

LEARNING OBJECTIVES

- Discuss the management of acute uncomplicated cystitis and asymptomatic bacteriuria
- Describe *Clostridium difficile*-associated disease, the reason for its increase, and its prevention
- Review the common clinical manifestations of community-acquired methicillin-resistant *Staphylococcus aureus* and resistance problems in gram-positive and gram-negative bacteria

The antibiotic challenge: Changing clinical management of infections

Common pathogens continue to evolve and learn in the process to evade antimicrobial intervention. Updated guidelines help to ensure successful treatment of these infections.

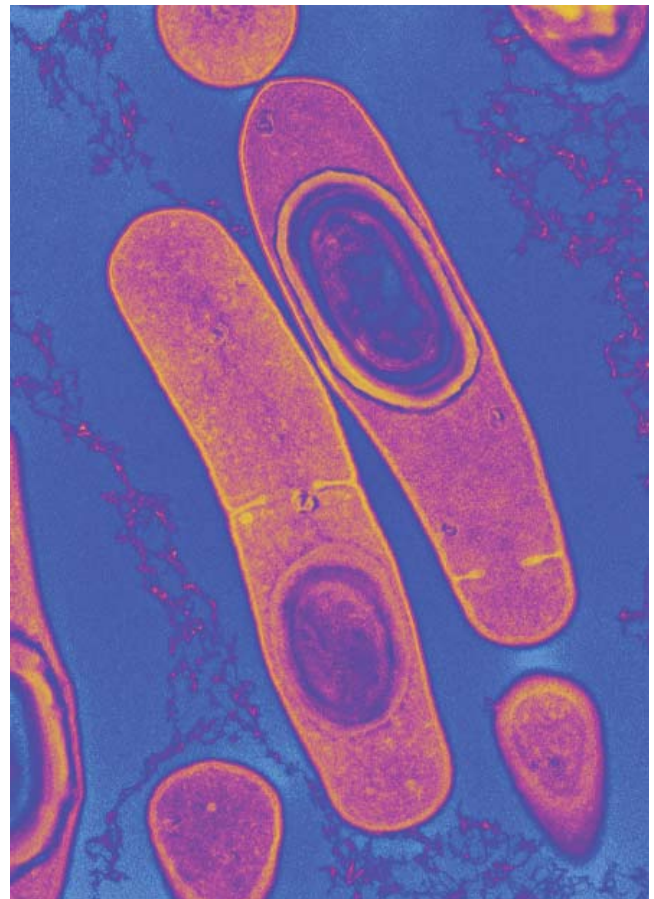
JoAnn Deasy, PA-C, MPH

Resistance is one of many reasons why antibiotic therapy can be ineffective. Efforts to forestall further development of antimicrobial resistance include judicious prescribing of antibiotics, implementing infection-control measures, and developing institutional stewardship of antimicrobial agents. This article, the third and final in a series on antibiotic resistance, discusses selected common infections that have changing epidemiology and/or for which the recommended evaluation and treatment guidelines have been updated.

Urinary tract infection (UTI) is the most frequently diagnosed bacterial infection among community-living women.¹ In the United States, UTIs account for approximately 8 million medical visits per year.² Acute cystitis is considered uncomplicated when a symptomatic infection occurs in an otherwise healthy, nonpregnant adult female. *Escherichia coli* is the causative organism in 80% to 85% of cases of acute cystitis; the causative organisms in the remaining cases are *Staphylococcus saprophyticus*, *Klebsiella pneumoniae*, and *Proteus mirabilis*.³

Increasing antimicrobial resistance of *E coli* urine culture isolates has made empirical treatment of UTIs more difficult. In 1999, the Infectious Diseases Society of America (IDSA) published guidelines for the treatment of UTIs.² These guidelines recommended a 3-day course of trimethoprim-sulfamethoxazole (TMP-SMX) as initial therapy for women with acute uncomplicated cystitis except in communities where resistance exceeds 10% to 20%. Other authors, however, suggested a threshold of 22% to 30%.⁴

A study published in 2007 evaluated adherence to the IDSA guidelines.⁵ The major outcomes measure was whether these



A course of broad-spectrum antibiotics can allow *Clostridium difficile*, a bacteria normally found in the gut, to flourish, causing a potentially fatal inflammation of the colon.

