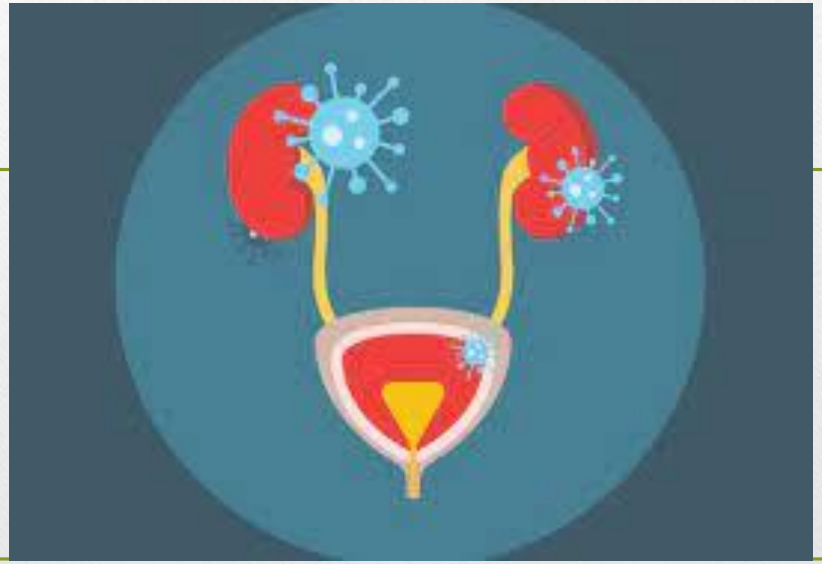
URINARY TRACT INFECTION



Dr. Khosravi

Clinical Pharmacist

Incidence, Prevalence, and Epidemiology

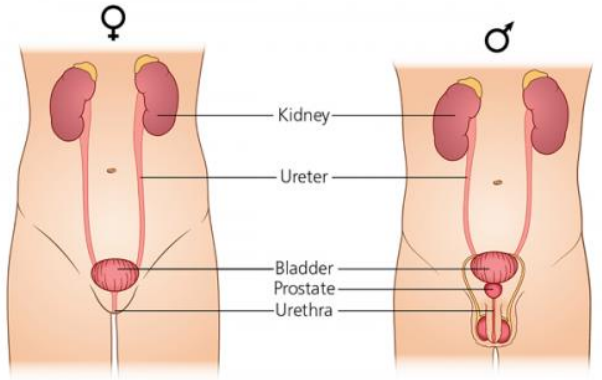
- UTI is an acute or chronic infection, usually bacterial in origin, that may affect any part of the upper or lower urinary system.

- Infections of the bladder ➲ **cystitis**
- Infections of parenchyma of the kidneys ➲ **pyelonephritis**

Incidence, Prevalence, and Epidemiology

- The most common bacterial infections in humans.
- From asymptomatic infection to acute pyelonephritis with sepsis
- Approximately 8-9 million cases of acute cystitis and 250,000 cases of acute pyelonephritis occur annually in the US ➲ >100,000 hospitalizations.

Prevalence



- **F= 30 M** (> 50% of all women experiencing at least one infection during their lifetime) probably because of anatomic and physiologic differences

❶ Female urethra is relatively short and allows bacteria easy access to the bladder.

❷ males are partly protected because the urethra is longer and antimicrobial substances are secreted by the prostate.

Epidemiology

- The incidence of UTI in neonates is about 1% and is more frequent in male neonates ➲ congenital structural abnormalities

- Prostatic obstruction, urethral instrumentation, and surgery influence the infection rate, incomplete bladder emptying caused by underlying diseases or medications, dementia, and urinary and fecal incontinence ➲ ↑ frequency of UTI in male > 50

UNCOMPLICATED VERSUS COMPLICATED INFECTIONS

- Uncomplicated UTI (cystitis or pyelonephritis) ➲ in women who have **normal structure and function** of the GU tract and who have no other factors which would put them at risk for more severe or complex infections
- Complicated UTI ➲ increase the risk for acquiring infection, the potential for serious outcomes, or the risk for therapy failure (GU tract abnormalities ➲ interfere with normal urine flow)

UNCOMPLICATED VERSUS COMPLICATED INFECTIONS

- Infections in men, children, and pregnant women ➲ **complicated**

❖ Other complicated infections:

✓ structural and neurologic abnormalities of the urinary tract,

✓ metabolic or hormonal abnormalities,

✓ impaired host responses,

✓ instrumentation and catheterization of the urinary tract,

✓ those caused by unusual pathogens (e.g., yeasts, Mycoplasma)

COMMUNITY-ACQUIRED INFECTIONS

- Gram-negative aerobic bacilli from the intestinal tract.

