



Urinary Tract Infections

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LEARNING OBJECTIVES

1. Analyze patient risk factors and examination data to distinguish different types of UTIs.
2. Design an appropriate empiric treatment plan according to the type and severity of UTI for a patient presenting in the inpatient or outpatient setting.
3. Justify pharmacotherapy management for special patient populations with asymptomatic bacteriuria.
4. Evaluate the role of antimicrobial and non-antimicrobial strategies for the prevention of recurrent UTI.

ABBREVIATIONS IN THIS CHAPTER

ABP	Acute bacterial prostatitis
ASB	Asymptomatic bacteriuria
CA-UTI	Catheter-associated urinary tract infection
CBP	Chronic bacterial prostatitis
CRE	Carbapenem-resistant Enterobacteriaceae
ESBL	Extended-spectrum β -lactamase
IDSA	Infectious Diseases Society of America
KPC	<i>K. pneumoniae</i> carbapenemase
MDR	Multidrug-resistant
NDM	New Delhi metallo- β -lactamase
SNF	Skilled nursing facility

[Table of other common abbreviations.](#)

INTRODUCTION

According to the CDC, UTIs are the most common bacterial infection requiring medical care, resulting in 8.6 million ambulatory care visits in 2007, 23% of which occurred in the ED (CDC 2011). Over 10.8 million patients in the United States visited the ED for the treatment of UTIs between 2006 and 2009 and 1.8 million patients (16.7%) were admitted to acute care hospitals (Sammon 2014). The economic burden of using the ED for the treatment of UTIs is estimated at \$2 billion annually. In addition, UTIs rank as the No. 1 infection that leads to an antibiotic prescription after a physician's visit (Abbo 2014).

Catheter-associated UTIs (CA-UTIs) are the most common type of health care-associated infections reported to the National Healthcare Safety Network, making up two-thirds of hospital-acquired UTIs (CDC 2017). The symptoms of UTIs are generally mild, and inappropriate use of antibiotics can lead to antibiotic resistance; therefore, it is important to establish the appropriate criteria for treatment using narrow-spectrum antibiotics for the optimal duration.

Epidemiology

Up to 60% of women have at least one symptomatic UTI during their lifetime. Around 10% of women in the United States have one or more episodes of symptomatic UTIs each year. Young, sexually active women 18–24 years of age have the highest incidence of UTIs. About 25% of these women have spontaneous resolution of symptoms, and an equal number become infected (Sobel 2014). The prevalence of UTIs in men is significantly lower than in women, occurring primarily in men with urologic structural abnormalities and in older adult men.

Pathophysiology

Lower UTIs, also known as cystitis, are significantly more prevalent in women than in men. This is primarily because of anatomic differences, including shorter urethral length and moist periurethral environment in women. Urinary tract infections typically start with periurethral contamination by a uropathogen residing in the gut, followed by colonization of the urethra and, finally, migration by the flagella and pili of the pathogen to the bladder or kidney. Bacterial adherence to the uroepithelium is key in the pathogenesis of UTI. Infections occur when bacterial virulence mechanisms overcome efficient host defense mechanisms.

Upper UTIs, also known as pyelonephritis, develop when uropathogens ascend to the kidneys by the ureters. Infections can occur when bacteria bind to a urinary catheter, a kidney, or a bladder stone or when they are retained in the urinary tract by a physical obstruction. In severe cases of pyelonephritis, the affected kidney may be enlarged, with raised

BASELINE KNOWLEDGE STATEMENTS

Readers of this chapter are presumed to be familiar with the following:

- Basic knowledge of UTI pharmacology, including mechanisms of action, adverse effects, and drug interactions

[Table of common laboratory reference values](#)

ADDITIONAL READINGS

The following free resources have additional background information on this topic:

- Sobel JD, Kaye D. Urinary tract infections. In: Mandell GL, Bennett JE, eds. *Principles and Practice of Infectious Diseases*, 8th ed. Philadelphia: Elsevier Saunders, 2014:886-913.
- Infectious Diseases Society of America (IDSA). [Guidelines for Acute Uncomplicated Cystitis and Pyelonephritis in Women](#), 2011.
- IDSA. [Guidelines for Catheter-Associated Urinary Tract Infection in Adults](#), 2010.
- IDSA. [Guidelines for Diagnosis and Treatment of Asymptomatic Bacteriuria in Adults](#), 2005.
- FDA Safety Information and Adverse Event Reporting Program. [Fluoroquinolones Antibacterial Drugs: Drug Safety Communication – FDA Advises Restricting Use for Certain Uncomplicated Infections](#).
- Grabe M, Bartoletti R, Bjerklund Johansen TE, et al, for the European Association of Urology. [Guidelines on Urological Infections](#). 2015.

abscesses on the surface (as revealed in imaging studies). *Staphylococcus aureus* bacteremia or endocarditis can lead to hematogenous seeding of the bacteria to the kidneys, causing suppurative necrosis or abscess formation within the renal parenchyma (Sobel 2014). In contrast, gram-negative bacilli rarely cause kidney infection by the hematogenous route. According to an experimental model of pyelonephritis, the main renal abnormality reported is the inability to maximally concentrate the urine (Sobel 2014). This concentration defect occurs early in the infection and is rapidly reversible with antibiotic therapy. An obstruction can lead to progressive destruction of the affected kidney and subsequent renal insufficiency.

Predisposing Factors

In the non-pregnant adult woman with a normal urinary tract, bacteriuria infrequently progresses to symptomatic cystitis or pyelonephritis. Common predisposing factors for UTIs are listed in Table 1-1. The urethra is usually colonized with bacteria, and sexual intercourse can force bacteria into the female bladder. Furthermore, spermicides increase colonization of the vagina with uropathogens and adherence of *Escherichia coli* to vaginal epithelial cells.

Patients with structural abnormalities develop UTIs largely from obstruction of the urine flow. Urinary stasis increases susceptibility to infection. Men of any age and pregnant women are susceptible to lesions that result in obstruction (Sobel 2014).

Typical Causative Organisms and Antibiotic Resistance

Urinary tract infections are primarily caused by gram-negative bacteria, but gram-positive pathogens may also be involved. More than 95% of uncomplicated UTIs are monobacterial. The most common pathogen for uncomplicated UTIs is *E. coli* (75%–95%), followed by *Klebsiella pneumoniae*, *Staphylococcus saprophyticus*, *Enterococcus faecalis*, group B streptococci, and *Proteus mirabilis* (Sobel 2014). Distribution of uropathogens may differ by type of infection or patient population (Table 1-2). *E. coli* can cause both uncomplicated and complicated UTIs. *P. mirabilis*, *Pseudomonas aeruginosa*, and *Enterococcus* spp. predominantly cause complicated infections and are more commonly isolated in hospitals and long-term care facilities. *Corynebacterium urealyticum* is an important nosocomial uropathogen associated with indwelling catheters. *S. saprophyticus* tends to cause infection in young women who are sexually active, accounting for 5%–15% of acute cystitis in the United States.

Coagulase-positive staphylococci can invade the kidney from hematogenous spread, resulting in renal abscesses. Fungi, particularly *Candida* spp., may cause UTIs in patients with indwelling catheters who are receiving antibiotic therapy.

Antibiotic resistance to *E. coli* has steadily been increasing; thus, incorporating the local antibiotic susceptibility patterns

Table 1-1. Predisposing Risk Factors for UTI

Patient Population	Risk Factors
Premenopausal women of any age	<ul style="list-style-type: none"> • Diabetes • Diaphragm use, especially those with spermicide • History of UTI or UTI during childhood • Mother or female relatives with history of UTIs • Sexual intercourse
Postmenopausal and older adult women	<ul style="list-style-type: none"> • Estrogen deficiency • Functional or mental impairment • History of UTI before menopause • Urinary catheterization • Urinary incontinence
Men and women with structural abnormalities	<ul style="list-style-type: none"> • <i>Extrarenal obstruction</i> associated with congenital anomalies of the ureter or urethra, calculi, extrinsic ureteral compression, or benign prostate hypertrophy • <i>Intrarenal obstruction</i> associated with nephrocalcinosis, uric acid nephropathy, polycystic kidney disease, hypokalemic or analgesic nephropathy, renal lesions from sickle cell disease

UTI = urinary tract infection.

Information from: Grabe M, Bartoletti R, Bjerklund Johansen TE, et al, for the European Association of Urology. [Guidelines on Urological Infections](#). 2015; and Sobel JD, Kaye D. Urinary tract infections. In: Mandell GL, Bennett JE, eds. Principles and Practice of Infectious Diseases, 8th ed. Philadelphia: Elsevier Saunders, 2014:886-913.

Table 1-2. Uropathogens by Type of UTIs

Type	Common Uropathogens
Uncomplicated UTI	<i>E. coli</i> <i>S. saprophyticus</i> <i>Enterococcus</i> spp. <i>K. pneumoniae</i> <i>P. mirabilis</i>
Complicated UTI	Similar to uncomplicated UTI Antibiotic-resistant <i>E. coli</i> <i>P. aeruginosa</i> <i>Acinetobacter baumannii</i> <i>Enterococcus</i> spp. <i>Staphylococcus</i> spp.
CA-UTI	<i>P. mirabilis</i> <i>Morganella morganii</i> <i>Providencia stuartii</i> <i>C. urealyticum</i> <i>Candida</i> spp.
Recurrent UTI	<i>P. mirabilis</i> <i>K. pneumoniae</i> <i>Enterobacter</i> spp. Antibiotic-resistant <i>E. coli</i> <i>Enterococcus</i> spp. <i>Staphylococcus</i> spp.

CA-UTI = catheter-associated urinary tract infection; UTI = urinary tract infection.

Information from: Sobel JD, Kaye D. Urinary tract infections. In: Mandell GL, Bennett JE, eds. Principles and Practice of Infectious Diseases, 8th ed. Philadelphia: Elsevier Saunders, 2014:886-913.

of *E. coli* into clinical decision processes is critical to optimal antibiotic selection. According to the Surveillance Network of urine isolates from female outpatients in the United States, *E. coli* resistance rates to nitrofurantoin, ciprofloxacin, and trimethoprim/sulfamethoxazole in 2012 were 0.9%, 11.8%, and 22.2%, respectively (Sanchez 2016). Susceptibility rates with cephalosporins and fluoroquinolones among 2013–2014 isolates were significantly lower in hospital- than in community-acquired UTIs, and *E. coli* resistance to ciprofloxacin was 29% in patients 65 and older (Sanchez 2016).

