Urinary Tract Infection Across the Lifespan: Latest Developments in Assessment, Prevention & Management

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Objectives

- Define urinary tract infection, its epidemiology and pathophysiology
- Outline prevention strategies, focusing on underlying evidence and investigational techniques
- Discuss evaluation of domiciliary and healthcare acquired UTI
- Review management of UTI including pharmacologic and behavioral interventions

UTI: Global Definitions

- Urinary Tract Infection (UTI)
  - Inflammatory response of urothelium to bacterial invasion; usually associated with bacteriuria & pyuria
  - Definitions in general dictionaries
    - Bacterial infection of urethra, bladder, ureters, kidneys
    - Infection of any part of the urinary tract, especially the urethra or bladder

2. Online Medical Dictionary. [http://cancerweb.ncl.ac.uk/cgi-bin/omd?query=urinary+tract+infection](http://cancerweb.ncl.ac.uk/cgi-bin/omd?query=urinary+tract+infection)
UTI: Laboratory Based Classifications

- **Bacteriuria**: bacteria in urine; may be symptomatic or asymptomatic; CFU > $10^5$ considered clinically relevant but correlation with clinical symptoms is weak.\(^1\)
- **Pyuria**: white blood cells (pus) in the urine, indicates inflammatory response to something, but not necessarily bacteria.\(^2\)
- **Asymptomatic bacteriuria**: sometimes called screening bacteriuria; resist intervention without indication.
- **Acute Pyelonephritis**: chills, fever and flank pain along with bacteriuria and pyuria.\(^2\)


UTI: Classification based on Environment

- **Community Acquired (Domiciliary) UTI** (formerly classified as uncomplicated):
  - Symptomatic UTI in otherwise healthy patient; is not associated with fever or history of urinary tract defects (majority of UTI from epidemiologic perspective; originally limited to women
  - Pathogen usually multidrug sensitive coliform bacterial species; most common is *E. coli*.
- **Nosocomial/ facility/ healthcare acquired UTI**
  - Historically this was one criterion of complicated UTI (others were gender and presenting symptoms)
  - Pathogens often differ from domiciliary; pathogens more likely to be resistant to multiple antimicrobials.

UTI: Classification Based on Natural History

- **First time/ isolated infection**: initial infection or more than 1 year from prior UTI
- **Recurrent UTI**: patient was infected, became well (infection free) and is infected again
- **Unresolved UTI**: bacteriuria persists despite antibiotic Rx
- **Chronic UTI**: little meaning or clinical relevance.

**Epidemiology**

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**UTI: Prevalence in Infancy & Childhood**

- Among female infants with fever (overall 7.0%, 95%CI 5.5-8.4%)
  - 0-3 mos: 7.5%
  - 3-6: 5.7%
  - 6-12 mos: 8.3%
  - >12 mos: 2.1%

- Among male infants with fever:
  - <3 mos: 2.4% (20.1% uncircumcised, highest of any group)

- Whites infants 8%; black infants 4.7%

- Among older children (<19 yrs) pooled prevalence of febrile and non-febrile UTI: 7.8%


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**UTI: Prevalence in Community Dwelling Women**

- 3.5% of adult, community dwelling women have bacteriuria, most are asymptomatic
- Cumulative risk for women: 10.8% per year; lifetime risk around 50%
- UTI account for
  - 7 million new clinic/office visits per year
  - 1 million visits to ED
  - 100,000 admissions to hospital

UTI: Prevalence & Incidence: Community Dwelling Men

- Occurrences in domiciliary men less frequent than women; account for approximately 20% of UTI prevalence in adults
- Annual incidence of UTI in men approximately 1318/100,000 (1.3%)
- Men with UTI more likely to have fever and more likely to require hospital admission
  - 424,000 ED visits by men found to be UTI related (majority were >65 years of age)\(^2\)
  - 100,000 hospital admissions


Healthcare Acquired UTI

- US Prevalence 4% (CI: 3.7; 95%CI: 3.7–4.4%) for calendar year 2010\(^1\,\(^2\)
- Majority of these (about 80%) are CAUTI
- Approximately 139,000 documented CAUTI occurred in 2007\(^3\)
  - Occurrence rates vary based on health care setting and focus of care within specific unit or ward (for example neurotrauma ICU vs psychiatric unit)