✓ E-coli (75% -95%)

✓ Coagulase-negative staphylococci (e.g., Staphylococcus saprophyticus) (5% - 20%)

✓ Other Enterobacteriaceae (e.g. Proteus mirabilis, Klebsiella) and Enterococcus faecalis

- Uncomplicated infections are nearly always caused by a single pathogen.

HEALTH CARE–ASSOCIATED INFECTIONS

- ✓ E. coli (the most common pathogen)
- ✓ Pseudomonas aeruginosa, Klebsiella, Proteus, Enterobacter, and Acinetobacter,
- ✓ Enterococcus
- ✓ UTIs because of Staphylococcus aureus are usually the result of hematogenous spread, although this pathogen is also associated with urinary catheterization
- ✓ Candida
- UTIs associated with structural abnormalities or indwelling urinary catheters are often caused by multiple pathogens

Table 71-1

Overview of Treatment of Urinary Tract Infections

Organisms Commonly Found	Antibacterial of Choice
Uncomplicated UTI	
Escherichia coli	TMP–SMX[a]
Proteus mirabilis	TMP–SMX[a]
Klebsiella pneumoniae	TMP–SMX[a]
Enterococcus faecalis	Ampicillin, amoxicillin
Staphylococcus saprophyticus	First-generation cephalosporin or TMP–SMX
Complicated UTI[b,c]	
E. coli	First-, second-, or third-generation cephalosporin; TMP–SMX[c]
P. mirabilis	First-, second-, or third-generation cephalosporin
K. pneumoniae	First-generation cephalosporin; fluoroquinolone
Enterococcus faecalis	Ampicillin or vancomycin ± aminoglycoside
Pseudomonas aeruginosa	Antipseudomonal penicillin ± aminoglycoside; ceftazidime; cefepime; fluoroquinolone; carbapenem
Enterobacter	Fluoroquinolone; TMP-SMX; carbapenem
Indole-positive *Proteus*	Third-generation cephalosporin; fluoroquinolone
Serratia	Third-generation cephalosporin; fluoroquinolone
Acinetobacter	Carbapenem; TMP-SMX
Staphylococcus aureus	Penicillinase-resistant penicillin; vancomycin

Pathogenesis and Predisposing Factors

- Ascending route
- A UTI usually begins with heavy and persistent colonization of the introitus (i.e., vaginal vestibule and urethral mucosa) with intestinal bacteria.
- Colonization of the urethra leads to retrograde infection of the bladder and the development of cystitis.

Pathogenesis

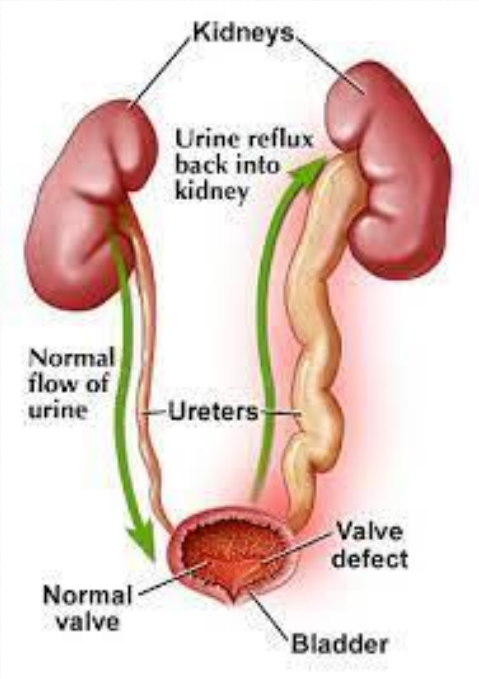
❖ Defense mechanisms of bladder:

- ✓ Urination washes bacteria out of the bladder and is effective if urine flows freely and the bladder is emptied completely.
- ✓ Substances in the urine, including **organic acids** (which contribute to low pH) and **urea** (which contributes to high osmolality) ➲ antibacterial
- ✓ The bladder mucosa ➲ antibacterial properties
- ✓ IgA and glycoproteins (e.g., Tamm–Horsfall protein) ➲ prevent adherence of bacteria to uroendothelial cells.

Pathogenesis

- Spread of bacteria via the ureters and may be facilitated by vesicoureteral reflux or decreased ureteral peristalsis ➲ pyelonephritis

- Pregnancy, ureteral obstruction, gram-negative bacterial endotoxins ➲ ↓ ureteral peristalsis



Predisposing Factors

- Bacterial virulence factors: specific adhesin molecules, bacterial polysaccharides, and bacterial enzymes.