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guidelines influenced antibiotic selection. The study reviewed 2,339 cases of uncomplicated UTI treated between 1996 and 2001. The data showed that the use of TMP-SMX did not change significantly; however, the use of ciprofloxacin increased significantly.⁵

Concern about increasing antimicrobial resistance to TMP-SMX is likely the reason that medical providers did not alter their prescribing habits in response to the IDSA guidelines. Prior to 1990, *E coli* resistance to TMP-SMX was 0% to 5%.⁶ In 2001, reported resistance among urine isolates of *E coli* obtained from female outpatients from across the United States was 16%; even allowing for considerable geographic variation, TMP-SMX resistance was higher than 10% in all nine US Census Bureau regions.⁷ However, resistance may be overestimated as uncomplicated cases of UTI are often treated empirically; therefore, isolates from laboratory cultures may have been obtained from women in whom previous antimicrobial treatment had failed or who had had underlying risk factors. Local hospital antibiograms often include both inpatient and outpatient isolates and, therefore, may also overstate the prevalence of *E coli* resistance as the cause of uncomplicated cystitis. Risk factors for *E coli* resistance to TMP-SMX include current use of antibiotics, use of TMP-SMX within the previous 3 months, diabetes, and recent hospitalization.⁸

An increase in the use of fluoroquinolones for cystitis may increase resistance, thereby limiting the effectiveness of this class of antibiotics for other types of infections. *E coli* isolates from outpatient urine cultures showed a greater than three-fold stepwise increase in resistance from 1995 (0.7%) to 2001 (2.5%).⁷ Given this concern, what would be the most appropriate treatment for uncomplicated cystitis if TMP-SMX cannot be used because of allergy, recent antibiotic administration, recent hospitalization, or a community-resistance prevalence greater than 20%? Nitrofurantoin should be considered for women with mild to moderate cystitis symptoms. This compound has activity against most uropathogenic *E coli* and gram-positive cocci; however, it is inactive against most *Proteus* species and some *Enterobacter* and *Klebsiella*

strains. Nitrofurantoin is administered for 5 to 7 days for cystitis; a 7-day regimen was recommended in the past, but a recent study demonstrated efficacy with 5 days of treatment.⁹ Nitrofurantoin should not be administered for complicated UTIs, including pyelonephritis, because it does not attain appreciable serum levels.¹⁰ Fluoroquinolones, such as ciprofloxacin, are excellent drugs for treating UTIs; however, because of increasing resistance, these agents should be reserved for women with more severe cystitis symptoms and a risk factor for TMP-SMX resistance. Limited use of fluoroquinolones for UTIs will help to maintain the efficacy of this important drug class.

ASYMPTOMATIC BACTERIURIA IN ADULTS

Asymptomatic bacteriuria is the isolation of bacteria from a urine specimen obtained from a person without symptoms or signs referable to UTI. Pyuria may or may not be present. Asymptomatic bacteriuria is a common occurrence, particularly among older adults because of the physiologic changes related to aging.¹¹

IDSA guidelines for diagnosis and treatment of asymptomatic bacteriuria in adults are based on published evidence.¹² Results of analyzed studies show that premenopausal women with asymptomatic bacteriuria are at increased risk for subsequent symptomatic UTI; however, an association between asymptomatic bacteriuria and long-term adverse outcomes, including hypertension, chronic kidney disease, cancer, or increased mortality, has not been found. Interestingly, antimicrobial treatment of asymptomatic bacteriuria neither decreases the frequency of symptomatic infection nor prevents future episodes of asymptomatic bacteriuria. Women with certain host factors appear to have increased susceptibility to both asymptomatic and symptomatic UTI that is not altered by treatment.¹²

