Adult Genito-Urinary Infections *Epidemiology, Etiology, and Diagnosis*

Geoffrey N. Box, M.D.
Assistant Professor
Director, Laparoscopic Urologic Surgery
The Ohio State University

Urinary Tract Infection

- **Definitions:**
  - ✓ **An inflammatory response of the urothelium to bacterial invasion that is usually associated with bacteriuria and pyuria.**
  - ✓ **Bacteriuria: presence of bacteria in the urine**
  - ✓ **Pyuria: WBCs in the urine**

Outline

- **Definitions**
- **Epidemiology**
- **Diagnosis**
- **Pathogenesis/Pathogens**
- **Bacterial Resistance**
- **Principles of Antimicrobial Therapy**
- **Asymptomatic Bacteriuria**
- **Preventative Strategies**

Classification - UTI

- **1) Status of the urinary tract**
  - **Uncomplicated UTI → Normal urinary tract**
  - **Complicated UTI → Structurally or functionally abnormal urinary tract**
- **2) Pattern of infections**
  - **Isolated/sporadic → separated by long intervals**
  - **Unresolved → fail antibiotic therapy (usually bacterial resistance)**
  - **Recurrent → *reinfection* (outside) or *persistence* (within)**
- **3) Site of infection**
  - **Cystitis: clinical syndrome→ Dysuria, Frequency, Urgency**
  - **Pyelonephritis: same as cystitis plus fever and flank pain**

Incidence & Epidemiology

- UTI is considered the most common bacterial infection
- >7 million office visits/yr
  - 1.2% of all ♀ visits and 0.6% of all ♂ visits
- Result in 100,000 hospitalizations/yr
- Community acquired UTI → $1.6 billion in US

Populations at ↑ Risk

- Pregnant women
- The elderly
- Spinal cord injury patients
- Patients with indwelling catheters
- Diabetes
- HIV

Incidence & Epidemiology

- 30% of women have had a UTI by age 24 and 50% will have one in their lifetime.
- Up to 15% of women develop UTIs each year (vs. 3% of men)
  - ✓ 25% have at least one recurrence

Differential Diagnosis

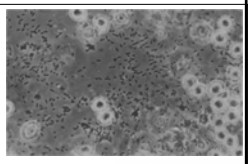
- Vaginitis
- Urethritis/Urethral pathology
- STDs
- Bladder cancer
- Interstitial cystitis

Diagnosis - History

- New onset frequency, dysuria, and urgency in the absence of vaginal discharge or pain → PPV 90%

Diagnosis

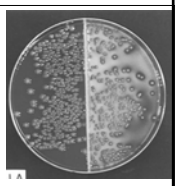
- Microscopic urinalysis
  - ✓ Pyuria
    - sen 95%, spec 70%
  - ✓ Bacteria
    - sen 70%, spec 90%
- Indirect Dipstick
  - ✓ Leukocyte esterace → pyuria
  - ✓ Nitrite → bacteria
    - Both positive: sen/spec ~95%



Diagnosis

- Urine Collection
  - ✓ Clean catch, mid-stream specimen
  - ✓ May need to catheterize some women to avoid contamination

Urine Culture



- Definitive test
- >10^2 cfu/ml (>10^5 cfu/ml)
- Not always necessary
- Indications to perform culture:
  - ✓ 1) Symptoms without bacteriuria/pyuria
  - ✓ 2) Recent antibiotic exposure
  - ✓ 3) Prior empiric therapy (unresolved UTI)

Evaluation

- None for uncomplicated UTIs
- Factors suggesting complicated UTI
  - Male gender
  - Hematuria
  - Elderly
  - Functional/structural abnormality
  - Immunosuppression
  - Diabetes Mellitus
  - Recent antimicrobial use

Pathogenesis – UTI

- Ascending event: outside → inside
- Colonization of vagina by uropathogenic bacteria.
- Replaces lactobacilli which are normally present and maintain acidic vaginal environment
- Primary bladder defense → complete emptying

Evaluation

- Recurrent infections and complicated UTIs
  - Post void residual urine
  - Urine culture
  - Consider imaging and cystourethroscopy
- In patients with recurrent UTIs, important to distinguish between persistence and reinfection

