Pharmacotherapy 2

Urinary Tract Infections

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Topic Outline

- Genitourinary Infections (General Principles)
- Asymptomatic Bacteruria
- Cystitis (Diagnosis, Treatment)
- Genitourinary Infections in Men (Cystitis, Prostatitis)
- Pyelonephritis (Diagnosis, Treatment)

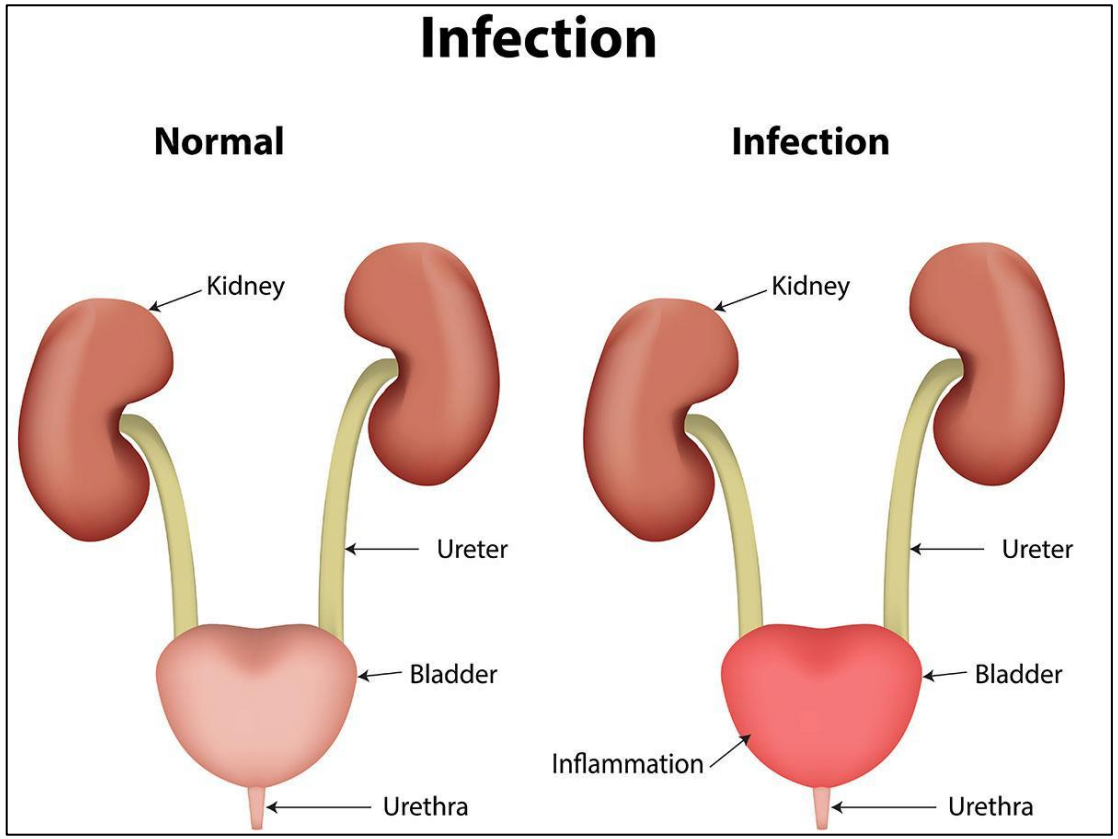
Genitourinary (GU) Infections

General Principles

✓ The spectrum of GU tract infections varies from uncomplicated to complicated, depending on host factors & underlying conditions.

✓ Diagnostic and therapeutic approaches to adult GU infections are determined by gender-specific anatomic differences, prior antimicrobial exposures, and the presence of catheters, etc.

✓ Infections are primarily caused by Enterobacteriaceae (E. coli, Proteus mirabilis, and K. pneumoniae) and Staphylococcus saprophyticus.



Asymptomatic Bacteriuria

- ✓ Asymptomatic bacteriuria is defined as the isolation of > 10^5 CFU/ mL of a single bacterial species in a specimen (men, catheters) or 2 consecutive specimens (women) in appropriately collected urine obtained from a person without symptoms of urinary infection.

- ✓ Asymptomatic bacteriuria is of limited clinical significance and should not be treated except in pregnant women or patients undergoing urologic surgery.

- ✓ Pregnant women should have screening urine culture near the end of the first trimester and be treated if positive.

- ✓ Treatment is not recommended for asymptomatic bacteriuria in the elderly, diabetics, institutionalized patients, spinal cord injury patients, or catheterized patients.