Likewise, screening and treatment of asymptomatic bacteriuria in women with diabetes, older persons who reside in the community, or elderly residents of long-term-care facilities are not beneficial. Symptomatic UTI is defined by the presence of symptoms referable to the GU tract; however, nonurinary

KEY POINTS

- Acute cystitis is considered uncomplicated when a symptomatic infection occurs in an otherwise healthy, nonpregnant adult female. *Escherichia coli* is the causative organism in 80% to 85% of cases of acute cystitis; the causative organisms in the remaining cases are *Staphylococcus saprophyticus*, *Klebsiella pneumoniae*, and *Proteus mirabilis*.
- Antimicrobial treatment of asymptomatic bacteriuria neither decreases the frequency of symptomatic infection nor prevents future episodes of asymptomatic bacteriuria. Women with certain host factors appear to have increased susceptibility to both asymptomatic and symptomatic urinary tract infection that is not altered by treatment.
- A recent increase in the incidence and severity of *Clostridium difficile*-associated disease (CDAD), both in the hospital and in the community, has been linked with a hypervirulent strain referred to as North American pulsed-field type 1.
- Prevention of CDAD in health care facilities is aimed at interrupting its transmission between persons. Evidence supports four interventions: (1) instituting policies that support the prudent use of antibiotics; (2) wearing gloves during contact with infected patients; (3) thoroughly cleaning and disinfecting patient rooms; and (4) using disposable, single-use thermometers.
- An important action institutions can take is to monitor drug resistance patterns among pathogens and to develop and routinely update antibiograms for clinicians. Local antibiograms that are site-specific to the pathogen and that separate outpatients from inpatients are the most useful.

tract-specific symptoms may indicate the presence of a UTI in elderly persons. Consensus-based criteria have been developed to define symptomatic UTI in nursing-home residents who do not have an indwelling catheter. Per these criteria, symptomatic UTI is identified if the person exhibits three of these four criteria: (1) fever 100.4°F (38°C) or higher; (2) new or increased burning sensation with urination, frequency, or urgency; (3) new flank or suprapubic pain or tenderness; and (4) worsening of mental or functional status.¹³

Women with asymptomatic bacteriuria during early pregnancy have a 20- to 30-fold increase in the risk of developing pyelonephritis.¹² Antimicrobial treatment is proven to decrease the risk of subsequent pyelonephritis, as well as the frequency of low birth weight and preterm delivery. Thus, the IDSA guidelines recommend that pregnant women be screened for bacteriuria by urine culture in early pregnancy and treated if test results are positive. Asymptomatic bacteriuria is also a risk for patients who undergo traumatic urologic interventions that involve mucosal bleeding. These patients should be treated prior to such interventions. For all other adults, the condition has not been shown to be harmful, and screening for, or treatment of, asymptomatic bacteriuria is not appropriate.¹²

Avoidance of treating asymptomatic UTIs in adults should reduce the risks of antimicrobial resistance. Treatment should be limited to those patients for whom therapy has been shown to have potential benefit. Antibiotic therapy for patients with diabetes, older persons, patients with or without indwelling catheters, or patients with spinal cord injuries who have asymptomatic bacteriuria has not been found to improve outcomes.¹¹

CLOSTRIDIUM DIFFICILE-ASSOCIATED DISEASE

Clostridium difficile is a gram-positive, spore-forming, toxin-producing bacillus that causes a spectrum of disease, including asymptomatic carriage, colitis (which usually manifests as diarrhea only), and occasionally life-threatening toxic megacolon. *C. difficile* accounts for 15% to 25% of cases of diarrhea occurring after antibiotic administration.¹⁴ Antimicrobial therapy is the primary risk factor for colonization with *C. difficile*; a greater increase in colonization risk is seen with older age, a prolonged antibiotic course, use of broad-spectrum antimicrobials, and administration of two or more antibiotics.¹⁵ Key steps in the pathogenesis of *C. difficile*-mediated diarrhea include disruption of normal colonic flora by antibiotics, colonization with *C. difficile* via fecal-oral transmission, elaboration of toxins, and mucosal injury and inflammation.¹⁶