Pathogenesis – UTI

- Host susceptibility factors
  - ✓ Genetic
    - ABO blood group antigens
  - ✓ Biologic
    - Anatomic abnormalities
    - Diabetes
    - Estrogen depletion
  - ✓ Behavioral
    - Sexual activity
    - Spermicide use
- Bacterial virulence

Pathogens

- **Uncomplicated UTI**
  - ✓ ***Escherichia coli*** **(80%)**
  - ✓ ***Staphylococus saprophyticus*** **(15%)**
  - ✓ ***Klebsiella pneumoniae***
  - ✓ ***Enterococcus faecalis***
- **Complicated UTI**
  - ✓ ***Escherichia coli***
  - ✓ ***Klebsiella pneumoniae***
  - ✓ ***Enterobacter cloacea***
  - ✓ ***Serratia marcescens***
  - ✓ ***Proteus mirabilis***
  - ✓ ***Pseudomonas aeruginosa***
  - ✓ ***Enterococcus faecalis***
  - ✓ **Group B strep**

Bacterial Resistance

- **Natural**
  - **I.E. all *proteus* species are resistant to nitrofurantoin**
- **Selection of resistant mutants (5-10%)**
  - **Chromosomal resistance**
  - **Antimicrobial drug concentration is not high enough to kill all of the bacteria**
- **Transferable, plasmid-mediated (5-45%)**
  - **Plasmids contain genetic material for resistance**
  - **Transferable within species and across genera**

Antibiograms

GRAM NEGATIVE RODS: ENTERICS % SUSCEPTIBLE

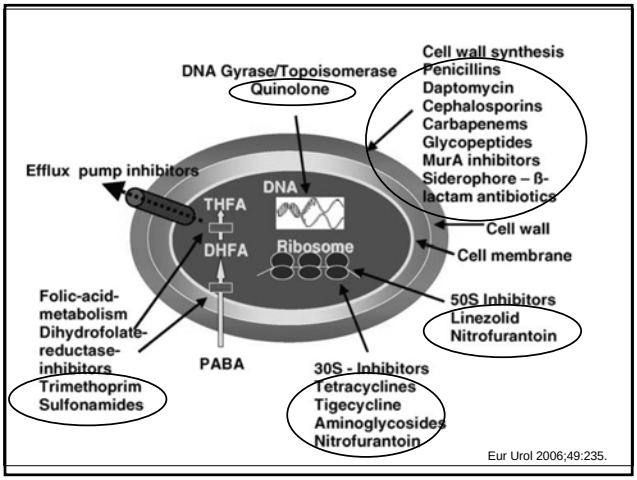
	# Isolates	Ampicillin/ Sulbactam	Piperacillin/ Tazobactam	Cefazolin	Cefepime	Imipenem	Ertapenem	Ciprofloxacin	Gentamicin	Tobramycin	Amikacin	Trimethoprim/ Sulfamethoxazole	Nitrofurantoin (urine only)
MIC breakpoints (µg/ml)		≤8/4	≤16/4	≤8	≤8	≤4	≤2	≤1	≤4	≤4	≤16	≤2/38	≤32
Escherichia coli	1421	44	95	87	100	100	100	67	88	89	100	64	98
Escherichia coli-ESBL	62					100	95	5	53	35	94	39	81
Klebsiella pneumoniae	511	83	98	95	100	100	100	95	98	97	100	89	67
Klebsiella pneumoniae-ESBL	71					99	89	14	38	27	97	27	41
Klebsiella oxytoca	96	57	85	35	100	100	100	94	99	98	100	96	91
Enterobacter cloacae	229		70		83	100	96	73	72	72	97	75	18
Enterobacter aerogenes	103		79		97	100	96	90	94	93	99	94	30
Citrobacter freundii	71	62	87		99	100	100	83	87	90	99	66	92
Citrobacter koseri	46	85	100	96	100	100	100	83	96	98	100	98	87
Serratia marcescens	153		85		99	97	99	86	97	88	100	92	
Proteus mirabilis	236	88	100	88	100	100	100	53	89	88	99	60	
Morganella morganii	55		98		100	100	100	47	71	89	98	51	
Providencia stuartii	43	16	98		100	100	100	7	12	9	100	65	