- Host: extremes of age, female sex, sexual activity, use of contraception, pregnancy, urinary tract instrumentation or catheterization, urinary tract obstruction, neurologic dysfunction, renal disease, previous antimicrobial use, and expression of A, B, and H blood group oligosaccharides on the surface of epithelial cells

Cont.

- Hormonal changes, anatomic changes, progressive urinary stasis, and glucose in the urine ➲ ↑ UTI in pregnancy
- Hormonal changes ➲ ↑ UTI in menopausal women
- Estrogen promotes an acidic vaginal pH and proliferation of normal flora such as Lactobacillus, both factors which reduce pathogenic colonization of the vagina.

Cont.

- 🡻 estrogen production during menopause ➲ significant colonization of the vaginal tract with E. coli and other enteric bacilli
- Renal disease ➲ 🡹 susceptibility of the kidney to infection.
- UTI in KT from 35%-80% without prophylactic antibiotic therapy.
- Spinal cord injuries, stroke, atherosclerosis, or diabetes may have neurologic dysfunction ➲ 🡹 UTI

Clinical Presentation

- Symptoms of cystitis: burning on urination (dysuria), frequency, suprapubic pain, hematuria, and back pain.
- Symptoms of acute pyelonephritis: loin pain, CVA tenderness, fever, chills, nausea, and vomiting.
- Clinical signs and symptoms correlate poorly with either the presence or the extent of the infection.

Clinical Presentation

- Many elderly patients with UTI are asymptomatic without pyuria. Additionally, because many patients have frequency and dysuria, it is difficult to distinguish between noninfectious and infectious causes based on symptoms.

- Nonspecific symptoms, such as failure to thrive and fever, may be the only manifestations of UTI in neonates and children < 2 years.

Diagnosis

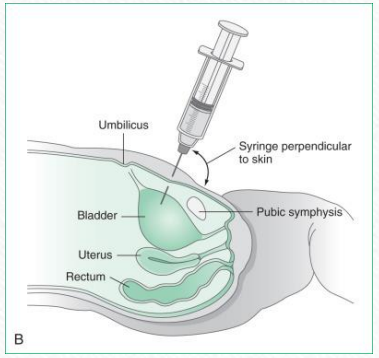
- Diagnosis of UTI based on clinical findings alone is accurate in only approximately 70% of patients.
- U/A in combination with appropriate clinical findings
- The nitrite test detects nitrite formation from the reduction of nitrates by bacteria.
- Although a positive nitrite reading is useful, false-negative results do occur.

Diagnosis

- Bacteruria (usually >20 per HPF)
- Pyuria (i.e., ≥8 WBC/mL of uncentrifuged urine or 2–5 WBC/HPF of centrifuged urine)
- WBC casts in the urine strongly suggest acute pyelonephritis

Diagnosis

- The gold-standard of diagnosis of UTI is the urine culture with a positive UA.
- Urinating into a sterile collection cup using the **midstream clean-catch technique** is the most practical method of urine collection.
- Suprapubic bladder aspiration



Diagnosis

- $>10^5$ colonies of bacteria/mL ➲ confirms a UTI
- Approximately 30%-50% of actual cases of acute cystitis have $<10^5$ bacteria/mL.
- In a symptomatic patient, using a definition of $\geq 10^2$ bacteria/mL is more accurate
- $>10^3$ bacteria/mL ➲ highly suggestive of UTI in men

LOWER UTI

- Selection of a specific antimicrobial based on:

(a) most likely pathogens,

(b) resistance rates within the specific geographic area,

(c) desired duration of therapy,

(d) clinical efficacy and toxicity profiles of various agents,

(e) cost and availability of specific agents

(f) patient characteristics such as allergies, compliance history, and underlying comorbidities.

ROLE OF URINE CULTURES

- The patient should be empirically treated with a conventional course of antibiotic therapy. If patient remains symptomatic 48 hours later, a C&S test can then be ordered.

- Use of C&S testing is therefore commonly recommended for treatment of complicated UTI in order to choose appropriate antibiotics

Overview of Drug Therapy

- The cornerstone of effective treatment of UTI is the appropriate selection and use of antibiotics

- IDSA/ESMID for as first-line antibiotics for **treatment of acute uncomplicated cystitis in women:**

✓ 5-day nitrofurantoin,

✓ 3-day trimethoprim–sulfamethoxazole (TMP–SMX)

✓ single dose of fosfomycin trometamol

Drug therapy

- Fosfomycin also has usefulness against MRSA, VRE, and ESBL- producing gram-negative bacteria.