3. Wise M. Abstract 3703. Society of Healthcare Epidemiology of America, April 2, 2011; Dallas TX.

Recurrent UTI

- Recurrent UTI occurs in 46% of women within 1 year
  - Most reinfections occur within 4-5 months\(^1,\(^2\)
  - Many are infected with different organism\(^2\)
  - Recurrence must be differentiated from chronic bacteriuria or persistent UTI

UTI: A Note of Caution

- Suspect Interstitial Cystitis when...
  - UTI like symptoms (frequent urination, LUT pressure/pain), occur but U/A is negative
  - Multiple UTI have been treated without relief from bothersome LUTS
  - Patient complains of "chronic UTI" & has seen multiple providers without relief
  - Empiric treatment of repeated UTI complaints with "partial response" after 2-4 weeks


UTI: Etiology & Pathophysiology

- General Principles
  1. UTI represents temporary loss in an ongoing skirmish between pathogens & host (patient), resulting colonization and overgrowth of pathogen to detriment of host
  2. Most pathogens are bacterial, fungal or tubercular; viral pathogens exits but are much less common
  3. Differences in anatomy of urinary tract in male and female results in differences in clinical manifestations and progression of infection left untreated
UTI: Etiology & Pathophysiology

- Pathogens usually enter urinary tract via urethra, rarer alternatives included
  - Hematogenous: critically ill, septic patient
  - Lymphatic: seen with retroperitoneal abscess or severe bowel infection

- Bacterial Reservoirs
  - Gastrointestinal Tract
  - Vaginal vault
  - Skin
  - Foreign object

UTI: Etiology & Pathophysiology

Multiple Contributing Factors

- Multitude of Associated/Risk Factors, these are especially prevalent
  - Sexual activity (↑ inoculation)
  - Spermicide (↑ binding)
  - Reduced estrogens (alters vaginal flora; ↑ binding)
  - Antimicrobial therapy (↓ normal flora)
  - Urinary stasis (↓ antegrade flow)
  - Inadequate fluid intake
  - Urinary or fecal incontinence
  - Incomplete bladder emptying
  - Foreign body in urinary tract

Health Care Associated UTI: Etiology & Pathophysiology

- Risk of CAUTI proportionally related to duration of catheterization.
- Bacterial species swarm catheter from urethral meatus toward vesicle; laboratory studies show *proteus* and *pseudomonas* species swarm in as little as 24 - 48 hours.
- Planktonic bacteria up-regulate specific genes to form biofilm, rendering them up to 1,000 fold more resistant to antimicrobial Rx.


Biofilm: polysaccharide surface formed by bacteria, slimy & densely adherent to surface of any foreign body in urinary tract.
- Primitive ‘circulatory’ system provides ↑ nutrients near surface, but bacteria near base live in near-starvation state; they are especially resistant to antimicrobial Rx.
- Silicone & latex catheters excellent surface for biofilm formation when colonized with virulent E. coli.

2. Figure: http://www.uweb.engr.washington.edu/images/research/biofilmtutorial.JPG

Most UTI in Adults are Bacterial: N = 22,830 domiciliary patients

Most UTI in Adults are Bacterial:
N = 5,563 hospitalized adults

Most UTI in Adults are Bacterial:
N = 2,777 elders in LTCF

Bacterial Virulence:
The Enemy’s Weapons
**Host Defenses**

- Figures on next 2 slides are integrative review on immune defenses in human urinary tract:

**Epithelial cells in the nephron secrete numerous substances that protect host against UTI and bacteria including**

- Uromodulin/Tamm-Horsfall glycoprotein: binds to fimbriae stopping bacteria from adhering to urinary tract
- Multiple interleukins (IL-1, IL-6, IL-8): recruit macrophages to area
- Other molecules remove essential nutrients from urine; for example, NGAL & siderophores remove or bind iron that is essential to bacterial growth and reproduction

**Urothelium of Bladder**

- Bladder defenses
  - After invading epithelium, urothelium ↑ cyclic AMP literally kicking bacterium back out into urine
  - Urothelium secretes antimicrobial proteins, peptides and chemokines
  - It all this is insufficient, the bladder will exfoliate/shed its superficial layer with bacterial content
  - All of this ultimately supported by local immune cells; mostly mast cells and Ly6C macrophages
Diseases & Disorders that Compromise Host Defenses

- **P1/P2 blood group phenotype (non secretors of P1/P2):** ↑ likelihood of bacteriuria, symptomatic UTI and febrile UTI.1,2
- **Diabetes mellitus:** predisposes to more severe infections, combined effect of glucosuria plus compromised immune response3
- **HIV:** immunocompromised and higher prevalence of virulent bacteria when UTI occurs.
- **Neurologic disease:** results in neurogenic bladder, obstruction, sphincter dyssynergia, greater likelihood of use of indwelling or intermittent catheterization.