A recent increase in the incidence and severity of *C. difficile*-associated disease (CDAD), both in the hospital and in the community, has been linked to a hypervirulent strain referred to as North American pulsed-field type 1 (NAP1). This strain of *C. difficile* produces increased levels of toxins A and B, as well as an extra toxin known as *binary toxin*. This strain, uncommon before 2000, has become epidemic and has also developed a high level of resistance to fluoroquinolones.¹⁷ Some studies of NAP1-related CDAD reported that fluoro-

quinolones were the antibiotic most closely associated with the acquisition of this disease.^{18,19} Another recently described but controversial risk factor for CDAD is the use of proton pump inhibitors (PPIs) to suppress acid secretion. Some investigators reported an association between PPI use and CDAD,²⁰ and other investigators reported that PPI use was not a risk factor.²¹

The patient who is newly exposed to *C. difficile*, not the patient who is already colonized with this bacillus, is at greatest risk of developing CDAD during a hospital stay. In health care facilities, workers' hands become contaminated with *C. difficile* spores easily, enabling the infection to spread from patient to patient.²² Although *C. difficile* is most often associated with health care settings, the bacillus can cause

“Antibiotic administration builds resistance in commensal bacteria as well as in the targeted pathogen, creating a resistance reservoir.”

disease in healthy persons in the community. Furthermore, some persons who acquire CDAD in the community may not have a history of antimicrobial use.²³

With these changes in the epidemiology of *C. difficile* infection, clinicians must maintain a high suspicion for CDAD. In addition to diarrhea, symptoms and signs often include fever, abdominal pain or cramping, and leukocytosis. CDAD without diarrhea may manifest as an acute abdominal syndrome or toxic megacolon. Diagnosis is made by demonstration of toxin in the stool. Testing should be performed only on diarrheal (unformed) stool unless ileus is suspected. The most commonly used assays are the enzyme immunoassays that provide rapid results. However, sensitivity ranges from 60% to 95%,²¹ and therefore, if findings from the first specimen are negative, testing a second stool specimen should be considered. Updated IDSA guidelines for the diagnosis and management of CDAD are expected to be published in Fall 2009.

Prevention of CDAD in health care facilities is aimed at interrupting its transmission between persons. Evidence supports four interventions: (1) instituting policies that support the prudent use of antibiotics; (2) wearing gloves during contact with infected patients; (3) thoroughly cleaning and disinfecting patient rooms; and (4) using disposable, single-use thermometers.²⁴ Hand-washing with soap and water is recommended; alcohol does not eradicate *C. difficile* spores. These spores can survive on dry surfaces for several months, and therefore, a policy should be in place for environmental cleaning, especially in the rooms and bathrooms used by patients with CDAD. Contact precautions should be used for all patients with known CDAD. Thus far, the use of probiotics is not an effective strategy for prevention or treatment of *C. difficile* infection.

Management of CDAD includes cessation of the inciting antibiotic as soon as possible. Oral metronidazole is the initial drug of choice for mild cases of CDAD; however, oral vancomycin is the preferred agent for moderate to severe disease. CDAD recurs in approximately 20% of cases after initial successful therapy; recurrence may represent reinfection or relapse. The mechanism of relapse in CDAD is not fully understood but may be caused by persistent spores from the initial infection. Patients who develop multiple recurrences may be particularly difficult to treat. Other antimicrobials, including rifaximin, which is approved for traveler's diarrhea, are being studied as potential treatment options for CDAD.²⁵ Nonantibiotic therapies, such as binding resins, are also being investigated.²⁶

METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS

Staphylococcus aureus is a common pathogen. Methicillin was introduced in 1959, and by the early 1960s, outbreaks of methicillin-resistant *S aureus* (MRSA) appeared. These infections occurred among hospitalized patients and were termed *health care-associated MRSA* (HA-MRSA). In the early 1990s, cases of MRSA among healthy persons without health care contact were reported, and these infections were labeled *community-associated MRSA* (CA-MRSA). Since 2002, the rate of CA-MRSA has increased in adults and children; CA-MRSA now accounts for most community-acquired skin and soft-tissue infections diagnosed in emergency departments.²⁷

Isolates of CA-MRSA are distinct from HA-MRSA isolates. CA-MRSA is susceptible to most nonbeta-lactam antibiotics; carries staphylococcal cassette chromosome IV; and frequently possesses the gene for production of the Panton-Valentine leukocidin toxin, which is capable of destroying human leukocytes and inflicting significant tissue damage. The strain that is most often isolated is USA300. In contrast, isolates of HA-MRSA are most often USA100 and USA200, are multidrug-resistant, and carry staphylococcal cassette chromosome II.²⁸ Antibiotic use correlates with risk for MRSA colonization and infection.²⁹

Common clinical manifestations of CA-MRSA include cellulitis, abscesses, carbuncles, and furuncles; however, severe, sometimes fatal, invasive disease can occur. A recently published study examined three types of cases of invasive MRSA disease diagnosed in 2005: community-associated infections without health care risk factors, community-onset infections with a health care risk factor, and hospital-onset infections. Of the observed cases, 14% were community-associated infections, 58% were community-onset infections, and 27% were hospital-onset infections.³⁰ The overall incidence rate was 31.8 per 100,000 persons, with a projected death rate of 18,650 in 2005. Incidence was highest among persons 65 years and older, blacks, and males.³⁰

A population-based survey and cross-sectional study identified clusters of a multidrug-resistant strain of USA300 in San Francisco and Boston.³¹ This strain was found to be more common among men who have sex with men but appears to be independent of HIV infection. The pathogen is a new

strain that is closely related to CA-MRSA seen in the general population; but in addition to resistance to methicillin and most other beta-lactam antibiotics, this pathogen is also resistant to tetracycline, clindamycin, and mupirocin. Most identified infections involved the buttocks, genitals, or perineum.³¹ Like other CA-MRSA, this strain spreads via skin-to-skin contact and contact with contaminated surfaces. New USA300 derivative strains are likely to emerge in the future.

OTHER PROBLEMS WITH RESISTANCE

Vancomycin has been the drug used to treat serious MRSA infections. However, intermediate-level vancomycin resistance has emerged among staphylococci as well as rare cases of fully resistant strains. New anti-MRSA agents have been introduced—linezolid, daptomycin, tigecycline, and quinupristin-dalfopristin—and are most welcome.

In addition to *S aureus*, other gram-positive bacteria have become multidrug-resistant. A dramatic increase in vancomycin-resistant enterococci (VRE) has been seen among hospitalized patients. Enterococci are inhabitants of the GI tract that act as opportunistic pathogens, causing surgical-site infections, UTIs, and bacteremia. Most VRE are *Enterococcus faecium*. Testing of isolates from 76 medical centers in the United States showed vancomycin resistance among *E faecium* to vary from 45% in the New England states to 85% in the east south-central states.³² VRE has intrinsic resistance to multiple antimicrobial drugs, making therapy difficult; fortunately, the newer agents—tigecycline, linezolid, and quinupristin-dalfopristin—have antibacterial activity against vancomycin-resistant *E faecium*.