- FQ, β-lactam antibiotics (amoxicillin–clavulanate or various cephalosporins) ➲ alternative agents for treating acute uncomplicated cystitis.

Table 71-2

Commonly Used Oral Antimicrobial Agents for Acute Urinary Tract Infections[1–3,5,29,47,48,91]

Drug	Usual Dose		Pregnancy[a]	Breast Milk[a]	Comments[b]
	Adult	Pediatric			
Amoxicillin	250 mg every 8 hours or 3 g single dose	20–40 mg/kg/day in 3 doses	Crosses placenta (cord) = 30% (maternal)[c]	Small amount present	High resistance rates, not for empiric use.
Amoxicillin + potassium clavulanate	500 + 125 mg every 12 hours	20 mg/kg/day (amoxicillin content) in 3 doses	Unknown	Unknown	
Ampicillin	250–500 mg every 6 hours	50–100 mg/kg/day in 4 doses	Crosses placenta	Variable amount; milk = 1–30% of serum[c]	High resistance rates, not for empiric use. Should be taken on an empty stomach.
Cephalexin	250–500 mg every 6 hours	15–30 mg/kg/day in 4 doses	Crosses placenta	Enters breast milk	Cephalosporins are alternate choices for patients allergic to penicillins, although cross-hypersensitivity can occur. May be associated with higher failure rates compared to other drug classes.
Cefaclor	250–500 mg every 8 hours	20–40 mg/kg/day in 2–3 doses	Crosses placenta	Small amount present	

Cefaclor	250–500 mg every 8 hours	20–40 mg/kg/day in 2–3 doses	Crosses placenta	Small amount present	
Cefpodoxime proxetil	100 mg every 12 hours	10 mg/kg/day in 2 doses	Crosses placenta	Variable amounts; milk = 0–16% of serum	
Cefdinir	300 mg every 12 hours or 600 mg every 24 hours	14 mg/kg/day in 1 or 2 doses	Crosses placenta	Not detectable after single 600 mg dose	
Norfloxacin[d]	400 mg every 12 hours	Avoid	Arthropathy in immature animals	Unknown	*Avoid antacids, divalent and trivalent cations, and sucralfate. Monitor INR in patients on warfarin. May cause dizziness.*[e]
Ciprofloxacin[d]	250–500 mg every 12 hours	Avoid	Arthropathy in immature animals	Unknown	Alternate choice for patients allergic to β-lactams.[e] Useful for pseudomonal infection.
Levofloxacin	250 mg every 24 hours	Avoid	Arthropathy in immature animals	Milk = 100% of serum[c]	
Nitrofurantoin	100 mg every 12 hours (e.g., Macrobid) 50–100 mg every 6 hours (e.g., Macrodantin)	5–7 mg/kg/day in 2–4 doses	Hemolytic anemia in newborn	Variable amounts; not detectable up to 30%; may cause hemolysis in G6PD-deficient baby	Alternate choice. *To be taken with food or milk. May cause brown or rust-yellow discoloration of urine.*
Sulfamethoxazole (SMX)	1 g every 12 hours	60 mg/kg/day in 2 doses	Crosses placenta; displacement of bilirubin may lead to hyperbilirubinemia and kernicterus, avoid after 32 weeks of gestation; teratogenic in some animal studies	Enters breast milk; displacement of bilirubin may lead to neonatal jaundice; may cause hemolysis in G6PD-deficient baby	Alters bowel flora to favor resistant organisms. *To be taken on an empty stomach with a full glass of water. Photosensitivity may occur.*

Table 71-2

Commonly Used Oral Antimicrobial Agents for Acute Urinary Tract Infections (*continued*)

Drug	Usual Dose		Pregnancy[a]	Breast Milk[a]	Comments[b]
	Adult	Pediatric			
Trimethoprim (TMP)	100 mg every 12 hours		Crosses placenta (cord) = 60%; (maternal) folate antagonism, avoid during first trimester; teratogenic in rats	(milk) >1 (serum)[c]	Alternate choice.
TMP–SMX	160 + 800 mg every 12 hours	10 mg/kg/day (TMP component in 2 doses)	Crosses placenta (cord) = 60%; (maternal) folate antagonism, avoid during first trimester; teratogenic in rats	(milk) >1 (serum)[c]	*To be taken on an empty stomach with a full glass of water. Photosensitivity may occur.* Monitor HIV-infected patients closely for development of adverse hematologic reactions.
					First-line agent for prostatitis.
Fosfomycin	3 g single dose	No data	Crosses placenta	Unknown	Recommended option for uncomplicated cystitis.