Cystitis

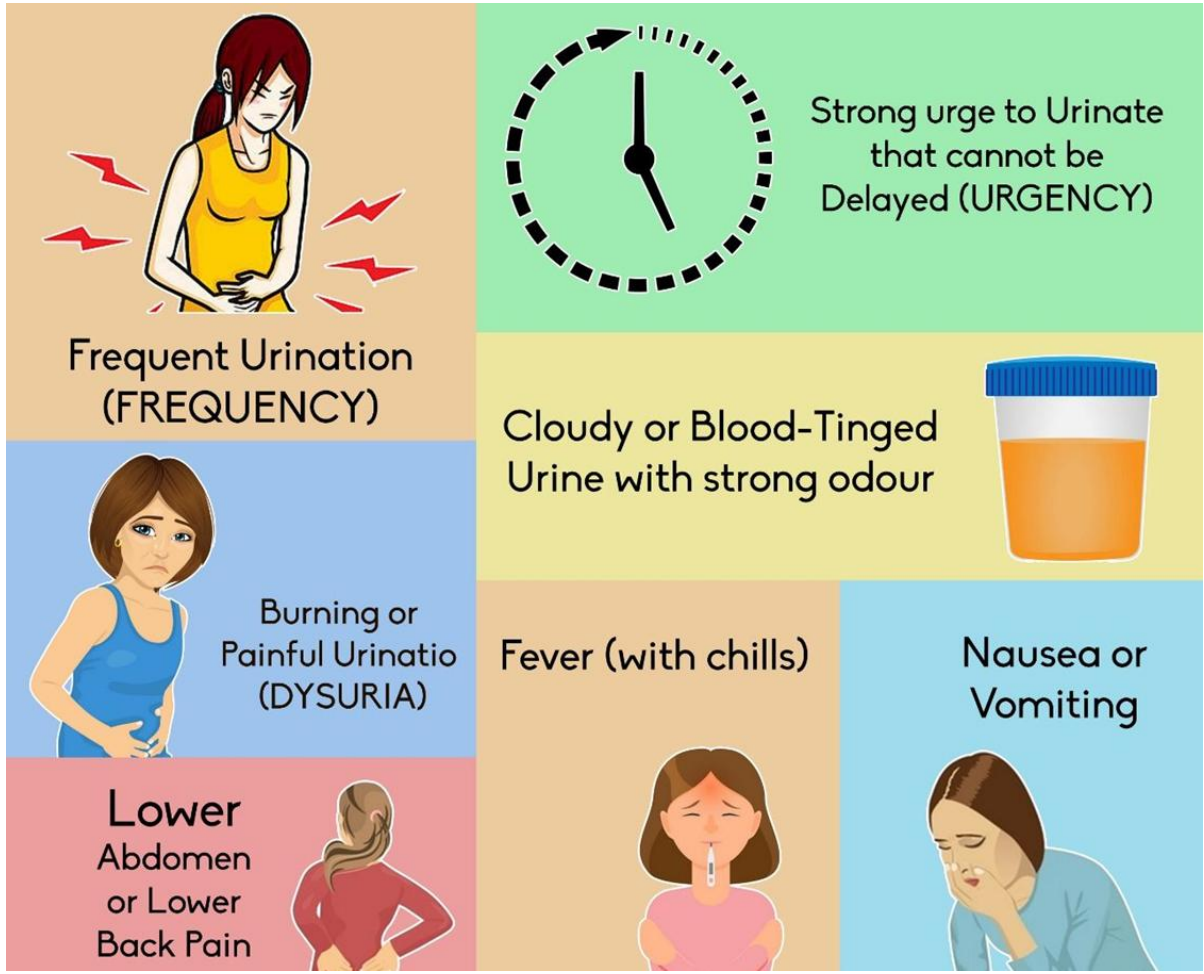
- ✓ Uncomplicated cystitis is defined as infection of the bladder or lower urinary tract in otherwise healthy, nonpregnant adult women.
- ✓ Complicated cystitis is defined based on several risk factors including anatomic abnormality, immunosuppression, pregnancy or indwelling catheters.
- ✓ Recurrent cystitis may be seen in women and is usually due to reinfection rather than relapse.

Diagnosis

✓ Clinical Presentation:

- Lower UTI is diagnosed based on clinical history of dysuria, urgency, frequency, or suprapubic pain associated with urinalysis abnormalities of pyuria and bacteriuria and urine culture.

- Fever is more likely if there is associated pyelonephritis.



CLINICAL PRESENTATION

Urinary Tract Infections in Adults

Signs and Symptoms

- Lower UTI: Dysuria, urgency, frequency, nocturia, and suprapubic heaviness
- Gross hematuria
- Upper UTI: Flank pain, fever, nausea, vomiting, and malaise

Physical Examination

- Upper UTI: Costovertebral tenderness

Laboratory Tests

- Bacteriuria
- Pyuria (WBC count more than 10/mm^3 [10×10^6/L])
- Nitrite-positive urine (with nitrite reducers)
- Leukocyte esterase-positive urine
- Antibody-coated bacteria (upper UTI)

✓ Diagnostic Testing:

Workup typically includes urinalysis and microscopic examination of a fresh, unspun, clean-voided, or catheterized urine specimen.

- Acute uncomplicated cystitis in women:
  - Many women are treated empirically without a urine culture.
  - A pretreatment urine culture is recommended for diabetics, patients who are symptomatic for > 7 days, individuals with recurrent UTI, women who use a contraceptive diaphragm, and individuals older than 65 years.

TABLE 134-1 Diagnostic Criteria for Significant Bacteriuria

$\geq 10^2$ CFU coliforms/mL (10^5 CFU/L) or $\geq 10^5$ CFU noncoliforms/mL (10^8 CFU/L) in a symptomatic female
$\geq 10^4$ CFU bacteria/mL (10^7 CFU/L) in a symptomatic male
$\geq 10^5$ CFU bacteria/mL (10^8 CFU/L) in asymptomatic individuals on two consecutive specimens
Any growth of bacteria on suprapubic catheterization in a symptomatic patient
$\geq 10^{2-5}$ CFU bacteria/mL (10^{5-8} CFU/L) in a catheterized patient

