Chapter 51: Urinary Tract Infections and Prostatitis

INTRODUCTION

- Infections of the urinary tract represent a wide variety of clinical syndromes including urethritis, cystitis, prostatitis, and pyelonephritis.
- A *urinary tract infection* (UTI) is defined as the presence of microorganisms in the urine that cannot be accounted for by contamination. The organisms have the potential to invade the tissues of the urinary tract and adjacent structures.
- Lower tract infections include cystitis (bladder), urethritis (urethra), prostatitis (prostate gland), and epididymitis. Upper tract infections involve the kidney and are referred to as *pyelonephritis*.
- *Uncomplicated* UTIs are not associated with structural or functional abnormalities that may interfere with the normal flow of urine or the voiding mechanism. *Complicated* UTIs are the result of a predisposing lesion of the urinary tract, such as a congenital abnormality or distortion of the urinary tract, stone, indwelling catheter, prostatic hypertrophy, obstruction, or neurologic deficit that interferes with the normal flow of urine and urinary tract defenses.
- *Recurrent* UTIs, two or more UTIs occurring within 6 months or three or more within 1 year, are characterized by multiple symptomatic episodes with asymptomatic periods occurring between these episodes. These infections are due to reinfection or to relapse. Reinfections are caused by a different organism and account for the majority of recurrent UTIs. Relapse represents the development of repeated infections caused by the same initial organism.

PATHOPHYSIOLOGY

- The bacteria causing UTIs usually originate from bowel flora of the host. Organisms typically gain entry into the urinary tract via three routes: the ascending, hematogenous (descending), and lymphatic pathways.
- The most common cause of uncomplicated UTIs is *E. coli*, accounting for more than 80%–90% of community-acquired infections. Additional causative organisms are *Staphylococcus saprophyticus*, *Klebsiella pneumoniae, Proteus* spp., *Pseudomonas aeruginosa*, and *Enterococcus* spp.
- The urinary pathogens in complicated or nosocomial infections may include *E. coli*, which accounts for less than 50% of these infections, *Proteus* spp., *K. pneumoniae, Enterobacter* spp., *P. aeruginosa*, staphylococci, and enterococci. Enterococci represent the second most frequently isolated organisms in hospitalized patients.
- Most UTIs are caused by a single organism; however, in patients with stones, indwelling urinary catheters, or chronic renal abscesses, multiple organisms may be isolated.
- Vancomycin-resistant *E. faecalis* and *E. faecium* (vancomycin-resistant enterococci) have become more widespread, especially in patients with long-term hospitalizations or underlying malignancies.

CLINICAL PRESENTATION

- The typical signs and symptoms of urinary tract infections are:
  - ✔ Lower UTI: Dysuria, urgency, frequency, nocturia, and suprapubic heaviness, gross hematuria, and costovertebral tenderness.
  - ✔ Upper UTI: Flank pain, fever, nausea, vomiting, and malaise.

- Symptoms alone are unreliable for the diagnosis of bacterial UTIs. The key to the diagnosis of a UTI is the ability to demonstrate significant numbers of microorganisms present in an appropriate urine specimen to distinguish contamination from infection.
- Older patients frequently do not experience specific urinary symptoms, but they will present with altered mental status, change in eating habits, or gastrointestinal (GI) symptoms.
- A standard urinalysis should be obtained in the initial assessment of a patient. Microscopic examination of the urine should be performed by preparation of a Gram stain of unspun or centrifuged urine. The presence of at least one organism per oil-immersion field in a properly collected uncentrifuged specimen correlates with greater than 100,000 colony-forming units (CFU)/mL (10^5 CFU/mL [$>10^8$ CFU/L]) of urine.
- A quantitative count of 10^5 CFU/mL (10^8 CFU/L) or more is considered indicative of a UTI; however, up to 50% of women will present with clinical symptoms of a UTI with lower counts (10^3 CFU/mL [10^6CFU/L]).
- The presence of pyuria (>10 white blood cells/mm^3 [10×10^6/L]) in a symptomatic patient correlates with significant bacteriuria. A count of 5–10 WBC/mm^3 (5×10^6–10×10^6/L) is accepted as the upper limit of normal.
- The nitrite test can be used to detect the presence of nitrate-reducing bacteria in the urine (eg, *E. coli*). The leukocyte esterase test is a rapid dipstick test to detect pyuria.
- The most reliable method of diagnosing UTIs is by quantitative urine culture. Patients with infection usually have more than 10^5 bacteria/mL (10^8/L) of urine, although as many as one-third of women with symptomatic infection have less than 10^5 bacteria/mL (10^8/L).

