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Infections in hospitalized patients: What is happening and who can help?

ABSTRACT

The continuing emergence of multidrug-resistant bacteria calls for new approaches to the management and treatment of infections in hospitalized patients. Health care–associated infections cause substantial morbidity and mortality while driving up health care resource use and costs worldwide. The continued spread of antimicrobial resistance requires a multidisciplinary approach and closer collaboration among health care providers, especially hospitalists, pharmacists, infection control practitioners, and infectious disease specialists. Such collaboration can potentially reduce treatment failures and minimize the spread of multidrug-resistant organisms between health care settings and the community.

KEY POINTS

Surveillance studies show that antimicrobial resistance among some community-associated pathogens and several key nosocomial pathogens is increasing at an alarming rate.

Widespread emergence of resistant pathogens and transmission of some pathogens between health care and community settings suggest that providers can no longer practice in an independent or isolated manner.

Greater partnership among providers in multiple disciplines and all health care settings is urgently needed to combat the challenge of multidrug-resistant bacteria.

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Nosocomial infections, also known as hospital-acquired or health care–associated infections, are a significant public health concern. These infections are estimated to occur in 5% to 10% of acute care hospitalizations in the United States, representing more than 2 million episodes per year.[1] The highest rates are seen in intensive care units and acute care surgical and orthopedic wards. Nosocomial infections are responsible for more than 90,000 US deaths per year and millions of additional days of hospitalization; the annual cost of treating these infections in the United States is estimated to exceed $4.5 billion.[1]

Despite these substantial effects in terms of morbidity, mortality, and health care costs, many nosocomial infections can be prevented if health care providers take proper precautions when caring for patients. Providers in a wide range of disciplines—intensivists, hospitalists, surgeons, infectious disease specialists, primary care clinicians, microbiologists, nurses, pharmacists—need to collaborate and arrive at a coherent control strategy to both minimize and effectively treat these infections.

This article sets the stage for the remainder of this supplement by outlining the challenges posed by antimicrobial resistance among key nosocomial and community-associated pathogens and the rationale for multidisciplinary collaboration in combatting these challenges.

THE HEART OF THE CHALLENGES: ANTIMICROBIAL RESISTANCE

Nosocomial infections have become more troublesome in the 21st century with the spread of antimicrobial resistance. Approximately 70% of nosocomial infections are attributable to antibiotic-resistant organisms,[2] including multidrug-resistant bacterial strains, which complicates the management of infections in all health care settings (hospital, office or clinic, and nursing home).[3–6] In an increasingly complex patient population, misuse and overuse of broad-

spectrum antibiotics, coupled with suboptimal infection control practice among health care providers and institutions, have contributed to the changing scope of nosocomial infections and created new treatment challenges.

Lower respiratory tract infections (eg, ventilator-associated pneumonia), postoperative wound infections, complicated intra-abdominal infections, catheter-associated bacteremia, and urinary tract infections are the most common nosocomial infections. Bacteria are responsible for the majority of these infections, with staphylococci, enterococci, Enterobacteriaceae, and *Pseudomonas* species recovered most often. Recent surveillance studies have demonstrated that antimicrobial resistance among key nosocomial pathogens is increasing at an alarming rate.[3–6] Over the past decade, several gram-positive and gram-negative organisms have become especially problematic[5]:

- Methicillin-resistant *Staphylococcus aureus* (MRSA)
- Vancomycin-resistant enterococci
- Beta-lactam–resistant and multidrug-resistant pneumococci
- *Klebsiella pneumoniae*, *Escherichia coli*, and *Proteus mirabilis* organisms with extended-spectrum beta-lactamases (ESBLs)
- *Enterobacter* species and *Citrobacter freundii* with high-level third-generation cephalosporin (Amp C) beta-lactamase resistance
- *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, and *Stenotrophomonas maltophilia* organisms with genes for multidrug resistance (to imipenem, fluoroquinolones, and third-generation cephalosporins).