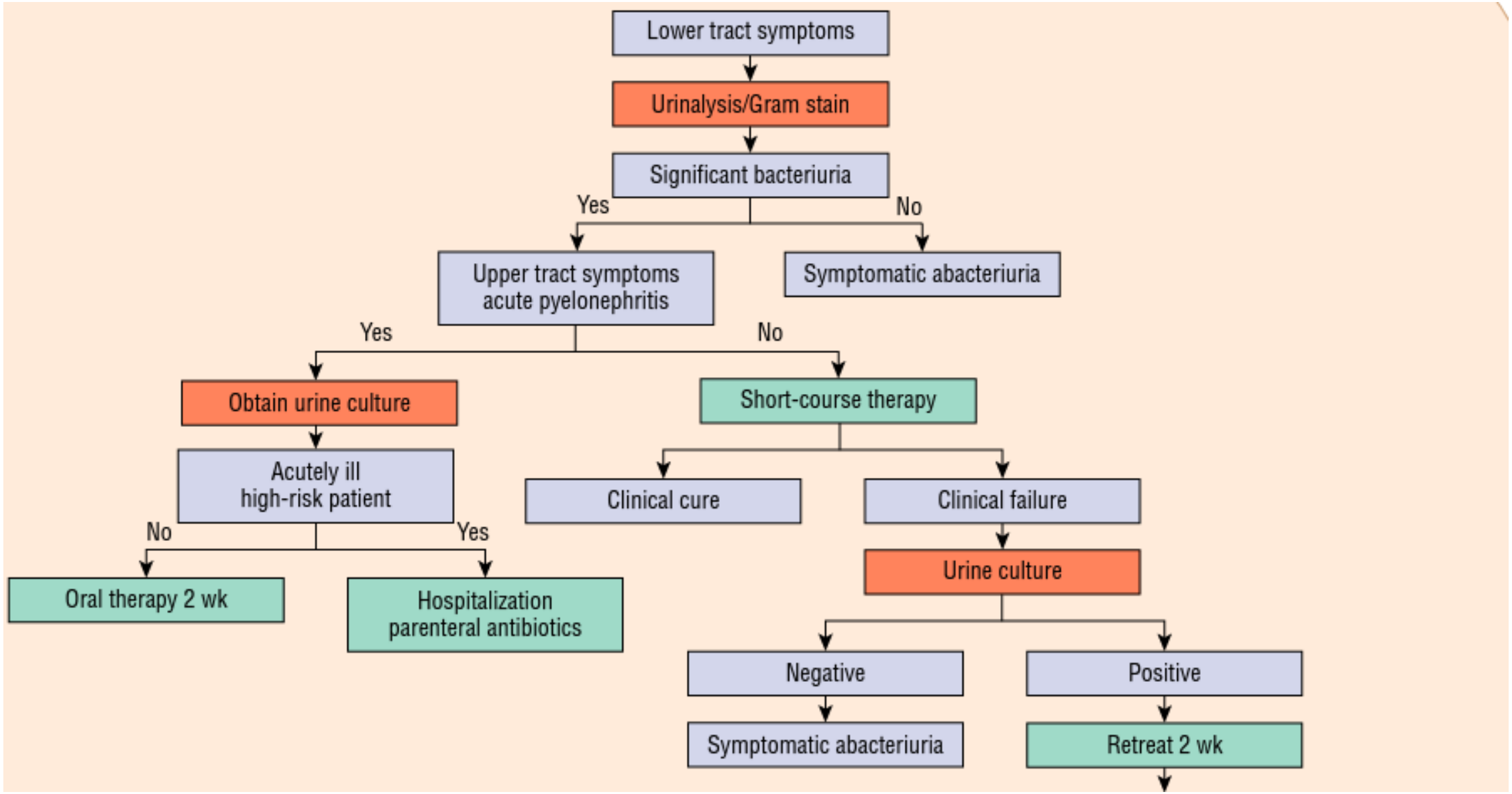
CFU, colony-forming unit.

Treatment

- ✓ See Tables.
- ✓ Acute uncomplicated cystitis in women:
  - A 5-day course of nitrofurantoin, a 3-day course of TMP-SMX, or a single dose of fosfomycin are recommended for empiric treatment.
  - Fluoroquinolones should not be used as first-line treatment.
  - Therapy should be extended to 7 days in pregnant patients and diabetics.
- ✓ Recurrent cystitis:
  - In women, it is usually due to reinfection (with a different organism) and may be challenging to manage.

- Risk factors include frequency of intercourse and spermicide use in young women and urologic abnormalities such as incontinence and cystocele in older women.

- Relapses (with the original infecting organism) that occur within 2 weeks of cessation of therapy should be treated for 2 weeks and may indicate a urologic abnormality.


Lower tract symptoms
Urinalysis/Gram stain
Significant bacteriuria
Yes
No
Upper tract symptoms
acute pyelonephritis
Symptomatic abacteriuria
Yes
No
Obtain urine culture
Short-course therapy
Acutely ill
high-risk patient
Clinical cure
Clinical failure
No
Yes
Urine culture
Oral therapy 2 wk
Hospitalization
parenteral antibiotics
Negative
Positive
Symptomatic abacteriuria
Retreat 2 wk