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Viral Urinary Tract Infections

- Rare in patients with competent immune system function; most commonly seen after organ transplantation.
- Asymptomatic viruria does occur; most common is BK virus.
- Most commonly associated with hemorrhagic UTI.
- Principal pathogens are cytomegalovirus, adenovirus and BK virus.

Paduch DJ. Current Urology Reports 2007; 8: 324.

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Fungal Urinary Tract Infections

- Most common in critically ill patients with ongoing or recent exposure to broad spectrum antibiotics.
- **Risk Factors include:**
  - Immunocompromised immune function, renal transplantation
  - Diabetes mellitus
  - Older
  - Renal failure, hemodialysis
- **Candidiasis** most common, Blastoschizomyces also occurs.

Parasitic Urinary Tract Infections

- From public health perspective schistosomiasis is the most significant parasitic infection of lower UTI in men (and women)
  - Parasite enters human host while bathing waters in tropical areas (Africa, Pacific rim)
  - Urothelium reacts to deposition of eggs with inflammation and secondary bacterial UTI
  - Reinfection, inadequate treatment result in progressive disorder with scarring, uropathy and high risk of urinary tract cancers

Ghoneim MA. BJU International 2002; 89 (Supplement 1): 22.

Evaluation & Diagnosis

Clinical Manifestations: Neonates & Infants

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Fever</td>
<td>67%</td>
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<tr>
<td>Irritability</td>
<td>55%</td>
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<tr>
<td>Poor Feeding</td>
<td>38%</td>
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<tr>
<td>Vomiting</td>
<td>36%</td>
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<tr>
<td>Diarrhea</td>
<td>36%</td>
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<tr>
<td>Abdominal distension</td>
<td>&lt;10%</td>
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<td>Jaundice</td>
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**Clinical Manifestations: Older Children**

- Dysuria in 15%-30%
- Vague lower abdominal pain, not well localized to flanks or suprapubic area
- Sudden change in LUTS
- Enuresis, urge UI
- Cloudy & malodorous urine (most common cause of cloudy urine: phosphaturia)


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**Classic Clinical Manifestations**

- Dysuria (burning, “voiding barbed wire”) tends to occur during and after void
- Suprapubic or lower back pain
- Voiding frequency
- Urgency
- Malaise


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**Clinical Manifestations: Older Adults >75 years**

- Lower urinary tract symptoms (LUTS) tend to be less “focused” than younger adults
- Greatest differences in very old (≥ 80 yrs) and very frail elders
- Retrospective review of 104 patients ≥70 yrs revealed confusion (30%), cough (27%), dyspnea (28%) with no reported LUTS despite bacteriuria, pyuria and fever – in absence of radiographic evidence of chest infection

Diagnosis

- Urine collection: Voided Specimen
  - Retract foreskin and cleanse in uncircumcised male and female
  - Collection bag or cloth diaper in infant
- Catheterization or suprapubic aspiration
  - Selected cases when voided specimen cannot be obtained
- Indwelling catheter
  - Consider changing long-term catheter that has been in for more than 3-5 days

Assessment: Routine Studies

- Urinalysis
  - Dipstick:
    - UTI (nitrites & leukocytes)
    - Diabetes mellitus (glucose)
    - Diabetes insipidus/ water intoxication (specific gravity)
    - LUT tumor (blood, RBC)
  - Microscopic examination
    - UTI (WBC & bacteria)
    - LUT (red blood cells)

UTI: Interpreting the U/A

- Bacteriuria: bacteria in urine; CFU > 10^5 considered clinically relevant but this criterion correlates poorly with clinical symptoms
- Pyuria: white blood cells (pus in the urine), indicates inflammatory response to something (like an indwelling catheter) but not necessarily bacteria
Urinalysis: How Accurate?