Basis of Bacterial Resistance

CLASS	Chromosomal	Plasmid
Beta-lactams	+	+
Aminoglycosides	-	+
Sulfonamides	-	+
Tetracycline	-	+
Trimethoprim	-	+
Nitrofurantoin	-	-
Quinolones	+	-

Principles of Antimicrobial Therapy

- Eliminate bacterial growth in the urinary tract.
  - Kill bacteria → bactericidal
  - Prevent growth of bacteria → bacteriostatic
- Urinary levels of antimicrobial agents is often several hundred times greater than serum levels.
- Efficacy dependent on the urinary levels and the duration this remains above the minimal inhibitory concentration (MIC)



Eur Urol 2006;49:235.

Principles of Antimicrobial Therapy

- Probable pathogen versus the antimicrobial agent's spectrum of activity
- Community and institutional susceptibilities
- Patient factors
  - History of allergic reaction
  - Renal and liver function
  - Pregnancy status

Asymptomatic Bacteriuria Prevalence

- Healthy adult woman: 2-5%
- Pregnant woman: 2-11%
- Diabetic women: 7-9%
- Elderly nursing home residents: 5-50%
- Spinal cord injury: 50%
- Chronic indwelling catheter: 100%

Prevention

- Cranberry Juice/Tablets
  - Contains proanthocyanidins → inhibits bacterial adherence to uroepithelial cells
  - ↓ Recurrent UTI by 30%
- Topical Estrogen (postmenopausal women)
  - ↓ Episodes of symptomatic bacteriuria
- Discontinuation of spermicide use

Pyelonephritis

- Cystitis very rarely progresses to pyelonephritis
  - ~20 to 1 ratio in patients with recurrent UTI
- Not as well defined as UTI
- Typical presentation:
  - Cystitis + flank pain and fevers
  - Septic shock is uncommon → important to consider an obstructive etiology
- *E. coli* in 90%
  - Unique virulence characteristics

Preventative Strategies

- No Proven Benefit
  - ✓ Frequent voiding
  - ✓ Increasing fluid intake
  - ✓ Postcoital voiding
  - ✓ Personal hygiene (i.e. wiping front to back)
  - ✓ Avoiding constipation

Conclusions

- UTIs are the most common bacterial infection and will affect more than 50% of women in their lifetime.
- If symptoms do not resolve following therapy, it is important to consider other potential etiologies.
- Complicated UTIs have special treatment considerations as these patients have increased chances of acquiring bacteria and therapy has decreased efficacy.
- Choice of antimicrobial therapy should be based on likely pathogen, local susceptibilities and patient factors.

Genito-Urinary Infections in the Adult *Management*

Jason P. Gilleran, MD

Assistant Professor, Dept of Urology

The Ohio State University Medical Center

Principles of Management

- **Identify uropathogen by culture/sensitivity**
- **Achieve adequate antimicrobial concentration**
  - ✓ **Compliance with full regimen**
  - ✓ **Dose appropriately**
- **Use of antimicrobial with lowest MIC (minimal inhibitory concentration) on sensitivity testing**
- **Documentation of sterility**
- **Prevent emergence or worsening of** resistance **to antimicrobial agent**

Outline

- **Cystitis**
  - ✓ **Antibiotic use and treatment courses**
- **Pyelonephritis**
- **Epididymitis**
- **Prostatitis**
- **Special Situations**
- **Indications for specialist referral**

Trimethoprim / Sulfamethoxazole (TMP-SMX)

- **Bactrim, Bactrim DS**
- **80-85% bacterial cure rate**
- **Eliminates pathogens from vaginal flora in addition to urine**
- **Considered first-line therapy (3 days)**
- **Allergies to sulfa-based medications common**
  - ✓ **TMP alone as effective as TMP-SMX**

Nitrofurantoin

- Effective against *E. coli* and most other uropathogens
- Universal resistance with *Proteus*
- Secreted solely in urine
  - ✓ Minimal risk of diarrhea, yeast infections
- Seven-day course
- Pulmonary fibrosis – rare but serious complication.
  - ✓ Symptoms of new cough while on drug, discontinue and obtain chest radiograph
  - ✓ More common in individuals on drug for extended periods of time as suppressive agent

