystitis
- Greatest risk of renal damage in first 5 years of life

**Elderly**
- Do not need to treat

**Diabetes**
- Treat as complicated UTI

**Pregnancy**
- Get culture and sensitivity
- Generally treat with 7-day course
  - Amoxicillin/Clavulanate
  - Cephalosporin
  - TMP/SMX
  - Nitrofurantoin
- No FQ
- No TMP/SMX during 3rd trimester
- F/U culture 1-2 weeks after treatment then monthly until delivery

**UTIs in Catheterized Patients or Patients with Spinal Cord Injuries**
- UTI is the most common nosocomial infection in these patients
- Patients with indwelling catheters acquire UTIs at a rate of 5%/day.
- After 30 days of catheterization, there is a 78-95% incidence of bacteriuria.
- 40% of patients with spinal cord injuries will die of renal related problems

**Treatment of Asymptomatic Bacteriuria**
- Remove catheter and monitor for symptoms

**Treatment of Symptomatic Bacteriuria/Complicated UTI**
- Culture urine
- Remove catheter
- Treat as complicated UTI (7-14 days)
**UTI Prevention**

Decrease or eliminate the use of spermicides and/or diaphragms

Cranberry juice

Estrogen in postmenopausal women

Antimicrobial prophylaxis

- ≥2 symptomatic UTIs over a 6-month period or ≥3 over 12 months
  - **Continuous**
    - Nitrofurantoin 50mg po QD
    - Trimethoprim 100mg po QD
    - TMP/SMX SS tab po QD or 3x/week
    - Norfloxacin 200 mg po 3x/week
  - **Post-coital**
    - TMP/SMX SS
    - TMP 100mg
    - Nitrofurantoin 50-100 mg
    - Cephalexin 250 mg
    - Norfloxacin 200-400mg
    - Ciprofloxacin 250mg
  - **Self-treatment**

**Funguria**

- A common nosocomial condition
- *Candida albicans* accounts for 40-65% of all fungal isolates from urine
- *C. tropicalis, C. krusei* and *C. glabrata*

*Lower tract infections*

Ascending route of infection

*Upper tract infections*

Hematogenous spread

**Diagnosis**

Any fungal isolate from urine should be considered abnormal and investigated further to determine whether it is colonization, infection or hematologic candidiasis.

**Risk factors for fungal UTIs**

Reversible

- Antibiotic therapy
- Indwelling urinary catheter
- Anatomical abnormality

Irreversible

- Female sex
- Diabetes
- Immunosuppression
**Treatment**

Spontaneous Resolution
- May take months to a year
- Only occurs at a rate of 23%

Non-pharmacological
- Remove any removable risk factors
- Any unnecessary antibiotics or catheters

Pharmacological

Fluconazole
- 200 mg x 1 then 100 mg/d x 4 days

Amphotericin B Bladder Irrigation
- Continuous low concentration vs. Intermittent high concentration

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<thead>
<tr>
<th>Advantages of Fluconazole</th>
<th>Disadvantages of Amphotericin B</th>
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<tr>
<td>70% of PO dose is excreted unchanged in urine</td>
<td>Does not clear funguria as rapidly</td>
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<tr>
<td>Good bioavailability</td>
<td>Optimum dosage and duration of therapy unknown</td>
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<tr>
<td>Greater sustained fungicidal effect</td>
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<tr>
<td>More convenient to administer</td>
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**Additional References**


Schaeffer AJ. The Expanding Role of Fluoroquinolones. *The American Journal of Medicine* 2002:113(1A):45S-54S.