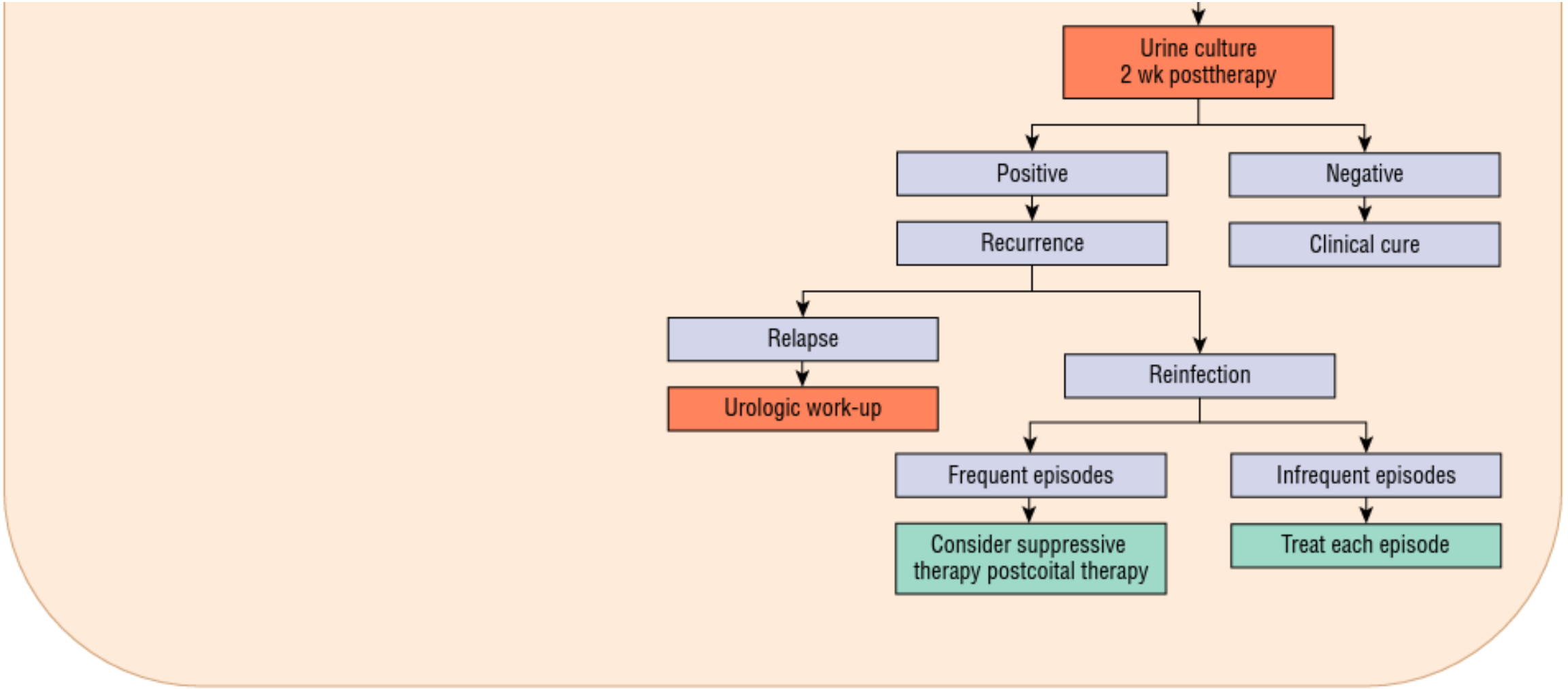


FIGURE 134-1 Management of urinary tract infections in females.

TABLE 134-4 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)* 2. Trimethoprim–sulfamethoxazole × 3 days (A,I)* 3. Fosfomycin trometamol × 1 dose (A,I)* 4. Fluoroquinolone × 3 days (A,I)* 5. β-Lactams × 3-7 days (B,I)* 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)* β-Lactams as a group are not as effective in acute cystitis then trimethoprim–sulfamethoxazole or the fluoroquinolones, do not use amoxicillin or ampicillin* Pivmecillinam not available in 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. Quinolone × 7 days (A,I)* 2. Trimethoprim–sulfamethoxazole (if susceptible) × 14 days (A,I)*	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. Quinolone × 4-6 weeks	Acute prostatitis may require IV therapy initially Chronic prostatitis may require longer treatment periods or surgery

*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.

Data from Reference 1.

TABLE 134-3 Overview of Outpatient Antimicrobial Therapy for Lower Tract Infections in Adults

Indications	Antibiotic	Oral Dose	Interval*	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	500 mg	Every 8 hours	5-7 days
	Pivmecillinam	400 mg	Twice a day	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
		1,000 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

TABLE 134-2 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	This combination is 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	This agent is 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	The fluoroquinolones have a greater spectrum of activity, including *P. aeruginosa*. These agents are 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, anaphylaxis), diarrhea, superinfections, and seizures	CBC, signs of rash, or hypersensitivity	There are no major advantages of these agents over other agents in the treatment of UTIs, and they are more expensive. These agents are not active against enterococci
Parenteral Therapy			
Aminoglycosides			
Gentamicin Tobramycin Amikacin	Ototoxicity, nephrotoxicity	Serum creatinine and BUN, serum drug concentrations, and individual pharmacokinetic monitoring	These agents are 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	These agents 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/tazaobactam 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

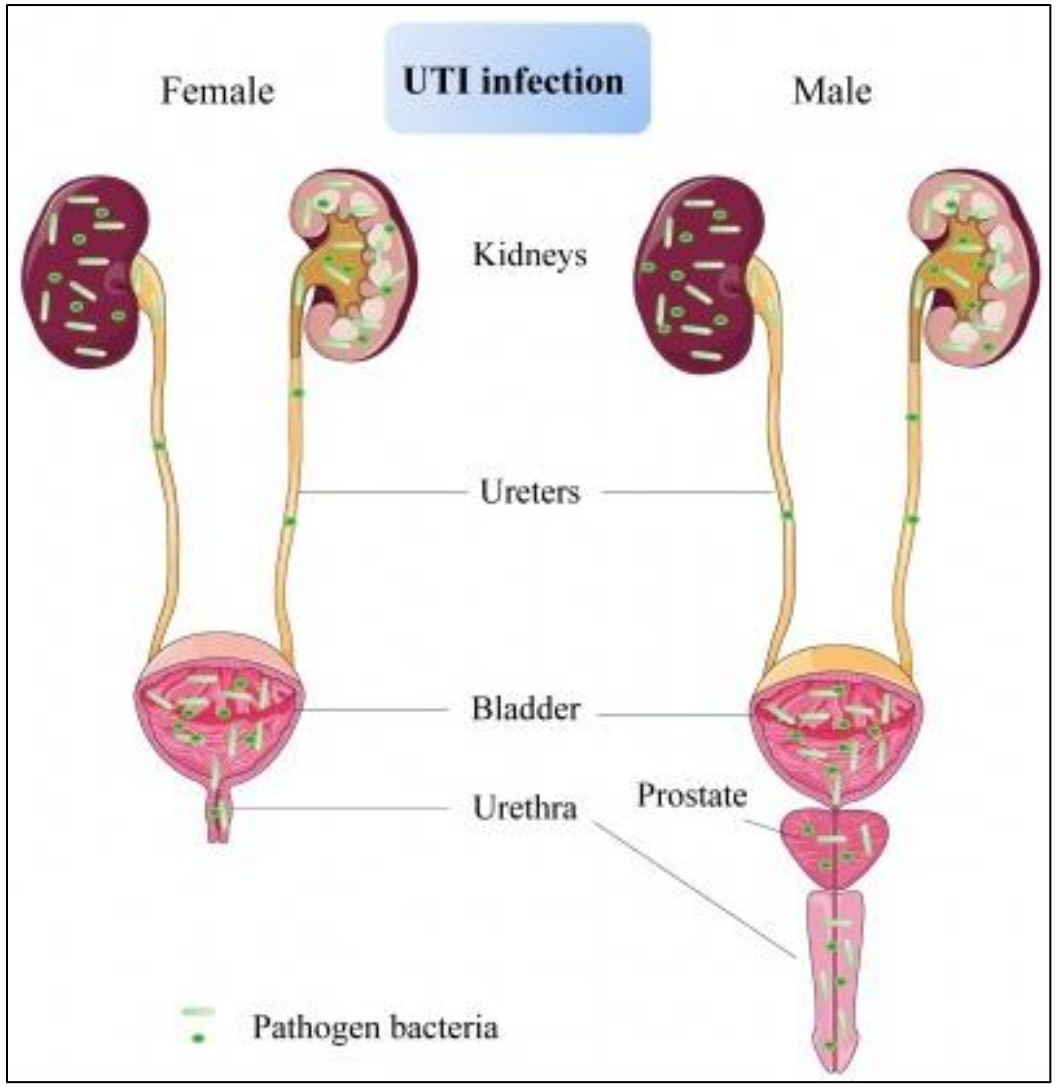
Carbapenems/monobactams			
Imipenem–cilistatin Meropenem Meropenem/vaborbactam Doripenem Ertapenem Aztreonam	Hypersensitivity (rash, anaphylaxis), diarrhea, superinfections, and seizures	CBC, signs of rash, or hypersensitivity	Carbapenems have a broad spectrum of activity, including gram-positive, gram-negative, 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	These agents have 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.