- Dipstick testing\(^1\)
  - Nitrite testing very specific (97\%) but less sensitive (43\%) when CFU <10\(^5\)
  - Leukocyte esterase specificity is 59\% and its sensitivity is 84\%
  - When combined…specificity is 98\% and sensitivity is 84\%

- Take home message: use a back up screening test whenever possible (microscopy)


Urinalysis: Microscopy

- Preparation of sample
  - 10-15 ml into test tube
  - Centrifuge at 5 minutes at 2000rpm or 2 minutes with high speed models
  - Pour off all but sludge in bottom
  - Agitate the sludge, place drop in center of slide
  - Cover with slip cover

- Examine with both eyes open, leave glasses on
- Use moderate light setting, most use too much
- Start with low setting (100x), then move to high (400x)
- Look around, concentrate on edges of slip cover as well as center
Urine Microscopy: Bacteriuria & Pyuria

URL: www.uwosh.edu/med_tech/teaching/microscopy.php

Urine Microscopy: Hematuria

URL: www.agora.crosemont.qc.ca/doceng/doc_013.htm

Urine Microscopy: Skin Cells

URL: www.ndt-educational.org/fogazzislidepart6.asp
UTI Diagnosis: Culture & Sensitivity Testing

- Selected cases in community acquired, generally obtained in all healthcare acquired
  - Colony count: standard for clinical relevance if >10^5 CFU/ml; there are some exceptions (as low as 10^3 in some E. coli & Enterococci)\(^1\)
  - Sensitivity testing still best means for guiding treatment for this particular UTI
  - Pay careful attention to “local antibiogram” and reach decision on treatment for individual patient accordingly

Prevention & Management

UTI Prevention: Behavioral Interventions

- Sexual activity (intercourse) well established risk factor for women, possible risk factor in men
- Very weak to moderate evidence supports the following interventions\(^1,2\)
  - Less frequent intercourse (<3 times weekly)
  - Limiting partners
  - Washing hands and genital area before and after intercourse
  - Voiding within 30 minutes of intercourse
  - Switching to different birth control method (diaphragm, spermicidal foam, even BCP have been connected; sexual activity is powerful confounding factor in these studies)

References:
UTI Prevention: Behavioral Interventions

- Wide variety of hygienic measures have been recommended; supporting evidence often weak or absent
  - Indirect but robust support for hand hygiene when in contact with fecal matter (recc. adapted from HAI literature), also adapted to advice about wiping from front to back following micturition or defecation
  - Weaker evidence for additives to bath water (“bubble baths” or “perfumed baths”, “scented soaps”), associated ↑risk for UTI, evidence traces its roots to very old case studies and multiple case series describing vulvovaginitis and LUTS in women and children rather than UTI occurrences


UTI Prevention: Behavioral Interventions

- Multiple other hygienic measures have been advocated that have no known evidence to support or refute…
  - Avoid tight fitting clothing
  - Breathable vs non-breathable undergarments
  - Shower versus tub bath
  - Tampons versus pads for containing menstrual flow
  - Voiding every __ hours, whether the individual desires to urinate or not, postponing urination, etc.
  - Void before or following physical activities

Preventing UTI & Recurrences

- Fluid Intake
  - Avoid extremes (consumption of high volumes of fluid or fluid restriction)
  - US Food & Science Board RDA for fluids: 30ml/kg/24 hr or ½ oz/lb/day (ambulatory person, moderate climate)
    - Approximately 1.5-2.2 liters in adult women, 1.5-2.3 in adult men; 1.2-2.3 in adults > 70 years of age
    - Children aged 1 to 3 years 1.0 to 1.5 liters; increase to 1.2 to 1.9 liters in older children

1. IOM/US Food & Science Board: Dietary Reference Intake for Water & Sodium. URL: http://www.iom.edu/Global/News%20Announcements/~/media/442A08B899F44DF9AAD083D86164C75B.ashx
Preventing UTI & Recurrences

**American cranberry (Vaccinium macrocarpon)**
- Principal antimicrobial action is *not* its ability to acidify urine; it is the concentration of Type a Pro-anthocyanins (PAC)
- Effective dose hypothesized to be >30mg administered twice daily; equals 2 8 ounce servings or juice or 2 capsules containing 36 mg PAC*
- Red cranberries have highest PAC concentration; avoid white cranberry juice