Penicillins/Cephalosporins

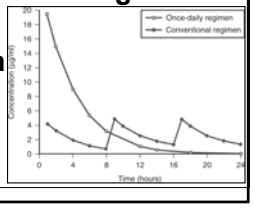
- Less effective
- Use of a β-lactamase inhibitor (amoxicillin-clavulinic acid) greatly improves susceptibility
- Cephalosporins do NOT cover *Enterococcus*

Quinolone Therapy

- Ciprofloxacin (Cipro), Levofloxacin (Levaquin), Moxifloxacin (Avelox)
- Highly effective, more expensive than nitrofurantoin or TMP-SMZ
- Second-line therapy if fails TMP-SMZ or allergic to sulfa meds
- Poor absorption with antacids
- Achilles tendon rupture – rare but serious complication

Aminoglycosides

- Preferred drug in combination with penicillin (ampicillin) in treatment of urosepsis
  - ✓ Emerging use of piperacillin-tazobactam
- Once-daily dosing vs q 8 hr dosing
  - ✓ 7 mg/kg if creatinine clearance > 60 mL/min
- Nephro-, ototoxicity



Uncomplicated Acute Cystitis

- Structurally normal urinary tract
- Otherwise healthy female
- No signs/symptoms of pyelonephritis, vaginitis, cervicitis
- Episodes can be treated by telephone consultation with follow-up culture

Low-Dose Prophylaxis

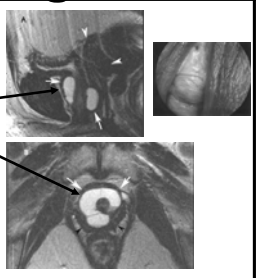
- Use of a daily (or other regimen) low-dose antibiotic to suppress bacterial growth
- Used for 3-12 months at a time
- Concerns for yeast infections and change in bowel flora
- TMP
- Nitrofurantoin

Treatment Uncomplicated Cystitis

- Trimethoprim (TMP) or Trimethoprim – Sulfamethoxazole (TMP-SMX) for 3 days
  - ✓ 93% success rate
- Quinolones (Ciprofloxacin, levofloxacin) for 3 days
  - ✓ Second-line therapy
  - ✓ Resistance to TMP-SMX > 20%
- Nitrofurantoin (Macrodantin 50 mg q.i.d., Macrobid 100 mg b.i.d.) for 7 days
- Fosfomycin single dose
  - ✓ Higher chance of recurrence

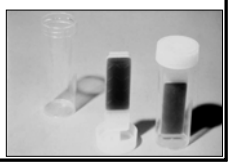
Recurrent UTI in Women Differential Diagnosis

- Abnormal vaginal flora
- Infection stone
- Urethral diverticulum
- Colovesical fistula
  - ✓ Pneumaturia, fecaluria
  - ✓ History of Crohn's, UC, diverticulitis
- Foreign body
- Upper tracts (ureter, nonfunctioning kidney, renal cysts)



Treatment of Recurrent, Uncomplicated UTIs

- Cranberry and push po fluids
  - ✓ Tablets vs juice (100% non-concentrate)
  - ✓ Mechanism of action - ?lower urinary pH
- Pre-/Post-coital prophylaxis
  - ✓ Macrodantin 50 mg or ½ strength TMP-SMX
- Self-start therapy
  - ✓ 3 day course of trimeothprim or quinolone at first signs and symptoms of UTI
  - ✓ Reasonable course of tx with consistent bacteria on urine cx
  - ✓ Home dipstick tests; mail-in cultures



Schaeffer A. AUA Instructional Course 2009

Management of Pyelonephritis

- Uncomplicated
  - ✓ Normal urinary tract; clinical status determines management
  - ✓ Outpatient/Inpatient
  - ✓ Oral / parenteral
  - ✓ Nitrofurantoin of little clinical use due to poor tissue penetration
- Complicated
  - ✓ Associated with hospitalization, catheterization, urologic surgery, or GU tract abnormality
  - ✓ Inpatient → parenteral – oral
  - ✓ Treat obstruction

CT scan showing enlarged right kidney with focal area of decreased uptake of contrast (aka "Lobar Nephronia")