TREATMENT

- Goals of Treatment: Eradicate the invading organisms, prevent or treat systemic consequences of infection, prevent recurrence of infection, and decrease the potential for collateral damage with excessively broad antimicrobial therapy.
- The management of a patient with a UTI includes initial evaluation, selection of an antibacterial agent and duration of therapy, and follow-up evaluation.
- The initial selection of an antimicrobial agent for the treatment of UTI is primarily based on the severity of the presenting signs and symptoms, the site of infection, and whether the infection is determined to be complicated or uncomplicated. Other considerations include antibiotic susceptibility, side-effect potential, cost, current antimicrobial exposure, and the comparative inconvenience of different therapies.

Pharmacologic Treatment

- Eradication of bacteria from the urinary tract is directly related to the sensitivity of the organism and the achievable concentration of the antimicrobial agent in the urine.
- Management of UTIs is best accomplished by first categorizing the type of infection: acute uncomplicated cystitis, symptomatic abacteriuria, asymptomatic bacteriuria, complicated UTIs, recurrent infections, or prostatitis.
- Most *E. coli* remain susceptible to **trimethoprim–sulfamethoxazole**, although resistance is increasing. In light of rising resistance and in order to decrease the overuse of broad-spectrum antimicrobials, agents such as **nitrofurantoin** and **fosfomycin** are now considered first-line treatments along with trimethoprim–sulfamethoxazole in acute uncomplicated cystitis.
- **Table 51-1** lists the most common agents used to treat lower UTIs in adults, along with comments concerning their general use.
- **Table 51-2** presents an overview of various therapeutic options for outpatient therapy for UTI.
- **Table 51-3** describes empiric treatment regimens for specific clinical situations.

TABLE 51-1

Commonly Used Antimicrobial Agents in the Treatment of UTIs

Drug	Adverse Drug Reactions	Monitoring Parameters	Comments
Oral therapy			
Trimethoprim–sulfamethoxazole	Rash, Stevens–Johnson syndrome, renal failure, photosensitivity, hematologic (neutropenia, anemia, etc.)	Serum creatinine, BUN, electrolytes, signs of rash, and CBC	Highly effective against most aerobic enteric bacteria except *P. aeruginosa*. High urinary tract tissue concentrations and urine concentrations are achieved, which may be important in complicated infection treatment. Also effective as prophylaxis for recurrent infections
Nitrofurantoin	GI intolerance, neuropathies, and pulmonary reactions	Baseline serum creatinine and BUN	Effective as both a therapeutic and prophylactic agent in patients with recurrent UTIs. Main advantage is the lack of resistance even after long courses of therapy
Fosfomycin trometamol	Diarrhea, headache, and angioedema	No routine tests recommended	Single-dose therapy for uncomplicated infections, low levels of resistance, use with caution in patients with hepatic dysfunction
Fluoroquinolones			
Ciprofloxacin Levofloxacin	Hypersensitivity, photosensitivity, GI symptoms, dizziness, confusion, and tendonitis (black box warning)	CBC, baseline serum creatinine, and BUN	Greater spectrum of activity, including *P. aeruginosa*. Effective for pyelonephritis and prostatitis. Avoid in pregnancy and children. Moxifloxacin should not be used owing to inadequate urinary concentrations
Penicillins			
Amoxicillin–clavulanate	Hypersensitivity (rash, anaphylaxis), diarrhea, superinfections, and seizures	CBC, signs of rash, or hypersensitivity	Due to increasing *E. coli* resistance, amoxicillin–clavulanate is the preferred penicillin for uncomplicated cystitis
Cephalosporins			
Cefaclor Cefpodoxime-proxetil	Hypersensitivity (rash,	CBC, signs of rash, or	No major advantages over other agents for treating UTIs, and they are more expensive. Not active against enterococci