1. Strothers L. Personal communication.
* = TheraCran (Theralogix), Rockville MD

Preventing UTI & Recurrences

**Mixed** evidence suggests consuming probiotics (lactobacillus) via dietary sources (yogurt, etc.) *might* reduce UTI risk

Particularly sparse evidence suggests that consumption of certain fruits & berries or juices from these may reduce risk of UTI³

Sparse evidence also suggest acupuncture may help (mechanism unclear, amy reduce residual urine in some)¹


Prevention of UTI or Recurrence: Angocin Anti-Infekt N

- Herbal produce containing Tropasoli majoris and Armoracia rusticanae radix (horse radish) for recurring UTI
- In vitro study demonstrated antimicrobial activity against E. coli, Pseudomonas aeruginosa, MRSA, Staphylococcus Pyogenes species¹
- Clinical study of 219 adults (women & men), aged 18-75 years with recurring UTI had fewer UTI over 90 day period²
- 2 serious AE in treatment group not associated with herbal preparation

Circumcision for Prevention of UTI

- Is circumcision protective against UTI?
  - Circumcision reduces UTI risk approximately 10-fold over first 6 months of life and demonstrable benefit up to 12 months, colonization of bacteria declines by age 5 years as foreskin grows and retraction is easier.
  - Controversy over whether benefit extends beyond extends beyond 1st year of life, cohort analysis needed.
  - Evidence supports reduced transmission rates of HIV & syphilis, mixed evidence concerning relative risk for transmission of chancroid, HSV-2.


Future of UTI Prevention: Vaccines?

- E. coli associated with 75% or more of UTIs in community dwelling women, various vaccine targets
  - Vaccine for FimH protein has shown promise in blocking adherence of E. coli to bladder wall
  - Vaccine for D-galactopyranoside receptors in vaginal wall and epithelial cells in kidney may protect against development of pyelonephritis
  - Vaccine for UpaG a auto-transporter may block E. coli’s ability to bind to bladder wall and from biofilm


Future of UTI Prevention: Vaccines?

- 2 RCT of vaccine, E. coli extract (unable to adhere to wall of bladder, activates innate antibodies against E. coli colonization)
  - Both tested in women with recurrent UTI (3 in 1 year); one was a capsule administered daily for 90 days, off for 60 days, then daily for first 10 days of months 7-9; the other was a weekly vaginal suppository for 90 days, then weekly suppository for additional 90 days
  - Both groups achieved significantly fewer recurrences than placebo group; neither are commercially available in US

Preventing CAUTI

- Intervention Bundle: no single intervention sufficient to reduce CAUTI incidence; evidence based winning strategies include
  - Reduce indwelling catheter days by implementing system for monitoring catheter insertion and removal\(^1\,^2\)
  - Use bladder scanners to aid in timely catheter removal\(^2\)
  - Evaluate all aspects of existing indwelling catheter policies\(^3\)
  - Enhance use of alternative means for urinary drainage: intermittent catheterization and external collection devices\(^1\,^3\)


Pharmacotherapy for Management of UTI and Prevention of Recurrences

Management of Community Acquired UTI

- Goals of treatment
  - Eradicate bacteriuria
  - Alleviate symptoms
  - Prevent recurrence
- Empiric therapy may be administered in otherwise healthy younger adults, culture & sensitivity recommended in adults with comorbid conditions, febrile or recurring UTI
UTI: Empiric Treatment

- Empiric treatment recommended for nonfebrile UTI in community dwelling women (IDSA 2010 CPG)
  - First Line Therapy
    - Nitrofurantoin ER 100 mg twice daily for 5 days
    - Trimethoprim/ Sulfamethoxazole DS 1 tablet twice daily for 3 days
  - Second Line Therapy
    - Ciprofloxacin 250 mg twice daily or 500 mg daily for 3 days

Gupta K et al. Clinical Infectious Disease 2011; 52:e103-e120.

Pharmacotherapy for UTI: Empiric Antimicrobial Therapy

- Infectious Disease Society of America initially recommended empiric therapy for women with uncomplicated UTI in 1999; guidelines updated in 2010/11; principal recommendations include:
  - Consider nitrofurantoin as first line agent (A-I)*
  - Add fosfomycin to your first line choices (A-I)*
  - Penicillamines should not be used alone for empiric therapy owing to high resistance throughout US (A-III)**
  - Penicillamine plus β-lactam should be considered when above agents cannot be used (B-I)^
  - Use the fluoroquinolones as second line treatments for empiric therapy (A-III)**

Gupta K et al. Clinical Infectious Disease 2011;52:e103-e120.