Shifting epidemiology of methicillin-resistant *S aureus*

One particular concern is the changing epidemiology of MRSA with the appearance of these typically nosocomial strains in the community setting (ie, community-acquired MRSA).[7] Notably, the incidence of community-acquired MRSA appears to be increasing with its emergence independent of a hospital reservoir.[8–10] Community-acquired MRSA, which typically occurs in healthy, immunocompetent individuals, has been associated with serious and sometimes fatal illness (eg, necrotizing pneumonia or fasciitis),[11] likely because of its greater number of virulence factors compared with hospital-acquired MRSA strains.[7,10] Even more disturbing, however, are recent reports of transmission of community-acquired MRSA strains back into the hospital environment as a cause of nosocomial infection.[12–14] In some cases, community-acquired MRSA has replaced hospital-acquired strains, thereby creating potential infection control challenges and future antimicrobial resistance issues (ie, emerging resistance to non–beta-lactam antibiotics).

Overall, the epidemiology, infection types, and antimicrobials of choice differ between community- and hospital-acquired MRSA infections.[15,16] To best manage their patients, clinicians need to be familiar with the unique properties of these infections.

Proliferation of problematic CTX-M enzymes

Another ominous concern from the past decade is the discovery of CTX-M enzymes (named for their predominant activity against cefotaxime), which have become the most prevalent ESBLs in health care and community settings alike.[17–20] Gram-negative organisms possessing these plasmids carry aminoglycoside, tetracycline, sulfonamide, or fluoroquinolone resistance genes. While nosocomially acquired CTX-M–producing *Enterobacter* or *Klebsiella* species were initially dominant, these resistant enzymes have migrated to many other Enterobacteriaceae organisms and to *P aeruginosa*. Furthermore, ESBLs of the CTX-M type also have invaded the community setting. CTX-M–producing *E coli* is a rapidly developing problem, especially among compromised patients with community-acquired urinary tract infections (eg, those with underlying disease, recent antibiotic use, or health care contact). Although the precise mode by which these organisms are spread remains unclear, they are being isolated more frequently and are no longer confined to hospitals.[19]

Other worrisome pathogens

Other emerging pathogens of concern include carbapenem-resistant *K pneumoniae* isolates[21] and a new, highly virulent strain of *Clostridium difficile*.[22] In addition to nosocomial infections, there has been a rise in the number of community-acquired cases of *C difficile*–associated diarrhea.[22] Because both *K pneumoniae* and *C difficile* are resistant to virtually all commonly used antibiotics, control of their spread—via active surveillance, antibiotic stewardship, and meticulous attention to contact precautions—is crucial.

MULTIDISCIPLINARY COLLABORATION NEEDED

The continued emergence of multidrug-resistant gram-positive and gram-negative bacteria in health care and community settings calls for a collaborative effort to reduce treatment failures and to minimize the spread of these bacteria between health care settings and within the community. All clinicians need to keep up-to-date on resistance patterns (with the

aid of laboratory surveillance) and to administer empiric regimens that address resistance phenotypes. Overall, antimicrobial therapy choices should be effective against any likely resistant bacteria, and the optimal antimicrobial regimen is one that has a low potential to induce resistance. As antimicrobial research and development languish,[23] rational policies for prescribing existing anti-infective agents and strict infection control measures are the current mainstay efforts for preventing and curtailing multidrug-resistant bacterial infections.

Three key provider groups

The widespread emergence of resistant pathogens, including transmission of some pathogens between health care and community environments, suggests that health care providers can no longer practice in an independent or isolated manner. Traditional provider roles are well recognized, but further collaboration is needed to deal with the proliferation of multidrug-resistant organisms. Key providers who can help include primary care clinicians, hospitalists, and infectious disease specialists.

The primary care clinician is the patient's first accessible health care contact and serves as an advocate for patients as well as an intermediary between patients and the health care system.[24] The previously mentioned emergence of MRSA and *C difficile* infections in community settings demands that primary care clinicians be aware of the features of these infections and aware of appropriate treatments and infection control measures.

Hospitalists represent a relatively new physician specialty whose primary focus is the care of hospitalized patients.[25–27] Hospital medicine has been recognized as a defined field in the United States for about 10 years and is the nation's fastest-growing physician specialty. The current number of hospitalists—approximately 15,000—is anticipated to at least double in the next 5 to 10 years. As originally conceived, the role of the hospitalist is to accept "hand-offs" of hospitalized patients from primary care physicians, provide expert inpatient care to these patients, and then return these patients to the care of their primary care physicians at discharge. Hospitalists also have the opportunity to serve as systems leaders by effecting changes to improve the health outcomes of hospitalized patients. They frequently serve on hospital committees, help develop clinical guidelines, and lead multidisciplinary teams to optimize patient care.