Genitourinary Infections in Men

Cystitis:

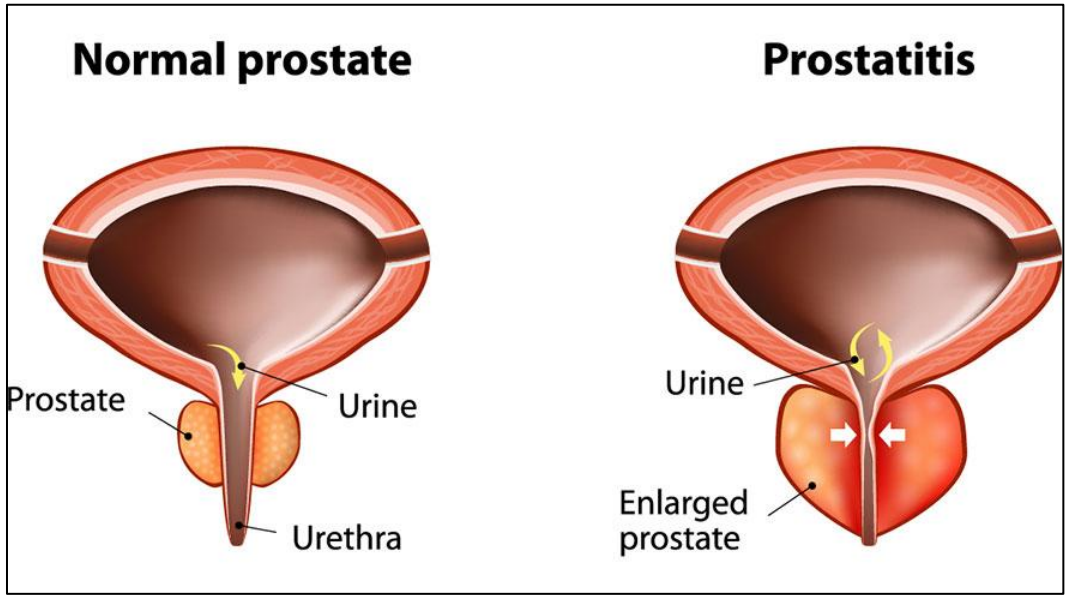
- ✓ Cystitis is uncommon in young men; E. coli is the most frequent pathogen.
- ✓ Risk factors include urologic abnormality, anal intercourse, and lack of circumcision.
- ✓ A pretreatment urinalysis and culture should be sent.
- ✓ Other urologic studies are appropriate if there are no underlying risk factors, when treatment fails, in recurrent infections, or when pyelonephritis occurs.



Prostatitis:

✓ Acute prostatitis:

- It usually presents with fever, chills, dysuria, pelvic pain, obstructive symptoms, and a boggy, tender prostate on examination.
- It is caused by E. coli and other gram-negative organisms.
- Diagnosis is made by physical examination and urine Gram stain and culture.
- Prostatic massage is contraindicated as it can lead to bacteremia.



✓ Chronic prostatitis:

- It is defined as presence of urinary symptoms for > 3 months.
- It is frequently noninfectious.
- Chronic bacterial prostatitis is caused by enteric gram-negative organisms. Symptoms include frequency, dysuria, urgency, perineal discomfort, and recurrent UTIs.
- Urine cultures should be obtained when the patient is symptomatic.
- Referral to a urologist for quantitative cultures before and after prostatic massage may be necessary.
- Transrectal ultrasound can be used if prostatic abscess is suspected.

CLINICAL PRESENTATION: Bacterial Prostatitis

Signs and Symptoms

- Acute bacterial prostatitis: High fever, chills, malaise, myalgia, localized pain (perineal, rectal, sacrococcygeal), frequency, urgency, dysuria, nocturia, and retention
- Chronic bacterial prostatitis: Voiding difficulties (frequency, urgency, dysuria), low back pain, and perineal and suprapubic discomfort