* A-I: strong recommendation based on good evidence
** A-III: strong rec based on expert opinion/consensus
^ B-I: moderate recommendation based on good evidence
**UTI: Empiric Treatment: Antibiotic Options for Pregnant Women**

- Multiple β-lactams may be considered in pregnant women


**Pharmacotherapy for UTI**

- Trimethoprim-Sulfamethoxazole (Bactrim DS, Septa DS)
  - IDSA recommends 160/800mg (double strength tablet) administered twice daily for 3 days
  - Adverse SE include significant hyperkalemia in patients with renal insufficiency, diabetes mellitus, older age or use of angiotensin-converting enzyme (ACE) inhibitor; study published in 2011 found incidence was 51.4 per 100,000; no association seen with fluoroquinolones or nitrofurantoin
  - Linked to bloody, antibiotic-associated diarrhea in children

1. Gupta K et al. Clinical Infectious Disease 2011;52:e103-e120

- Nitrofurantoin (Macroantin, Macrobid)
  - Administer as 100 mg twice daily for 5 days
  - Achieves high urinary levels effective for *E. coli* and many other common domiciliary pathogens; less penetration in serum – do not use if evolving pyelonephritis suspected
  - Typically offers limited activity against *Proteus*, *Pseudomonas*, *Serratia* (~3-4% sensitivity)
  - Recent RCT found equivalent or superior efficacy to 3 day course of TMP/SMZ
  - Linked to risk of *C. Difficile* associated diarrhea

1. Gupta K et al. Clinical Infectious Disease 2011;52:e103-e120
Pharmacotherapy for UTI

- **Fosfomycin (Monurol)**\(^1\)\(^2\)
  - Administer as a 3 gram sachet in single dose in 90-120 ml of water; drug is not bound to plasma proteins, reaches high urinary levels in 2-2.5 hours and persisting for 36-48 hours; primarily excreted in urine
  - Efficacy shown non-inferior to norfloxacin, ofloxacin, ceftriaxone in several RCT
  - Carries risk for *C. Difficile* associated diarrhea, other SE include diarrhea, nausea, headache
  - IND and primary clinical experiences in women

1. Gupta K et al. Clinical Infectious Disease 2011;52:e103-e120

Pharmacotherapy for UTI

- **Fluoroquinolones (Cipro, Levaquin)**\(^1\)
  - *Second line agents*, administer ciprofloxacin as 500 mg twice daily or levofloxacin as 500 mg once daily
  - Levofloxacin offers broader coverage for gram positive organisms; some prefer ciprofloxacin for empiric
  - Linked to *C difficile* associated diarrhea
  - *In vitro* study finding suggests that ciprofloxacin activity may be augmented by *Pelargonium graveolens*, an essential oil\(^2\)

1. Gupta K et al. Clinical Infectious Disease 2011;52:e103-e120.

Bacterial Resistance

- Prevalent, clinically relevant, alarming\(^1\)
  - With repeated exposure to an antibiotic, bacteria will self-select (evolve) to favor lines that are resistant to that agent
  - No antimicrobial to date has proved immune to this process
  - Exposure is the key to evolution of resistance; secondary keys include pharmacokinetics of a given exposure
  - Example: recent study of ciprofloxacin resistance found the following predictors of resistance in elderly who were proven non-resistant 1 year ago:
    - 3 or more prescriptions in past year (OR 3.38; 95%CI 1.92-5.97)
    - Pork, chicken calcium supplements (ORs 3.68, 2.72, 2.51 respectively)

Pharmacotherapy for LUT Pain/Discomfort

- Consider short-term urinary analgesic
  - Phenazopyridine (Pyridium, 200mg three times daily): reduces burning and alleviates dysuria
  - MOA unknown, turns urine deep orange capable of staining clothing, some patients mistakenly identify color as indicating hematuria
  - Adverse side effects include fever, confusion, uncommon to rare SE impaired renal or liver function, hemolytic anemia (anemia risk rises with prolonged use).