INITIAL ANTIBIOTIC SELECTION

- TMP–SMX ➲ effective Gram-positive and gram-negative organisms, with the notable exceptions of Enterococcus, P. aeruginosa, and anaerobes.

- Individually, trimethoprim and sulfamethoxazole are bacteriostatic, but in combination they are bactericidal against most urinary pathogens.

TMP–SMX

- Furthermore, this combination is almost uniformly successful in the treatment of uncomplicated UTI, even against organisms that originally were resistant to either agent alone.

- Urinary concentrations of trimethoprim and sulfamethoxazole far exceed the MIC for most susceptible urinary pathogens.

Nitrofurantoin

- Almost completely absorbed after oral administration, but it barely reaches detectable levels in the plasma because it is rapidly eliminated (t ½=20 min) into the urine and bile ➲ high urine levels are 50-250 mg/L and are well in excess of the MIC for most common pathogens causing UTI.

- Food ➲ 🡻 the rate of absorption, 🡹 the total BA of nitrofurantoin from both the macrocrystalline capsules and the microcrystalline tablets by about 40%.

- This effect lengthens the duration of therapeutic urine concentrations by about 2 hours.

Nitrofurantoin

- Coverage of E. coli, some strains of Pseudomonas, S. saprophyticus, streptococci, and enterococci
- Proteus, Enterobacter, and Klebsiella are more likely to be resistant (susceptibility <60%).

Adverse effects

❶ Nausea (dose related)

- The mechanism is not clear by which nitrofurantoin produces nausea is central or local.

- Taking nitrofurantoin with food may reduce nausea either through serving as a buffer or slowing the rate of absorption and reducing peak concentrations of the drug.

Adverse effects

- Use of the macrocrystalline preparation may also reduce adverse effects through slowing rates of dissolution and absorption, and producing lower serum levels.

❷ Pulmonary reactions (fever, dyspnea, and cough; eosinophilia) ➲ rechallenge is contraindicated

Adverse effects

❸ Peripheral neuropathy (symmetric dysesthesia and paresthesia in the distal extremities, which progresses in a central and ascending fashion)

- ✓ Neuropathy usually occurs within the first 60 days of chronic nitrofurantoin treatment and is rarely seen during shorter courses of therapy
- ✓ Symptom severity is not dose-related and is generally reversible, although more severe cases may require up to several months to resolve completely.
- ✓ Renal failure ➲ ↑ neurotoxicity and pulmonary toxicity

Fosfomycin

- Phosphonic acid derivative ➲ irreversibly block bacterial cell wall synthesis through inhibition of early cytoplasmic stages of peptidoglycan synthesis.

- It has bactericidal activity against E. coli and other Enterobacteriaceae, P. aeruginosa, and Enterococcus as well as many MRSA, VRE, and ESBL-producing gram-negative bacilli

Fosfomycin

- Fosfomycin is approximately 40% absorbed after oral administration as granules marketed in a sachet form and is rapidly and almost completely excreted unchanged in the urine.
- Fosfomycin achieves mean urinary concentrations > 500 mg/L within 6-8 hours after administration and maintains concentrations >100 mg/L for a duration of >26 hours after a single oral dose.
- Single 3-g oral doses

Drug therapy

- IDSA/ESMID for treatment of acute pyelonephritis in women:

- FQ, cephalosporins, AG, TMP–SMX, extended-spectrum penicillins (i.e., piperacillin–tazobactam), or a carbapenem

- The duration of therapy for acute pyelonephritis: 5-14 days and is dependent on which specific antibiotic is being used.

Monitoring

- Resolution of clinical signs and symptoms, and repeat urinary cultures are not usually required.

- Patients with complicated UTI or recurrent infections may require additional monitoring and long-term follow-up, and antibiotic selection must be guided by culture and susceptibility (C&S) testing.

Others

- FQ ➲ not be routinely used as preferred agents in the treatment of uncomplicated UTI because ↑ rates of resistance among common uropathogens and significant collateral effects on normal flora (Clostridium difficile infection)

- β-lactams (Amoxicillin–clavulanate and several oral cephalosporins) to be generally comparable to TMP–SMX, but less clinically or microbiologically effective than the FQ.

Others

- β-lactams ➲ longer durations of treatment ➲ 🡻 patient adherence and 🡹 rates of drug-related adverse effects and 🡹 frequent emergence of bacterial resistance, including ESBL-producing gram-negative bacilli.