Nosocomial infections caused by multidrug-resistant gram-negative bacteria, particularly *Klebsiella* species, *E coli*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*, have increased, especially among patients in ICUs. Few new antibiotics are being developed to treat these infections. Of the newer antimicrobial agents, only tigecycline has activity against gram-negative pathogens, but it has no clinically relevant activity against *Pseudomonas* species.³³

Adequate antimicrobial therapy, administered early, has a significant impact on the outcome of patients with bacteremia and sepsis. The most common reason for inadequate therapy is resistance to the administered regimen.³⁴ The mechanisms of resistance in these gram-negative bacteria are impermeability of the outer bacterial membrane, efflux pumps, and production of extended-spectrum beta-lactamases (ESBLs).³⁵ ESBLs are enzymes that confer resistance to most beta-lactam antibiotics, including penicillin, aztreonam, and cephalosporins, by opening the beta-lactam ring with resultant inactivation of the antibiotic. The mutant genes for ESBLs are encoded on transferable plasmids and encode resistance to a variety of antimicrobials in addition to beta-lactam agents. *K pneumoniae* and *E coli* are ESBL-producing organisms; *P aeruginosa* and *A baumannii* have extremely impermeable outer membranes and use a variety of mechanisms of resistance that may include ESBL production. Carbapenems, such as imipenem-cilastatin and meropenem,

are the drugs of choice for serious infections caused by ESBL-producing bacteria.

Risk factors for colonization and nosocomial infection with multidrug-resistant gram-negative bacteria include patient-to-patient transmission, antibiotic use during a hospital stay, and antibiotic use in the person. Prevention methods incorporate infection-control measures and strategies for minimizing total antibiotic use in the hospital. Nosocomial resistant isolates lack options for drug treatment and represent a serious public health concern.

CONCLUSION

The changing epidemiology and resistance patterns of bacteria are making effective treatment of bacterial infections more difficult. Antimicrobial therapy enhances the multiplication of existing drug-resistant bacteria and the exchange of resistance mechanisms among bacteria. Antibiotic administration builds drug resistance in the commensal bacteria that are part of the patient’s normal flora as well as in the targeted pathogen, thereby creating a resistance reservoir. Therefore, antibiotic overuse contributes to antimicrobial resistance. Monitoring drug-resistance patterns among pathogens, developing antibiograms for clinicians, and routinely updating the antibiograms are important actions institutions can take to increase awareness of antimicrobial resistance. Local antibiograms that are site-specific to the pathogen and that separate outpatients from inpatients are the most useful. The benefits versus the risks of prescribing antibiotics must be considered. Antibiotic administration puts the patient at risk for allergic reactions, adverse reactions, and drug-drug interactions, as well as increases the likelihood that a newly acquired bacterial infection will be caused by an antibiotic-resistant strain. From a public health standpoint, indiscriminate use of antibiotics increases the rates of antibiotic resistance in a society. **JAAPA**

JoAnn Deasy is on the faculty at Pace University-Lenox Hill Hospital Physician Assistant Program, New York, New York. She has indicated no relationships to disclose relating to the content of this article.

DRUGS MENTIONED

Aztreonam (Azactam)	Nitrofurantoin (Furadantin, Macrobid,
Ciprofloxacin (Cipro, Proquin, generics)	Macrochantin, generics)
Clindamycin (Cleocin, generics)	Penicillin
Daptomycin (Cubicin)	Quinupristin-Dalfopristin (Synercid)
Imipenem-cilastatin (Primaxin)	Rifaximin (Xifaxan)
Linezolid (Zyvox)	Tetracycline (Bristacycline, Sumycin)
Meropenem (Merrem)	Tigecycline (Tygacil)
Methicillin	Trimethoprim-sulfamethoxazole
Metronidazole (Flagyl, generics)	(Bactrim, Septra, Sulfatrim, generics)
Mupirocin (Bactroban, generics)	Vancomycin (Vancocin, generics)