The Study for Monitoring Antimicrobial Resistance Trends reported that among 3498 *E. coli* isolates from hospitals in Canada and the United States, extended-spectrum β -lactamase (ESBL) rates increased from 7.8% in 2010 to 18.3% in 2014 (Lob 2016). Of note, percent susceptibilities of *E. coli* isolates collected in 2014 in the United States to ceftriaxone, cefepime, ciprofloxacin, levofloxacin, piperacillin/tazobactam, and amikacin were 80.5%, 83.4%, 64.7%, 65.3%, 96.2%, and 99.4%, respectively (Lob 2016).

In recent years, worldwide spread of ESBL-producing *E. coli* such as CTX-M-15 has emerged as a significant cause of community-associated UTIs (Sobel 2014). Highly antibiotic-resistant uropathogens, including AmpC β -lactamase- or carbapenemase-producing Enterobacteriaceae (e.g., New Delhi metallo- β -lactamase [NDM]) and *Acinetobacter* spp., are increasingly being reported among health care-associated complicated UTIs (Sobel 2014). Carbapenem-resistant Enterobacteriaceae (CRE) is a growing concern worldwide. According to the CDC, an isolate is considered a CRE if it is resistant to imipenem, meropenem, doripenem, or ertapenem by susceptibility testing or if it is identified to have a carbapenemase by genotype testing (CDC 2015). The CDC is tracking CRE types such as *K. pneumoniae* carbapenemase (KPC), NDM, IMP-1, and OXA β -lactamases. Among these, KPC is the most prevalent type in the United States, and NDM is the most antibiotic resistant type, often resistant to new cephalosporin/ β -lactamase inhibitor combinations (CDC 2017).

GENERAL TREATMENT CONSIDERATIONS

The first step in treating UTIs is to classify the type of infection, such as acute uncomplicated cystitis or pyelonephritis, acute complicated cystitis or pyelonephritis, CA-UTI, asymptomatic bacteriuria (ASB), or prostatitis (Coyle 2017). The Infectious Diseases Society of America (IDSA) recommends that empiric regimens for uncomplicated UTIs be guided by the local susceptibility, particularly to *E. coli*. They recommend considering trimethoprim/sulfamethoxazole if the local resistance rate is less than 20% and fluoroquinolones if the resistance rate is less than 10% (Gupta 2011). The empiric regimen for complicated UTIs should also be guided by local susceptibility trends of uropathogens, and definitive regimens should be tailored according to susceptibility results, when available (Sobel 2014).

Collateral damage should be considered when deciding on treatment for uncomplicated UTIs (Gupta 2011). Collateral damage refers to ecological adverse effects, including the selection of drug-resistant organisms from antibiotic use, particularly when broad-spectrum cephalosporins and fluoroquinolones are used to treat UTIs. Broad-spectrum cephalosporins have been associated with subsequent infections caused by vancomycin-resistant enterococci, ESBL-producing *K. pneumoniae*, β -lactam-resistant *A. baumannii*, and *Clostridium difficile* infection. Prior use of fluoroquinolones has been linked to subsequent colonization or infections with methicillin-resistant *S. aureus* or fluoroquinolone-resistant *P. aeruginosa* (Paterson 2004). The preserved in vitro susceptibility of *E. coli* to nitrofurantoin and fosfomycin suggests that they cause limited collateral damage, perhaps because of their minimal effects on bowel flora. Antibiotics with a lower potential for collateral damage are preferred for uncomplicated cystitis because the infection is often self-limiting, even without treatment, and the risk of progression to tissue invasion or sepsis is minimal. In fact, studies have shown that 25%–42% of women with uncomplicated cystitis achieved clinical cure even though they did not receive antibiotic treatment or received an inactive antibiotic (Hooton 2012).

Clinical Presentation

Patients with cystitis commonly present with dysuria, hematuria, frequency, and occasionally suprapubic pain. Pyelonephritis usually presents with costovertebral angle tenderness, fevers, urgency, dysuria, chills, nausea, and vomiting. Urinary tract infections are classified into complicated or uncomplicated, depending on the presence or absence of structural abnormality, pregnancy, sex, and renal obstructions. See Table 1-3 for definitions of types of UTIs.

Diagnosis

A urinalysis is often used to detect UTIs, and a clean-catch dipstick leukocyte esterase test is a rapid screening test for detecting pyuria, with a high sensitivity and specificity for detecting more than 10 WBC/mm³ in urine (Sobel 2014). Of note, the presence of pyuria is nonspecific and does not always indicate clinical UTI. Furthermore, bacteriuria alone is not a disease and usually does not necessitate treatment. For symptomatic UTIs, most patients have more than 10 leukocytes/mm³; however, negative tests for bacteriuria may occur because of low bacterial burden. Organisms like *E. coli*, *Klebsiella* spp., *Enterobacter* spp., *Proteus* spp., *Staphylococcus* spp., and *Pseudomonas* spp. reduce nitrate to nitrite in the urine, and the presence of nitrite on a urinalysis is another marker of UTIs.

Urine culture is not recommended for managing acute uncomplicated cystitis. However, for acute pyelonephritis and any type of complicated UTIs, a urine culture should be obtained before empiric therapy to optimize the subsequent

Table 1-3. Definition of Types of UTIs

Category	Definition
Uncomplicated UTI	<ul style="list-style-type: none"> Lower urinary symptoms (dysuria, frequency, and urgency) in otherwise healthy non-pregnant women
Complicated UTI	<ul style="list-style-type: none"> Pregnant women, men, obstruction, immunosuppression, renal failure, renal transplantation, urinary retention from neurologic disease, and individuals with risk factors that predispose to persistent or relapsing infection (e.g., calculi, indwelling catheters or other drainage devices) Health care associated
CA-UTI	<ul style="list-style-type: none"> Presence of indwelling urinary catheters with signs and symptoms of UTI and no other source of infection Presence of $\geq 10^3$ CFU/mL in a single catheter urine specimen or in a midstream urine, despite removal of urinary catheter in the previous 48 hr
Asymptomatic bacteriuria	<ul style="list-style-type: none"> <i>Women:</i> Two consecutive voided urine specimens with isolation of the same bacteria at $\geq 10^5$ CFU/mL <i>Men:</i> A single, clean-catch, voided urine specimen with 1 bacteria isolated 10^5 CFU/mL A single catheterized urine specimen with 1 bacteria isolated $\geq 10^2$ CFU/mL

CA-UTI = catheter-associated UTI.

Information from: Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis* 2011;5:e103-20; Nicolle LE, Bradley S, Colgan R, et al. Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. *Clin Infect Dis* 2005;5:643-54; Hooton TM, Bradley SF, Cardenas DD, et al. Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America. *Clin Infect Dis* 2010;5:625-63.

definitive antibiotic regimen once the susceptibility results are available. Most symptomatic UTIs have 10^5 CFU/mL or greater, indicating a 95% probability of infection. One study of 226 healthy premenopausal women with acute cystitis showed that the detection of 10 – 10^2 CFU/mL of *E. coli* in voided clean-catch midstream urine was highly predictive of bladder infection (Hooton 2013). However, detection of *Enterococcus* spp. and group B streptococci at any colony count in this population was not predictive of cystitis but suggested urethral contamination (Hooton 2013).

Urine in the bladder is normally sterile. In contrast, the urethra and periurethral areas are not sterile, and contamination can occur during urine collection. Therefore, proper cleansing before urine collection is critical, especially in women, to avoid contamination with bacteria from the urethral areas. Of note, gram-positive organisms and fungi may not reach 10^5 CFU/mL in patients with infection. Specimens with 10^4 CFU/mL or less may contain skin organisms, such as diphtheroids, *Neisseria* spp., and staphylococci.

Screening for ASB is necessary for select patients (pregnant women, individuals undergoing invasive genitourinary procedures, and renal transplant recipients) (Nicolle 2005). If screening is indicated, urine should be collected by clean-catch midstream, catheterization, or suprapubic aspiration.

Goals of Therapy

Symptomatic relief is a high priority in patients with UTIs. With appropriate antibiotic therapy, clinical response occurs within 24 hours for cystitis and within 48–72 hours for pyelonephritis. Lack of response within 72 hours warrants a further workup with imaging studies. Patients should receive treatment with agents that are low in toxicity and that have low potential of changing the normal bowel flora. Resolution of bacteriuria is anticipated to correlate with the susceptibility of the pathogen relative to the antibiotic concentration in the urine, not the serum (Sobel 2014). However, data are currently limited correlating the antibiotic concentration in the urine in anuric or dialysis patients with clinical outcomes, and additional studies in this topic would be useful.

Hydration

During UTI management, hydration dilutes the uropathogen and removes infected urine by frequent bladder emptying (Sobel 2014). However, the bacterial count returns to the prehydration level after hydration is discontinued. Potential problems with forcing fluids include urinary retention in a patient with a partially obstructed bladder and decreased urinary antibiotic concentration. Although hydration removes the infected urine, there is no clear evidence that hydration improves the outcomes of UTI.

Overview of Select Antibiotics to Treat UTIs

Most uncomplicated UTIs are treated in the outpatient setting. However, patients who present with fevers or systemic symptoms of infection (e.g., systemic inflammatory response with a suspected urinary source) should be hospitalized and treated with parenteral antibiotics. Initial therapy is based on the local susceptibility patterns of *E. coli* and other uropathogens. For the treatment of cystitis, an adequate urinary antibiotic concentration is important to ensure response to therapy (Sobel 2014). For all oral antibiotics commonly used in UTIs, adequate urinary concentrations are usually achieved. Further research is necessary to help clinicians determine effective treatment of UTIs in patients with renal insufficiency, including anuric patients.

Nitrofurantoin

Nitrofurantoin is recommended for the treatment of cystitis. It is highly active against *E. coli*, with 0.9% resistance among female outpatients (Sanchez 2016). Nitrofurantoin achieves high urinary concentration but does not penetrate well into the renal parenchyma; therefore, it should not be used for the treatment of pyelonephritis. According to the package insert, nitrofurantoin should be avoided in individuals with a CrCl of 60 mL/minute/1.73 m² or less because of lack of efficacy and the potential for peripheral neuropathy and pulmonary adverse effects. Before 2015, nitrofurantoin was listed on the American Geriatrics Society's Beers Criteria of medications potentially inappropriate for use in older adults. In the 2015 Beers Criteria update, the threshold for CrCl was decreased to 30 mL/minute/1.73 m² because of the results of a large cohort study, which found similar effectiveness and low rates of serious adverse effects associated with nitrofurantoin. Serious adverse effects, including renal failure in infected women 18 and older with an estimated glomerular filtration rate of 30–50 mL/minute/1.73 m², were comparable with those with an estimated glomerular filtration rate greater than 80 mL/minute/1.73 m² (Geerts 2013). However, use of nitrofurantoin for long-term suppression of UTIs remains potentially inappropriate in older adult patients because of the risk of adverse effects.