	anaphylaxis), diarrhea, superinfections, and seizures	hypersensitivity	
Parenteral therapy			
Aminoglycosides			
Gentamicin Tobramycin Amikacin	Ototoxicity, nephrotoxicity	Serum creatinine and BUN, serum drug concentrations, and individual pharmacokinetic monitoring	Renally excreted and achieve good concentrations in the urine. Amikacin generally is reserved for multidrug-resistant bacteria
Penicillins			
Ampicillin–sulbactam Piperacillin–tazobactam	Hypersensitivity (rash, anaphylaxis), diarrhea, superinfections, and seizures	CBC, signs of rash, or hypersensitivity	Generally are equally effective for susceptible bacteria. The extended-spectrum penicillins are more active against *P. aeruginosa* and enterococci and often are preferred over cephalosporins. They are very useful in renally impaired patients or when an aminoglycoside is to be avoided
Cephalosporins			
Ceftriaxone Ceftazidime Cefepime Ceftozolane/Tazobactam Ceftazidime/Avabactam	Hypersensitivity (rash, anaphylaxis), diarrhea, superinfections, and seizures	CBC, signs of rash, or hypersensitivity	Second- and third-generation cephalosporins have a broad spectrum of activity against gram-negative bacteria, but are not active against enterococci and have limited activity against *P. aeruginosa*. Ceftazidime and cefepime are active against *P. aeruginosa*. They are useful for nosocomial infections and urosepsis due to susceptible pathogens
Carbapenems/Monobactams			
Imipenem–cilistatin Meropenem Meropenem/Vaborbactam Doripenem Ertapenem Aztreonam	Hypersensitivity (rash, anaphylaxis), diarrhea, superinfections, and seizures	CBC, signs of rash, or hypersensitivity	Carbapenems have a broad spectrum of activity, including gram-positive, gram-negative, and anaerobic bacteria. Imipenem, meropenem, and doripenem are active against *P. aeruginosa* and enterococci, but ertapenem is not. Aztreonam is a monobactam that is only active against gram-negative bacteria, including some strains of *P. aeruginosa*. Generally useful for nosocomial infections when aminoglycosides are to be avoided and in penicillin-sensitive patients
Fluoroquinolones			

Ciprofloxacin Levofloxacin	Hypersensitivity, photosensitivity, GI symptoms, dizziness, confusion, and tendonitis (black box warning)	CBC, baseline serum creatinine, and BUN	Broad-spectrum activity against both gram-negative and gram-positive bacteria. They provide urine and high-tissue concentrations and are actively secreted in reduced renal function

BUN, blood urea nitrogen; CBC, complete blood count; GI, gastrointestinal; UTIs, urinary tract infections.

TABLE 51-2

Overview of Outpatient Antimicrobial Therapy for Lower Tract Infections in Adults