Complicated Cystitis

- Men
- Children
- Structural or abnormal function
  - ✓ Neurogenic bladder, prior or recent urologic history, use of catheter or foreign body
- Assess for reflux in children (VCUG)
- Consider treatment for 7-21 days with follow-up culture

Complicated Pyelonephritis

- Fluoroquinolone - parenteral to oral
- Duration of Therapy
  - ✓ Uncomplicated – 7 days
  - ✓ Complicated – 21 days
- Repeat urine cultures
  - – 5-7 days after initiation of therapy
  - – 4-6 weeks after discontinuation of therapy

Talan et al. JAMA 2000; 283: 1583-1590

Complications of Pyelonephritis

- Renal/perinephric abscess
  - ✓ Percutaneous drainage
  - ✓ 14-21+ day course of parenteral vs oral antibiotics
- Xanthogranulomatous pyelonephritis
  - ✓ Associated with stone
  - ✓ May mimic renal cancer
  - ✓ Nephrectomy

MRSA and VRE

- Methicillin-resistant Staph aureus
  - ✓ May account for 30-50% of hospital isolates
  - ✓ Incidence in outpatient setting is rising
  - ✓ Resistance rate with quinolones 70-80%
  - ✓ If sensitive, can be treated with quinolone or TMP-SMX + rifampin
  - ✓ Cautious use of Vancomycin
- Vancomycin-resistant Enterococcus
  - ✓ Linezolid (Zyvox) 400-600 mg po q12 hrs
  - ✓ Watch for myelosuppression

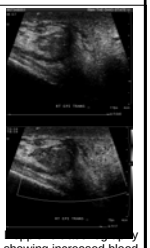
Uropathogen Resistance

	% Susceptible	
Antimicrobial	***E.Coli***	***S.saprophyticus***
Ampicillin	**60.6%**	**29.3%**
TMP-SMX	**81.7%**	**93.9%**
Ceftazidime	**99.1%**	**No data**
Ceftriaxone	**99.7%**	**74.5%**
Ciprofloxacin	**97.4%**	**99.1%**
Levofloxacin	**97.0%**	**98.2%**
Ofloxacin	**97.0%**	**100%**

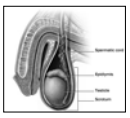
Schaeffer A. AUA Instructional Course 2009

Epididymo-Orchitis

- Acute bacterial infection of epididymitis
- Retrograde mechanism
- Common uropathogens (***E.coli***, ***Klebsiella***, ***Staph***)
  - ✓ Urine culture often indicative of pathogen
- Isolated episodes may not need specialist evaluation
  - ✓ Treatment 10-14 days of TMP-SMX or quinolones
  - ✓ Poor tissue penetration by nitrofurantoin
- Recurrent episodes
  - ✓ Consider evaluation for bladder outlet obstruction



showing increased blood flow



Prostatitis

- Most common urologic diagnosis in men younger than 50
- Dysuria, perineal and penile pain
- Fever, chills, retention → urosepsis
- Urine culture often not indicative
  - ✓ Post-prostatic massage urine culture

Special Situations

Prostatitis

- Acute Bacterial vs Chronic Bacterial
- Patients may require 4-6 weeks of therapy with quinolone or TMP-SMX, with additional 6 weeks if prostate cultures remain positive
- Chronic non-bacterial (CPPS)

UTI in the Pregnant Patient

- Screen in first trimester
- Prevalence of bacteriuria 4-7%
- Acute pyelonephritis in 25-35% of untreated bacteriuria
- Women with pyelonephritis in pregnancy at higher risk for:
  - ✓ Pre-term labor
  - ✓ SGA infants
  - ✓ Fetal mortality
  - ✓ Low birth-weight infants

Treatment in the Pregnant Patient

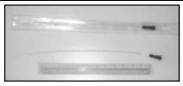
- SAFE
  - ✓ Penicillins, cephalosporins
- USE WITH CAUTION
  - ✓ TMP-SMX → antifolate (1st trimester) and hyperbilirubinemia (3rd trimester)
  - ✓ Nitrofurantoin → hemolytic anemia in G6PD deficiency; avoid at term