Trimethoprim/Sulfamethoxazole

Trimethoprim/sulfamethoxazole remains a highly effective agent for the treatment of uncomplicated cystitis, with cure rates of 90%–100%. It is also effective in the treatment of UTIs in men. Trimethoprim/sulfamethoxazole was noninferior to ciprofloxacin for early clinical and bacterial cure rates (Arredondo-Garcia 2004). A 20% resistance rate has been recommended as the threshold to avoid treatment with trimethoprim/sulfamethoxazole (Gupta 2011). However, trimethoprim/sulfamethoxazole may remain effective at a clinical cure rate of 85%, even when the resistance rate is 30% (Gupta 2001).

Fluoroquinolones

Fluoroquinolones (e.g., levofloxacin or ciprofloxacin) are recommended for the treatment of uncomplicated pyelonephritis

and complicated UTIs, including urosepsis when the local resistance is less than 10% (Gupta 2011). In addition to collateral damage, the FDA's drug safety communication issued in 2016 states that the serious adverse events (e.g., tendinitis, peripheral neuropathy, and CNS effects) outweigh the benefits in patients with uncomplicated cystitis when other treatment options are available. Alternatives to fluoroquinolones such as nitrofurantoin or amoxicillin/clavulanate are recommended for uncomplicated UTIs (Alternatives to fluoroquinolones 2016). Of note, according to the manufacturer's package insert, about 20% of moxifloxacin is excreted unchanged in the urine, and moxifloxacin is currently not recommended for the treatment of UTIs.

Fosfomycin Trometamol

Fosfomycin trometamol has in vitro activity against most Enterobacteriaceae spp. including ESBL-producing isolates and *Enterococcus* spp. (regardless of vancomycin susceptibility). Given the high *E. coli* susceptibility rates and its low potential for collateral damage, fosfomycin is one of the agents recommended by the IDSA for uncomplicated UTIs. However, increased use of fosfomycin has been associated with increased resistance; thus, routine use of fosfomycin for uncomplicated cystitis remains unclear. A study evaluating 17,602 UTI cases caused by *E. coli* showed that fosfomycin resistance among ESBL-producing *E. coli* increased from 2.2% in 2003 to 21.7% in 2008 with the increased use of fosfomycin by 50% (Oteo 2009). The price of fosfomycin remains relatively high. The average wholesale price for each 3-g sachet is \$86.99, and insurance coverage is variable, which may limit its routine use for uncomplicated cystitis.

Oral β -Lactam Agents

Studies of β -lactam antibiotics (e.g., amoxicillin/clavulanate, cefaclor, cefdinir, cefpodoxime, and ceftriaxone) report lower efficacy than with fluoroquinolones and trimethoprim/sulfamethoxazole. β -Lactam antibiotics are considered alternative agents in managing uncomplicated UTIs. Although cephalexin is not recommended by the IDSA for the treatment of uncomplicated UTI, it is commonly used in the outpatient setting and is an acceptable alternative for treating uncomplicated cystitis and ASB (Gupta 2011). Amoxicillin and ampicillin are currently not recommended for empiric therapy because of the increased prevalence of resistance, but they may be prescribed for the treatment of ASB or UTIs when culture data show susceptibility, especially to *E. faecalis*.

TYPES OF INFECTIONS AND ANTIBIOTIC THERAPY

Uncomplicated UTIs in Women

Antibiotic recommendations by the IDSA and the European Association of Urology and their doses are summarized in Table 1-4.

Table 1-4. Antibiotic Recommendations According to Type of UTIs

Antibiotics	Dose	Therapy Duration	Comments
Acute Uncomplicated Cystitis			
<i>Recommended Agents</i>			
Nitrofurantoin ^a monohydrate/ macrocrystal	100 mg PO BID	5 days	
Trimethoprim/sulfamethoxazole ^c	160/800 mg PO BID	3 days	
Trimethoprim	100 mg PO BID	3 days	
Fosfomycin	3 g PO once	Once	
<i>Alternative Agents</i>			
Amoxicillin/clavulanate	500/125 mg PO q8hr	5–7 days	
Cefpodoxime proxetil	100 mg PO BID	5–7 days	
Cefdinir	300 mg PO BID	5–7 days	
Cephalexin	500 mg PO BID	5–7 days	Widely used, but limited data
Ciprofloxacin ^b	250 mg PO BID	3 days	
Levofloxacin ^b	250–500 mg PO daily	3 days	
Acute Uncomplicated Pyelonephritis			
<i>Recommended Antibiotics for Outpatient Management</i>			
Ciprofloxacin ^b	500 mg PO BID	7 days	If local FQ resistance is > 10%, give ceftriaxone 1 g IV once or a dose of an aminoglycoside ⁹ pending culture results
Ciprofloxacin ^b	1 g ER PO daily	7 days	
Levofloxacin ^b	750 mg PO daily	5 days	
<i>Alternatives or Definitive Therapy after susceptibility is confirmed</i>			
Trimethoprim/sulfamethoxazole ^c	160/800 mg PO BID	14 days	Give ceftriaxone 1 g IV once or aminoglycoside ⁹ pending culture results
Cefpodoxime proxetil	200 mg PO BID	10–14 days	
Amoxicillin/clavulanate	500 mg PO TID	10–14 days	
<i>Inpatient management or in those unable to take oral medications</i>			
Ciprofloxacin	400 mg IV q12hr	7 days	May add aminoglycoside ⁹ pending culture results. Complete the course with PO antibiotics after afebrile for 48 hr
Levofloxacin	500 mg IV q24hr	7 days	
Ceftriaxone	1 g IV q24hr	14 days	
Cefepime	1–2 g IV q12hr		
Piperacillin/tazobactam	3.375 g IV q6hr		
Acute Complicated Cystitis or CA-UTI without upper tract symptoms			
<i>Recommended Empiric Therapy</i>			
Ciprofloxacin	500 mg PO BID	5–7 days	Empiric therapy on the basis of local antibiotic resistance patterns; then streamline on the basis of cultures and treat for 5–7 days
Ciprofloxacin	1 g ER PO daily	5–7 days	
Levofloxacin	750 mg PO daily	5–7 days	
Ampicillin/sulbactam	1.5–3 g IV q6hr		
Ceftriaxone	1 g IV q24hr		

Table 1-4. Antibiotic Recommendations According to Type of UTIs (*continued*)

Antibiotics	Dose	Therapy Duration	Comments
Gentamicin/tobramycin	3–5 mg/kg IV once		
Pathogen-specific treatment	If susceptible, Nitrofurantoin, trimethoprim/sulfamethoxazole, fosfomycin, or PO β -lactams for 7 days		
ESBL <i>E. coli</i> Nitrofurantoin or fosfomycin		7 days	
Acute Complicated Pyelonephritis or Urosepsis or CA-UTI patients who are severely ill			
<i>Recommended Empiric Therapy for inpatient, not severely ill</i>	See Inpatient Management of Acute Uncomplicated Pyelonephritis		
<i>Recommended Empiric Therapy for inpatient, severely ill including urosepsis</i>			
Ceftriaxone	1 g IV q24hr		Add aminoglycoside initially (i.e., gentamicin 5–7 mg/kg once daily).
Ceftazidime	1–2 g IV q8hr		
Cefepime	1 g IV q12hr		Direct antibiotic therapy according to susceptibility results and treat for total of 14 days
Piperacillin/tazobactam	3.375–4.5 g IV q6hr		
Aztreonam	1–2 g IV q8hr		
Meropenem ^d	1 g IV q8hr		
Ertapenem ^d	1 g IV q24hr		
Doripenem ^d	500 mg IV q8hr		
Antibiotic-resistant (e.g., CRE or <i>Acinetobacter</i> spp.) Colistin	Loading dose of CBA (mg) = C _{ss} , average target (mg/L) \times 2.0 \times ideal body weight (kg) up to 300 mg CBA; then maintenance dose according to the look-up table		
Definitive therapy if susceptible to trimethoprim/sulfamethoxazole	160/800 mg PO BID	14 days	
Ciprofloxacin	500 mg PO BID	5 days	
Levofloxacin	750 mg PO daily	5 days	
CA-UTI (see acute complicated cystitis for stable patients)			
UTIs and Asymptomatic Bacteriuria in Pregnant Women^e			
Nitrofurantoin monohydrate/ macrocrystals ^f	100 mg PO BID	5–7 days	Except during first trimester or near term
Amoxicillin	500 mg PO TID	3–7 days	
Amoxicillin/clavulanate	500 mg PO TID	3–7 days	
Cephalexin	500 mg PO QID	3–7 days	
Cefpodoxime	100 mg PO BID	3–7 days	

Table 1-4. Antibiotic Recommendations According to Type of UTIs (*continued*)

Antibiotics	Dose	Therapy Duration	Comments
Fosfomycin	3 g PO once	Once	
Trimethoprim/sulfamethoxazole	160/800 mg PO BID	3 days	Except during first trimester or near term
Prevention of Recurrent UTIs			
Nitrofurantoin	50 mg PO qhs		
Trimethoprim/sulfamethoxazole	40/200 mg PO daily		
UTIs in Men: See recommendations for acute complicated cystitis and pyelonephritis and treat for at least 7 days			
Acute Bacterial Prostatitis			
Ceftriaxone	1–2 g IV q24hr		Follow by PO FQs for 2–4 wk
Ciprofloxacin	400 mg IV q12hr		
Levofloxacin	500 mg IV q24hr		
Chronic Bacterial Prostatitis			
Ciprofloxacin	500 mg PO BID	4–6 wk	
Levofloxacin	500 mg PO daily	4–6 wk	
Trimethoprim	100 mg PO BID	4–12 wk	
Doxycycline	100 mg PO BID	4 wk	

Note: Dosage listed assumes normal renal function (e.g., CrCl > 60 mL/min/1.73 m²).

^aAvoid if early pyelonephritis is suspected.

^bUse empirically if *E. coli* resistance to FQs is < 10%.

^cUse empirically if *E. coli* resistance to trimethoprim/sulfamethoxazole is < 20%.

^dThe decision to use a carbapenem for empiric therapy should be individualized on the basis of local resistance data followed by timely de-escalation to ensure judicious use.

^eOral antibiotics should be used for asymptomatic bacteriuria and cystitis and parenteral antibiotics for pyelonephritis in pregnant women.

^fNot used for pyelonephritis because of inadequate therapeutic concentrations in the kidneys.

^gGentamicin or tobramycin 5–7 mg/kg IV once.