Indications	Antibiotic	Oral Dose	Interval[a]	Duration
Lower tract infections				
Uncomplicated	Trimethoprim–sulfamethoxazole	1 DS tablet	Twice a day	3 days
	Nitrofurantoin monohydrate	100 mg	Twice a day	5 days
	Fosfomycin trometamol	3 g	Single dose	1 day
	Ciprofloxacin	250 mg	Twice a day	3 days
	Levofloxacin	250 mg	Once a day	3 days
	Amoxicillin–clavulanate Pivmecillinam	500 mg 400 mg	Every 8 hours Twice a day	5–7 days 3 days
Complicated	Trimethoprim–sulfamethoxazole	1 DS tablet	Twice a day	7–10 days
	Ciprofloxacin	250–500 mg	Twice a day	7–10 days
	Levofloxacin	250 mg	Once a day	10 days
		750 mg	Once a day	5 days
	Amoxicillin–clavulanate	500 mg	Every 8 hours	7–10 days
Recurrent infections	Nitrofurantoin	50 mg	Once a day	6 months
	Trimethoprim–sulfamethoxazole	1/2 SS tablet	Once a day	6 months
Acute pyelonephritis	Trimethoprim–sulfamethoxazole	1 DS tablet	Twice a day	14 days
	Ciprofloxacin	500 mg	Twice a day	14 days
		1000 mg ER	Once a day	7 days
	Levofloxacin	250 mg	Once a day	10 days
		750 mg	Once a day	5 days
	Amoxicillin–clavulanate	500 mg	Every 8 hours	14 days

[a]Dosing intervals for normal renal function.

DS, double strength; SS, single strength.

TABLE 51-3

Evidence-Based Empirical Treatment of UTIs and Prostatitis

Diagnosis	Pathogens	Treatment Recommendation	Comments
Acute uncomplicated cystitis	*Escherichia coli*, *Staphylococcus saprophyticus*	1. Nitrofurantoin × 5 days (A,I)[a] 2. Trimethoprim–sulfamethoxazole × 3 days (A,I)[a] 3. Fosfomycin trometamol × 1 dose (A,I)[a] 4. Fluoroquinolone × 3 days (A,I)[a] 5. β-Lactams × 3–7 days (B,I)[a] 6. Pivmecillinam × 3–7 days (A,I)	Short-course therapy more effective than single dose Reserve fluoroquinolones as alternatives to development of resistance (A-III)[a] β-Lactams as a group are not as effective in acute cystitis than trimethoprim–sulfamethoxazole or the fluoroquinolones, do not use amoxicillin or ampicillin[a] Pivmecillinam not available in the United States
Pregnancy	As above	1. Amoxicillin–clavulanate × 7 days 2. Cephalosporin × 7 days 3. Trimethoprim–sulfamethoxazole × 7 days	Avoid trimethoprim–sulfamethoxazole during the third trimester
Acute pyelonephritis			
Uncomplicated	*E. coli*	1. Fluoroquinolone × 7 days (A,I)[a] 2. Trimethoprim–sulfamethoxazole (if susceptible) × 14 days (A,I)[a]	Can be managed as outpatient
	Gram-positive bacteria	1. Amoxicillin or amoxicillin–clavulanic acid × 14 days	
Complicated	*E. coli* *P. mirabilis* *K. pneumoniae* *P. aeruginosa* *Enterococcus faecalis*	1. Quinolone × 14 days 2. Extended-spectrum penicillin plus aminoglycoside	Severity of illness will determine duration of IV therapy; culture results should direct therapy Oral therapy may complete 14 days of therapy

Prostatitis	*E. coli* *K. pneumoniae* *Proteus* spp. *P. aeruginosa*	1. Trimethoprim–sulfamethoxazole × 4–6 weeks 2. Fluoroquinolone 4–6 weeks	Acute prostatitis may require IV therapy initially Chronic prostatitis may require longer treatment periods or surgery

[a]Strength of recommendations: A, good evidence for; B, moderate evidence for; C, poor evidence for and against; D, moderate against; E, good evidence against. Quality of evidence: I, at least one proper randomized, controlled study; II, one well-designed clinical trial; III, evidence from opinions, clinical experience, and expert committees.