- β-lactam antibiotics (with the exception of pivmecillinam) are currently only recommended for empirical treatment of uncomplicated cystitis when none of the other agents previously discussed can be used.

Cont.

- Ampicillin and amoxicillin ➲ ↑ resistance rates ➲ discouraged for empirical treatment of UTI

- FQ ➲ preferred agents for initial treatment of complicated UTI with subsequent antibiotic therapy guided by the results of C&S testing

FLUOROQUINOLONE THERAPY

- Norfloxacin, ciprofloxacin, and levofloxacin
- Excellent in-vitro activity against most gr – and gr + organisms, including P.aeruginosa, S. saprophyticus.
- The activity of many FQ in vitro is antagonized by urine (acidic pH, divalent cations); however, this is unlikely to be clinically significant because urine concentrations are several hundred-fold greater than serum levels.

Cont.

- FQ are recommended as appropriate alternatives for patients with allergies or other contraindications to the use of other first-line agents, or for patients infected with organisms resistant to multiple antibiotics, such as P. aeruginosa.

- FQ are effective in treating patients with structural or functional abnormalities of the urinary tract and other complicated infections.

Fluoroquinolones

- Contraindicated in children and adolescents < younger than 18 years of age because of concerns regarding potential musculoskeletal toxicities in juvenile populations.

- Although not approved for pediatric use, FQ have been formally studied for febrile neutropenia, infectious gastroenteritis, otitis media, bacterial meningitis, and other uses in pediatric patients

Fluoroquinolones

- Tendinopathy or other musculoskeletal toxicities ➲ usually mild, reversible, and occurring at rates comparable to that seen in adults.
- AAP: FQ may be considered in special circumstances including (a) infections caused by MDR pathogens for which there are no other safe and effective alternatives and (b) times when parenteral therapy is not feasible and no other effective oral agent is available.

Treatment of UTI caused by MDR, gram-negative pathogens are specifically mentioned as a potentially appropriate use for FQ in pediatric patients.

Phenazopyridine

- A urinary tract analgesic, occasionally is prescribed alone or along with an antibacterial agent for the symptomatic relief of dysuria.
- Although phenazopyridine at a dose of 200 mg TDS may relieve dysuria, it is ineffective in the actual eradication of true UTI.
- Short trial (1–2 days) of phenazopyridine

Adverse effects

❶ Azo dye ➲ discolor the urine to an orange–red, orange–brown, or red color that can stain clothes.

❷ In vivo, about 50% of phenazopyridine is metabolized to aniline, which can cause methemoglobinemia and hemolytic anemia (primarily in patients with G6PD deficiency)

❸ Reversible AKI and allergic hepatitis (rare)

DURATION OF ANTIBIOTIC THERAPY

❖ **Outpatients with acute, uncomplicated UTI:**

✓ traditional 7-14 day course of oral medications ➲ now is considered excessive for most patients with uncomplicated infections

✓ a shorter 3-5-day course of therapy,

✓ single-dose therapy

TMP–SMX is recommended as the preferred agent for 3-day treatment regimens; the FQ may also be used in this shorter duration.

DURATION OF ANTIBIOTIC THERAPY

- β-Lactam ➲ courses of 3-7 days

- Longer treatment courses are also used in cases of treatment failure after regimens of shorter duration, as well as in the treatment of complicated UTI where longer courses of therapy (7–14 days) are associated with higher clinical success rates and improved outcomes.

Cont.

❶ Bacteria disappear from the urine within hours after antibacterial therapy has been initiated.

❷ urinary bladder's ability to defend itself through micturition, acidification, and inherent antibacterial activity ➲ a large single dose of an antibiotic can eradicate a UTI.

- Very high urinary concentrations of Fosfomycin are maintained for >24 hours after a single 3-g oral dose and contribute to the favorable clinical efficacy observed in comparative trials.

Cont.

- Female patients with history or clinical presentation suggestive of complicated infection (e.g., systemic manifestations of infection, renal disease, anatomic abnormalities of the urinary tract, DM, pregnancy), a history of antibiotic resistance, or a history of relapse after single-dose therapy ➲ should not receive single-dose regimens.

- Single dose therapy is also not appropriate for male patients with UTI.

Cont.

- The advantages of single-dose treatment: ↑compliance, ↓ cost, proven efficacy in a defined population of patients (i.e., young women with acute, uncomplicated lower UTI), minimal side effects, and ↓incidence of bacterial resistance associated with antibiotic overuse.