BID = twice daily; CBA = colistin base activity; CRE = carbapenem-resistant Enterobacteriaceae; ER = extended release; ESBL = extended-spectrum β-lactamase; FQ = fluoroquinolone; IV = intravenous(ly); PO = orally; q = every; QD = once daily; qhs = at night; QID = four times daily; TID = three times daily.

Information from: Coyle EA, Prince RA. Urinary tract infections and prostatitis. In: DiPiro JT, Talbert RL, Yee GC, et al, eds. *Pharmacotherapy: A Pathophysiologic Approach*, 10th ed. New York: McGraw-Hill, 2017; Grabe M, Bartoletti R, Bjerklund Johansen TE, et al, for the European Association of Urology. [Guidelines on Urological Infections](#). 2015; Sobel JD, Kaye D. Urinary tract infections. In: Mandell GL, Bennett JE, eds. *Principles and Practice of Infectious Diseases*, 8th ed. Philadelphia: Elsevier Saunders, 2014;886-913; Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis* 2011;5:e103-20; Hooton TM, Bradley SF, Cardenas DD, et al. Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America. *Clin Infect Dis* 2010;5:625-63; and Nation RL, Garonzik SM, Thamlikitkul V, et al. Dosing guidance for intravenous colistin in critically ill patients. *Clin Infect Dis* 2017;64:565-71.

Patient Care Scenario

A 54-year-old woman (height 66 inches, weight 71 kg) with well-controlled type 2 diabetes presents to the ED with burning during urination, costovertebral angle tenderness, chills, and nausea. Your ED attending physician turns to you for a recommendation on empiric antibiotic therapy for the patient's UTI. Urinalysis was remarkable for WBC greater than 182 per high-power field, nitrite

positive, and large leukocyte esterase. She reports that she has not had UTIs for a few years. Her SCr is 1.1 mg/dL, and she is allergic to trimethoprim/sulfamethoxazole, which causes maculopapular rash. One dose of ondansetron 4 mg intravenous push was administered a few minutes ago. Formulate the initial antibiotic regimen for this patient.

ANSWER

This patient has costovertebral angle tenderness with burning during urination, chills, and nausea, which suggest acute pyelonephritis. She does not have urologic structural abnormalities or immunosuppression; thus, her condition is considered uncomplicated. If available, the empiric regimen is determined on the basis of local susceptibility trends. If *E. coli* resistance to fluoroquinolones is below 10%, ciprofloxacin 400 mg intravenously every 12 hours or levofloxacin 500 mg intravenously every 24 hours can be prescribed empirically until her nausea subsides. If *E. coli* resistance to fluoroquinolones is 10% or greater, a third-generation cephalosporin such as ceftriaxone 1 g intravenously every 24 hours with or without

a consolidated dose of aminoglycoside such as gentamicin or tobramycin once can be given with the initial regimen. This patient weighs 71 kg, with ideal body weight of 58.7 kg, and gentamicin 5–7 mg/kg (300–440 mg) intravenously once is the suggested dosage. For acute pyelonephritis, urine culture should be obtained and the antibiotic regimen tailored to susceptibility results. If the culture and susceptibility results confirm the susceptibility to ciprofloxacin or levofloxacin, or trimethoprim/sulfamethoxazole, this patient can be transitioned to oral ciprofloxacin or levofloxacin to complete the treatment course of 7 days for uncomplicated pyelonephritis.

1. Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: a 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis* 2011;5:e103-20.
2. Coyle EA, Prince RA. Urinary tract infections and prostatitis. In: DiPiro JT, Talbert RL, Yee GC, et al, eds. *Pharmacotherapy: A Pathophysiologic Approach*, 10th ed. New York: McGraw-Hill, 2017.

Acute Uncomplicated Cystitis

Acute uncomplicated cystitis is a mild infection for which 25%–42% of women have early resolution of symptoms, even without active antibiotic treatment (Hooton 2012). Narrow-spectrum oral antibiotics with a low potential for collateral damage are preferred. The recommended antibiotics for uncomplicated cystitis are trimethoprim/sulfamethoxazole (if uropathogen resistance is 20% or less), nitrofurantoin monohydrate/macrocrystal, or fosfomycin trometamol.

Oral β -lactams, including amoxicillin/clavulanate, cefdinir, cefaclor, and cefpodoxime, are recommended as alternatives (Gupta 2011). Oral β -lactams used for 3–5 days have a clinical efficacy of 89% and are less effective than trimethoprim/sulfamethoxazole or fluoroquinolones (Hooton 2012). Efficacy data are limited on narrow-spectrum cephalosporins such as cephalexin, and they are currently not recommended by the IDSA (Hooton 2012).

Fluoroquinolones such as ciprofloxacin and levofloxacin have overall high clinical efficacy rates for uncomplicated cystitis. However, because of the concern for increased fluoroquinolone resistance and serious adverse events, fluoroquinolones should be reserved as an alternative treatment option when other UTI agents cannot be used (FDA 2016; Gupta 2011).

Therapy duration for most uncomplicated cystitis is short, 3–7 days. Nitrofurantoin is recommended for 5 days, trimethoprim/sulfamethoxazole for 3 days, fluoroquinolones for 3 days, fosfomycin for a single dose, and oral β -lactams for 3–7 days (Gupta 2011).

Acute Uncomplicated Pyelonephritis

Most patients with acute uncomplicated pyelonephritis are treated as outpatients with oral antibiotics that achieve high serum and renal tissue concentrations. For clinically stable patients who do not require hospitalization and if local fluoroquinolone resistance is less than 10%, oral ciprofloxacin for 7 days or levofloxacin for 5 days with or without an initial intravenous dose of ciprofloxacin or levofloxacin is recommended (Gupta 2011). If the fluoroquinolone resistance rate is 10% or greater, a dose of ceftriaxone 1 g or a consolidated aminoglycoside (e.g., gentamicin 5–7 mg/kg once) is recommended at the initiation of therapy (Gupta 2011). Oral trimethoprim/sulfamethoxazole is not an optimal agent for empiric therapy because of increasing rates of resistance; however, it is highly effective in pyelonephritis and appropriate if the pathogen is susceptible. Compared with trimethoprim/sulfamethoxazole, oral β -lactams are not as effective because of higher relapse rates. When the susceptibility to

trimethoprim/sulfamethoxazole is unknown or when an oral β -lactam is used, an initial parenteral dose of ceftriaxone or consolidated aminoglycoside is recommended (Gupta 2011).

Patients with severe symptoms, hemodynamic instability, inability to tolerate oral medications, poor adherence, or any complicating factors (i.e., renal stones) are treated as inpatients initially with parenteral antibiotics. Patients hospitalized with pyelonephritis should be treated with an initial parenteral regimen including a fluoroquinolone, an aminoglycoside with or without ampicillin, or an extended-spectrum cephalosporin, or penicillin with or without an aminoglycoside (Gupta 2011). The antibiotic selection must be tailored to available susceptibility results. The European Association of Urology suggests initial therapy with an aminoglycoside or carbapenem if ESBL-producing *E. coli* rates are high (i.e., greater than 10%), followed by a transition to oral antibiotics if susceptibility results indicate that oral agents are active (Grabe 2015).

The recommended therapy for uncomplicated pyelonephritis is 7 days for fluoroquinolones, 14 days for trimethoprim/sulfamethoxazole, and 10–14 days for β -lactam agents (Gupta 2011). Persistent high fevers or positive blood cultures (i.e., over the first 3–4 days) suggest the need to investigate for complications, including urinary obstruction and abscess (intrarenal or perinephric). Renal ultrasonography, CT, MRI, and urologic consultation may be useful in this scenario.

ASB and UTIs in Pregnancy

Asymptomatic bacteriuria is common during pregnancy, occurring in 2%–10% of pregnant women, and increases the risk of symptomatic UTIs (particularly pyelonephritis) during pregnancy (Nicolle 2005). Pregnant women should be screened for ASB using a urine culture at least once during pregnancy, preferably at 12–16 weeks of gestation (Angelescu 2016). The most common pathogen causing both ASB and symptomatic UTI during pregnancy is *E. coli*. Cystitis and ASB during pregnancy are usually treated with oral antibiotics. For pyelonephritis during pregnancy, parenteral antibiotics should be administered for 48 hours before transitioning to oral therapy.

The safety of antibiotics in pregnancy is of foremost importance when selecting therapy in pregnant women. Teratogenic concerns with the use of fluoroquinolones, tetracyclines, and sulfonamides at term significantly limit these antibiotics as treatment options. Trimethoprim/sulfamethoxazole should be avoided during the first trimester of pregnancy because it can cause folate-sensitive birth defects. Trimethoprim/sulfamethoxazole should also be avoided after 32 weeks of gestation because it can displace bilirubin from albumin and cause kernicterus.

β -Lactams, nitrofurantoin, and fosfomycin have been used in pregnant women for ASB and UTIs. All β -lactams (except for ceftriaxone because it may cause kernicterus by bilirubin displacement if administered the day before parturition) and fosfomycin are generally considered safe during pregnancy.

Among the parenteral β -lactams, piperacillin/tazobactam and the carbapenems should be reserved for severe pyelonephritis or for patients with an impaired immune system or incomplete urinary drainage. Imipenem/cilastatin has caused adverse fetal effects in animals and should be avoided in pregnant women.

Trimester-specific cautions must be considered for nitrofurantoin. Nitrofurantoin can be used during the second trimester but should be avoided in the first trimester because of its effects on organogenesis. Nitrofurantoin is contraindicated near term (i.e., 38–42 weeks) and during labor because of its potential to cause hemolytic anemia in the newborn. For ASB and cystitis, therapy duration is 3–7 days, except for single-dose fosfomycin. Fluoroquinolones should be avoided during pregnancy, according to animal studies, because of their toxic effect on the developing cartilage and high rate of therapeutic abortions in humans (Bar-Oz 2009; Loebstein 1998).

Special Considerations in Lactating Women

Urinary tract infections in lactating mothers are treated with antibiotics that are considered safe in lactation. Factors that determine the passage of antibiotics into breast milk are summarized in Table 1-5. In general, trimethoprim/sulfamethoxazole, nitrofurantoin, and most β -lactam agents are considered compatible with breastfeeding with minimal risk of toxicity to infants. The American Association of Pediatrics issued a report and concluded that only a few medications (primarily radioactive agents and select psychotropic agents) are contraindicated in breastfeeding mothers or are associated with adverse effects in infants (Sachs 2013). Clinicians are referred to LactMed for the most current data on individual antibiotics. Although the potential for direct toxicity associated with antibiotic exposure through breast milk in infants is low, hypersensitivity reactions and changes in bowel flora in infants leading to diarrhea must be monitored while the nursing mother is taking antibiotics.