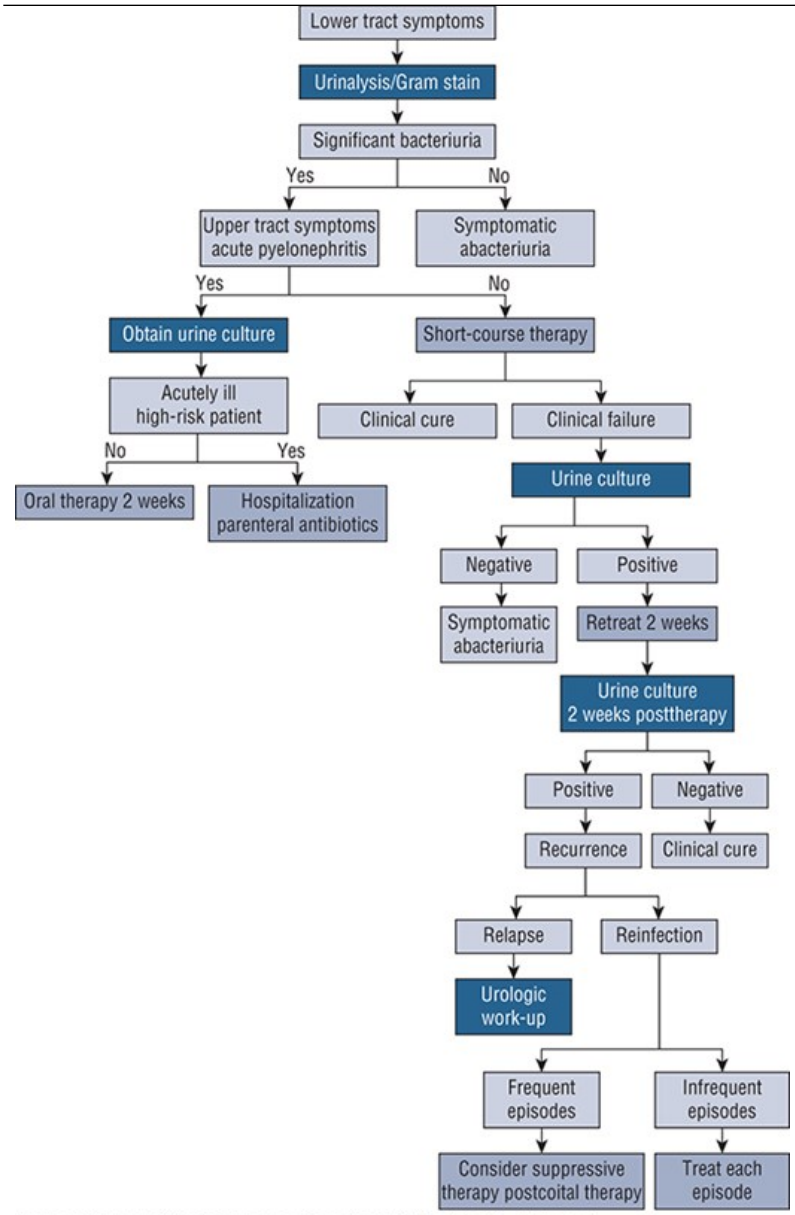
UTI, urinary tract infection.

Acute Uncomplicated Cystitis

- These infections are predominantly caused by *E. coli,* and antimicrobial therapy should be directed against this organism initially. Because the causative organisms and their susceptibilities are generally known, a cost-effective approach to management is recommended that includes a urinalysis and initiation of empiric therapy without a urine culture (**Figure 51-1**).
- Short-course therapy (3-day therapy) with **trimethoprim–sulfamethoxazole** or a **fluoroquinolone** (eg, **ciprofloxacin** or **levofloxacin**, but not moxifloxacin) is superior to single-dose therapy for uncomplicated infection. Fluoroquinolones should be reserved for patients with suspected or possible pyelonephritis due to the collateral damage risk. Instead, a 3-day course of trimethoprim–sulfamethoxazole, a 5-day course of nitrofurantoin, or a one-time dose of **fosfomycin** should be considered as first-line therapy. In areas where there is more than 20% resistance of *E. coli* to trimethoprim–sulfamethoxazole, nitrofurantoin or fosfomycin should be utilized. Amoxicillin or ampicillin is not recommended because of the high incidence of resistant *E. coli.* Follow-up urine cultures are not necessary in patients who respond.