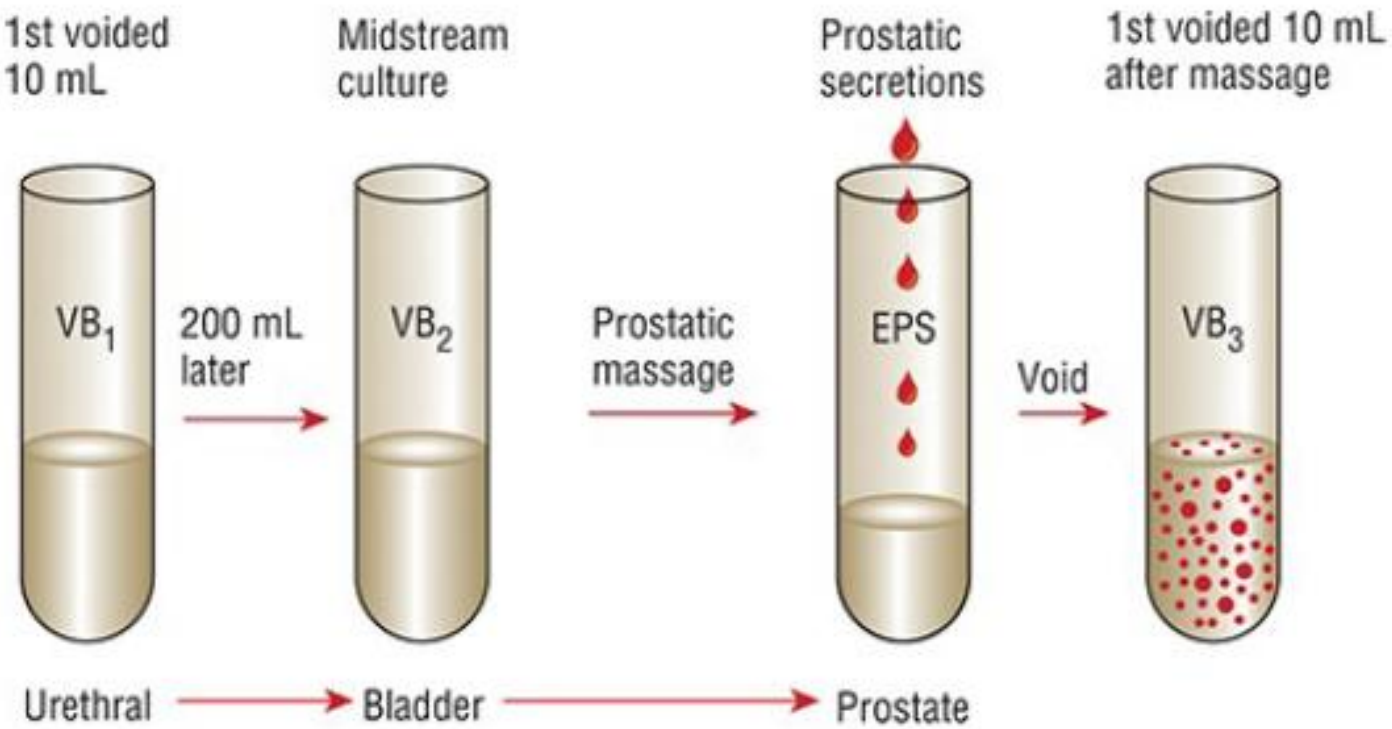
Physical Examination

- Acute bacterial prostatitis: Swollen, tender, tense, or indurated gland
- Chronic bacterial prostatitis: Boggy, indurated (enlarged) prostate in most patients

Laboratory Tests

- Bacteriuria
- Bacteria in EPSs

Segmented cultures of the lower tract in men. (VB_1, voiding bladder 1; VB_2, voiding bladder 2; VB_3, voiding bladder 3.)