Complicated UTIs

Complicated UTIs usually occur in individuals with underlying conditions that increase the risk of treatment failure. These underlying conditions include poorly controlled diabetes, pregnancy, symptoms for 7 or more days before receiving medical care, hospital-acquired UTIs, renal failure, urinary tract obstruction, presence of an indwelling urinary catheter, stent, nephrostomy tube or urinary diversion, functional or anatomic abnormality of the urinary tract, renal transplantation, and immunosuppression.

Urinary tract infections in men are uncommon and increase with age. They are often associated with structural or functional abnormality. Therefore, any man presenting with a UTI should be evaluated for structural abnormalities of the urinary tract, with the UTI treated as a complicated UTI until proven otherwise (Sobel 2014).

Table 1-5. Factors That Determine the Passage of Antibiotics into Breast Milk

Factors	Effect
Gradient of concentration	Antibiotics transfer to lactocytes by passive diffusion, and it is important to recognize expected time to reach peak serum concentration to determine appropriate plans to minimize drug exposure to infants. “Pump and dump” strategy can be applied to minimize the risk to infants
Molecular weight	Antibiotics with smaller molecular weights (i.e., < 300 Da) transfer to the breast milk easily, whereas those with 900 Da or higher diffuse poorly
Volume of distribution	Medications with a large volume of distribution achieve low concentrations in the milk and are generally compatible with breastfeeding
Protein binding	Medications with high protein binding (e.g., > 90%) are associated with low concentrations in the breast milk
Half-life	Antibiotics with a longer half-life are more likely to transfer to the breast milk from the maternal blood

Information from: de Sa Del Fiol F, Barberato-Filho S, de Cassia Bergamaschi C, et al. Antibiotics and breastfeeding. *Chemotherapy* 2016;61:134-43.

Acute Complicated Cystitis

Treatment of acute complicated cystitis with any antibiotic with confirmed susceptibility results is recommended because of the lack of superiority data for any particular agent (Grabe 2015). Empiric antibiotic options include fluoroquinolones, nitrofurantoin, fosfomycin, trimethoprim/sulfamethoxazole, and β -lactam with or without aminoglycoside (Grabe 2015; Sobel 2014). Oral antibiotics with activity against resistant pathogens such as ESBL- or AmpC- β -lactamase-producing bacteria are limited to nitrofurantoin and fosfomycin. These agents are effective for the treatment of cystitis (Giancola 2017; Qiao 2013). Of note, fosfomycin, when compared with ertapenem as a step-down therapy for an ESBL UTI in outpatients, had similar UTI-related 30-day hospital readmission, or ED/clinic visits (12 of 89 vs. 13 of 89, respectively) (Veve 2016). When diagnosis of cystitis versus pyelonephritis is unclear, trimethoprim/sulfamethoxazole is an acceptable choice if susceptibility is available.

Cystitis in men is treated with trimethoprim/sulfamethoxazole or fluoroquinolones. Nitrofurantoin, fosfomycin, and β -lactams are used in men if pyelonephritis and prostatitis are ruled out. The treatment duration for cystitis in men is 7–14 days. Two large studies showed that prolonged treatment with fluoroquinolones or trimethoprim/sulfamethoxazole was associated with an increase in late recurrence and the risk of *C. difficile* infection (Mospan 2016; Drekonja 2013). As such, in men with no symptoms suggestive of severe pyelonephritis or prostatitis, 7 days may be considered until additional studies are conducted.

Acute Complicated Pyelonephritis

In mildly to moderately ill patients with acute complicated pyelonephritis who can take oral medications, oral ciprofloxacin or levofloxacin is recommended initially (Coyle 2017; Sobel 2014). Alternative agents include trimethoprim/sulfamethoxazole or amoxicillin/clavulanate after the patient is given an initial long-acting agent such as ceftriaxone (Coyle 2017).

In severely ill patients, empiric antibiotics should be parenteral broad-spectrum antibiotics (e.g., third- or fourth-generation cephalosporin, piperacillin/tazobactam with or without an aminoglycoside, or a carbapenem) and be tailored to susceptibility results (Sobel 2014). Because of increasing carbapenem resistance including CRE, the decision to prescribe a carbapenem for severe infections of urinary source should be individualized; a β -lactam/ β -lactamase inhibitor such as piperacillin/tazobactam may be a more judicious option. According to a surveillance study of complicated UTIs in North America and Europe, piperacillin/tazobactam was susceptible to 78.6% of ESBL *E. coli* and 42.8% of ESBL *K. pneumoniae* (Hoban 2012). In a multivariate analysis of clinical efficacy of piperacillin/tazobactam compared with ertapenem in the treatment of acute pyelonephritis caused by ESBL *E. coli*, the type of antibiotic was not associated with treatment failure (Yoon 2017). In addition, other investigators conducted a meta-analysis to investigate the outcomes of patients who received carbapenems or β -lactam/ β -lactamase inhibitors (Muhammed 2017). Their analysis of 13 studies that evaluated empiric therapy showed no statistically significant difference in mortality of patients with ESBL Enterobacteriaceae

bloodstream infections who were treated with carbapenems (22.1%) compared with those treated with β -lactam/ β -lactamase inhibitors (20.5%) with RR 1.05 (95% CI, 0.83–1.37). The analysis of seven studies that reported data on definitive therapy indicated similar mortality rates at 15.2% (115 of 767) for carbapenem recipients and 16.2% (32 of 199) for β -lactam/ β -lactamase inhibitor recipients (RR 0.62; 95% CI, 0.25–1.52). Therefore, available data do not support routine use of carbapenems as a preferred class for empiric or definite treatment of patients with ESBL Enterobacteriaceae bloodstream infections of urinary source. β -Lactam/ β -lactamase inhibitors are appropriate treatment options. Cefepime is another agent with a potential role as a carbapenem-sparing agent for the treatment of ESBL UTIs. In a study of 106 patients with ESBL UTIs, 17 patients received cefepime and 89 patients received a carbapenem without clinical or microbiological failures (Kim 2017). Additional studies of cefepime for this indication are needed to better define the role of cefepime.

For multidrug-resistant (MDR) organisms, alternatives such as colistin or tigecycline may be necessary (Sobel 2014). Colistin was recently recognized as the preferred polymyxin for the treatment of complicated UTIs because it is renally excreted (Bader 2017; Zavascki 2008). The optimal dosage of colistin is an evolving topic because of considerable interindividual variation in plasma concentrations, administration of colistimethate (the prodrug of colistin), and increased risk of nephrotoxicity when the colistin concentration exceeds 2.5 mg/L (Nation 2016). According to recent studies, equations for loading and maintenance doses of colistin aim for an average colistin concentration of 2 mg/L at steady state (Nation 2017). Because of its nephrotoxicity and neurotoxicity, colistin is reserved primarily for complicated UTIs associated with MDR organisms that are resistant to aminoglycosides and carbapenems. Tigecycline is often active against ESBL-producing bacteria or *Acinetobacter* spp. *in vitro*. However, tigecycline achieves low urinary and serum concentrations because of a large volume of distribution; therefore, tigecycline is not a recommended agent for UTIs, especially those with concurrent bacteremia, unless there are no appropriate alternative agents. For patients with serious penicillin allergy, aztreonam is an appropriate empiric option. The recommended therapy is 10–14 days; however, when complicated by abscesses, longer duration and drainage should be considered (Grabe 2015; Sobel 2014).

Recently, two cephalosporins with β -lactamase inhibitor combinations were approved for the management of complicated UTIs: ceftolozane/tazobactam and ceftazidime/avibactam. Ceftolozane is a new cephalosporin (similar to ceftazidime) with a pyrazole side chain that prevents hydrolysis by AmpC β -lactamases (van Duin 2016). For the management of complicated UTIs, ceftolozane/tazobactam was compared with levofloxacin in a randomized, double-blind, phase III trial (Wagenlehner 2015). Most patients in

the study had pyelonephritis (656 of 800 patients enrolled), and *E. coli* was the most commonly isolated uropathogen (629 [78.6%] patients), followed by *K. pneumoniae* (7.3%) and *P. aeruginosa* (2.9%). The resistance rate to ceftolozane/tazobactam was 2.7% and that to levofloxacin was 26.7% at baseline. Ceftolozane/tazobactam was superior to levofloxacin in microbiologic eradication for the per-protocol groups with Enterobacteriaceae infections (88.9% vs. 78.0%). However, this superiority was not observed when only levofloxacin-susceptible pathogens were analyzed (Wagenlehner 2015). The second combination agent, ceftazidime/avibactam, has avibactam, which is a non- β -lactam β -lactamase inhibitor. Avibactam prevents the hydrolysis of ceftazidime by diverse types of β -lactamases such as TEM, SHV, CTX-M, AmpC- β -lactamases, and most KPC, but not by the metallo- β -lactamases such as NDM (van Duin 2016). In a phase II trial of complicated UTIs, 68 patients received ceftazidime/avibactam, and 67 patients received imipenem/cilastatin (Vazquez 2012). Sixty-four patients were evaluated, and a favorable clinical response occurred in 24 of 28 (86%) in the ceftazidime/avibactam group and 29 of 36 (81%) in the imipenem/cilastatin group. *E. coli* was the most commonly isolated uropathogen, occurring at over 92% in both treatment groups. Overall, microbiological responses were similar for the ceftazidime/avibactam group and the imipenem/cilastatin group at 70% and 71%, respectively (Vazquez 2012). These two new agents play a potential role in the treatment of complicated UTIs caused by MDR *P. aeruginosa* or Enterobacteriaceae spp., particularly CRE strains that are not NDM producers (Alatoom 2017). Of note, until additional data are available, these agents must be used judiciously for serious infections caused by MDR organisms, and their empiric use for infections because of a urinary source in the absence of MDR organisms must be avoided.

The optimal treatment of CRE infections originating from urinary source is a complex topic with limited data and heterogeneity of study designs. Due to wide variations in local rates of CRE infections and prevalence of CRE types, treatment strategies differ by region. According to a retrospective cohort study, monotherapy with aminoglycoside was effective for treatment of CRE UTIs (Alexander 2012). In addition, *in vitro* data suggest synergy with double carbapenem therapy, and case series have demonstrated positive outcomes among patients with sepsis or septic shock who received double carbapenem therapy as salvage therapy for complicated UTIs (some patients with concurrent bacteremia) (Souli 2017; Oliva 2017; Bulik 2011). However, the published data regarding the role of combination therapy for CRE UTIs are inconclusive. A study from the New York/New Jersey region, the CRE epicenter of the United States of KPC-2 and KPC-3 types, indicated that the overall 14-day mortality rate of CRE bacteremia is high at 34%, regardless of whether monotherapy or combination therapy was used for definitive therapy

(Satlin 2017). Furthermore, CRE bacteremia of urinary source was an independent factor associated with decreased mortality (adjusted OR 0.25; 95% CI, 0.07–0.99; $p=0.049$). Additional research on treatment options for CRE infections of urinary source is necessary.