FIGURE 51-1

Management of urinary tract infections in women.



Source: Terry L. Schwinghammer, Joseph T. DiPiro, Vicki L. Ellingrod, Cecily V. DiPiro: *Pharmacotherapy Handbook, 11e*

Complicated Urinary Tract Infections

Acute Pyelonephritis

- The presentation of high-grade fever (>38.3°C [100.9°F]) and severe flank pain should be treated as acute pyelonephritis, and aggressive management is warranted. Severely ill patients with pyelonephritis should be hospitalized and IV drugs administered initially. Milder cases may be managed with oral antibiotics in an outpatient setting.
- At the time of presentation, a Gram stain of the urine should be performed, along with urinalysis, culture, and sensitivities.
- In the mild to moderately symptomatic patient for whom oral therapy is considered, an effective agent should be administered for 7–14 days, depending on the agent used. Fluoroquinolones (**ciprofloxacin** or **levofloxacin**) orally for 7–10 days are the first-line choice in mild-to-moderate pyelonephritis. Other options include **trimethoprim–sulfamethoxazole** for 14 days. If a Gram stain reveals gram-positive cocci, *Streptococcus faecalis* should be considered and treatment directed against this pathogen (**ampicillin**).

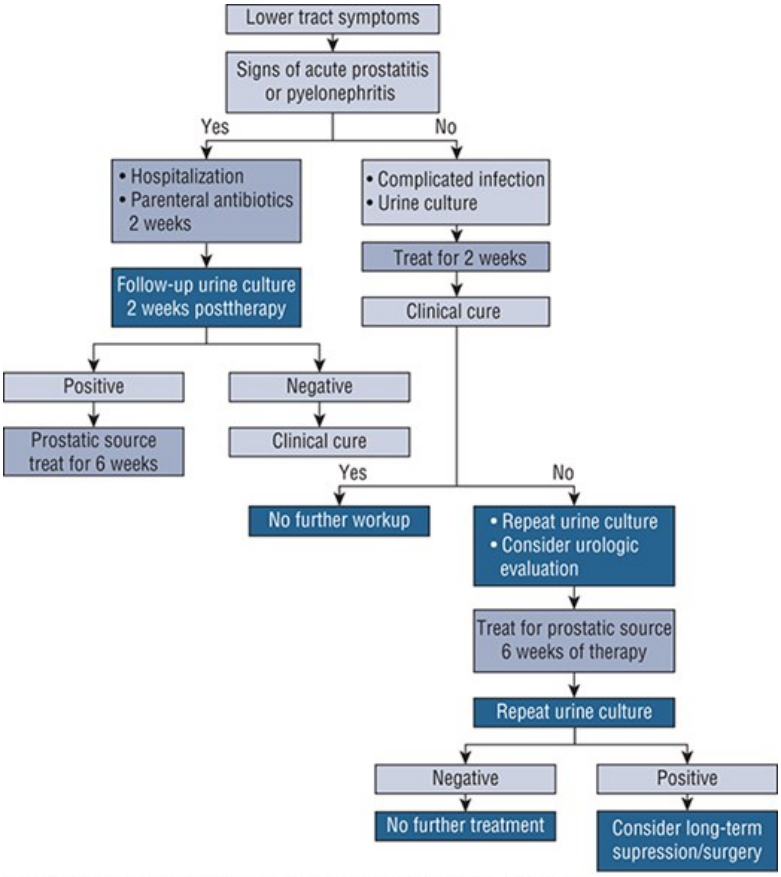
- In the seriously ill patient, the traditional initial therapy is an IV fluoroquinolone, an aminoglycoside with or without ampicillin, or an extended-spectrum cephalosporin with or without an aminoglycoside.
- If the patient has been hospitalized in the last 6 months, has a urinary catheter, or is in a nursing home, the possibility of *P. aeruginosa* and enterococci infection, as well as multiple-resistant organisms, should be considered. In this setting, **ceftazidime**, **ticarcillin–clavulanic acid**, **piperacillin**, **aztreonam**, **meropenem**, or **imipenem**, in combination with an aminoglycoside, is recommended. If the patient responds to initial combination therapy, the aminoglycoside may be discontinued after 3 days.
- Follow-up urine cultures should be obtained 2 weeks after the completion of therapy to ensure a satisfactory response and to detect possible relapse.