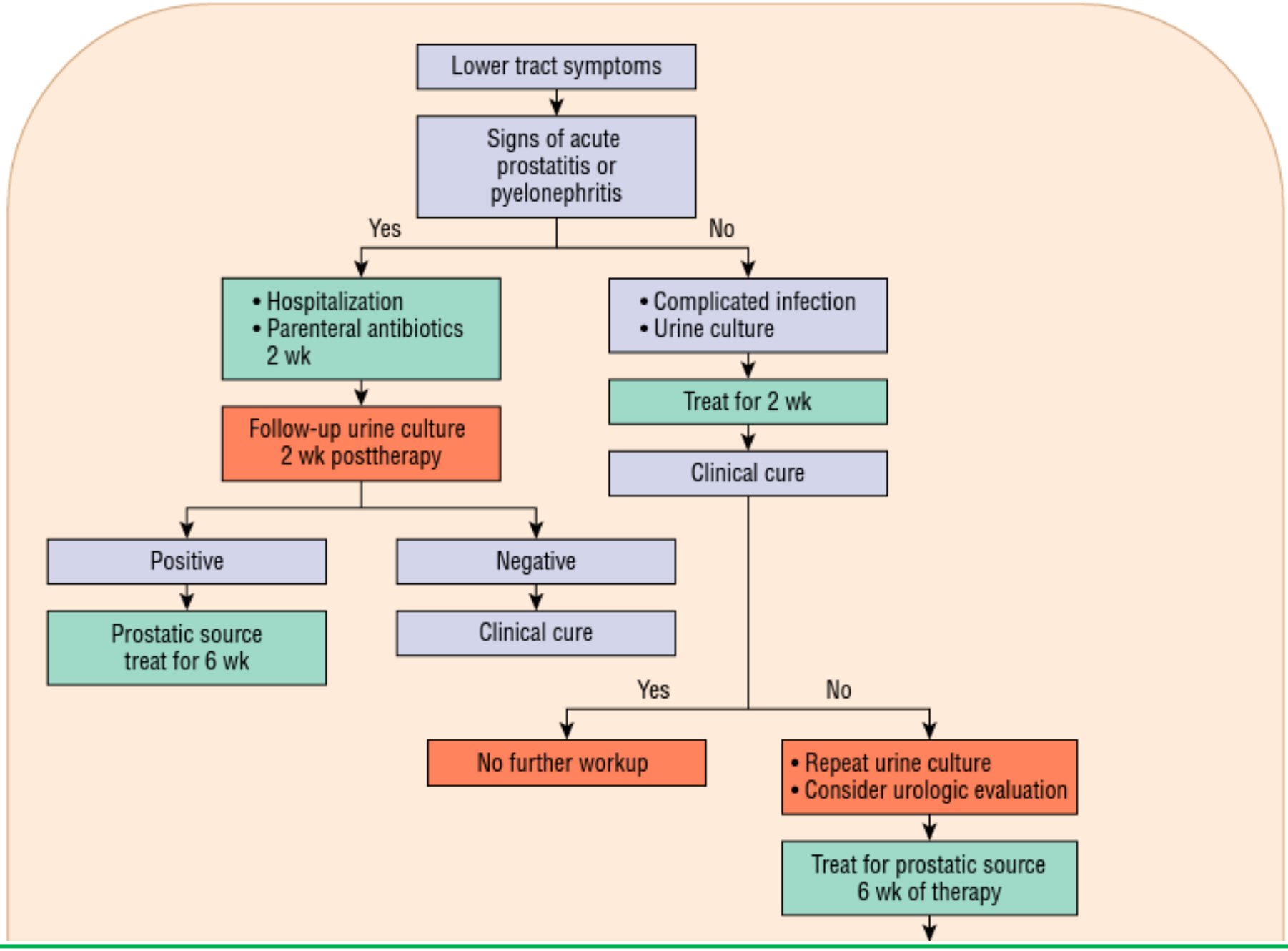


Source: Stuart T. Haines, Thomas D. Nolin, Vicki L. Ellingrod, Lisa M. Holle, Jennifer Cocohoba, L. Michael Posey: *DiPiro's Pharmacotherapy: A Pathophysiologic Approach, 13th Edition*

✓ Treatment:

- Acute bacterial prostatitis should be treated with a 6 week course of either ciprofloxacin 500 mg PO q12h or TMP-SMX 160 mg/ 800 mg (DS) PO q12h.

- Chronic prostatitis is difficult to treat. Culture-positive chronic bacterial prostatitis should receive prolonged therapy (for at least 4– 6 weeks with a fluoroquinolone or TMP-SMX).


Lower tract symptoms
Signs of acute prostatitis or pyelonephritis
Yes
No
• Hospitalization
• Parenteral antibiotics 2 wk
• Complicated infection
• Urine culture
Follow-up urine culture 2 wk posttherapy
Treat for 2 wk
Clinical cure
Positive
Negative
Prostatic source treat for 6 wk
Clinical cure
Yes
No
No further workup
• Repeat urine culture
• Consider urologic evaluation
Treat for prostatic source 6 wk of therapy

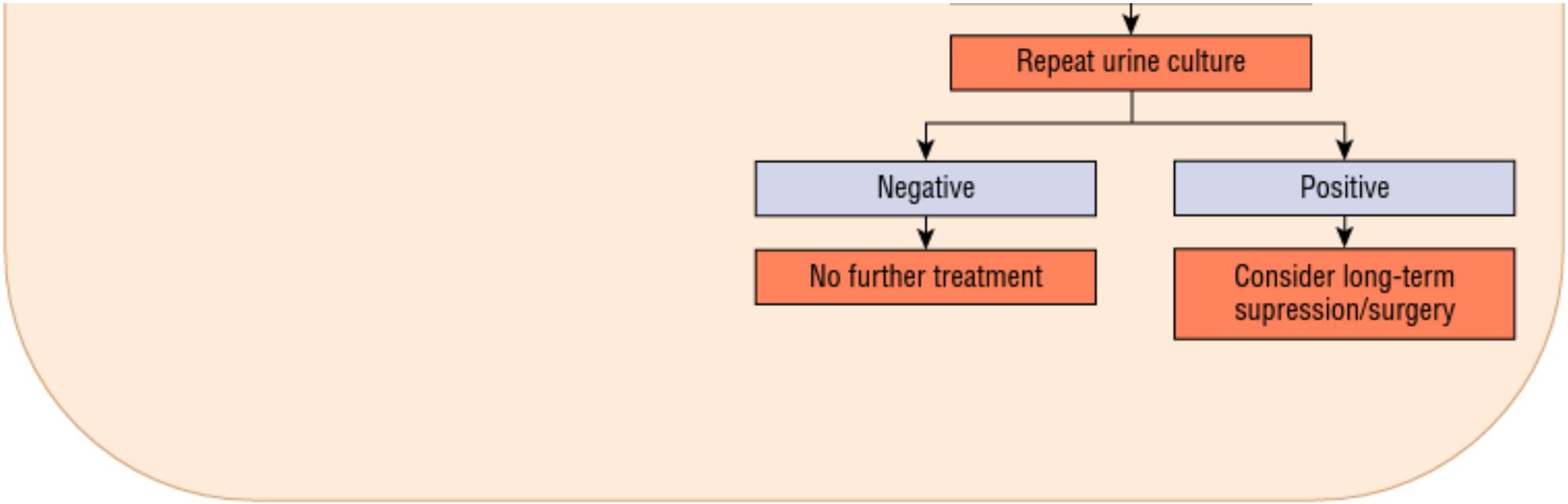


FIGURE 134-2 Management of urinary tract infections in males.

Pyelonephritis

- ✓ Pyelonephritis is infection of the kidney, usually due to ascending infection from the lower urinary tract.
- ✓ The causative agents are typically Enterobacteriaceae such as E. coli or Proteus spp.
- ✓ The incidence of MDRO is rising, especially in patients with recent use of broad-spectrum antibiotics or exposure to health-care facilities.

Diagnosis

✓ Clinical Presentation:

- Patients present with fever, chills, flank pain, nausea/ vomiting, and costovertebral angle tenderness, often along with cystitis symptoms.

- Patients may present with sepsis or multiorgan dysfunction, especially if they have urinary obstruction and recent instrumentation or are elderly or diabetic.