REFERENCES

1. Gupta K, Hooton TM, Stamm WE. Increasing antimicrobial resistance and the management of uncomplicated community-acquired urinary tract infections. *Ann Intern Med.* 2001;135(1):41-50.
2. Warren JW, Abrutyn E, Hebel JR, et al. Guidelines for antimicrobial treatment of uncomplicated acute bacterial cystitis and acute pyelonephritis in women. Infectious Diseases Society of America (IDSA). *Clin Infect Dis.* 1999;29(4):745-758.
3. Hooton TM, Besser R, Foxman B, et al. Acute uncomplicated cystitis in an era of increasing antibiotic resistance: a proposed approach to empirical therapy. *Clin Infect Dis.* 2004;39(1):75-80.
4. Le TP, Miller LG. Empirical therapy for uncomplicated urinary tract infections in an era of increasing antimicrobial resistance: a decision and cost analysis. *Clin Infect Dis.* 2001;33(5):615-621.

5. Taur Y, Smith MA. Adherence to the Infectious Diseases Society of America guidelines in the treatment of uncomplicated urinary tract infection. *Clin Infect Dis.* 2007;44(6):769-774.
6. Gupta K. Emerging antibiotic resistance in urinary tract pathogens. *Infect Dis Clin North Am.* 2003;17(2):243-259.
7. Karlowsky JA, Kelly LJ, Thomsberry C, et al. Trends in antimicrobial resistance among urinary tract infection isolates of *Escherichia coli* from female outpatients in the United States. *Antimicrob Agents Chemother.* 2002;46(8):2540-2545.
8. Wright SW, Wrenn KD, Haynes LM. Trimethoprim-sulfamethoxazole resistance among urinary coliform isolates. *J Gen Intern Med.* 1999;14(10):606-609.
9. Gupta K, Hooton TM, Roberts PL, Stamm WE. Short-course nitrofurantoin for the treatment of acute uncomplicated cystitis in women. *Arch Intern Med.* 2007;167(20):2207-2212.
10. Reckendorf HK, Castringius RG, Spingler HK. Comparative pharmacodynamics, urinary excretion, and half-life determinations of nitrofurantoin sodium. *Antimicrob Agents Chemother.* 1962;2:531-537.
11. Juthani-Mehta M. Asymptomatic bacteriuria and urinary tract infection in older adults. *Clin Geriatr Med.* 2007;23(3):585-594.
12. Nicolle LE, Brandley S, Colgan R, et al; Infectious Diseases Society of America; American Society of Nephrology; American Geriatric Society. Infectious Diseases Society of America guidelines for the diagnosis and treatment of asymptomatic bacteriuria in adults. *Clin Infect Dis.* 2005; 40(5):643-654.
13. McGreer A, Campbell B, Emori TG, et al. Definitions of infection for surveillance in long-term care facilities. *Am J Infect Control.* 1991;19(1):1-7.
14. Bartlett JG. Antibiotic-associated diarrhea. *Clin Infect Dis.* 1992;15(4):573-581.
15. Dubberke ER, Reske KA, Yan Y, et al. *Clostridium difficile*-associated disease in a setting of endemicity: identification of novel risk factors. *Clin Infect Dis.* 2007;45(12):1543-1549.
16. Mandell GL, Bennett JE, Dolin R. *Principles and Practice of Infectious Diseases.* 6th ed. Oxford, England: Churchill Livingstone; 2005.
17. McDonald LC, Killgore GE, Thompson A, et al. An epidemic toxin gene-variant strain of *Clostridium difficile*. *N Engl J Med.* 2005;353(23):2433-2441.
18. Muto CA, Pokrywka M, Shutt K, et al. A large outbreak of *Clostridium difficile*-associated disease with an unexpected proportion of deaths and colectomies at a teaching hospital following increased fluoroquinolone use. *Infect Control Hosp Epidemiol.* 2005;26(3):273-280.
19. Gaynes R, Rimland D, Killum E, et al. Outbreak of *Clostridium difficile* infection in a long-term care facility: association with gatifloxacin use. *Clin Infect Dis.* 2004;38(5):640-645.
