SHEA POSITION PAPER

Enhancing Patient Safety by Reducing Healthcare-Associated Infections: The Role of Discovery and Dissemination

The Research Committee of the Society of Healthcare Epidemiology of America

(See the commentary by Stevenson and Gordon, on pages 124–126.)

Healthcare-associated infections (HAIs) take a major human toll on society and reduce public confidence in the healthcare system. The current convergence of scientific, public, and legislative interest in reducing rates of HAI can provide the necessary momentum to address and answer important questions in HAI research. This position paper outlines priorities for a national approach to HAIs: scrutinizing the science base, developing a prioritized research agenda, conducting studies that address the questions that have been identified, creating and deploying guidelines that are based on the outcomes of these studies, and then initiating new studies that assess the efficacy of the interventions.

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BURDEN OF HEALTHCARE-ASSOCIATED INFECTIONS

In the past few years, national surveillance data and public health research have demonstrated that healthcare-associated infections (HAIs) take a major human toll on society. The overall morbidity and mortality associated with HAI are enormous. Five to 10% of all hospital admissions are complicated by HAI, in both the United States and Western Europe.[1] In the United States, an estimated 1.7–2 million people per year develop an HAI, and nearly 100,000 die.[2] By these estimates, HAIs are among the top 10 leading causes of death in the United States.[2]

The economic burden of HAIs is substantial and increasing. The total cost of HAIs has been estimated at $20 billion per year. The healthcare costs of hospital-acquired catheter-associated bloodstream infections in the United States have been estimated to be $10,000–$20,000 per case,[3] and the cost of each episode of *Clostridium difficile* infection has been estimated to be approximately $5,000.[4]

These figures do not reflect the loss of productivity and other less quantifiable human and economic costs associated with a serious HAI. Finally, HAIs result in another, less tangible toll on the healthcare system: loss of consumer confidence in the healthcare system. In response to the realization of the magnitude of the problem, consumer advocacy groups, federal and state governments, and professional societies have stepped up pressure to make reduction of HAIs a national priority. In a notable example, the Centers for Medicare and Medicaid Services have engaged in "payment reform" in the battle against HAIs and have ceased reimbursing hospitals for expenses related to certain HAIs. By placing that economic burden on the shoulders of hospitals, the Centers for Medicare and Medicaid Services have given hospitals a very concrete incentive to enhance efforts to prevent HAIs.

Healthcare costs continue to spiral upward at an alarming rate, virtually mandating substantial healthcare reform in the United States. President Barack Obama and his new administration have identified healthcare reform as one of their highest priority projects. Improved understanding of the pathogenesis, epidemiology, prevention, and treatment of HAIs should be an integral part of any discussion of healthcare reform. Because of the substantial and unnecessary costs associated with HAIs, addressing the problem of HAIs will improve healthcare quality while simultaneously resulting in substantial cost savings.

The past decade has witnessed increasing national and international momentum for addressing HAIs. In December 2008, the European Union declared HAI prevention a top policy priority. In the United States, national and state consumer groups have raised public and media awareness of both HAIs and multidrug-resistant organisms. Prevention of HAI has become a major patient safety initiative; indeed, the 2 objectives are inextricably linked, both within and outside healthcare settings.[5,6]

In the spirit of patient safety, one-half of all states have, in the past 7 years, established mandatory reporting of HAIs, and some have required screening for certain multidrug-re-

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sistant organisms. Legislatures and consumer advocacy groups argue that mandatory screening and reporting will reduce the incidence of HAIs, although no data yet support this assertion. A major shortcoming of this approach is that it is based on inadequate scientific data. Much of what has been recommended for infection control interventions over the past 2 decades has been based on experience, empiricism, and common sense. Often such approaches seem rational on the basis of our limited science base. Unfortunately, the evidence base is inadequate to support the mandatory implementation of many of these interventions or to guide the manner of their implementation. The Department of Health and Human Services, in a multiagency effort, has developed a National Action Plan to Prevent Healthcare-Associated Infections. This aggressive plan focuses on reporting rates of HAI and enforcing existing guidelines, but it pays insufficient attention to shoring up the research foundation that would, if available, provide the critical underpinnings for science-based guidelines. An approach that mandates the implementation of practices based on inadequate scientific understanding may prove ineffective or, worse, may have unintended consequences, in addition to depleting critical infection control resources.