Pharmacotherapy: Special Considerations in Children

- Diagnosis requires urinalysis plus culture in all infants and children with febrile UTI, microscopy strongly recommended – look for ≥ 10 WBC/hpf
  - Lower threshold for hospital admission, especially in infants & young children (↑ likelihood of sepsis)
  - 7-14 days of antibiotic therapy for all febrile UTIs; 2-4 days for afebrile episodes – begin with empiric selection and confirm
  - Look for antimicrobials available as liquid or suspension
  - Nitrofurantoin and cephalosporin often used as first line (greater likelihood of Enterococcus species); penicillamine use limited by E coli resistance


Pharmacotherapy for LUT Pain/Discomfort

- Combination agents for short-term analgesia contain one or more of the following agents
  - Pharmacologic actions of individual agents
    - Hyoscyamine (atropine): anticholinergic
    - Methanemine: urinary antiseptic, antimicrobial agent that acts by concentrating formaldehyde in low concentrations
    - Methylene blue: mild antiseptic effect
    - Sodium biphosphate: mild antiseptic effect
    - Phenyl salicylate: ASA with typical analgesic response
**Pharmacotherapy for LUT Pain/Discomfort**

- 4 agent formulations contain:
  - Hyoscyamine sulfate 0.06 - 0.12 mg, usually (Urised, Prosed)
    - Also list low dose atropine but this is a bit unclear. The dose appears to have changed to hyoscyamine.
  - Methenamine 81.2 - 118.4 mg
  - Methylene blue 10 - 10.8 mg
  - Sodium biphosphate 40.8 mg
  - Phenyl salicylate 36-40 mg

  - Typically prescribed as 1 tablet up to 4 times daily.
  - Multiple branded names (Uribel, Prosed, Urised, Urogescic blue); contain similar active agents, doses vary slightly (check with local pharmacy).

**Pharmacologic Strategies for Preventing Recurrent UTI**

- Consider ongoing course of suppressive antibiotic course for adults with recurrent UTI:
  - Daily dose; usually treat with a first line drug for empiric UTI treatment (nitrofurantoin, trimethoprim/sulfamethoxazole).
  - Consider baseline liver function panel and possibly chest x-ray if contemplating long-term suppression with nitrofurantoin.
  - I recommend a 6 month trial; some extend to 1 year trial.

**Pharmacologic Strategies for Preventing Recurrent UTI**

- Consider self-start antibiotic therapy:
  - 3 day course of antibiotic prescribed that patient stores in home.
  - Provide specimen cup for urinalysis ± urine culture with standing order with local laboratory.
  - Teach patient to monitor for symptoms.

- Consider post-coital antibiotic therapy:
  - Prescribe antibiotic as above and instruct patient to take single dose following intercourse.
Preventing Recurrent UTI: Methenamine

- Methenamine (Hiprex, Mandelamine, Urex)
  - Extensively excreted in urine, converting hexamine to formaldehyde, ↓ urinary pH exert antiseptic activity
  - Magnitude of effect (and clinical effectiveness) remains controversial
  - Cochrane Review indented 13 studies (2013 subjects); Overall study quality rated as low and heterogeneity too great for meta-analysis
  - Methenamine more effective than placebo in reduction of bacteriuria (RR 0.56, 95% CI 0.37-0.83) and symptomatic UTI (RR 0.24, 95% CI 0.07-0.89); sued short term (1 week or less); no differences when used in patients with urinary tract abnormalities (e.g. NGB) or indwelling catheters


Preventing UTI Recurrence in Postmenopausal Women

- Sparse evidence suggests benefit from intravaginal estrogen in women with urogenital atrophy
  - Systematic review pooled data from 4 studies (2798 women) found that oral estrogens did not reduce risk for recurring UTI, RR 1.08, 95% CI: 0.89-1.33
  - Non-pooled results from 2 studies suggest that intravaginal estrogens (cream or ring device) may reduce risk for recurrence RR 0.25, 95% CI: 0.13 - 0.50 and RR 0.64, 95% CI: 0.47-0.86

Perrotta C et al. Cochrane Database of Systematic Reviews, (CD005131, 2008).

