Health Care–Associated Infections: Major Issues in the Early Years of the 21st Century

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Health care–associated bloodstream infections are associated with an attributable mortality that makes them equivalent to the eighth leading cause of death in the United States. Increasing levels of antibiotic resistance and the problems associated with biofilms surrounding prostheses and vascular catheters pose special challenges. These issues and potential solutions are addressed in the present article.

Health care–associated infections are those that are not present or incubating at the time when patients enter a clinic or hospital. In general, they become manifest ≥48 h after initial patient care. Although comprehensive data on infection rates after clinic visits are lacking, it is known that 5%–10% of patients admitted to acute care hospitals in the United States will acquire a nosocomial infection. Under the assumption that 40 million admissions occur annually, each year there are 2–4 million nosocomial infections, which are generally distributed anatomically as follows: 35% involve the urinary tract, 25% the surgical site, 10% the lung, 10% the bloodstream, and 10% other sites.

Consistent studies have shown that health care–associated infections add incremental morbidity, mortality, and costs to those expected from the underlying diseases alone. In the United States, the attributable mortality from bloodstream infections alone (200,000–400,000 episodes annually) makes them equivalent to the eighth leading cause of death, leading to ≥260,000 years of life lost annually [1].

One key issue in infection control in the early 21st century involves bloodstream infections with antibiotic-resistant pathogens. The reasons for the focus on this problem include the high attributable mortality [2] due to the bloodstream infections and the incremental mortality that results when clinicians institute ineffective empirical antibiotic therapy. Specifically, 25%–30% of patients with nosocomial bloodstream infections die (50,000–120,000 deaths annually), and the attributable mortality (directly due to the infection after accounting for the underlying diseases) is at least 15% (half of the total mortality) [1], accounting for 25,000–60,000 deaths. In critical care settings, patients with nosocomial bloodstream infections who did not receive an appropriate antibiotic within the first 24 h of illness had a crude mortality rate that was twice that among those who received an effective drug [3]. Thus, a thorough knowledge of likely pathogens and their antibiograms is essential for the modern clinician.

The current landscape of antibiotic resistance among bloodstream pathogens is formidable. The leading causes of nosocomial bloodstream infections [4, 5], in order from most common to least common, are coagulase-negative staphylococci, Staphylococcus aureus, enterococci, and Candida species. More than 90% of coagulase-negative staphylococci and 60% of S. aureus isolates are resistant to methicillin, >30% of enterococci are resistant to vancomycin, and >10% of Candida organisms are resistant to first-generation triazoles. Fortunately, new agents are available that have in vitro activity, but few studies have shown improved efficacy compared with that of available agents.

The Surveillance and Control of Pathogens of Epidemiologic Importance (SCOPE) Project surveillance system showed that 70% (140,000–280,000 annually) of all nosocomial bloodstream infections are associated with a central venous catheter [5]. Several recent studies have indicated that chemically bounded catheters (anti-
biotics, antiseptics, or metals bonded chemically to the polymer materials) can reduce nosocomial bloodstream infections by 70%–90%. Even if only half of the 70% of the bloodstream infections represent a true cause-and-effect association with the use of a central venous catheter, modern catheter bonding will have had a substantial impact, saving thousands of lives per year. The point is that proof of concept has been established for an important preventive measure, and the next steps are (1) to find optimal bonding chemicals, preferably not antibiotics used commonly to treat patients, and (2) to provide wide patient access to the catheters.

More recently, it has been recognized that the bacterial biofilms are important in favoring the pathogens that are colonizing and infecting bioprosthesis, including vascular catheters. Specifically, biofilms not only provide a protected environment, allowing horizontal gene transfers that code for antibiotic resistance, but they create an amazingly complex environment with important biological gradients [6, 7]. Moreover, as one examines bacteria residing increasingly more closely to the prosthesis, the bacteria are more difficult to culture and less likely to be antibiotic susceptible than are those residing distantly in the biofilm from the bioprosthesis. Furthermore, the organisms closer to the surface of the biomaterials are less aggressive and have lower metabolic activity.