Professional organizations, such as the Society for Healthcare Epidemiology of America (SHEA), which is a major scientific organization dedicated to healthcare epidemiology and infection prevention,[7-9] the Infectious Diseases Society of America,[9,10] and the Association of Professionals in Infection Control,[7,11] have developed policy statements recommending prioritization of research on the pathogenesis and prevention of HAIs. Any national effort designed to address the problem of HAIs should begin with the following priorities: scrutinizing the science base, developing a prioritized research agenda, conducting studies that address the questions that have been identified, creating and deploying guidelines that are based on the outcomes of these studies, and then initiating studies that assess the efficacy of the interventions.

MAJOR CATEGORIES OF HAI

Five clinical syndromes are responsible for the vast majority of HAIs, as outlined below:

Catheter-associated bloodstream infection. In 2002, nearly 250,000 Americans developed a healthcare-associated bloodstream infection; the overwhelming majority of these infections were due to the presence of intravascular devices. These infections, which account for 14% of all HAIs, are often caused by multidrug-resistant organisms and are responsible for nearly one-third of all HAI-related deaths.[2]

Ventilator-associated pneumonia. Approximately 15% of all HAIs are cases of pneumonia.[2] The incidence of ventilator-associated pneumonia, a subset of healthcare-associated pneumonia, is approximately 1–10 cases per 1,000 ventilator-days, and the attributable mortality rate associated with ventilator-associated pneumonia is at least 10%.[12]

Catheter-associated urinary tract infection. This is the most common type of HAI, accounting for approximately 32% of all HAIs occurring in hospitals,[2] with an attributable mortality rate as high as 13% in cases of HAI complicated by bacteremia.

Surgical site infection. This type of infection occurs in approximately 2% of all surgical procedures and is responsible for approximately 20% of all cases of HAI.[2]

C. difficile *infection.* The incidence of *C. difficile* infection among adults has doubled over the past 5 years,[13] with more than 310,000 cases occurring among hospitalized adults in 2006. A worldwide epidemic strain has caused more severe disease, as evidenced by the quadrupling of the attributable mortality rate associated with *C. difficile* infection and its complications over the past decade.[14]

A handful of multidrug-resistant organisms are responsible for approximately 10%–20% of all HAIs[15] (including some of the aforementioned syndromes), as discussed below.

Methicillin-resistant Staphylococcus aureus. The epidemic of community-associated methicillin-resistant *S. aureus* (MRSA) infection has dramatically increased the overall incidence of MRSA infection, complicating the nosocomial epidemiology and confounding some of the prevention strategies that have been proffered for this perplexing pathogen. MRSA as a cause of HAI has remained essentially stable over the past few years.[15] MRSA is a frequent cause of surgical site infection as well as all classes of device-related infection.

Vancomycin-resistant enterococci. These organisms are responsible for approximately 4% of all HAIs. Vancomycin-resistant enterococci (VRE) are primarily found in bloodstream infections and catheter-related urinary tract infections. One-third of the *Enterococcus* isolates recovered from patients with HAI are resistant to vancomycin.[15]

Highly resistant gram-negative organisms. These types of organisms include multidrug-resistant *Acinetobacter baumannii* and *Pseudomonas aeruginosa,* carbapenemase-producing gram-negative bacilli, and β-lactamase– and cephalosporinase-producing gram-negative rods. Incidence of HAI due to this category of organisms has risen dramatically during the past decade, portending a serious clinical and epidemiological predicament. Infections with these organisms, primarily ventilator-associated pneumonia, bloodstream infection, and catheter-related urinary tract infection, may be nearly impossible to treat.

GAPS IN KNOWLEDGE

The research agenda for addressing the substantial challenges presented by HAIs must be multifaceted. To determine the preventability of infections, we first need to understand how

and why these infections occur. To develop credible prevention strategies, we need the basic research to elucidate the etiology and pathogenesis of these infections. A comprehensive national research agenda on HAIs must include at least 3 major categories of research: pathogenesis, epidemiology, and infection prevention strategies. A fourth area of equal, if not greater, importance is the development, as well as consistent use, of improved approaches to the design and conduct of healthcare epidemiology studies. However, additional scientific research is needed to address the complex problem posed by HAIs.