Catheter-Associated UTIs

Urea-splitting organisms such as *Proteus* spp., *M. morgani*, and *P. stuartii* are often isolated in patients with indwelling urinary catheters (Grabe 2015). Urinary catheters may become coated with a biofilm that acts as a reservoir for microorganisms and can compromise the action of antibiotics and host defenses. Therefore, urinary catheters should be removed and replaced when CA-UTI is suspected. Catheter-associated UTIs linked to short-term catheterization are usually caused by a single organism, whereas polymicrobial infections are more common with long-term catheterization lasting 30 days or longer (Grabe 2015).

Individuals symptomatic with CA-UTI are treated similarly to those with acute complicated cystitis in the absence of upper tract symptoms or complicated pyelonephritis if upper tract symptoms are present (Sobel 2014). A urine culture should be obtained before initiation of antibiotic therapy, if possible, from a newly placed catheter because the bacterial biofilm on the existing catheter can render the culture results less useful (Hooton 2010). In addition, an indwelling catheter that has been in place for 7 days or longer should be removed or replaced before initiating antibiotics (Grabe 2015). The optimal treatment duration for CA-UTI has not been well defined. However, the IDSA and the European Association of Urology recommend treating CA-UTI for 7 days in patients who have timely resolution of symptoms and for 10–14 days in those with a delayed clinical response, bacteremia, hypotension, or signs of severe sepsis (Grabe 2015; Hooton 2010). In the absence of symptoms indicative of pyelonephritis, women younger than 65 with CA-UTI may be treated for 3 days after the indwelling catheter is removed (Hooton 2010). Other patients with CA-UTI who are not severely ill may be treated with levofloxacin for 5 days.

Asymptomatic candiduria is common among hospitalized patients with an indwelling urinary catheter. Changing or removing the indwelling catheter clears 20%–40% of asymptomatic candiduria (Sobel 2000). Treatment of asymptomatic candiduria with fluconazole effectively eradicates candiduria initially, but 2 weeks after discontinuing therapy, the recurrence rate was 40% among patients with an indwelling catheter (Sobel 2000). Therefore, routine antifungal treatment of asymptomatic candiduria is not recommended, and treatment is reserved primarily for patients undergoing urologic procedures. However, if candiduria persists and a deep-seated infection is suspected, reasons for persistent candiduria should be investigated by performing imaging studies. Fluconazole is the only azole that achieves high urinary concentrations. Patients with candiduria with symptoms of *Candida*

cystitis or pyelonephritis should be treated with fluconazole, except for fluconazole-resistant *Candida* such as *Candida glabrata* and *Candida krusei* (Fisher 2011). Flucytosine may be used for *Candida* cystitis caused by fluconazole-resistant *Candida* strains, but it must be used with caution because of its bone marrow suppression adverse effect and development of resistance when used alone. Amphotericin B bladder irrigation is going out of favor because of the lack of adequate efficacy data and because its role is limited to patients with *C. krusei* or fluconazole-resistant *C. glabrata* cystitis.

Urosepsis

Most cases of urosepsis are health care associated and occur in patients older than 65 with renal stones who are undergoing lithotripsy. Risk factors associated with urosepsis are obstruction of the urinary tract because of stones, tumor obstruction, prostate enlargement, urethral stricture, or congenital anomalies (Wagenlehner 2015). According to a prevalence study in health care–associated UTIs, among 1866 patients with a diagnosis of health care–associated UTIs, 70.4% were men, and the mean age was 59.9 years for both men and women (Tandogdu 2016). Urinary tract infections presenting with signs of severe sepsis with hypotension or organ dysfunction must be treated with parenteral broad-spectrum antibiotics initially similar to acute complicated pyelonephritis. Definitive therapy should be optimized on the basis of susceptibility results.

Prostatitis

The presence of fever with symptoms of cystitis in men may indicate acute bacterial prostatitis (ABP). When symptoms persist for more than 3 months, chronic bacterial prostatitis (CBP) occurs. Most men with CBP have a condition called chronic pelvic pain syndrome. Four main symptoms of CBP and chronic pelvic pain syndrome are urogenital pain, lower urinary tract symptoms including voiding or storage symptoms, psychological issues, and sexual dysfunction (Rees 2015).

The most common pathogen for ABP is *E. coli*, but the spectrum of pathogens is more variable for CBP, including *E. coli*, *E. faecalis*, *K. pneumoniae*, *P. mirabilis*, *P. aeruginosa*, *S. aureus*, and streptococcal spp. (Grabe 2015). In patients with ABP, a clean-catch midstream urine culture is the most important diagnostic test, together with a physical examination of the abdomen, external genitalia, perineum, and prostate (Nickel 2011).

Acute Bacterial Prostatitis

Acute bacterial prostatitis requires parenteral therapy initially with bactericidal antibiotics, including broad-spectrum penicillin, third-generation cephalosporin, or a fluoroquinolone (Grabe 2015; Nickel 2011). An aminoglycoside can be added to the initial therapy and be continued until the patient becomes afebrile. In less severe cases, an oral fluoroquinolone is prescribed for 10 days (Grabe 2015).

Chronic Bacterial Prostatitis

For CBP, ciprofloxacin and levofloxacin are the drugs of choice because of good penetration to the prostate, high bioavailability, and activity against *P. aeruginosa*. Patients are treated for 4–6 weeks (Grabe 2015). For fluoroquinolone resistance or intolerance, trimethoprim is an appropriate alternative because it has good penetration into the prostate and high bioavailability; however, trimethoprim requires a longer treatment of 4–12 weeks (Grabe 2015). In patients with chronic pelvic pain syndrome, management should include antibiotics, α -adrenergic antagonists, and analgesics (Rees 2015). α -Adrenergic antagonists such as tamsulosin, alfuzosin, doxazosin, terazosin, and silodosin reduce symptoms and improve quality-of-life scores. The combination of antibiotics and α -blockers reduces the recurrence of CBP and is optional for patients with obstructive symptoms (Nickel 2011).

ASB in Special Patient Populations

Urologic Intervention

In addition to pregnancy, screening for and treatment of ASB is recommended for those with plans to undergo transurethral resection of the prostate or urologic procedures during which mucosal bleeding is anticipated (Nicolle 2005). Antibiotic prophylaxis and treatment of ASB reduce postprocedural urosepsis from 4.4% to 0.7% in these patients (Wollin 2017). A urine culture should be obtained several days before the procedure, followed by therapy with a third-generation cephalosporin or another appropriate agent initiated 12 hours before the procedure. The antibiotic therapy should be discontinued immediately after the procedure; however, some clinicians continue therapy until the urethral catheter is removed. Patients with bladder cancer who are undergoing cystoscopy do not require antibiotic prophylaxis because postprocedure UTIs are uncommon and are easily treated with oral antibiotics.

Urinary tract infections (including urosepsis) are the most common complications in patients with renal stone intervention. Bacteria involved in renal stones may enter the urine and spread systemically, leading to sepsis. In patients undergoing percutaneous nephrolithotomy or ureteroscopy, attempts should be made to retrieve stone fragments under sterile conditions (Wollin 2017). Urine cultures are obtained before and after percutaneous nephrolithotomy. Extracted stones should be tested for culture and susceptibility because the results can guide antibiotic selection if sepsis occurs after the procedure.

Use of newer disposable wires and baskets to access the ureter and kidney has significantly decreased the complications associated with ureteroscopy. However, infectious complications are still of utmost concern. In patients with negative preoperative urine cultures, pre- or perioperative antibiotic prophylaxis does not appear to reduce postoperative UTIs (de la Rosette 2014). The European Association of Urology recommends antibiotic prophylaxis for therapeutic (and not diagnostic) ureteroscopy. In contrast, the American Urological Association currently recommends perioperative

prophylaxis with one dose of oral levofloxacin 500 mg, ciprofloxacin 500 mg, or trimethoprim/sulfamethoxazole 160/800 mg before the procedure for all patients undergoing ureteroscopy (Wolf 2008).

Renal Transplant Recipients

Urinary tract infections are the most common infectious complications after kidney transplantation and are associated with poor allograft survival. Reported rates of UTIs after kidney transplantation range widely, with around 25% of allograft recipients having UTIs within 1 year of transplantation (Ariza-Heredia 2013). Of note, UTIs increase the likelihood of complications (including transplant failure or rejection) in renal transplant recipients by 2- to 3-fold (Becerra 2015).

Although ASB is a risk factor for developing allograft pyelonephritis, screening and prophylaxis for ASB do not appear to prevent pyelonephritis 24 months after transplantation (Origüen 2016; Singh 2016). The IDSA guidelines do not recommend routine screening for ASB in renal transplant recipients. The usefulness of screening remains controversial, and clinical practices vary among transplant centers (Nicolle 2006).

Most renal transplant recipients receive trimethoprim/sulfamethoxazole prophylaxis for 6 months to prevent *Pneumocystis jiroveci* pneumonia, and this antibiotic probably serves a secondary purpose of preventing UTI. In fact, compared with those who received inhaled pentamidine or oral dapsone, *P. jiroveci* prophylaxis with trimethoprim/sulfamethoxazole was associated with fewer UTIs (HR 0.41; 95% CI, 0.27–0.62; $p < 0.0001$), particularly the first year posttransplantation (Ariza-Heredia 2013).

Skilled Nursing Facility Residents

Asymptomatic bacteriuria occurs in 15%–50% of older adult women and men residing in skilled nursing facilities (SNFs) (Grabe 2015). Contributing factors to the development of ASB are dementia, neurologic effects on the bladder, and inability to independently use bathrooms. A major concern in SNFs is the inappropriate use of antimicrobials to treat UTIs in asymptomatic residents. About 50% of asymptomatic SNF residents are prescribed broad-spectrum antibiotics for suspected UTIs. Furthermore, around 80% of the antibiotic use was based on urinalysis results and prescribed for individuals with an indwelling urinary catheter in the absence of UTI symptoms (Phillips 2012).

Routine screening for ASB is not recommended for SNF residents (Nicolle 2005). Contamination of the urine samples is common in older adult patients. If the patient does not have a urinary catheter, dipsticks may be useful because negative tests are associated with a low probability of bacteriuria. Antibiotic therapy for bacteriuria is only indicated in patients in SNFs who are symptomatic because treatment of ASB does not prevent symptomatic UTIs.