✓ Diagnostic Testing:

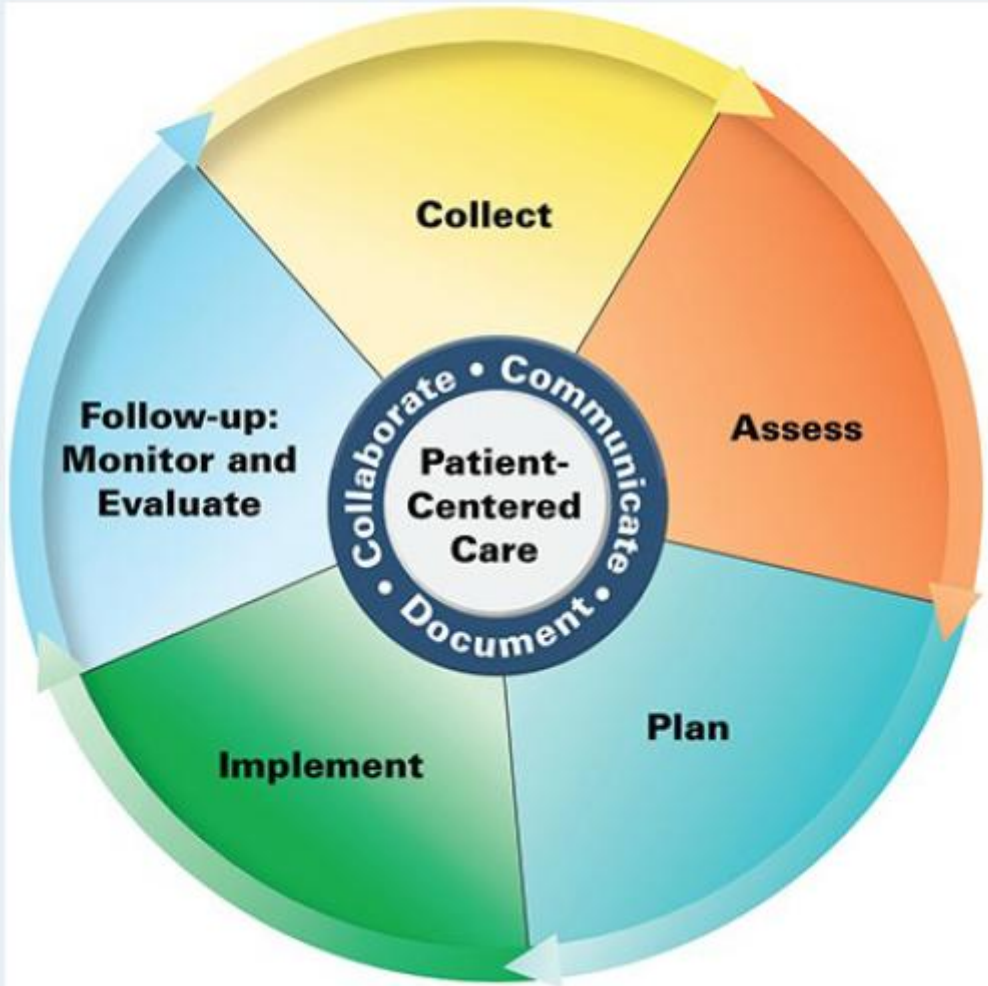
- Urinalysis reveals significant bacteriuria, pyuria, red blood cells, and occasional leukocyte casts.
- A urine culture should be sent. Blood cultures should be obtained in hospitalized patients as bacteremia is present in 15%– 20% of cases.
- Imaging may be considered if symptoms persist despite 48– 72 hours of appropriate antibiotics or for suspected urinary tract obstruction.
- Ultrasonography, CT scan, or IV pyelogram may demonstrate the presence of a renal abscess or renal calculi, which may require more invasive management.

Treatment

- ✓ Start empiric antibiotics promptly. See Tables.
- ✓ Patients with mild to moderate illness who are able to take oral medications can typically be treated in the outpatient setting.
- ✓ Patients with more severe illness and pregnant patients should be treated initially with IV therapy.

PATIENT CARE PROCESS

Patient Care Process for Urinary Tract Infection



Collect

- Patient characteristics (eg, age, sex, pregnant, immunocompetent)
- Patient symptoms (see Clinical Presentation box)
- Patient medical history (including history of past UTIs)
- Social history (eg, sexually active) and dietary habits
- Current medications including nonprescription and/or herbal products, dietary supplements
- Objective data
    - Vital signs: blood pressure (BP), heart rate (HR), respiratory rate (RR), height, weight, O_2 saturation, temperature
    - Labs including WBC count, serum creatinine (SCr)
    - Urinalysis (eg, nitrite or leukocyte esterase positive) +/− culture and sensitivity data
    - Urine dipstick test
    - Physical exam (eg, abdominal tenderness, costovertebral tenderness)

Assess

- Hemodynamic stability (eg, systolic BP <90 mm Hg >110 beats/min)
- Mental status
- Urinary catheter present

Plan

- Drug therapy regimen, including drug name, dose, route, frequency, and duration (see Tables 144-2, 144-3, and 144-4)
- Monitoring parameters, including efficacy (eg, afebrile, WBC, urinalysis, resolution of symptoms), decrease in urinary discomfort and safety (eg, signs and symptoms of antibiotic hypersensitivity, SCr, WBC, hemodynamics)
- Patient education (eg, purpose of treatment, personal hygiene, drug-specific information, medication administration instructions, when to follow-up if no improvement observed; see Table 144-3)
- Self-monitoring for resolution of symptoms (eg, urinary discomfort, flank pain, fever, mental status changes)
- Referrals to other providers when appropriate (eg, urologist)

Implement*

- Provide patient education regarding all elements of treatment plan
- Use motivational interviewing and coaching strategies to maximize adherence
- Schedule follow-up if necessary

Follow-up: Monitor and Evaluate

- Resolution of urinary symptoms (eg, burning, discomfort during urination, flank pain, tenderness)
- Normalization of labs (eg, WBC, SCr)
- Urinalysis presence of adverse effects (eg, rash, diarrhea)
- Patient adherence to treatment plan using multiple sources of information
- Reevaluate if the patient does not respond adequately to treatment

**Collaborate with patient, caregivers, and other healthcare professionals.*

Thank You