Pathogenesis. In parallel, basic science and translational research are needed to form a solid scientific basis for understanding the biology of HAIs, including the mechanism(s) of acquisition of these pathogens, the host factors associated with increased risks for colonization and infection, as well as the specific mechanisms responsible for colonization and transmission. Improved knowledge of the pathogenesis of HAIs will lead to more consistent definitions of HAIs as well as to more biologically plausible preventive measures. Table 1 provides an example of the critical factors related to the pathogenesis of HAIs that simply must be addressed in order to provide an adequate science base for making recommendations and implementing effective interventions. The following examples represent only a small fraction of the unanswered questions that need to be addressed:

Biofilms. Further understanding of biofilm chemistry and ecology would almost certainly open the door to interventions that could have a dramatic impact on device-related HAIs. Currently, our understanding of the behavior of microorganisms in biofilms is rudimentary, at best. Research characterizing the behavior of organisms in a biofilm, as well as studies defining the interactions between the immune system and biofilms, likely would lead to the development of materials that have superior resistance to colonization by pathogenic organisms.

Toxins. Despite the fact that *C. difficile*–associated diarrhea was identified as a significant problem associated with the administration of broad-spectrum antimicrobials more than 3 decades ago, research on the roles of the various *C. difficile* toxins in the pathogenesis of the infection remains a hot topic in 2009. Such studies, carefully designed and conducted, would likely lead to the development of improved diagnostic tests as well as additional targets for prophylactic and therapeutic agents.

Virulence factors. Clarification of the role individual virulence factors play in the pathogenesis of HAIs would likely lead to the identification of new targets for therapeutic intervention, as well as new strategies and approaches to interventions.

Mucosal immunity. Our understanding of the role of mucosal immunity in the host defense against specific HAIs is quite superficial. Learning more about the function of the mucosal immune system in the setting of critical illness and/or in circumstances in which foreign material is present may lead to insights into the pathogenesis of HAIs and would likely result in new interventions to prevent ventilator-associated pneumonia.

TABLE 1. Critical Factors Relating to the Pathogenesis of Healthcare-Associated Infections (HAIs) That Must Be Addressed to Develop a Science-Based Discipline of Healthcare Epidemiology

1. Characterization of the chemistry, biology, and ecology of biofilms in vivo.
2. Delineation of the specific contributions of microbial toxins to the pathogenesis of a variety of HAIs caused by staphylococci, streptococci, enterococci, *Clostridium difficile, Pseudomonas aeruginosa,* and a host of additional pathogens associated with HAIs.
3. Identification of specific microbial virulence factors, as well as the contributions of the individual virulence factors to the pathogenesis of colonization and infection caused by important healthcare-associated pathogens.
4. Precise definition of the role of mucosal immunity in the defense against specific HAI syndromes (eg, ventilator-associated pneumonia, among others).

Epidemiology of HAIs. We have an incomplete understanding of the basic epidemiology of most HAIs. An enormous gap remains in our knowledge of the factors influencing bacterial colonization and transmission that result in HAIs in a variety of healthcare settings, for example:

Bacterial transmission. We must further elucidate the respective roles the environment, fomites, other patients, and the hands of healthcare workers play in transmission of *C. difficile,* MRSA, VRE, and highly resistant gram-negative organisms.

Screening for drug-resistant organisms. To learn whether screening individuals for colonization by VRE, MRSA, or drug-resistant gram-negative organisms is useful, we need to establish the optimal body sites for that screening, the duration of colonization, the specific healthcare settings in which screening is effective, and the types of institutions in which this approach is beneficial.

Antimicrobial stewardship. Broad-spectrum antimicrobial use is implicated in the generation and selection of multidrug-resistant bacteria. Several common approaches to this problem have been proposed, but no consensus has been reached regarding optimal techniques for maintaining antimicrobial stewardship in an organization or institution. Studies designed to evaluate specific approaches for reducing an institution's rate of colonization and infection with drug-resistant bacteria using well-defined interventions that address antimicrobial use (eg, restriction, rotation, or other manipulation of antibiotic use) are sorely needed.