New drugs, such as lysostaphin, with the ability to destroy biofilm structure and the organisms within may be used in the future [8]. Lysostaphin works rapidly—in <20 min—and at very low concentrations, whereas standard antibiotics at high concentrations have no effect on the architecture of the biofilm. In addition, it is now recognized that, at higher concentrations—a “quorum”—bacteria can “communicate” with each other to coordinate the production of toxins or of biofilm. This process, quorum sensing, offers the possibility for developing new drugs that inhibit the process [9, 10]. Therefore, the identification of drugs that inhibit or destroy biofilms offers new hope for infection control. It is likely that, in the next decade, there will be adjunctive therapies for infections associated with the insertion of foreign bodies.

Related to catheter-related bloodstream infections are health care provider behavioral issues—for example, hand washing (hygiene) and the use of proper technique in inserting and managing catheters. Hand hygiene is the key issue, and prospective studies have shown access to easy-to-use alcohol preparations to be a strong influence on increasing hygiene compliance [11]. Comprehensive programs with a motivated infection control team exhorting hand washing have also been quite beneficial [12]. Because an earlier observation from a prospective study of optimal hand washing agents in critical care units showed that a 25% increase in hand washing was associated with a 25% decline in intensive care unit–related bloodstream infections [13], it is time for hospitals to insist on health care worker compliance with hand hygiene.

An obvious reason to champion infection control issues is the continual emergence of antibiotic-resistant pathogens as major health care–associated microbes. As an example, a key issue early in the 21st century is the threat of community-acquired methicillin-resistant S. aureus (CA-MRSA) infections entering the hospital and becoming a major health care–associated infection. The problems are 2: (1) resistance to methicillin and (2) the increased virulence of the strain relative to other circulating strains of S. aureus.

It is recognized that virulent strains of S. aureus, CA-MRSA, have emerged in the community. Causing primarily skin and soft tissue infections, these strains contain new molecular markers of virulence. Less often, infections have been associated with necrotizing pneumonias or serious bloodstream infections. Elegant molecular studies by Diep et al. [14] have shown that most strains have genes coding for Panton-Valentine leukocidin, enterotoxins, and an arginine deiminase pathway that enables growth and survival at low pH. Diep et al. [14] have also shown that the genes coding for the arginine deiminase pathway very likely arose from colonizing strains of Staphylococcus epidermidis, because 67% of the latter were found to possess the genes. Thus, the exchange of genetic material among bacterial species has generated a more virulent pathogen. Furthermore, the key circulating clone—USA 300—contains a plasmid that could serve as a recipient of a gene coding for vancomycin resistance [9]. Thus, this virulent organism might be the perfect reservoir for a new clonal expansion of fully vancomycin-resistant strains of S. aureus.

In recent years, a concern has been the possible emergence of nosocomial CA-MRSA infections causing serious illness in hospitalized patients. Early reports showed such infections on an obstetrics-gynecology ward [15] and on an orthopedic ward among patients with hip and knee prostheses [16]. More recently, a hospital in Atlanta has reported that 20% of its nosocomial S. aureus bloodstream infections were comprised of CA-MRSA [17]. A host of challenging new questions arise for infection control, if CA-MRSA maintains a foothold in a hospital:

1. What should be the empirical antibiotic treatment for intensive care unit–related bloodstream infections and pneumonia? For postsurgical infections?
2. What should toxic shock syndrome be treated with, recognizing that increasing resistance to clindamycin is occurring among strains of CA-MRSA? How important is clindamycin resistance for therapy?
3. What perioperative, prophylactic antibiotics should be prescribed? At what surgical site infection rate should a hospital change its strategy regarding prophylaxis against CA-MRSA strains?
4. Can we improve rates of proper isolation of patients with *S. aureus* infections? Can we finally improve rates of hand hygiene and proper use of gloves?

These may be among the most important questions related to the control of health care–associated infections in the early years of the 21st century.