20. Dial S, Delaney JA, Barkun AN, Suissa S. Use of gastric acid-suppressive agents and the risk of community-acquired *Clostridium difficile*-associated disease. *JAMA.* 2005;294(23):2989-2995.
21. Lowe DO, Mamdani MM, Kopp A, et al. Proton pump inhibitors and hospitalization for *Clostridium difficile*-associated disease: a population-based study. *Clin Infect Dis.* 2006; 43(10):1272-1276.
22. Blossom DB, McDonald LC. The challenges posed by reemerging *Clostridium difficile* infection. *Clin Infect Dis.* 2007;45(2):222-227.
23. Centers for Disease Control and Prevention (CDC). Severe *Clostridium difficile*-associated disease in populations previously at low risk—four states, 2005. *MMWR Morb Mortal Wkly Rep.* 2005;54(47):1201-1205.
24. Valiquette L, Cossette B, Garant MP, et al. Impact of a reduction in the use of high-risk antibiotics on the course of an epidemic of *Clostridium difficile*-associated disease caused by the hypervirulent NAP1/027 strain. *Clin Infect Dis.* 2007;45(suppl 2):S112-S121.
25. Marchese A, Salemo A, Pesce A, et al. In vitro activity of rifaximin, metronidazole and vancomycin against *Clostridium difficile* and the rate of selection of spontaneously resistant mutants against representative anaerobic and aerobic bacteria, including ammonia-producing species. *Chemotherapy.* 2000;46(4):253-266.
26. Louie TJ, Peppe J, Watt CK, et al; Tolevamer Study Investigator Group. Tolevamer, a novel nonantibiotic polymer, compared with vancomycin in the treatment of mild to moderately severe *Clostridium difficile*-associated diarrhea. *Clin Infect Dis.* 2006;43(4):411-420.
27. Moran GJ, Krishnadasan A, Gorwitz RJ, et al; EMERGEncy ID Net Study Group. Methicillin-resistant *S. aureus* infections among patients in the emergency department. *N Engl J Med.* 2006;355(7):666-674.
28. Naimi TS, DeLell KH, Como-Sabetti KM, et al. Comparison of community- and health-care associated methicillin-resistant *Staphylococcus aureus* infection. *JAMA.* 2003;290(22):2976-2984.
29. Tacconelli E, De Angelis G, Cataldo MA, et al. Does antibiotic exposure increase the risk of methicillin-resistant *Staphylococcus aureus* (MRSA) isolation? A systematic review and meta-analysis. *J Antimicrob Chemother.* 2008;61(1):26-38.
30. Klevens RM, Morrison MA, Nadle J, et al; Active Bacterial Core surveillance (ABCs) MRSA Investigators. Invasive methicillin-resistant *Staphylococcus aureus* infections in the United States. *JAMA.* 2007;298(15):1763-1771.
31. Diep BA, Chambers HF, Graber CJ, et al. Emergence of multidrug-resistant, community-associated, methicillin-resistant *Staphylococcus aureus* Clone USA300 in men who have sex with men. *Ann Intern Med.* 2008;148(4):249-257.
32. Denys GA, Koch KM, Dowzicky MJ. Distribution of resistant gram-positive organisms across the census regions of the United States and in vitro activity of tigecycline, a new glycolycycline antimicrobial. *Am J Infect Control.* 2007;35(8):521-526.
33. Milatovic D, Schmitz FJ, Verhoef J, Fluit AC. Activities of the glycolycycline tigecycline (GAR-936) against 1,924 recent European clinical bacterial isolates. *Antimicrob Agents Chemother.* 2003;47(1):400-404.
34. Ibrahim EH, Sherman G, Ward S, et al. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. *Chest.* 2000;118(1):146-155.
35. Rice LB. Emerging issues in the management of infections caused by multidrug-resistant gram-negative bacteria. *Cleve Clin J Med.* 2007;74(suppl 4):S12-S20.