- AVOID
  - ✓ Fluoroquinolones → cartilage abnormalities
  - ✓ Tetracyclines → teeth and liver abnormalities
  - ✓ Erythromycin → jaundice

UTI in the Geriatric Population

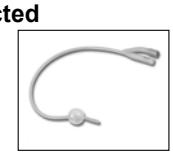
- Asymptomatic bacteriuria in women over 65 approximately 20% in women and 10% in men
- 25-75% rate of bacteriuria in female nursing home residents over 65
- Treat urea-splitting organisms on culture
  - ✓ *Proteus*, *Klebsiella*
  - ✓ *E coli* NOT a urea-splitting organism

UTI in the presence of a urinary catheter

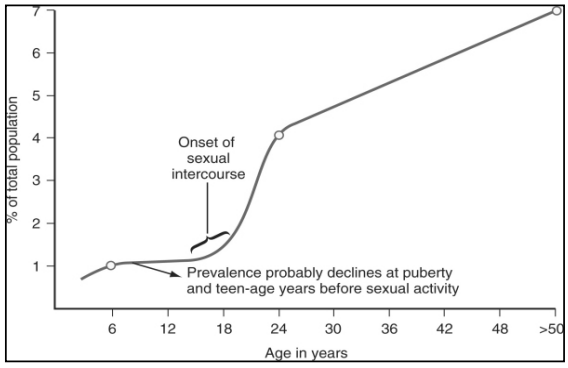


"Frictionless" catheter

- Clean intermittent catheterization (CIC)
- Indwelling Foley catheter
  - ✓ Aseptic technique
  - ✓ Maintain closed system
  - ✓ Change catheter if acutely infected
- Candida albicans or other fungal pathogen → removal of Foley
- Do NOT treat positive culture if patient asymptomatic



Prevalence of Bacteriuria



Topical Vaginal Estrogen

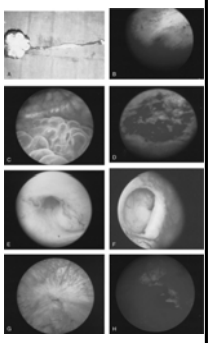
Variable	Estriol (n=50)	Placebo (n=43)
Episodes of Bacteriuria	12.0	111.0
Symptomatic	10.0	103.0
Asymptomatic	2.0	8.0
Total person- months observed	310.0	225.0
Urinary Tract Infections	0.5	5.9*

p<0.005

Raz and Stamm NEJM 1993; 329 (11): 753

Genitourinary Tuberculosis

- Rare chronic GU infection
  - ✓ Kidney, ureter, bladder, prostate
  - ✓ Immunosuppressed, immigrants
- Sterile pyuria
  - ✓ Leukocytes and negative standard urine culture
- Diagnosis requires 3 morning first void samples
  - ✓ Acid-fast bacilli (AFB) → 42 days

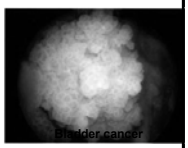


UTI in the Immunosuppressed

- Poorly-controlled diabetics
  - ✓ Assess bladder function, sensation and emptying (post-void residual, PVR)
  - ✓ Tighter diabetic control
- HIV +
  - ✓ Viral, fungal and parasitic
- Transplant patients or chronic steroid use for autoimmune disease
  - ✓ Retained, non-functional renal units

Indications for Urologic Referral

- Hydronephrosis
- Repeated negative urine cultures with symptoms
  - ✓ Interstitial Cystitis (IC)
- Microscopic or gross hematuria
  - ✓ > 5 RBC/hpf on urinalysis or > 2-3/hpf on 2 out of 3 specimens
- Persistent irritative symptoms (with/without bacteria) in a smoker



Current Areas of Research

- Vaccine
  - ✓ Uro-vaxom® and Strovac®
  - ✓ Only available in Europe as of now
- Probiotics
  - ✓ Lactobacillus intake to alter vaginal flora
- Biofilm formation
  - ✓ Re-emergence vs "eruption" of bacteria within bladder epithelium

Wagenlehner F et al. Eur Urol 49(2006):235-244

Conclusions

- Treatment based on type of infection
- Consider identifiable and correctible causes of infection
- Judicious use of antibiotics in appropriate cases, doses, and lengths