Urinary Tract Infections in Men

- Therapy in men requires prolonged treatment (**Figure 51-2**).
- A urine culture should be obtained before treatment, because the cause of infection in men is not as predictable as in women.
- If gram-negative bacteria are presumed, trimethoprim–sulfamethoxazole or a fluoroquinolone is a preferred agent. Initial therapy is for 10–14 days. For recurrent infections in men, cure rates are much higher with a 6-week regimen of trimethoprim–sulfamethoxazole.

FIGURE 51-2

Management of urinary tract infections in men.



Source: Terry L. Schwinghammer, Joseph T. DiPiro, Vicki L. Ellingrod, Cecily V. DiPiro: *Pharmacotherapy Handbook, 11e*

Recurrent Infections

- Recurrent episodes of UTI (reinfections and relapses) account for a significant portion of all UTIs. These patients are most commonly women and can be divided into two groups: those with fewer than two or three episodes per year and those who develop more frequent infections.
- In patients with infrequent infections (ie, fewer than three infections per year), each episode should be treated as a separately occurring infection. Short-course therapy should be used in symptomatic female patients with lower tract infection.
- In patients who have frequent symptomatic infections, long-term prophylactic antimicrobial therapy may be instituted (see **Table 51-2**). Therapy is generally given for 6 months, with urine cultures followed monthly.
- In women who experience symptomatic reinfections in association with sexual activity, voiding after intercourse may help prevent infection. Also, self-administered, single-dose prophylactic therapy with **trimethoprim–sulfamethoxazole** taken after intercourse significantly reduces the incidence of recurrent infection in these patients.
- Women who relapse after short-course therapy should receive a 2-week course of therapy. In patients who relapse after 2 weeks, therapy should be continued for another 2–4 weeks. If relapse occurs after 6 weeks of treatment, urologic examination should be performed, and therapy for 6 months or even longer may be considered.

SPECIAL CONDITIONS

Urinary Tract Infection in Pregnancy

- In patients with significant bacteriuria, symptomatic or asymptomatic treatment is recommended to avoid possible complications during the pregnancy. Therapy should consist of an agent with a relatively low adverse-effect potential (**cephalexin, amoxicillin**, or **amoxicillin/clavulanate**) administered for 7 days.
- Tetracyclines should be avoided because of teratogenic effects and sulfonamides should not be administered during the third trimester because of the possible development of kernicterus and hyperbilirubinemia. Also, the fluoroquinolones should not be given because of their potential to inhibit cartilage and bone development in the newborn.

Catheterized Patients

- When bacteriuria occurs in asymptomatic, short-term catheterized patients (<30 days), the use of systemic antibiotic therapy should be withheld and the catheter removed as soon as possible. If the patient becomes symptomatic, the catheter should again be removed, and treatment as described for complicated infections should be started.
- The use of prophylactic systemic antibiotics in patients with short-term catheterization reduces the incidence of infection over the first 4–7 days. In long-term catheterized patients, however, antibiotics only postpone the development of bacteriuria and lead to emergence of resistant organisms.

See Chapter 134, Urinary Tract Infections and Prostatitis, authored by Julianna M. Fernandez and Elizabeth A. Coyle, for a more detailed discussion of this topic.