Educational programs (including small-group sessions with facility nurses and physicians, guidelines adapted for

the local context, and feedback on prescribing) were implemented in Swedish long-term care facilities to improve antimicrobial use (Pettersson 2011). Although the educational interventions did not affect fluoroquinolone use for the treatment of UTIs at the end of the 2-year intervention period, overall antimicrobial use for all infections decreased, and the “wait-and-see” approach (with delay in empiric antibiotics) increased (Pettersson 2011).

Recurrent UTIs

Recurrent UTI is defined as at least two infections within 6 months, or at least three infections within 1 year. The recurrence of a UTI may be relapse (i.e., caused by the same uropathogen) or reinfection (i.e., caused by different uropathogens). Most recurrences are likely reinfection rather than relapse. The frequency of infections caused by *Proteus*, *Pseudomonas*, *Klebsiella*, *Enterobacter* spp., antibiotic-resistant *E. coli*, enterococci, and staphylococci increases significantly with recurrent complicated UTIs involving structural abnormalities.

Risk Factors

Recurrent UTIs in women are caused by uropathogens that adhere well to the uroepithelial cells. Recurrent UTIs may occur in women of any age, and there may be a genetic predisposition because some women are more likely to develop subsequent infections after the first episode of UTI. One study showed that after a first episode of cystitis caused by *E. coli* in young women, 24% had a second infection within 6 months (Sobel 2014).

Antibiotic Prophylaxis

Women with recurrent cystitis can be treated with self-administration of a short-course therapy (3–5 days) at symptom onset. In addition, sexually active women with recurrent UTI can take prophylactic antibiotics (e.g., a single-strength trimethoprim/sulfamethoxazole, nitrofurantoin 50 mg or 100 mg, or a dose of ciprofloxacin 250 mg) at the time of intercourse; they should also avoid the use of a spermicide-containing contraceptive. In young women with a history of recurrent UTI, treating ASB with antibiotics was actually associated with an increased risk of recurrence (RR 1.31; 95% CI, 1.21–1.42; $p < 0.0001$). This increased risk occurred even at 12 months after treatment (Cai 2012). Antibiotic prophylaxis should be considered a last resort after behavioral changes (e.g., avoiding spermicide-containing products, early postcoital voiding, and liberal fluid intake) have proven unsuccessful. The potential risks of long-term antibiotic therapy should be discussed with the patient. Long-term antibiotic therapy for 4 weeks may be considered when prevention is clinically warranted and patients with frequent symptomatic relapses desire antibiotic prophylaxis.

In acidic urine, methenamine is hydrolyzed to ammonia and formaldehyde, which has nonspecific bactericidal activity. Methenamine hippurate 1 g twice daily appears to reduce UTIs in patients without structural abnormalities

(specifically, RR for symptomatic UTI of 0.24; 95% CI, 0.07–0.89; and bacteriuria of 0.56; 95% CI, 0.37–0.83) (Lee 2012). According to the manufacturer’s package insert, methenamine is contraindicated in patients with impaired renal function.

Non-antimicrobial Preventive Strategies

Cranberry inhibits one of the adhesins called P-fimbriae and blocks the adherence of bacterial P-fimbriae to uroepithelial cells (Costantini 2017). As a result, cranberry products including juice, tablets, or capsules may reduce the frequency of recurrent UTIs in women. However, a meta-analysis of 24 studies of 4473 participants showed that cranberry products did not significantly reduce the occurrence of symptomatic UTIs (Jepson 2013). Cranberry capsules are an option in pregnant women to prevent ASB (Wing 2015).

Other adhesin blockers such as D-mannose are used by women to prevent cystitis, but data to support their use are limited. In women with recurrent UTIs, oral administration of D-mannose 2 g or nitrofurantoin 50 mg daily for 6 months, compared with no treatment, significantly decreased the risk of recurrent UTIs. Recurrent UTI rates were 14.6%, 20.4%, and 60.8% for D-mannose, nitrofurantoin, and the no-prophylaxis group, respectively (Kranjcec 2014).

In postmenopausal women, replacement with topical estrogen therapy normalizes the vaginal flora and has been shown to reduce the risk of recurrent UTI. Use of 0.5 mg of estriol vaginal cream at night for 2 weeks followed by twice-weekly administration for 8 months significantly reduced the incidence of UTIs compared with placebo (Raz 1993). In addition, estriol use was associated with an increase in vaginal lactobacilli from 0% to 60% and a decrease in vaginal colonization with Enterobacteriaceae spp. from 67% to 31% (Raz 1993).

Probiotics protect the vagina from bacterial colonization by blocking attachment and producing hydrogen peroxide that is microbicidal to *E. coli* and other uropathogens. *Lactobacillus* appears to be promising as an antibiotic-sparing agent. In a study of postmenopausal women, a mixture of *Lactobacillus* (including *L. rhamnosus* GR-1 and *L. reuteri* RC-14) administered orally twice daily was compared with trimethoprim/sulfamethoxazole prophylaxis over 1 year (Beerepoot 2012). The mean time to the first UTI was 3 and 6 months for *Lactobacillus* and trimethoprim/sulfamethoxazole, respectively. Resistance to trimethoprim/sulfamethoxazole and amoxicillin increased in women who received trimethoprim/sulfamethoxazole, but not in those who received *Lactobacillus* (Beerepoot 2012).

ROLE OF ANTIMICROBIAL STEWARDSHIP PROGRAMS

Antimicrobial stewardship programs are essential to promote appropriate antibiotic use to optimize therapeutic outcomes and minimize adverse events (including the development of resistance and collateral damage) for UTIs. The diagnosis of UTI is primarily based on clinical presentation rather than

laboratory findings, particularly in the outpatient setting. Selection of empiric antibiotics for UTIs should be based on the severity of the infection and local susceptibility patterns. When antibiotics are indicated, short courses are effective for uncomplicated UTIs, especially cystitis, and in otherwise healthy women.

Routine screening and treatment for ASB may lead to unnecessary antibiotic use, unnecessary diagnostic testing, development of antimicrobial resistance, and adverse drug effects. Therefore, the decision to screen for bacteriuria in asymptomatic individuals or to initiate antibiotic treatment in the setting of ASB must be weighed carefully to ensure judicious use of antibiotics and to prevent the development of antibiotic resistance. Of importance, screening for ASB is not indicated for most patients, including SNF residents and those undergoing non-urologic procedures (Drekonja 2013).

In women with uncomplicated UTIs, trying analgesic agents such as ibuprofen for symptomatic relief rather than an immediate antibiotic prescription may be prudent to spare antibiotic use (Gagyor 2012). Of note, in a comparative study with fosfomycin, ibuprofen (400 mg three times daily for 3 days) relieved UTI symptoms in two-thirds of women with uncomplicated UTIs who recovered without any antibiotic use. Therefore, initial symptomatic treatment rather than immediate antibiotic use should be considered in women with uncomplicated UTIs (Gagyor 2012).

An antibiotic stewardship program could provide educational programs and cascade the reporting of antibiotic susceptibility results as effective strategies to improve antibiotic prescribing behavior.

In a university-based internal medicine clinic, the aggregate concordance with antibiotic type, frequency, and duration according to the IDSA guidelines was surprisingly low at 34% (Kim 2015). An antibiotic stewardship program intervention that incorporates prospective review and feedback (i.e., for selected cases after positive urine cultures) within health care systems may reduce urine culture ordering and antibiotic prescribing for catheter-associated ASB (Trautner 2015). In addition, developing and implementing institutional guidelines to manage catheter-associated ASB may improve appropriate antibiotic use.

CONCLUSION

As the most common bacterial infection that requires medical care, UTIs vary greatly by clinical presentation and therapeutic management. Urinary tract infections affect a variety of patients with different biological and procedural risk factors (e.g., age, sex, pregnancy, catheters and urologic interventions). However, not all bacteriurias require antibiotic therapy, particularly in the presence of ASB. Antibiotic stewardship practices are essential to promote judicious antibiotic use for UTIs. This can significantly reduce antibiotic resistance because UTIs are the most common infections leading to an antibiotic prescription.

Practice Points

In determining appropriate antibiotic regimens for the treatment of UTIs, consider the following:

- Which type of UTI does the patient have?
- What are the local susceptibility rates of *E. coli* to trimethoprim/sulfamethoxazole and the fluoroquinolones?
- What is the most appropriate empiric antibiotic regimen with a low potential for collateral damage for the type of UTI the patient has?
- What is the most appropriate definitive antibiotic regimen with a low potential for collateral damage for the type of UTI the patient has, given the susceptibility results?
- Which antibiotics are safe to use for UTIs during pregnancy, or which are compatible with breastfeeding?
- What is the recommended therapy duration for the type of UTI the patient has?
- When the patient has UTIs caused by MDR organisms, what are the treatment options?
- What is the role of newer cephalosporin/β-lactamase inhibitor combinations for the treatment of complicated UTIs?
- Does the patient have any risk factors for recurrence?
- For patients with recurrent UTIs, what are appropriate strategies to prevent future recurrences?
- For patients undergoing urologic procedures, especially renal stone procedures, what is the optimal strategy to minimize the potential for urosepsis postoperatively?

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Self-Assessment Questions

- L.P. is a 21-year-old female college student, otherwise healthy, who presents to the clinic with complaints of burning during urination and frequent urination for 2 days. She denies fevers, chills, or flank pain. L.P. has no known allergies. According to last year's antibiogram from the student health office, trimethoprim/sulfamethoxazole resistance to urinary pathogens is estimated to be 24%, and ciprofloxacin resistance is estimated to be 8%. L.P.'s urine dipstick is positive for leukocyte esterase and nitrites. Which one of the following is best to recommend for L.P.?
 - Amoxicillin/clavulanate 500mg/125mg by mouth twice daily for 5 days
 - Levofloxacin 750 mg by mouth once daily for 5 days
 - Nitrofurantoin monohydrate macrocrystals 100 mg by mouth twice daily for 5 days
 - Trimethoprim/sulfamethoxazole 1 double-strength tablet by mouth twice daily for 3 days
- A 49-year-old woman with uncontrolled diabetes is hospitalized with significant flank pain, chills, and a temperature of 101.3°F (38.5°C). In her home state, the *E. coli* resistance rate to ciprofloxacin is 19% and the rate to trimethoprim/sulfamethoxazole is 30%. She is very uncomfortable because of flank pain, and her vital signs are blood pressure 140/95 mm Hg, heart rate 85 beats/minute, and respiratory rate 23 breaths/minute. Her laboratory test results are remarkable only for a WBC of 11.3×10^3 cells/mm³. The patient has a history of a maculopapular rash associated with penicillin G. She has no history of renal insufficiency. Which one of the following is best to recommend for this patient?
 - Ampicillin/clavulanate 3 g intravenously every 6 hours
 - Ceftriaxone 1 g intravenously every 24 hours
 - Aztreonam 1 g intravenously every 8 hours
 - Levofloxacin 750 mg intravenously every 24 hours

Questions 3–6 pertain to the following case.