So little is known about the epidemiologic profile of and optimal treatments for CA-MRSA infections that the approaches to answering these questions are not simple. The long-term goal must be to create an effective vaccine that will prevent infections with most strains of *S. aureus*. In the meantime, we know that ~20% of strains of CA-MRSA are resistant to clindamycin, that in vitro testing with clindamycin and linezolid have shown down-regulation of the production of Panton-Valentine leukocidin [18], and that anecdotal reports exist of patients with pneumonia due to CA-MRSA improving only when a second drug—probably one inhibiting toxin production—was added to vancomycin [19]. Recognizing these issues, however, it remains unclear whether Panton-Valentine leukocidin causes toxicity independently or is only a marker of toxicity linked to the true cause. What can the clinician consider while awaiting more data from clinical trials?

Given the above, it is reasonable to begin empirical therapy for life-threatening CA-MRSA bloodstream infections with 2 drugs, one that targets the organisms’ growth and another that inhibits protein toxin production. Vancomycin and linezolid would be an example of such a combination. However, it should be emphasized that no clinical trial data are yet available to show the efficacy of such combinations, yet the information from such trials is urgently needed. Recently, an argument has been made for the use of intravenous immunoglobulin in life-threatening CA-MRSA infections [20].

With respect to toxic shock syndrome due to CA-MRSA arising either in the community or in the hospital, linezolid—a drug that also inhibits protein synthesis—would be a reasonable substitution for clindamycin, if antibiotic resistance is important [21]. Perhaps no change in perioperative antibiotics is needed currently; however, if a larger proportion of *S. aureus* strains become CA-MRSA clones, and if the rates of infection remain at or above historical thresholds, antibiotics to be considered might include vancomycin, tigecycline, linezolid, and daptomycin, all of which currently show extremely high levels of activity. However, proper studies of the use of each of these drugs as perioperative prophylaxis are needed.

With respect to basic infection control, there needs to be little tolerance for any lack of hand hygiene. The lack of hygiene compliance is a major failing of modern physicians and other health care workers that implies both medical and ethical breaches. It cannot be tolerated, because it is a key quality-of-care issue, and it should be made unacceptable, a part of the annual review process, and a reason for disciplinary action in hospitals.

In summary, the epidemiologic profile of nosocomial infections has been well described in terms of the morbidity, mortality, and economics of life-threatening infections. New drugs and new technologies to influence both biofilm architecture and quorum sensing may be forthcoming in the next decade. The emergence of strains of CA-MRSA in US hospitals creates an urgent issue for infection control. The circulating clones are more virulent than other strains of *S. aureus*, and they are increasingly resistant to other antibiotics and may serve as a springboard for clonal expansion of fully vancomycin-resistant *S. aureus* infections.

**DR. THEODORE E. WOODWARD**

I met Dr. Theodore E. Woodward when I was an applicant to the internal medicine residency program at the University of Maryland in 1965. He was the chairman of the department at the time and a close personal friend of my advisor, Ken Goodner, the chair of the Department of Microbiology at Jefferson Medical College. I had expressed an interest in experiencing medicine in developing countries, and Dr. Woodward promised to send me to Bangladesh for 3 months of my second year of residency. I remained at the University of Maryland as a resident, fellow in infectious diseases, and chief resident. Dr. Woodward and his Chief of Infectious Diseases, Dick Hornick, had begun surveying in the hospital for nosocomial infections, an area of infectious diseases receiving virtually no focus in the late 1960s. The single surveyor was struggling with simple ways to identify high-risk patients. Although I had no direct involvement in that process, I recalled it immediately when I was hired as the first hospital epidemiologist at the University of Virginia. More importantly, Dr. Woodward kept abreast of my career, continually maintained contact, and was always a friend.

**Acknowledgments**

*Supplement sponsorship.* This article was published as part of a supplement entitled “Tribute to Ted Woodward,” sponsored by an unrestricted grant from Cubist Pharmaceuticals and a donation from John G. McCormick of McCormick & Company, Hunt Valley, Maryland.

*Potential conflicts of interest.* R.P.W. has received recent research funding from Pfizer and is a consultant for Pfizer, Methylgene, and Replydine.

**References**