RECURRENT UTIs

Relapse versus Reinfection

- Recurrent infections develop in approximately 20%-30% of women with acute cystitis.
- Relapse ➲ recurrence of bacteriuria caused by the same microorganism within 1-2 weeks after the completion of therapy
- Relapses often are associated with an inadequately treated upper UTI (e.g. medication non-adherence), structural abnormalities of the urinary tract, or chronic bacterial prostatitis

Relapse versus Reinfection

- Reinfection ➲ recurrence of bacteriuria with a different organism than was present before therapy and occur at any time during or after the completion of treatment, but most appear several weeks to several months later.
- Approximately 80% of recurrences are caused by reinfection.
- Reinfection is generally caused by introital colonization with Enterobacteriaceae from the lower intestinal tract; of these, E. coli is the most common.

Relapse versus Reinfection

- Patients with reinfection should be investigated for modifiable predisposing factors such as use of a diaphragm with or without spermicides.

- Patients with frequent reinfections should also be evaluated for risk factors such as anatomical abnormalities, undiagnosed glucose intolerance or diabetes, or other factors.

Treatment for Reinfection

- Because reinfection is not caused by failure of previous therapy, TMP–SMX may be a reasonable choice once again.

- If several months elapse between each episode of antimicrobial therapy, normal fecal bacterial flora become reestablished and the risk of infection with resistant pathogens is reduced.

Treatment for Reinfection

- Nitrofurantoin is generally a useful agent for the treatment of recurrent E. coli, S. saprophyticus, and Enterococcus infections.
- The fluoroquinolones also are useful in this setting, especially in geographic areas with high rates of TMP–SMX resistance.
- Cephalosporins (e.g., cefuroxime, cefpodoxime proxetil) and trimethoprim have also been recommended as alternative agents in this setting.

Antibiotic Selection for Treatment of Relapse

- Additional reasons for treatment failure, including failure to adhere to previously prescribed medication regimens, should also be investigated in patients with apparent recurrent infections.

- Same or different antibiotic (according to culture)

Duration of therapy

- For relapsing infections usually is 14 days.
- In patients who relapse after a second 2-week course of therapy, treatment for 6 weeks should be instituted.
- If relapse occurs after a 6-week course, some experts recommend longer courses of 6 months to 1 year.

Chronic Prophylaxis

- The frequency of urinary infections probably is the main determinant of whether chronic suppressive therapy should be used, because repeated treatment of recurrent infections eventually will result in a decreased incidence of subsequent infections.

- Long-term prophylactic therapy clearly reduces the frequency of symptomatic infections in nearly all patients.

Chronic Prophylaxis

- For women with ≥ 3 episodes of cystitis per year, prophylaxis clearly is more cost-effective than treating individual infections.

- Therefore, it is recommended that chronic antimicrobial prophylaxis may be considered in any adult patient with ≥ 2 episodes of UTI per year.

Duration of prophylactic therapy

- Prophylaxis should be continued for 6 months in patients with < 3 UTIs per year and for at least 12 months in adult patients with ≥ 3 UTIs per year.

- Age also should be considered when contemplating chronic antimicrobial therapy (elderly patient taking many other medications is usually not an ideal candidate for chronic prophylactic treatment).

Prophylactic therapy

- Before chronic antimicrobial suppressive therapy is initiated, active infections must be completely eradicated with a full course of appropriate antibiotic therapy.

- The low doses of antimicrobials used for chronic prophylaxis suppress bacterial growth but do not eliminate active infection.

Prophylactic therapy

- TMP–SMX (extensive experience, proven efficacy, infrequent toxicities, and low cost).
- TMP–SMX ➲ 🡻 vaginal colonization with uropathogens
- TMP–SMX single strength, either one-half or one full tablet daily

Table 71-5

Antimicrobial Agents Commonly Used for Chronic Prophylaxis Against Recurrent UTIs[1–3,5,77–79,82]

Agent	Adult Dose	Comments[a]
Nitrofurantoin	50–100 mg nightly	Contraindicated in infant <1 month of age. *To be taken with food or milk. May cause brown or rust-yellow discoloration of urine.*
Trimethoprim	100 mg nightly	Not recommended in children <12 years of age.
Trimethoprim 80 mg + sulfamethoxazole 400 mg	0.5–1 tablet nightly *Or* 3/week	Not recommended for use in infants <2 months. *To be taken on an empty stomach with a full glass of water. Photosensitivity may occur.*
Norfloxacin	200 mg/day	*Avoid antacids*; monitor theophylline levels.
Cephalexin	125–250 mg/day	
Cefaclor	250 mg/day	
Sulfamethoxazole	500 mg/day	

Cont.