Infectious disease specialists are often consulted in cases of undiagnosed symptoms or conditions. They diagnose and treat infections, scrutinize microbial susceptibility patterns, serve on infection control and formulary committees, establish antibiotic guidelines, provide consultation on optimal antimicrobial use in the hospital setting, and supervise parenteral antimicrobial use outside the hospital.

All of these specialties need to work together to develop a health care delivery system that will combat the urgent challenges posed by multidrug-resistant pathogens.

A need for new multidisciplinary approaches

New approaches are needed for the management and treatment of nosocomial infections caused by multidrug-resistant organisms. While several specific strategies have been suggested to improve the outcomes of patients with severe bacterial infections—such as the use of treatment guidelines, antibiotic prophylaxis restrictions, the use of antibiotics in combination, de-escalation therapy, cycling therapy,[28] and short-course therapy—a multidisciplinary approach is essential. Closer collaboration among hospitalists, pharmacists, infection control practitioners, and infectious disease specialists can potentially bridge the gap between global strategies and individual patient needs. Such collaboration also must extend to primary care clinicians and continuity-of-care providers. The need for teamwork is highlighted in recently published guidelines from the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America on developing an institutional program to enhance antimicrobial stewardship.[29]

Finally, it is impossible to overstate the importance of appropriate infection control measures and continued surveillance of resistance patterns. In many cases, surveillance efforts will require institutional support in the form of information technology services to ensure that accurate real-time information is available to clinicians and policymakers.

THE SCOPE OF THIS SUPPLEMENT

It is in this context that this journal supplement aims to update clinicians on the challenges of infections in hospitalized patients and increasing antimicrobial resistance in the 21st century. Dr. Thomas M. File, Jr, takes the supplement from here with a detailed overview of the impact of community-acquired MRSA in the hospital setting. Next, Dr. Louis B. Rice discusses emerging issues in the treatment of infections caused by multidrug-resistant gram-negative organisms. Drs. James I. Merlino and Mark A. Malangoni then describe empiric treatment options for compli-

cated skin and soft-tissue infections, and Dr. John A. Weigelt outlines empiric treatment options for complicated intra-abdominal infections. Finally, Drs. Morton P. Goldman and Radhika Nair explore the role of pharmacoeconomics in the antimicrobial formulary decision-making process as well as the economic impact of antimicrobial resistance.

Our hope is that readers will come away from this supplement better equipped to contribute to the multidisciplinary efforts urgently needed to combat the challenges posed today by serious infections. Success will demand that we all be informed and involved.