C.M. is a 36-year-old woman (height 66 inches, weight 57.2 kg) who presents to the transplant nephrology clinic for a scheduled follow-up appointment. She has a history of hypertension and diabetes, both of which are well controlled. C.M. underwent kidney-pancreas transplantation 6 years ago and currently takes atenolol 50 mg by mouth once daily, tacrolimus 2 mg by mouth twice daily, and prednisone 5 mg by mouth daily. C.M. states that she started to have increased burning during urination yesterday, had to go to the bathroom three times last night, has some hematuria, and is feeling tired this morning. She denies fever, nausea, and vomiting. Clean-catch midstream urine sample has been collected for

- urinalysis, culture, and susceptibility. Her SCr is 1.1 mg/dL. C.M.'s vital signs are otherwise within normal limits.
- Which one of the following types of UTI does C.M. most likely have?
 - Asymptomatic bacteriuria (ASB)
 - Uncomplicated cystitis
 - Uncomplicated pyelonephritis
 - Complicated cystitis
 - Which one of the following risk factors most likely contributed to C.M.'s urinary symptoms?
 - Age
 - Immunosuppressive therapy
 - Diabetes
 - Hypertension
 - Pending results of the urine culture and susceptibility for outpatient management, which one of the following oral therapies is best to recommend as empiric treatment given C.M.'s clinical presentation?
 - Cefpodoxime 100 mg twice daily
 - Ciprofloxacin 500 mg twice daily
 - Fosfomycin 3 g every 2 days
 - Trimethoprim/sulfamethoxazole 160 mg/800 mg 1 tablet twice daily
 - Two days after her clinic visit, C.M.'s urine culture is positive for greater than 100,000 CFU/mL of vancomycin-resistant *Enterococcus faecium* with the susceptibility results as follows. The laboratory also provided the result of daptomycin ETEST with the MIC of 4 mcg/mL.

> 100,000 CFU/mL of vancomycin-resistant <i>E. faecium</i>	
Antibiotic	Interpretation
Ampicillin	Resistant
Ciprofloxacin	Resistant
Levofloxacin	Resistant
Linezolid	Susceptible
Nitrofurantoin	Susceptible
Penicillin	Resistant
Tetracycline	Resistant
Tigecycline	Susceptible

- Which one of the following is best to recommend for C.M.'s UTI?
- Linezolid 400 mg by mouth twice daily for 7 more days
 - Fosfomycin 3 g by mouth once

- C. Nitrofurantoin monohydrate macrocrystals 100 mg by mouth twice daily for 7 more days.
- D. Daptomycin 350 mg intravenously every 24 hours for 7 more days

7. A 70-year-old woman (height 64 inches, weight 51.4 kg) is brought to the ED from a skilled nursing facility (SNF) with a temperature of 100.9°F (38.3°C) and altered mental status. The patient has neurogenic bladder secondary to spinal stenosis and performs self-catheterization three times a day. She is also an active smoker. The patient has a history of UTIs (i.e., three in the current year). For the last episode (about 4 weeks ago) she received ceftriaxone for *P. mirabilis*. Her caretaker reports that the patient is urinating more often than usual. Her WBC is 12.5×10^3 cells/mm³ and SCr is 0.9 mg/dL. Urinalysis reveals WBC greater than 182 per high-power field, large leukocyte esterase, and positive nitrite. Her urine culture results are as follows:

<i>P. aeruginosa</i> > 100,000 CFU/mL		
Antibiotic	MIC (mcg/mL)	Interpretation
Amikacin	4	Susceptible
Cefepime	16	Intermediate
Ceftazidime	32	Resistant
Ciprofloxacin	2	Intermediate
Gentamicin	≥ 16	Resistant
Imipenem	≥ 16	Resistant
Levofloxacin	≥ 8	Resistant
Meropenem	≥ 16	Resistant
Piperacillin	≥ 64	Resistant
Piperacillin/tazobactam	64	Intermediate
Polymyxin B	1	Susceptible
Tobramycin	≥ 16	Resistant

Which one of the following is the best intravenous regimen to recommend as definitive therapy for this patient's UTI?

- A. Amikacin 700 mg every 36 hours
- B. Cefepime 2 g over 30 minutes every 8 hours
- C. Meropenem 2 g over 3 hours every 8 hours
- D. Polymyxin B 500,000 units every 12 hours

Questions 8 and 9 pertain to the following case.

H.D. is a 60-year-old man with quadriplegia caused by coccidoidal meningitis requiring lifelong suppressive therapy with fluconazole and a chronic tracheostomy. He developed new bilateral staghorn calculi and was subsequently admitted to the hospital for percutaneous nephrolithotomy as definitive stone management. H.D. has a right nephrostomy tube, and

urine culture obtained 2 days before admission showed the following:

<i>K. pneumoniae</i> > 100,000 CFU/mL		
Antibiotic	MIC (mcg/mL)	Interpretation
Ampicillin	≥ 32	Resistant
Ampicillin/sulbactam	≥ 32/16	Resistant
Amikacin	≥ 64	Resistant
Cefazolin	≥ 8	Resistant
Cefepime	≥ 64	Resistant
Ceftazidime	≥ 64	Resistant
Ciprofloxacin	≥ 4	Resistant
Ertapenem	≥ 4	Resistant
Gentamicin	8	Resistant
Imipenem	≥ 16	Resistant
Levofloxacin	≥ 8	Resistant
Meropenem	≥ 16	Resistant
Nitrofurantoin	256	Resistant
Piperacillin	≥ 128	Resistant
Piperacillin/tazobactam	≥ 128/4	Resistant
Polymyxin B	0.5	Susceptible
Tobramycin	≥ 16	Resistant

8. Which one of the following is best to recommend for H.D.?
- A. Start meropenem 1 g intravenous every 8 hours
 - B. Obtain another urine culture to determine the need for antibiotic therapy
 - C. Start colistin
 - D. Start polymyxin B
9. H.D. undergoes percutaneous nephrolithotomy successfully, and intraoperative renal pelvic urine cultures grow *K. pneumoniae* with the same susceptibility as with the preoperative urine culture, except for a polymyxin B MIC of 8 mcg/mL. Today, on postoperative day 2, H.D. has a temperature of 102.7°F (39.3°C) with chills and rigors. His vital signs are blood pressure 71/53 mm Hg, heart rate 121 beats/minute, and respiratory rate 21 breaths/minute. He is currently not receiving any antibiotic therapy. Blood and urine cultures have been collected. Which one of the following antibiotic susceptibility tests would be best to request from the microbiology laboratory before initiating treatment in H.D.?
- A. Fosfomycin
 - B. Colistin
 - C. Ceftazidime/avibactam
 - D. Ceftolozane/tazobactam

Questions 10 and 11 pertain to the following case.

C.T. is a 39-year-old man with congenital urethral stricture who presents to the ED with a temperature of 102.4°F (39.1°C), chills, dysuria, frequency, and pelvic pain for 2 days. His laboratory results are remarkable for a WBC of 14×10^3 cells/mm³. A urine specimen has been collected for culture and susceptibility testing.

10. Which one of the following conditions does C.T. most likely have?
- A. Acute complicated cystitis
 - B. Acute bacterial prostatitis
 - C. Acute uncomplicated pyelonephritis
 - D. Urosepsis
11. C.T.'s urine culture was finalized with *E. coli* that was susceptible to ceftriaxone, ciprofloxacin, and nitrofurantoin. Which one of the following is best to recommend for C.T.?
- A. Levofloxacin 500 mg by mouth once daily for 14 days
 - B. Trimethoprim/sulfamethoxazole 160 mg/800 mg by mouth twice daily for 4 weeks
 - C. Ceftriaxone 2 g intravenously once daily for 4 weeks
 - D. Moxifloxacin 400 mg by mouth once daily for 14 days
12. In a placebo-controlled, randomized clinical trial of pregnant women, cranberry capsule ingestion was evaluated for the prevention of ASB. Seven episodes of ASB occurred in five patients: 2 of 24 (8%) in the cranberry group and 3 of 25 (12%) in the placebo group. Which one of the following best describes the number needed to treat with cranberry capsules to prevent ASB?
- A. 1
 - B. 8
 - C. 12
 - D. 25
13. A 53-year-old man has a medical history of diabetes, hypertension, dementia, and neurogenic bladder requiring the long-term use of urethral indwelling catheters. Last month he was admitted to an SNF because of his worsening dementia. The patient has a history of UTIs (usually once a year) and had his catheter replaced several times in the past 2 years. Currently, his vital signs are Tmax 98.6°F (37°C), blood pressure 135/85 mm Hg, heart rate 75 beats/minute, and respiratory rate 18 breaths/

minute. He only has complaints of pain caused by a pressure ulcer on his right back. Which one of the following initial approaches of care is best for this patient?

- A. Monitor vital signs and conduct physical examination
 - B. Obtain a urine sample for urinalysis
 - C. Obtain a urine sample for urine culture
 - D. Initiate antibiotic therapy using a class of antibiotic that is different from what the patient has received previously
14. Which one of the following patient populations is most likely to benefit from the specified non-antimicrobial preventive strategy?
- A. Pregnant women; cranberry juice
 - B. Men with recurrent UTIs; d-Mannose
 - C. Premenopausal women; estriol cream
 - D. Postmenopausal women; probiotics
15. A 49-year-old woman with systemic lupus erythematosus presents to the ED with dysuria, nausea, and costovertebral angle tenderness. She had an episode of cystitis caused by *E. coli* 5 months ago and was treated with amoxicillin/clavulanate. Her initial vital signs in the ED were temperature 100.2°F (37.9°C), blood pressure 120/82 mm Hg, heart rate 75 beats/minute, and respiratory rate 18 breaths/minute. Her laboratory results were remarkable for SCr 1.6 mg/dL, Hct 10.1 g/dL, and Hgb 8.9 g/dL. You and the ED physician reviewed the urine culture results for her last episode of cystitis and gave the patient ceftriaxone 1 g intravenously 4 hours ago. Her current vital signs are temperature 101.8°F (38.8°C), blood pressure 80/54 mm Hg, heart rate 135 beats/minute, and respiratory rate 22 breaths/minute. The microbiology laboratory reports that one of the two sets of her blood culture has gram-negative rods. The ED physician wants to optimize this patient's antibiotic therapy. Which one of the following is best to recommend for this patient?
- A. Colistin
 - B. Meropenem
 - C. Piperacillin/tazobactam
 - D. Tigecycline with gentamicin