Preventing UTI Recurrence

- Recurrent UTI defined as 3 occurrences in 12 months or 2 in 6 months
- All primary preventive strategies should be considered for preventing recurrence
- Consider obtaining urine culture for recurrent UTI to exclude possibility of persistent bacteriuria
- Consider referral or imaging of urinary tract for urinary stone, anatomic defect of urinary tract, obstructive uropathy, etc.

Febrile UTI: 
Principles of Management

- Determine need for hospitalization
  - Evidence of sepsis
  - High fever
  - High WBC
  - Vomiting and dehydration precluding ability to take oral medications or fluid/electrolyte balance
  - Lack of resources in home

Pharmacotherapy for Febrile UTI

- Begin with empiric therapy; IDSA/EMSID guidelines recommend ciprofloxacin twice daily.*
  - Consider single parenteral dose of antimicrobial agent before starting empiric oral therapy; often aminoglycoside, ceftriaxone, or fluoroquinolone
  - Tailor antibiotic selection based on sensitivity panel
  - If hospital admission required, start with aminoglycoside ± aminopenicillin, fluoroquinolone, extended spectrum (3rd or 4th generation) cephalosporin (example is ceftazidime)

* Level of Recommendation = A-III

1. Gupta K et al. Clinical Infectious Disease 2011; 52:e103-e120.
Pharmacotherapy for Febrile UTI

- Antibiotic options for febrile UTI:
  - Fluoroquinolone: ciprofloxacin 500 mg twice daily for 7 days or levofloxacin once daily for 5 days (B-II)*
  - Trimethoprim-sulfamethoxazole (160/800 mg, DS) for 14 days (A-I)*
  - β-lactams less effective than these suggestions, recommend initial parenteral dose or beginning with initial dose of aminoglycoside (B-II, B-III)*; optimal duration of therapy is unknown – possibly 10-14 days

* = Level of Recommendation

1. Gupta K et al. Clinical Infectious Disease 2011; 52:e103–e120.

Community-Based Management

- 7-14 day course of ciprofloxacin (more effective than 14 days of TMP-SMX: 96% vs. 83%)*
- Oral ciprofloxacin taken as directed provides serum levels comparable to parenteral administration
- Repeat culture 5-7 days if response questioned
- Repeat culture 14 days after treatment completed; 10%-16% will recur
- Extend treatment to 6 weeks if necessary and exclude abscess or complicating condition


Extended Evaluation in Infants, Children & Adults
Infants & Children

- Febrile UTI in child associated with ↑ risk of vesicoureteral reflux and renal damage (big bang hypothesis)
  - Controversy exists as to proper evaluation of infants and children who experience first (or 2nd) febrile UTI
  - Extended evaluation usually involves one or more of the following
    - Ultrasonography
    - Voiding urethrogram
    - Radionuclide cystogram or imaging of upper urinary tracts
    - Gadolinium MRI
  - Extend evaluation after 1st or 2nd UTI?
  - Is VCUG necessary?

American Academy of Pediatrics Revised their Guidelines for Infants 3 months to 2 years

- Diagnosis should include urinalysis and positive urine culture
- Infants with proven febrile infants should undergo renal and bladder ultrasonography
- VCUG routinely only when:
  - Ultrasound reveals hydronephrosis, scarring, or other findings that would suggest high-grade VUR or obstructive uropathy
- *VCUG indicated after 2nd febrile UTI

Top Down Algorithm

Febrile UTI

- DMSA scan
  - Cortical defect (Pyelonephritis)
    - VCUG
  - Normal
    - Central photopenia (Hydronephrosis)
      - No further W/U* = Ultrasound
      - *Recurrent febrile UTI
    - VCUG (*AAP Guideline)

*Algorithm courtesy H Gil Rushon, MD
**Additional Diagnostic Studies for Febrile of Healthcare Acquired UTI**

- Upper tract imaging: ultrasound or spiral CT when renal colic present or urinary calculi suspected
- Abdominal CT for unresolved (persistent) UTI to exclude abscess or anatomic abnormality
- Doppler enhanced ultrasound when epididymitis suspected
- Referral and cystourethroscopy in selected cases

**Conclusions**

- UTI prevalent in both genders
- Lifetime risk greatest for women vs men
- Classification of UTI, diagnosis and treatment based on where UTI was acquired (community vs healthcare setting)
- Management must go beyond short course antimicrobials to include multiple non-pharmacologic interventions to prevent or limit recurrences