REFERENCES

1. **Centers for Disease Control and Prevention.** Healthcare-associated infections (HAIs). Available at: http://www.cdc.gov/ncidod/dhqp/healthDis.html. Accessed February 15, 2007.
2. **Burke JP.** Infection control: a problem for patient safety. N Engl J Med 2003; 348:651–656.
3. **Clark NM, Hershberger E, Zervosc MJ, Lynch JP III.** Antimicrobial resistance among gram-positive organisms in the intensive care unit. Curr Opin Crit Care 2003; 9:403–412.
4. **Clark NM, Patterson J, Lynch JP III.** Antimicrobial resistance among gram-negative organisms in the intensive care unit. Curr Opin Crit Care 2003; 9:413–423.
5. **Jones RN.** Resistance patterns among nosocomial pathogens: trends over the past few years. Chest 2001; 119(Suppl 2):397S–404S.
6. **Okeke IN, Laxminarayan R, Bhutta ZA, et al.** Antimicrobial resistance in developing countries. Part I: recent trends and current status. Lancet Infect Dis 2005; 5:481–493.
7. **Weber JT.** Community-associated methicillin-resistant *Staphylococcus aureus*. Clin Infect Dis 2005; 41(Suppl 4):S269–S272.
8. **Crum NF, Lee RU, Thornton SA, et al.** Fifteen-year study of the changing epidemiology of methicillin-resistant *Staphylococcus aureus*. Am J Med 2006; 119:943–951.
9. **Huang H, Flynn NM, King JH, Monchaud C, Morita M, Cohen SH.** Comparisons of community-associated methicillin-resistant *Staphylococcus aureus* (MRSA) and hospital-associated MRSA infections in Sacramento, California. J Clin Microbiol 2006; 44:2423–2427.
10. **Daum RS, Ito T, Hiramatsu K, et al.** A novel methicillin-resistance cassette in community-acquired methicillin-resistant *Staphylococcus aureus* isolates of diverse genetic backgrounds. J Infect Dis 2002; 186:1344–1347.
11. **Crum NF.** The emergence of severe, community-acquired methicillin-resistant *Staphylococcus aureus* infections. Scand J Infect Dis 2005; 37:651–656.
12. **Linde H, Wagenlehner F, Strommenger B, et al.** Healthcare-associated outbreaks and community-acquired infections due to MRSA carrying the Panton-Valentine leucocidin gene in southeastern Germany. Eur J Clin Microbiol Infect Dis 2005; 24:419–422.
13. **David MD, Kearns AM, Gossain S, Ganner M, Holmes A.** Community-associated meticillin-resistant *Staphylococcus aureus*: nosocomial transmission in a neonatal unit. J Hosp Infect 2006; 64:244–250.
14. **Ko KS, Park S, Peck KR, et al.** Molecular characterization of methicillin-resistant *Staphylococcus aureus* spread by neonates transferred from primary obstetrics clinics to a tertiary care hospital in Korea. Infect Control Hosp Epidemiol 2006; 27:593–597.
15. **Rice LB.** Antimicrobial resistance in gram-positive bacteria. Am J Med 2006; 119(Suppl 1):S11–S19; discussion S62–S70.
16. **Kowalski TJ, Berbari EF, Osmon DR.** Epidemiology, treatment, and prevention of community-acquired methicillin-resistant *Staphylococcus aureus* infections. Mayo Clin Proc 2005; 80:1201–1207.
17. **Livermore DM, Woodford N.** The beta-lactamase threat in Enterobacteriaceae, *Pseudomonas* and *Acinetobacter*. Trends Microbiol 2006; 14:413–420.
18. **Pitout JD, Nordmann P, Laupland KB, Poirel L.** Emergence of Enterobacteriaceae producing extended-spectrum beta-lactamases (ESBLs) in the community. J Antimicrob Chemother 2005; 56:52–59.
19. **Livermore DM, Hawkey PM.** CTX-M: changing the face of ESBLs in the UK. J Antimicrob Chemother 2005; 56:451–454.
20. **Canton R, Coque TM.** The CTX-M beta-lactamase pandemic. Curr Opin Microbiol 2006; 9:466–475.
21. **Bratu S, Landman D, Haag R, et al.** Rapid spread of carbapenem-resistant *Klebsiella pneumoniae* in New York City: a new threat to our antibiotic armamentarium. Arch Intern Med 2005; 165:1430–1435.
22. **Oldfield EC III.** *Clostridium difficile*-associated diarrhea: resurgence with a vengeance. Rev Gastroenterol Disord 2006; 6:79–96.
23. **Spellberg B, Powers JH, Brass EP, Miller LG, Edwards JE Jr.** Trends in antimicrobial drug development: implications for the future. Clin Infect Dis 2004; 38:1279–1286.
24. **Moore G, Showstack J.** Primary care medicine in crisis: toward reconstruction and renewal. Ann Intern Med 2003; 138:244–247.
25. **Kelley MA.** The hospitalist: a new medical specialty? Ann Intern Med 1999; 130:373–375.
26. **Baudendistel TE, Wachter RM.** The evolution of the hospitalist movement in the USA. Clin Med 2002; 2:327–330.
27. **Freed DH.** Hospitalists: evolution, evidence, and eventualities. Health Care Manag (Frederick) 2004; 23:238–256.
28. **Esposito S, Leone S, Noviello S.** Management of severe bacterial infections. Expert Rev Anti Infect Ther 2005; 3:593–600.
29. **Dellit TH, Owens RC, McGowan JE Jr, et al.** Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis 2007; 44:159–177.

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