- Cranberries and probiotics have long been of interest for their potentially beneficial effects in preventing UTI.

- Cranberries contain known compounds (i.e., flavonols, anthocyanidins, proanthocyanidin-tannins) ➲ prevent E. coli from adhering to uroepithelial cells in the urinary tract.

Cont.

- Probiotics (particularly Lactobacillus strains) may prevent colonization with pathogens associated with UTI. Studies of probiotics for prophylaxis, however, are inconclusive at this time.

- Lack of standardization of ingredients (i.e. purity, dosage strengths) among available products and paucity of well-designed clinical studies are among the reasons for lack of clear recommendations regarding probiotics for this use.

UTI and Sexual Intercourse

- Studies also indicate that introital colonization by fecal bacteria has a definite role in recurrent infections related to intercourse.

- The migration of these colonizing bacteria into the bladder appears to be facilitated during intercourse, but the exact mechanism remains unclear.

Cont.

- Postcoital antibiotic prophylaxis is useful when recurrent UTI results from sexual intercourse.

- Patients should be instructed to empty their bladder just after intercourse and before taking the medication to minimize the number of bacteria present in the bladder and to reduce dilution of the drug in the urine.

Cont.

- However, this practice is not recommended in patients with structural abnormalities of the urinary tract or decreased renal function.
- Symptomatic infection must be completely treated before beginning prophylaxis.
- **Postcoital prophylaxis:** TMP–SMX or nitrofurantoin is the most commonly recommended agent; however, other agents such as FQ and cephalexin may be used.

UTI and Pregnancy

- Untreated bacteriuria ➲ acute symptomatic lower UTI or pyelonephritis
- UTI during pregnancy ➲ ↑ preterm labor, premature delivery, and lower birth-weight infants

- Nitrofurantoin is often recommended during pregnancy because teratogenic effects have not been observed clinically.

- During lactation, nitrofurantoin ➲ hemolytic anemia in a G6PD-deficient nursing infant; however, only small amounts have been detected in breast milk.
- FQ ➲ contraindicated in pregnancy because of the arthropathy observed in immature animals

UTI and Pregnancy

- The penicillins and cephalosporins are safe for use during pregnancy.
- Trimethoprim and TMP–SMX ➲ avoided because of the folate antagonist actions of trimethoprim and concerns regarding neural tube and cardiovascular defects potentially associated with maternal folate deficiency during the first trimester.

UTI and Pregnancy

- It is recommended that pregnant patients receive either a 3-day regimen or a 7- to 10-day regimen rather than single-dose therapy.

- Appropriate follow-up of patients is crucial.
- Clinicians must document elimination of pathogens 1-2 weeks after therapy and follow the patient monthly for the remainder of gestation.

ASYMPTOMATIC BACTERIURIA

Antibiotic Treatment

- The treatment depends on the clinical setting in which it is found.

- Recommendations for treatment of asymptomatic patients with significant bacteriuria (two consecutive voided urine specimens showing $\geq 10^5$ bacteria/mL of urine in women, or a single clean-catch voided specimen in men) are based on specific **age**, **sex**, and **clinical characteristics.**

Antibiotic Treatment

- **Antibiotic treatment** for patients with urinary tract structural abnormalities, immunosuppressive therapy, and procedures requiring urinary tract instrumentation or manipulation.

- Short-course regimens (i.e., single-dose or 3-day) are usually recommended when treatment is desired, although longer regimens have also been recommended.

Antibiotic Treatment

- UTIs in infants and preschool children (predominantly girls) ➲ renal tissue damage.
- Asymptomatic bacteriuria of childhood is also important because it may be a manifestation of an anatomic or mechanical defect in the urinary tract.
- Screening for bacteriuria in children and treating those with positive cultures, regardless of their clinical presentation, seems reasonable and is frequently recommended.

Pregnant Patients, the Elderly, and Other Adult Populations

- Asymptomatic bacteriuria does not require treatment in most adult patients who have no evidence of mechanical obstruction or renal insufficiency.

- Antimicrobial therapy is appropriate during pregnancy because as many as 40% of pregnant women with asymptomatic bacteriuria later develop symptomatic UTI, particularly pyelonephritis.

Cont.

- 20% of all women and 10% of all men > 65 years and older have bacteriuria.
- Therapy is not recommended for the asymptomatic older patient because the expense, side effects, and potential complications of drug therapy appear to outweigh the benefits.
- The treatment of asymptomatic bacteriuria in women with diabetes does not reduce complications and is not currently recommended.