Infection prevention strategies. Many of the time-honored current practices in HAI control and prevention are, surprisingly, not based on solid scientific data. Many crucial questions related to the efficacy of interventions remain to

be answered. For these and many other gaps in our armamentarium of infection prevention strategies to be filled, numerous uncertainties must be resolved:

Hand hygiene. From the time of Ignaz Semmelweis and Oliver Wendell Holmes, healthcare professionals have been instructed in the principles and importance of hand hygiene. One hundred fifty years later, we still have an incomplete scientific basis for the efficacy of hand hygiene to prevent infections[16] and healthcare workers' adherence to hand hygiene recommendations.[17] Despite the widespread consensus that hand hygiene adherence is a cornerstone of infection control, there is a paucity of high-quality data to support its efficacy.[16] Although we have learned that alcohol-based hand hygiene products may increase healthcare worker adherence to hand hygiene recommendations, we also know that alcohol-based hand gels do not eliminate *C. difficile* spores. Conversely, despite the existence of recommendations for hand hygiene in the setting of *C. difficile* infection, we do not have science-based guidelines for optimal hand hygiene strategies for health providers caring for *C. difficile*-infected patients.

When to isolate. Recent evidence from cases of asymptomatic *C. difficile* colonization suggests that, historically, we may have been too lenient with regard to isolating patients who have *C. difficile* infection.[18-20] This suggestion is illustrative of the types of studies that need to be performed to provide an adequate science base for the use of isolation as an intervention. Such approaches are deserving of additional scrutiny. Furthermore, we are currently immersed in a controversy about the utility of universal screening and isolation of patients colonized with MRSA, VRE, and multidrug-resistant gram-negative bacteria.

Use of "bundles." Although reasonably strong evidence supports the use of "bundling" preventive practices together to reduce catheter-associated bloodstream infection,[21-23] it remains unclear whether such an approach will reduce other HAIs, such as catheter-associated urinary tract infection.

Decolonization. The issue of decolonization is extremely complex. The questions of when, how, and for whom to attempt MRSA decolonization are far from settled.

Selective digestive tract decontamination and/or oropharyngeal decontamination. Despite several studies that have attempted to address digestive tract decontamination and/or oropharyngeal decontamination, the definitive role of these modestly effective strategies for specific HAI syndromes remains to be established.

Study design. Carefully designed multicenter prospective clinical trials are needed to establish the effectiveness of prevention and control strategies. Over the years, data from many well-intentioned healthcare epidemiology studies have been dismissed because of flaws in study design, some of which were only appreciated years later. Much of the literature of the 1980s and 1990s is dominated by single-site studies using quasi-experimental design (ie, "before and after" intervention studies). Although the limitations of this study design and methodology have been underscored in recent years,[24,25] several varied approaches may help optimize the design of such studies. The ORION Statement published in Europe provides standards for the design of high-quality quasi-experimental studies.[26] In addition, many of the studies that have delineated pathogenetic mechanisms for HAI have been conducted in the setting of ongoing epidemics of these infections. The relationship of pathogenesis in an epidemic setting to pathogenesis in an endemic setting is unknown and needs to be evaluated. Often the major criticisms of these studies relate to their design. The optimal design for such studies remains a matter of debate. Many studies are underpowered for the clinically important outcome and would benefit by coordination and collaboration in multicenter studies.

With respect to design, time-series analyses may be useful for studying a single intervention in a single setting. Cluster-randomized studies, in which groups of individuals are randomly allocated to interventions, have emerged as a useful and credible design, although they require significant resources and the gathering of a broad partnership of institutions and investigators to yield useful results. Those that involve a large, heterogeneous set of hospitals may yield more generalizable results. The discipline of healthcare epidemiology must develop science-based, systematic approaches to the design of these studies, to provide definitive answers to these critical questions. We must develop ways to avoid recreating the wheel with each new study.

Although prospective, randomized trials are one important method of answering narrow healthcare epidemiology questions, they cannot capture the nuanced, real-world impact of diverse and divergent cultural and practical approaches to infection prevention across international boundaries.[27] Cross-country comparisons of macroepidemiologic data and practices, a technique that is frequently used in the social sciences, allow an ecologic approach that can complement interventional and observational infection control studies based on individual patient-level data.

Technology

As we continue into the 21st century, the science of healthcare epidemiology will continue to move into previously uncharted territory. As noted throughout this paper, we believe that we must first conduct the studies that provide the scientific infrastructure for our discipline and then anticipate where technology and scientific progress will guide us. Technology in our discipline is moving rapidly. For example, patient health records, the electronic medical record, and electronic data collection and data mining systems now provide innovative, sophisticated, and unprecedented data sources. The creative design and construction of healthcare facilities that integrate these technological advances may facilitate adherence to isolation protocols or may contribute to the creation of new approaches to the prevention of HAI. For these

reasons, healthcare epidemiologists will undoubtedly be investing intellectual and fiscal resources in technology for the foreseeable future.

RECOMMENDATIONS

The principal recommendations of the SHEA Research Committee are listed in Table 2. A brief overview of each of these recommendations follows:

Creation of a national research agenda. SHEA must articulate a comprehensive, cohesive research agenda that reflects the gaps in knowledge about the pathogenesis, epidemiology, and prevention of HAI and that points the society toward the technology of the future. The agenda must include the major categories of HAI and the multidrug-resistant organisms that are responsible for the vast majority of these infections. The agenda must also address the issues relating to study design. To address these issues, in the fall and winter of 2008–2009, the SHEA Research Committee conducted a survey of the SHEA membership about the most pressing research questions facing the discipline of healthcare epidemiology. In order of priority, the top 5 issues identified by the membership of SHEA were (1) preventing the spread of multidrug-resistant aerobic gram-negative bacilli (eg, *Acinetobacter* species and *Pseudomonas* species) in healthcare settings; (2) implementing effective strategies to ensure antimicrobial stewardship in healthcare settings; (3) preventing the spread of MRSA infection in healthcare settings; (4) developing effective strategies to ensure adherence to hand hygiene standards; and (5) developing strategies to prevent *C. difficile* in healthcare settings.

Creation of a national research consortium. As noted above, because individual institutions may not be able to accrue enough patients to address many of these questions effectively, much of the work yet to be done in this healthcare epidemiology agenda necessitates the creation of a national infection prevention research network. This network will comprise hospitals of varying size, with varying patient demographics, and from different geographic locations. Investigators from these institutions will participate in the design and conduct of these studies, and these institutions will regularly contribute patients and resources to investigator-initiated healthcare epidemiology clinical trials.

Increased funding for basic and applied research. Support for basic, translational, and epidemiological research on HAIs has not been a priority of major funding bodies. Despite the fact that HAIs are among the top 10 causes of death in the United States annually, scientists studying these infections have received relatively little funding, compared with their colleagues in many other disciplines. In 2008, the National Institutes of Health estimated that it spent more than $2.9 billion dollars on funding for HIV/AIDS research, approximately $2.0 billion on cardiovascular disease research, and approximately $664 million on obesity research; by comparison, the National Institute of Allergy and Infectious Diseases provided approximately $18 million for MRSA research. Because the magnitude of the problem has become part of the dialogue on healthcare reform, the SHEA Research Committee believes that now is the time for funding organizations to put resources behind this approach to HAI.

TABLE 2. Society of Healthcare Epidemiology of America Research Committee Recommendations to Address the Increasing Problem of Healthcare-Associated Infections (HAIs)

1. Creation of a national research agenda to identify the most pressing problems in healthcare epidemiology.
2. Creation of a national research consortium of experts in healthcare epidemiology and participating institutions to address the most pressing questions in healthcare epidemiology.
3. Advocating for a substantial increase in funding for basic and applied research in healthcare epidemiology proportionate to the clinical significance of HAIs.

The limited federal funding available to study HAI has the effect of steering young investigators interested in pursuing research on HAI toward other, better-funded fields. Although industry funding is available, the potential conflicts of interest, particularly in the area of infection prevention technologies, make this option seriously problematic.

CONCLUSION

As the United States' population and the world's population age, and as an increasing number of individuals live with immunocompromised states, people will, of necessity, spend increasing amounts of time in hospitals or long-term care facilities. Such patients will be at risk for morbidity and mortality associated with HAI. Infection control and prevention programs were the bellwethers for the patient safety movement and provide a basic paradigm for improving patient safety.[21,28] Although some studies have demonstrated that HAIs can be reduced greatly by concerted, targeted initiatives that emphasize adherence and implementation of bundled interventional strategies,[21] this approach has yet to be realized on a larger scale. Although these efforts are laudable and deserving of increased resource support, as well, our discipline is faced with the need to bundle, implement, and adhere to interventions that we believe to be successful, while simultaneously conducting the basic, epidemiological, pathogenetic, and translational studies that are needed to move our discipline to the next level of evidence-based patient safety. The current convergence of scientific, public, and legislative interest in reducing rates of HAI can provide the necessary momentum to address and answer important questions in HAI research. We must direct our research resources to meet the expectations of our patients that we will keep them safe from infection when they are under our care in medical facilities.

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